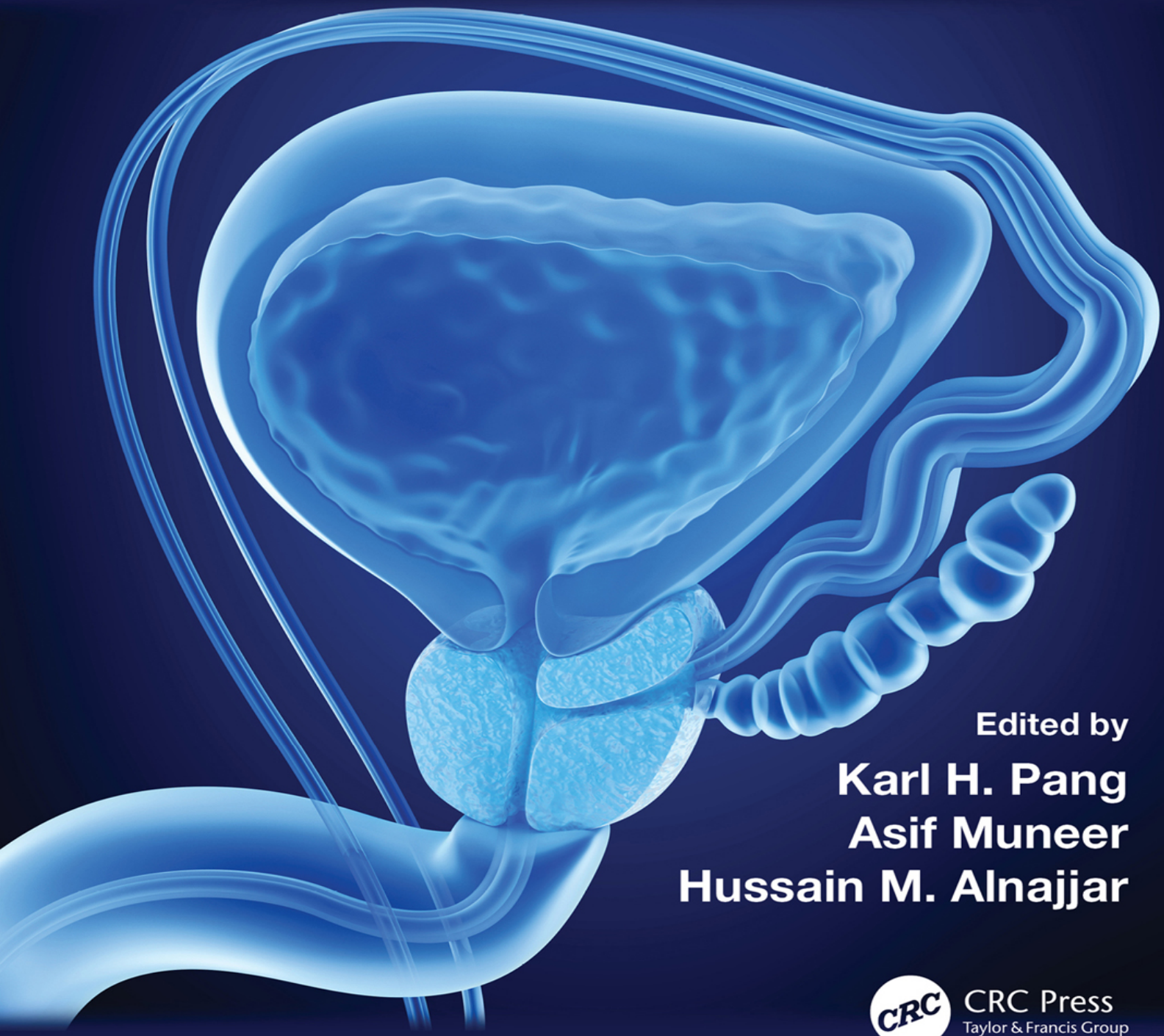
CLINICAL ANDROLOGY

A PRACTICAL HANDBOOK

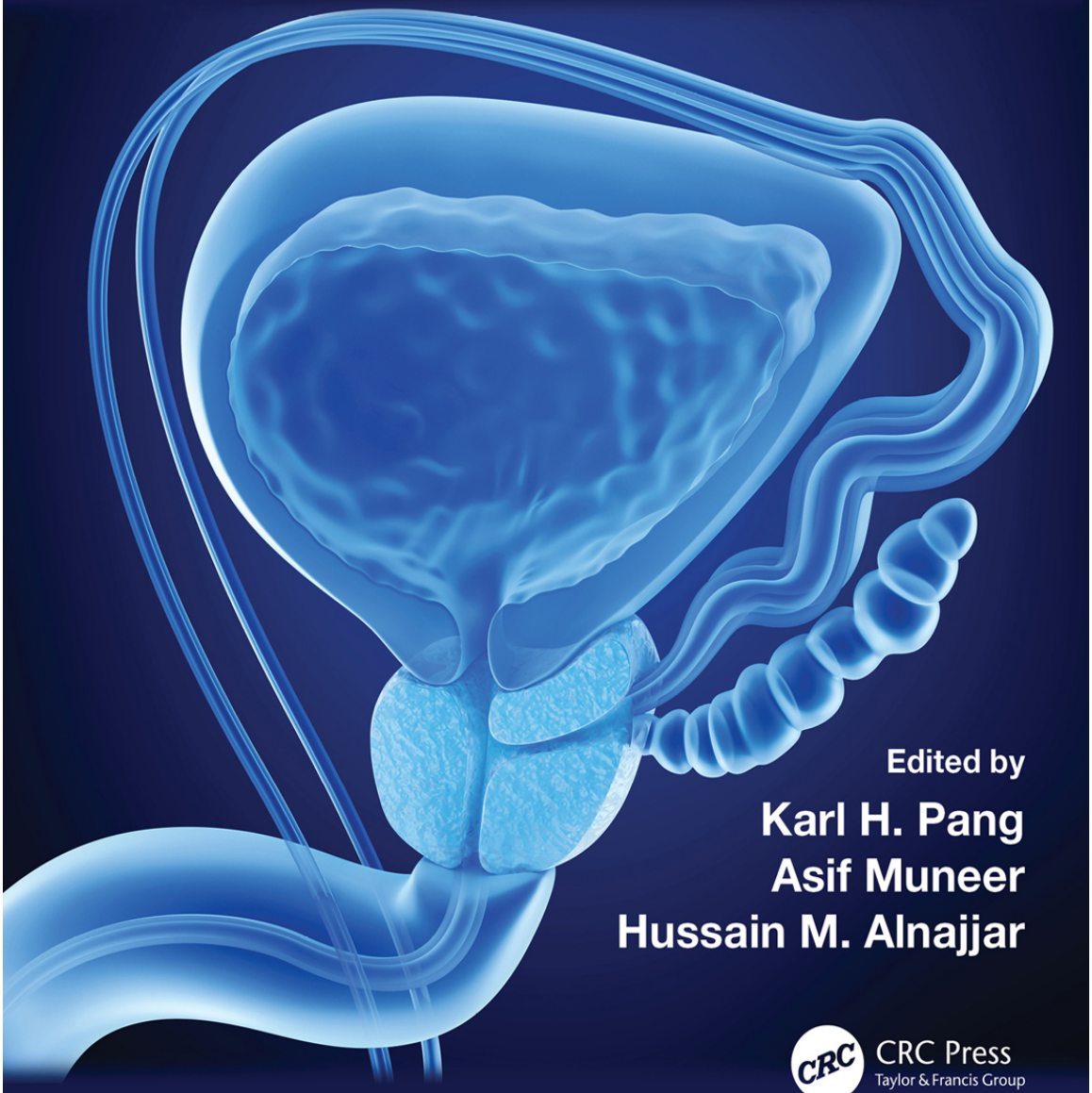


Edited by
Karl H. Pang
Asif Muneer
Hussain M. Alnajjar

CRC Press
Taylor & Francis Group

CLINICAL ANDROLOGY

A PRACTICAL HANDBOOK



Edited by
Karl H. Pang
Asif Muneer
Hussain M. Alnajjar

CRC Press
Taylor & Francis Group

CLINICAL ANDROLOGY

This practical handbook serves as both a comprehensive revision tool for the FRCS (Urol) and FEBU examinations and a concise reference to the theoretical and clinical aspects of andrology – an often underrepresented subspecialty in medical education and postgraduate training.

Covering key topics such as reproductive system anatomy, embryology and physiology, the guide also addresses clinical and surgical management of common and complex andrological conditions, including erectile dysfunction, ejaculatory disorders, penile curvature, infertility, penile emergencies and penile and testicular cancers.

Designed to support a wide range of healthcare professionals, this resource is not only valuable for those preparing for specialist exams, but also for practising consultants seeking a focused update on contemporary andrology practice. Its practical approach makes it a useful tool for refining clinical decision-making in both acute and elective settings. In addition, it offers accessible guidance for specialist nurses, primary care physicians and psychosexual counsellors involved in the multidisciplinary care of patients with andrological concerns.

CLINICAL ANDROLOGY

A Practical Handbook

Edited by

Karl H. Pang, Asif Muneer and Hussain M. Alnajjar

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

Designed cover image: Shutterstock

First edition published 2026
by CRC Press
2385 NW Executive Center Drive, Suite 320, Boca Raton FL 33431

and by CRC Press
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN

CRC Press is an imprint of Taylor & Francis Group, LLC

ISBN: 9781032284576 (hbk)
ISBN: 9781032282862 (pbk)
ISBN: 9781003296911 (ebk)

DOI: 10.1201/b22940

Typeset in Advent Pro
by Deanta Global Publishing Services, Chennai, India

Contents

About the Editors

Karl H. Pang MBChB, BSc (Hons), MSc, PhD, AFHEA, FRCS (Urol), FEBU

Karl Pang is a Consultant Urological Surgeon and Andrologist (locum) at Chelsea and Westminster Hospital NHS Foundation Trust, and an Honorary Associate Professor at University College London. He underwent specialist training in the Yorkshire and Humber Deanery and received fellowship training in andrological surgery at University College London Hospital. He was Clinical Assistant Professor within the Department of Surgery, University of Hong Kong and Queen Mary Hospital between 2023 and 2024. He obtained his intercalated BSc in Immunobiology from King's College London, and his MSc in Medical Research and PhD in Cancer Epigenetics from the University of Sheffield. He received funding from the Urology Foundation and the Royal College of Surgeons of England for his PhD and ongoing research.

He was the chief editor of *Basic Urological Science (CRC Press)* and *Challenging Cases in Urological Surgery (Oxford Press)*. The former book received an annual BMA book award. He previously served in both the EAU-YAU Men's Sexual and Reproductive Health Group and the Penile and Testis Cancer Group, and is currently a senior associate of the EAU Guidelines Office and a member of the ISSM Young Researchers Committee. His clinical and research interests are in men's sexual and reproductive health and male genital cancer.

Asif Muneer MBChB, MD, PhD, FRCS (Urol)

Asif Muneer is a Professor of Urology and Surgical Andrology at University College London. He is a Consultant Urological Surgeon and

Andrologist based at University College London Hospital. Having completed his research degree (MD) at UCL, he went on to complete his higher surgical training in Oxford. He has also completed a PhD and published widely on all aspects of urology, with his main interest being andrology and male genital cancers. He has edited several books including *Textbook of Penile Cancer*, *Atlas of Male Genitourethral Surgery* and *Prosthetic Surgery in Urology*. He has lectured and delivered training courses both nationally and internationally and is the Past President of the British Society for Sexual Medicine and past Chair of the BAUS Section of Andrology. He is also past honorary Secretary of BAUS.

He has received a number of awards including the Keith Yeates Gold Medal for the intercollegiate FRCS and the Harold Hopkins Golden Telescope award from the British Association of Urological Surgeons.

Hussain M. Alnajjar BSc (Medical Sciences), MBBS, ChM (Urol), FEBU, FRCS (Urol)

Hussain M. Alnajjar is a Consultant Urological and Andrological Surgeon at University College London Hospitals (UCLH) and an Honorary Associate Professor at University College London (UCL). He leads a high-volume, specialised andrology practice, with a national quaternary referral base for complex cases.

His clinical expertise includes advanced surgical management of Peyronie’s disease, penile prosthesis implantation, male infertility, penile and testicular cancer, and male genital reconstruction. His practice is defined by excellence in care, innovation in technique and commitment to outcomes-driven surgery.

Mr Alnajjar has been awarded numerous prestigious awards for his outstanding clinical and academic achievements. He is also widely published in leading peer-reviewed journals and has authored and co-edited several influential textbooks and chapters in the field of andrology. He remains actively involved in clinical research and academia. Mr Alnajjar is a national and international speaker.

He was recently elected Secretary of the Andrology Executive Committee of the British Association of Urological Surgeons (BAUS). A dedicated educator and mentor, he trains senior andrology fellows and acts

as a proctor for penile prosthesis implantation and complex andrological surgeries. He is an examiner for the Membership of the Royal College of Surgeons of England (MRCS) and has formerly served on the European Board of Urology Examination Committee, as well as the scientific committees of the European Society for Sexual Medicine (ESSM) and the Middle East Society for Sexual Medicine (MESSM).

List of Contributors

Kamran Ahmed
Sheikh Khalifa Medical City
Abu Dhabi, UAE
Khalifa University
Abu Dhabi, UAE
King's College London
London, UK

Hussain M. Alnajjar
University College London Hospitals
NHS Foundation Trust
London, UK
Division of Surgery and Interventional Science
University College London, London, UK

Ali Alrawahneh
University College London Hospitals
NHS Foundation Trust
London, UK

Nasreen Aziz
Barts Health NHS Trust

London, UK

Matthew H.V. Byrne
University of Oxford
Oxford, UK

Walter Cazzaniga
The Royal Marsden NHS Foundation Trust
London, UK

Francesco Claps
University of Trieste
Trieste, Italy
Cattinara Hospital – ASUGI
Trieste, Italy

Nipun Lakshitha de Silva
General Sir John Kotelawala Defence University
Rathmalana, Sri Lanka

Muslim Dogan Deger
Tekirdag City Hospital
Tekirdag, Turkey

Ankit Desai
Watford General Hospital, West Hertfordshire Teaching Hospitals NHS Trust
Watford, UK

Ian Eardley

Leeds Teaching Hospitals NHS Trust
Leeds, UK

Amr Elmekresh
Dubai Hospital
Dubai, UAE

Christina Fontaine
Southmead Hospital, Bristol Urological Institute
Bristol, UK

Giulio Garaffa
Whittington Hospital, Whittington Health NHS Trust
London, UK

Selcuk Guven
Necmettin Erbakan University Rectorate
Konya, Turkey

Paul Hadway
Royal Berkshire NHS Foundation Trust
Reading, UK

Muhammad Haider
Barts Health NHS Trust
London, UK

Neil James Harvey
Bolton NHS Foundation Trust
Farnworth, UK

Rozh Jalil
Mubadala Health Dubai and Orchid Fertility and Andrology centre
Dubai, UAE

Channa N. Jayasena
Imperial College London
London, UK

Adam Jones
Manchester University NHS Foundation Trust
Manchester, UK

Odunayo Kalejaiye
Southmead Hospital, Bristol Urological Institute
Bristol, UK

Jas Kalsi
Frimley Health NHS Foundation Trust
Frimley, UK

Niall Kelly
Galway University Hospital
Galway, Ireland

Pinky Kotecha
Barts Health NHS Trust
London, UK

Giovanni Liguori
University of Trieste

Trieste, Italy
Cattinara Hospital – ASUGI
Trieste, Italy

Jamie Lindsay
North Central and East London Deanery
London, UK

Suks Minhas
Imperial College Healthcare NHS Trust
London, UK

Vaibhav Modgil
Manchester University NHS Foundation Trust
Manchester, UK
University of Manchester, Faculty of Biology, Medicine, and Health, UK

Chloe Mount
Buckinghamshire Healthcare NHS Trust
Buckinghamshire, UK

Asif Muneer
University College London Hospitals
NHS Foundation Trust
London, UK
Division of Surgery and Interventional Science, University College London
London, UK

David Nicol
The Royal Marsden NHS Foundation Trust
London, UK

Luca Ongaro
University of Trieste
Trieste, Italy
Cattinara Hospital – ASUGI
Trieste, Italy

Nadir I. Osman
Sheffield Teaching Hospitals NHS Foundation Trust
Sheffield, UK

Karl H. Pang
Division of Surgery and Interventional Science, University College London
London, UK

Ian Pearce
Manchester Royal Infirmary, Manchester University NHS Foundation Trust
Manchester, UK

Hannah Pendegast
Chesterfield Royal Hospitals NHS Foundation Trust
Chesterfield, UK

Prabhakar Rajan
Barts Health NHS Trust

London, UK

David J. Ralph
University College London Hospitals
NHS Foundation Trust
London, UK
The Institute of Urology London and St Peter's
Andrology Centre
London, UK

Karen Randhawa
Western Health & Social Care Trust
Londonderry, Northern Ireland, UK

Rowland Rees
University Hospital Southampton
NHS Foundation Trust
Southampton, UK

Matthew J. Rewhorn
Glasgow Royal Infirmary, NHS Greater Glasgow & Clyde
Glasgow, UK

Philippa Sangster
University College London Hospitals
NHS Foundation Trust
London, UK

Xenia Sara
Pinderfields Hospital, Mid Yorkshire Hospitals

NHS Trust
Wakefield, UK

Maria Satchi
King’s College Hospital NHS Foundation Trust
London, UK

Kirby F. Sebro
George Eliot Hospital
Nuneaton, UK

Ege Can Serefoglu
Biruni University
Istanbul, Turkey

Majed Shabbir
Guy’s and St Thomas’ NHS Foundation Trust
London, UK

C. J. Shukla
NHS Lothian
Edinburgh, UK

Stanley Tang
University College London Hospitals
NHS Foundation Trust
London, UK

Carlo Trombetta
University of Trieste

Trieste, Italy
Cattinara Hospital – ASUGI
Trieste, Italy

Hermione Tsoi
Sheffield Teaching Hospitals NHS Foundation Trust
Sheffield, UK

Shafi Wardak
Royal Berkshire NHS Foundation Trust
Reading, UK

Sachin Yallapa
University Hospitals Birmingham NHS Foundation Trust
Birmingham, UK

Mark Yao
Dartford and Gravesham NHS Trust
Dartford, UK

Preface

The term andrology is derived from the Greek word *andros*, meaning ‘male’. It is a surgical subspeciality concerned with disorders of the male genital and reproductive systems. In our opinion, andrology is both an important and fascinating specialty. However, we feel that from our experience, andrology is undertaught at the undergraduate level and underemphasised in postgraduate urology training programmes worldwide. This may be in part due to its highly specialised nature, with services commonly centralised in high-volume expert centres –particularly in the UK. Trainees often find andrology challenging when it comes to postgraduate exams. This is mainly because trainees are less familiar with this subspeciality. With this in mind, we produced this book to summarise the key elements of andrology most relevant to medical students, trainees, senior fellows, newly qualified specialist clinicians and consultants.

This book covers various benign surgical andrology and male genital cancer topics, including erectile dysfunction, ejaculatory disorders, penile curvature, male infertility, penile cancer and testicular cancer. In also addresses common andrological emergencies, such as priapism, Fournier’s gangrene and genital trauma are covered.

Each chapter has been led by an expert in the field, and we sincerely thank all our contributors for their hard work in helping to put this book together. We hope you enjoy reading it.

Karl H. Pang, Asif Muneer and Hussain M. Alnajjar

1 Embryology of the Male Reproductive System

Mark Yao, Majed Shabbir and Maria Satchi

DOI: 10.1201/b22940-1

Introduction

Fertilisation is the fusion of DNA from a spermatozoon (male gamete) and an oocyte (female gamete) [1, 2]. This usually occurs in the fallopian tube and marks the beginning of gestation.

A blastocyst (ball of cells) forms after fertilisation and implants in the uterine lining around day 6 [1]. The process of gastrulation then occurs, where a single layer of cells develops into multiple layers [3]. During this time, 2 cavities form: the amniotic cavity, which is closer to the endometrial lining, and the yolk sac. The embryo forms at the interposition of these two cavities.

By day 16, the blastocyst has developed into a structure called the trilaminar or embryonic disc [1]. This structure is composed of 3 germ layers: ectoderm, mesoderm, and endoderm. The mesoderm, which arises in part from the movement of cells from the amniotic cavity, gives rise to the reproductive system, kidneys, and other organs and tissues.

By day 21, the mesoderm has folded. It can be differentiated into the paraxial mesoderm, intermediate mesoderm, and the lateral plate mesoderm [1], where the intermediate mesoderm will develop into the kidneys, gonads, and ductal system [4].

Developing from the intermediate mesoderm, the mesonephros is a temporary excretory organ which functions between weeks 4–8 [5]. A 2-duct system develops lateral to the mesonephros: the mesonephric (Wolffian) duct and laterally the paramesonephric (Müllerian) duct. While

the mesonephric ducts drain bilaterally into the anterior cloaca, the paramesonephric ducts fuse and terminate as a single structure at the same site [6, 7]. In the male, the Wolffian ducts give rise to the vas deferens, epididymides, seminal vesicles, and central zone of the prostate, whereas in females they regress [1]. The Mullerian ducts regress in males; whereas in females, it goes on to form the majority of the female genital system.

Abnormal formation of the mesonephric ducts can cause malformations in both urinary and genital systems. Approximately 80% of cases of congenital bilateral absence of the vas deferens are caused by mutations in the cystic fibrosis transmembrane conductance gene (CFTR, chromosome 7) and account for 2% of male infertility [8]. Ectopic ureters are often associated with ipsilateral renal agenesis and are caused by a more cephalad development of the ureteric bud [9]. This prevents normal insertion into the bladder trigone, and the ureter instead remains attached to the distal mesonephric duct, draining more caudally nearer to other structures arising from the distal mesonephric duct, such as the seminal vesicles and ejaculatory ducts. Further development of the mesonephric ducts relies on androgens from Leydig cells [10]. Mutations in androgen receptor genes can cause a spectrum of androgen insensitivity syndromes (AIS). Subtypes include complete, partial, or mild AIS [11]. Patients with complete or partial AIS are 46,XY males with feminised external genitalia, absent/underdeveloped Müllerian structures, normal testosterone, and normal testes with impaired spermatogenesis. Both complete- and partial-androgen-insensitivity syndrome individuals present with normal female external genitalia with a lack of internal female genitalia; however, patients with partial AIS will have partially virilised external genitalia (clitoromegaly, fusion of posterior labia). Mild AIS patients will have normal external male genitalia with possible impaired spermatogenesis, often presenting during adolescence with gynaecomastia and under-virilised secondary sexual characteristics.

The urogenital ridge appears at week 5 and will subsequently differentiate into the medial gonadal ridge and the lateral nephrogenic cord (or nephrogenic ridge) [12]. The urogenital ridge is formed of mesenchyme and mesonephric cells. Primordial germ cells migrate from the epiblast (yolk sac), across the coelomic cavity via the vitelline duct at weeks 4–5 [13]. They infiltrate proliferating epithelial cells of the urogenital ridge.

Through a process called reciprocal interaction, the primordial germ cells and epithelial cells form the primitive sex cords [14]. The primordial germ cells will go on to give rise to the subsequent gametes (oocytes or spermatozoa).

Initially, the mesonephros and the gonadal ridge are continuous, but with continued development, the gonadal ridge separates from the mesonephros but remains attached by a peritoneal fold (mesovarium in females or mesorchium in males) [15].

Testis Development

Until week 6, the embryological development between the sexes is the same [6]. Sex is determined by the 23rd pair of chromosomes; either XX for female or XY for male. Gonads will by default develop down the female pathway unless stimulated into male differentiation by the testis-determining gene. The testis-determining gene encodes for testis-determining factor (TDF) or the sex-determining region Y protein (SRY), found on the Y chromosome short arm (Yp11) [6]. The gonadal medulla differentiates in male development whereas the gonadal cortex differentiates in female development.

By week 7 in the male foetus, the central mass of the gonad separates into testicular cords and interstitial tissue. Transcription factor SOX9 is activated by the SRY gene within the pre-Sertoli cells to activate anti-Müllerian hormone (AMH), also known as Müllerian inhibiting substance (MIS), and promotes the migration of cells from the mesonephric mesenchyme into the developing gonad [6]. The pre-Sertoli cells then assemble to surround the germ cells and are subsequently referred to as Sertoli cells [16].

From week 7, the pre-Sertoli cells secrete AMH/MIS, a glycoprotein responsible for regression of the paramesonephric (Müllerian) ducts. In males, this regression may leave a vestigial remnant such as the prostatic utricle and appendix testis (or hydatid of Morgagni) [10]. Torsion of the appendix testis can mimic testicular torsion in its clinical presentation [17]. From week 9, Leydig cells begin to secrete testosterone and insulin-like

growth factor 3, the latter of which causes the transabdominal (first stage) of testicular descent [6].

From week 8, Leydig cells are formed from mesenchymal cells in the interstitial space [6]. The testicular cords organise towards the hilum and form a network which will become the rete testis. Seminiferous tubules differentiate further from the hilum and connect to the rete testis. On the periphery of the gonad, the basement membrane of the gonadal ridge will become the tunica albuginea.

During weeks 8–12, under the influence of testosterone secreted by the Leydig cells, the upper part of the mesonephric duct will lengthen and fold, developing into the epididymis [10]. The mesonephric duct will also develop tubules towards the testis to form the efferent ductules, which integrates into the rete testis connecting the epididymis to the seminiferous tubules [6].

The testis is initially connected cranially via the cranial suspensory ligament to the posterior abdominal wall, and caudally to the labioscrotal folds by fibrous bands [10]. Testicular descent occurs from their developing position within the embryonic abdomen to the scrotum in 2 stages (Table 1.1) (Figure 1.1):

Table 1.1 Stages of Testicular Descent⏎

	Week	Hormone	Site of release	Action
Transabdominal stage	8–15	AMH/MIS	Sertoli cells	• Descent along posterior abdominal wall to internal inguinal ring • Gubernaculum extends from inguinal region to scrotum
Inguinoscrotal stage	24–35	Androgens	Leydig cells	• Weeks 24–28: Passage through inguinal canal • Weeks 28–35: Descent into scrotum

Abbreviations: AMH, Anti-Müllerian Hormone; MIS, Müllerian Inhibiting Substance.

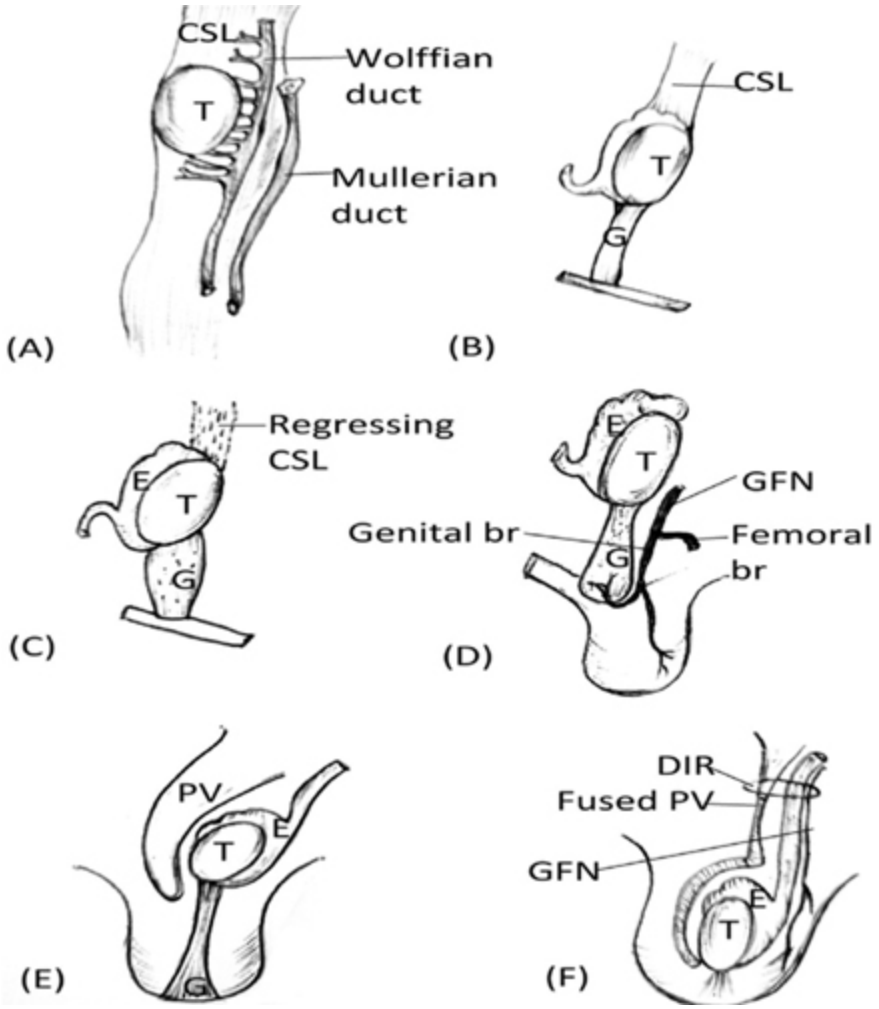


Figure 1.1 Diagram showing testicular descent.⏎

1. **Transabdominal stage** of descent occurs between weeks 8–15 [10].
    - This process is mediated by AMH and insulin-like factor 3 secreted by Leydig cells.
    - By week 12, the cranial suspensory ligaments are no longer present. The caudal fibrous bands develop into the gubernaculum, which pulls the testis down along the posterior abdominal wall to the internal inguinal ring.
2. **Inguinoscrotal stage** of descent occurs between weeks 24–35 [10].
    - This process is mediated by androgens.
    - Testis traverses the inguinal canal between weeks 24–28.
    - Pulled into the scrotum in weeks 28–35.
    - During descent through the inguinal canal, it takes a fold of peritoneum from the abdominal cavity – the processus vaginalis – and pulls layers of the muscles and fascia of the abdominal wall. These will form the layers of the spermatic cord: external oblique

forming external spermatic fascia, internal oblique forming cremasteric fascia, and tranversalis fascia forming internal spermatic fascia.

By the time the testis has reached its terminal position, the processus vaginalis is connected to the abdominal cavity only by its superior aspect. Shortly after birth, the processus vaginalis typically obliterates, and the remaining scrotal part will become the tunica vaginalis. Failure to obliterate its connection results in patent processus vaginalis, clinically presenting as a congenital inguinal hernia or hydrocele [18]. Abnormalities with either stage of descent presents as undescended testes, which can be intrabdominal, within the inguinal canal, or at the scrotal neck [10]. The testis will stay at the internal inguinal ring until the third trimester.

Development of the Prostate, Seminal Vesicles, and Vas Deferens

Caudally to the developing gonad, the mesonephric duct is surrounded by smooth muscle and will become the vas deferens. In 95% of patients with cystic fibrosis, mutation in the CFTR gene can cause congenital bilateral absence of the vas deferens [19]. The vas deferens terminates at the urogenital sinus, either side of the Müllerian tubercle, where the paramesonephric ducts join the urogenital sinus [20]. The seminal vesicles develop from an outpouching at the distal mesonephric duct at week 12 in response to testosterone.

Testosterone acts on target cells, which contain the enzyme 5-alpha reductase, and converts testosterone to dihydrotestosterone (DHT). DHT is a more potent androgen with a 2-fold greater affinity for androgen receptors than testosterone [21]. It plays an important role in differentiation of the male external genitalia, the penis, scrotum, and prostate [10].

The prostate begins to develop at week 10, from the lower part of the urogenital sinus under the influence of DHT [22]. Paired epithelial prostatic buds form on the posterior urogenital sinus. The buds elongate, branch and canalise simultaneously from week 12. The top pair arises from mesoderm and forms periurethral/transitional zones, and the lower pair arises from endoderm to form the peripheral zone. A pair of buds at the level of the

Müllerian tubercle will fuse with it and go on to canalise at week 18 to form the prostatic utricle.

A Müllerian duct cyst occurs as a lack of complete regression of the distal ends of the paramesonephric (Müllerian) duct and can occur anywhere along its line of regression. When it presents in the prostate midline, it can be difficult to differentiate from a prostate utricle cyst [23]. Utricle cysts always occur in the midline at the level of the verumontanum. Both Müllerian duct cysts and utricle cysts can cause ejaculatory duct obstruction. Patients may present with infertility, haematospermia, pelvic pain, or dysuria. Diagnosis is typically made using transrectal ultrasound or MRI of the prostate, which may reveal dilated ejaculatory ducts, with or without dilated seminal vesicles. Surgical management can be offered in selected cases with transurethral resection of the ejaculatory ducts (TURED). Müllerian duct cysts are rarer, usually larger, and have more lateral extension compared to the centrally located utricle cysts and therefore respond less well to TURED in comparison.

Up to week 15, the endodermal lining of the urethra and mesenchyme undergo reciprocal induction [24]. These tissues form the glandular acini and canalise to form the prostatic ducts, draining into the urethra [6]. The prostate develops around the urethra, in a concentric manner [22]. Mesenchyme gives rise to the prostatic capsule and smooth muscle. The mesonephric duct contributes to the formation of the central zone of the prostate, as well as the intraprostatic vas deferens and ejaculatory ducts. In the mature prostate, the glandular tissue near ducts is secretory, whereas glandular tissue at the peripheries is less secretory but exhibits a higher mitotic index [22].

The bulbourethral glands (Cowper’s glands) develop at a similar time to the prostate, also under the action of DHT, in the urogenital sinus, from the region that will become the membranous urethra [25]. These paired exocrine glands secrete clear mucus prior to ejaculation, serving both as a lubricant and to neutralise the acidity of the seminal fluid in the urethra.

Development of the Penis and Scrotum

The urogenital folds fuse with the cloacal membrane in the midline to form the genital tubercle, composed of mesoderm and ectoderm. Virilisation of the external genitalia is stimulated by DHT [10]. It stimulates the differentiation of ectoderm into penile shaft skin and prepuce, and mesoderm of the genital tubercle into corpus cavernosa and the glans penis. After these structures have developed, the urethral groove is visible on the ventral genital tubercle.

Around week 6, labioscrotal swellings develop laterally to the urogenital folds and surround the opening of the urogenital sinus (ostium). Fibrous bands connect the labioscrotal swellings to the caudal developing testis. These bands will develop into the gubernaculum in males and the round ligament in females [6].

The labioscrotal folds fuse towards the midline on the ventral aspect, creating the epithelial seam (midline raphe in maturity) and what will become the scrotum. Fusion of the labioscrotal folds closes the urethral groove, creating a patent lumen by week 15. Abnormalities of closure present as hypospadias [2].

A–**C** shows trans-abdominal phase. **A** shows testis (T) on urogenital ridge with Müllerian (paramesonephric), Wolffian (mesonephric) ducts, and cranial suspensory ligament (CSL). **B** Thickening of gubernaculum (G) positions testis (T). **C** Development of epididymis (E) and regression of cranial suspensory ligament (CSL). **D**–**F** shows inguinoscrotal phase. **C** gubernaculum (G) enlarges due to *insulin-like 3 hormone* (Leydig cells), supported by AMH. **D** The genital branch of genitofemoral nerve (GFN) supplies the gubernaculum and scrotal wall. During the inguinoscrotal phase, **E** and **F** demonstrate the migration and elongation of the gubernaculum, along with the processus vaginalis (PV), as they move through the deep inguinal ring (DIR) to reach the scrotum (26).

Summary Table

Testes	• Undifferentiated sex gonad until week 6 • Sex-determining region Y protein (SRY), of the Y chromosome, causes differentiation into testes • 2 stages of testicular descent • AMH and INSL-3 stimulates transabdominal stage, weeks 8–15 • Androgens stimulate inguinoscrotal stage, weeks 24–35
Vas deferens, epididymis, seminal vesicles	• Mesonephric (Wolffian) duct develops into the vas deferens, epididymis, and seminal vesicles (SV) • Epididymis develops at weeks 8–12 • SVs develop as an outpouching of the mesonephric duct from week 12
Prostate	• Prostate starts to develop from week 10 • Central gland arises from the mesonephric duct • Transitional zone arises from mesoderm • Peripheral zone arises from endoderm
Scrotum	• Develops under action of dihydrotestosterone (DHT) from labioscrotal folds • Fusion of labioscrotal folds and formation of urethra by week 15 • Hypospadias is caused by failure of fusion of the labioscrotal folds
Penis	• Develops under action of DHT • Penile shaft skin and prepuce arises from endoderm • Corpus cavernosa and the glans penis arises from the mesoderm of the genital tubercle

References

1. Thomas DF. Embryology. In: *Essentials of Paediatric Urology*. 2nd ed. CRC Press; 2008.⏎
2. Thomas DFM. Embryology. In: *The Scientific Basis of Urology*. 3rd ed. CRC Press; 2010.⏎
3. Muhr J, Arbor TC, Ackerman KM. Embryology, Gastrulation. In: *StatPearls*: StatPearls Publishing; 2024 [cited 2024 Mar 22]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK554394/⏎

4. Johnston A, Amer T, Aboumarzouk O, Hashim H. Embryology, Anatomy, and Physiology of the Bladder. In: *Basic Urological Sciences*. CRC Press; 2021.⏎
5. Sturch P, Madaan S, Sriprasad S. Embryology, Anatomy, and Physiology of the Kidneys and Ureters. In: *Basic Urological Sciences*. CRC Press; 2021.⏎
6. Rey R, Josso N, Racine C. Sexual Differentiation. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, *et al.*, editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2024 Mar 22]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK279001/⏎
7. Wieder J. *Pocket Guide to Urology*. 6th ed J. Wieder Medical; 2021.⏎
8. Lin CH, Huang TY. Congenital bilateral absence of the vas deferens (CBAVD) with bilaterally present seminal vesicles. *Urol Case Rep*. 2020 Mar 10;31:101131.⏎
9. Rickwood AM, Boddy NPM and SAM. Duplication anomalies, ureterocoeles and ectopic ureters. In: *Essentials of Paediatric Urology*. 2nd ed. CRC Press; 2008.⏎
10. Satchi M, Muneer A. Embryology, anatomy, and physiology of the male reproductive system. In: *Basic Urological Sciences*. CRC Press; 2021.⏎
11. Gottlieb B, *Trifiro MA.* Androgen Insensitivity Syndrome. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJ, *et al.*, editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2024 Mar 22]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1429/⏎
12. Bowles J, Koopman P. 33 - Gonads–Müllerian Ducts. In: Lanza R, Gearhart J, Hogan B, Melton D, Pedersen R, Thomson J, *et al.*, editors. *Handbook of Stem Cells* [Internet]. Burlington: Academic Press; 2004 [cited 2024 Mar 22]. pp.

345–357. Available from: https://www.sciencedirect.com/science/article/pii/B9780124366435500420⏎
13. Cheng H, Shang D, Zhou R. Germline stem cells in human. *Signal Transduct Target Ther*. 2022 Oct 2;7(1):1–22.⏎
14. Pirouz M, Klimke A, Kessel M. The reciprocal relationship between primordial germ cells and pluripotent stem cells. *J Mol Med*. 2012 Jul;90(7):753–761.⏎
15. Aslan AR, Kogan BA, Gondos B. Chapter 191 - Testicular Development. In: Polin RA, Fox WW, Abman SH, editors. *Fetal and Neonatal Physiology*. 3rd ed [Internet]. Philadelphia (PA): W.B. Saunders; 2004 [cited 2024 Mar 22]. pp. 1950–5. Available from: https://www.sciencedirect.com/science/article/pii/B9780721696546501946⏎
16. Pelosi E, Koopman P. Development of the Testis. In: *Reference Module in Biomedical Sciences* [Internet]. Elsevier; 2017 [cited 2024 Mar 22]. Available from: https://www.sciencedirect.com/science/article/pii/B9780128012383998544⏎
17. Murphy FL, Fletcher L, Pease P. Early scrotal exploration in all cases is the investigation and intervention of choice in the acute paediatric scrotum. *Pediatr Surg Int*. 2006 May;22(5):413–416.⏎
18. Madden NP. Testis, hydrocoele and varicocoele. In: *Essentials of Paediatric Urology*. 2nd ed. CRC Press; 2008.⏎
19. de Souza DAS, Faucz FR, Pereira-Ferrari L, Sotomaior VS, Raskin S. Congenital bilateral absence of the vas deferens as an atypical form of cystic fibrosis: reproductive implications and genetic counseling. *Andrology*. 2018 Jan;6(1):127–135.⏎
20. Jin ZW, Abe H, Hinata N, Li XW, Murakami G, Rodríguez-Vázquez JF. Descent of mesonephric duct to the final position

of the vas deferens in human embryo and fetus. *Anat Cell Biol*. 2016 Dec;49(4):231–240.⏎
21. Kinter KJ, Amraei R, Anekar AA. Biochemistry, Dihydrotestosterone. In: *StatPearls*: StatPearls Publishing; 2024 [cited 2024 Mar 22]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK557634/⏎
22. Tam J, Ahmed H. Embryology, anatomy, and physiology of the prostate. In: *Basic Urological Sciences*. CRC Press; 2021.⏎
23. Devaraju S, Nerli RB, *Hiremath MB. A large mullerian duct cyst presenting as an abdominal mass with ipsilateral renal agenesis: an unusual presentation*. *Nephro-Urol Mon*. 2012;4(4):640–643.⏎
24. Cunha GR, Vezina CM, Isaacson D, Ricke WA, Timms BG, Cao M, *et al.* Development of the human prostate. *Differ Res Biol Divers*. 2018;103:24–45.⏎
25. Chughtai B, Sawas A, O'Malley RL, Naik RR, Ali Khan S, Pentyala S. A neglected gland: a review of Cowper's gland. *Int J Androl*. 2005 Apr;28(2):74–77.⏎
26. Reny SE, Mukherjee A, Mol PM. The curious case of testicular descent: factors controlling testicular descent with a note on cryptorchidism. *Afr J* 2023 Mar 2;29(1):12.⏎

2 Anatomy and Physiology of the Male Reproductive System

Adam Jones, Christina Fontaine, Odunayo Kalejaiye and Vaibhav Modgil

DOI: 10.1201/b22940-2

ANATOMY

Testes

The testes (Figure 2.1) are paired male reproductive organs responsible for spermatogenesis and steroidogenesis. They are located within the scrotum, which allows for temperature regulation to aid spermatogenesis. The testes are ovoid, with average volume 12–20 ml and a longitudinal length of 4.5–5.1 cm [1].

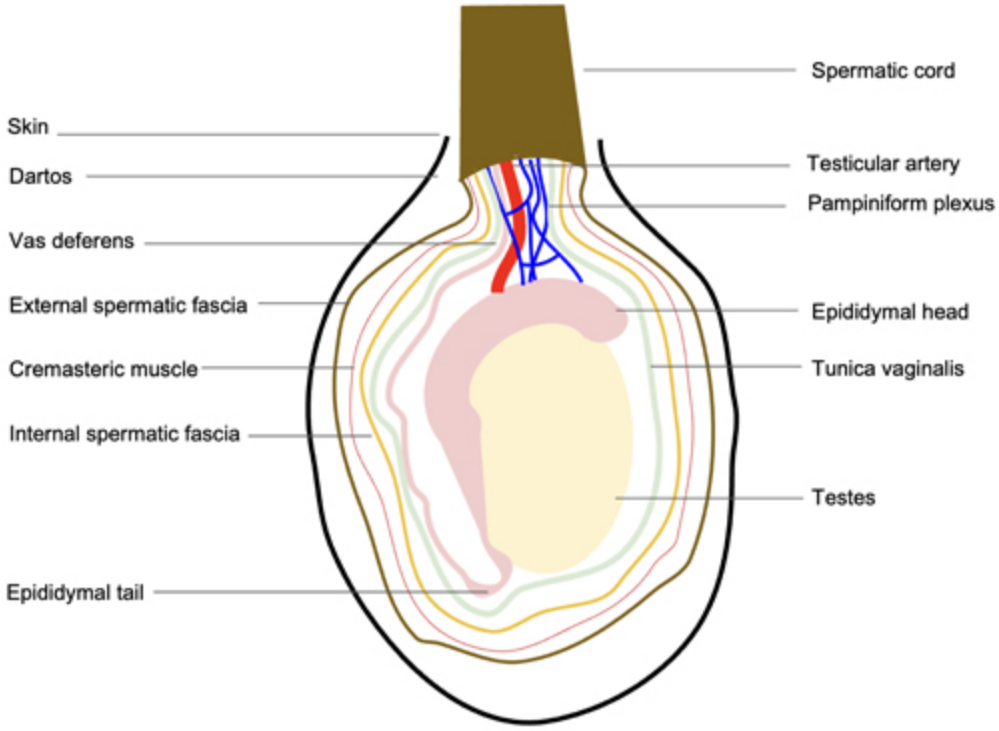


Figure 2.1 Scrotal structures.⏎

The parenchyma of each testis is surrounded by a thick, pearly, fibrous capsule – tunica albuginea, and projects within the testis to form 200–300 compartments (lobules). Within each lobule are the seminiferous tubules and interstitial tissue.

The interstitial tissue is composed of Leydig cells, lymphovasculature, mast cells and macrophages.

The seminiferous tubules contain:

- Primordial germ cells: Located at the basement membrane of the seminiferous tubules, these are precursor cells for spermatogonia.
- Supporting Sertoli cells: Provide nourishment for germ cells throughout their growth cycle and provide a protective barrier to larger molecules owing to inter-Sertoli cell junctions (the blood–testis barrier). This barrier is derived from a basal lamina formed by peritubular hyoid cells that line the seminiferous tubules [2].

The terminal ends of the seminiferous tubules extend as straight extensions and these form an anastomosing network of tubules called the rete testis [3].

The rete testis is a series of efferent ducts that form the duct of the epididymis [3].

Arterial Supply

1. Testicular arteries are paired arteries that arise directly from the abdominal aorta (L2), below the level of the renal artery, and become a component of the spermatic cord [1].
2. Cremasteric arteries arise from the inferior epigastric artery.
3. Deferential arteries (artery to the vas deferens) arise from the inferior vesical artery.

The medial and lateral aspects of the superior pole have the lowest density of superficial vessels compared to the inferior and anterior portions of the testis.

Venous Drainage

A plexus of veins emerges at the upper pole of the testis, collectively known as the pampiniform plexus. Each plexus ascends and surrounds the testicular artery, forming the basis of the countercurrent heat exchange mechanism that contributes to temperature regulation. Each pampiniform plexus drains to paired testicular (gonadal) veins:

- The right gonadal vein drains directly into the inferior vena cava (IVC).
- The left gonadal vein drains to the IVC via the left renal vein.

Lymphatics drain into the lumbar and para-aortic lymph nodes.

Innervation

The testes share a common level of autonomic innervation to the kidneys due to their embryological origin. Sympathetic innervation arises from the T10-L1 spinal segment, which accounts for 90% of overall innervation. The remaining innervation is derived from the parasympathetic S2-4 level. Superior spermatic nerves, which arise from the inter-mesenteric plexus, explain the ‘kick to stomach’ pain associated with testicular injury. The

middle spermatic nerve originates from the superior hypogastric plexus; its course passes close to the mid-ureter and subsequently along the internal ring with the vas deferens. This may explain the radiation of pain associated with ureteric colic to the scrotum. The inferior spermatic nerve originates from the inferior hypogastric plexus [4].

Accessory Ducts

These include the epididymis, vas deferens and ejaculatory duct.

Epididymis

The epididymis is a single, heavily coiled duct that connects the testicular efferent ducts (rete testis) to the vas deferens [2]. It is the site of sperm maturation, transport and storage. It is situated at the posterior aspect of the testis, where it is attached at the superior and inferior poles and is divided into three regions (superior to inferior):

- Caput (globus major) – head
- Corpus – body
- Cauda (globus minor) – tail

The tunica vaginalis covers each epididymis apart from posteriorly, where connective tissue attaches the epididymis to the scrotum and spermatic cord [2].

The superior and inferior epididymal branches of the testicular artery supply the caput and corpus epididymis, and the deferential artery supplies the cauda epididymis.

The venous drainage communicates directly with pampiniform plexus, deferential and cremasteric veins.

Vas Deferens

The vas deferens is a tubular structure connecting the cauda epididymis to the seminal vesicle and ejaculatory ducts. It is divided into 5 zones:

- Epididymal (proximal)
- Scrotal
- Inguinal

- Pelvic
- Ampulla (distal)

The vas is approximately 30–40 cm in length. It ascends superiorly through the inguinal canal, then descends on the posterolateral wall of the pelvis and turns medially, running between the bladder and ureter. It terminates where its distal portion (ampulla) meets the seminal vesicle to form the ejaculatory ducts.

It is comprised of three muscular layers: an outer and inner longitudinal layer and an inner circular layer. These muscular layers function to propel sperm to the ejaculatory ducts.

The vas is supplied by the deferential artery, and venous drainage is via the deferential vein.

The vas is innervated by sympathetic and parasympathetic nerves, which regulate contraction and relaxation of smooth muscle during ejaculation. Sympathetic fibres carry a rich adrenergic supply that causes smooth muscle contraction. These fibres are derived from the hypogastric nerve and account for the majority of the innervation. The parasympathetic fibres arise from the pelvic splanchnic nerves and contribute to smooth muscle relaxation.

The lymphatic drainage is via the external and internal iliac lymph nodes.

Ejaculatory Duct

The ejaculatory ducts are formed by the union of the seminal vesicle and vas deferens on each side. They are approximately 2 cm in length and originate at the prostate base, terminating at the verumontanum in the prostatic urethra (seminal colliculus). The duct is divided into proximal, middle and distal thirds. Lymphovasculature and innervation are similar to the vas deferens.

Accessory Glands

Seminal Vesicle

These are paired glands located posterior to the prostate and inferior to the bladder fundus. The seminal vesicle (SV) is a single, blind-ending tube with irregular pouches, measuring 3–5cm in length. It has three distinct layers: an inner mucosal layer, a muscular layer (inner circular and outer longitudinal layers) and an outer adventitial layer. The SV functions to contribute alkaline fluid, which makes up around 70% of the seminal fluid. This fluid also contains fructose (to provide energy to spermatozoa) and semenogelin, a protein that results in the formation of a gel-matrix that prevents capacitation of spermatozoa.

The arterial supply arises from the middle and inferior vesical and middle rectal vessels. Venous drainage is via the vesical venous plexus into the internal iliac veins

The lymphatics drain to the internal and external iliac lymph nodes.

The secretory glandular tissue is under parasympathetic control, while the smooth muscle is under both sympathetic and parasympathetic influence. The emission phase of ejaculation is mediated through sympathetic fibres from the hypogastric nerve plexus [5].

Bulbourethral Glands (Cowper's Glands)

These are paired exocrine glands located posterolateral to the membranous urethra. They provide lubricating mucus secretion that contains glycoproteins, contributing to the final volume of seminal fluid and helping to neutralise residual acidity in the male urethra.

The glands are supplied by the arteries to the bulb of the penis, and lymphatics drain into the internal and external iliac lymph nodes.

Prostate

This is a fibromuscular gland located inferiorly to the bladder, it surrounds the proximal urethra, and the ejaculatory ducts enter the prostate as they emerge from the seminal vesicles. The prostate's relations are:

- *Anterior*: Pubic symphysis (separated by prostatic venous plexus)
- *Posterior*: Rectum (separated by Denonvilliers fascia)
- *Superior*: Bladder
- *Inferior*: External urethral sphincter

- *Lateral*: Levator ani

McNeal described zonal anatomy of the prostate:

- *Central zone*: 25% glandular tissue that surrounds ejaculatory ducts
- *Peripheral zone*: 70% glandular tissue; surrounds most of the central zone and the distal prostatic urethra
- *Transition zone*: 10% glandular tissue; surrounds a portion of the urethra between the urinary bladder and verumontanum
- *Anterior fibromuscular stroma*: Contains no glandular components; composed of muscle and fibrous tissue

The inferior vesical artery is the major arterial supply, derived from the anterior branch of the internal iliac artery. The prostate also receives blood from the middle rectal and internal pudendal arteries. Venous drainage is via the prostatic plexus, which drains into the internal iliac veins. Lymphatics drain into the internal iliac lymph nodes and sacral lymph nodes.

The prostate is innervated by autonomic fibres from the inferior hypogastric plexus. Sympathetic nerves arise from the hypogastric nerve, and parasympathetic nerves arise from the pelvic plexus. Both the hypogastric and pelvic nerves provide sensory input [6].

External Genitalia

Scrotum

The scrotum is a fibromuscular cutaneous sac that functions to assist thermoregulation. It contains:

- External spermatic fascia
- Testes and epididymis
- Spermatic cord

The left- and right-sided structures are separated into two compartments by a midline scrotal septum. Two muscle fibres contribute to this fibromuscular structure:

- *Dartos muscle*: Smooth muscle deep to the skin

- *Cremasteric muscle*: A paired muscle formed in two parts – medial cremaster (originates from the pubic tubercle) and the lateral cremaster (originates from the internal oblique muscle).

The scrotal wall consists of fascial layers (superficial to deep):

- Skin
- Dartos fascia
- External spermatic fascia (from external oblique muscle)
- Cremaster muscle (fascia from internal oblique muscle)
- Internal spermatic fascia (from transversals fascia)
- Tunica vaginalis (parietal layer from peritoneum and visceral layer)

The scrotum is supplied by:

- *Anterior scrotal artery*: A branch of the external pudendal arteries (from femoral arteries)
- *Posterior scrotal artery*: A branch of the internal pudendal artery
- *Cremasteric branch*: From the inferior epigastric artery
- These arteries form arteriovenous anastomoses along with subcutaneous plexuses

The venous drainage mirror the corresponding arterial supply, and these scrotal veins drain into the external pudendal veins. The lymphatics drain into the superficial inguinal nodes.

Innervation

The anterior innervation is via the genital branch of the genitofemoral nerve, which is formed at the anterior rami of L1–L2 lumbosacral plexus. The genitofemoral nerve passes inferiorly along the psoas major and descends in the retroperitoneum, deep to the ureter and gonadal vessels. At the level of the inguinal ligament, the nerve penetrates the psoas fascia and divides into genital and femoral branches. The genital branch enters the inguinal canal via the deep ring and provides motor innervation to the dartos and cremaster muscles. It also provides sensory innervation to the upper, anterior scrotum.

The ilioinguinal nerve provides sensory innervation to the superior medial thigh and anterior third of the scrotum. It emerges from the lateral edge of the psoas major at L1 and the anterior rami of the lumbar plexus. It passes anterolaterally, travelling along the quadratus lumborum to reach the

deep inguinal ring, exiting at the superficial inguinal ring by piercing the external spermatic fascia.

The posterior scrotum is supplied by the perineal branches of the pudendal nerve. The posterior femoral cutaneous nerve also provides sensory innervation.

Cremasteric reflex – the ilioinguinal nerve (sensory) and genitofemoral nerve (motor) carry a sensory synapse to activate a physiological reflex. This functions to assist temperature regulation. The reflex is elicited by stroking the skin in the medial upper thigh to cause ipsilateral cremasteric contraction [7].

Penis

The penis functions for reproduction through erections and ejaculatory output, which is a shared route for micturition (Figure 2.2). It is located in the urogenital triangle, between the perineal membrane and deep perineal fascia. The penis is divided into three parts:

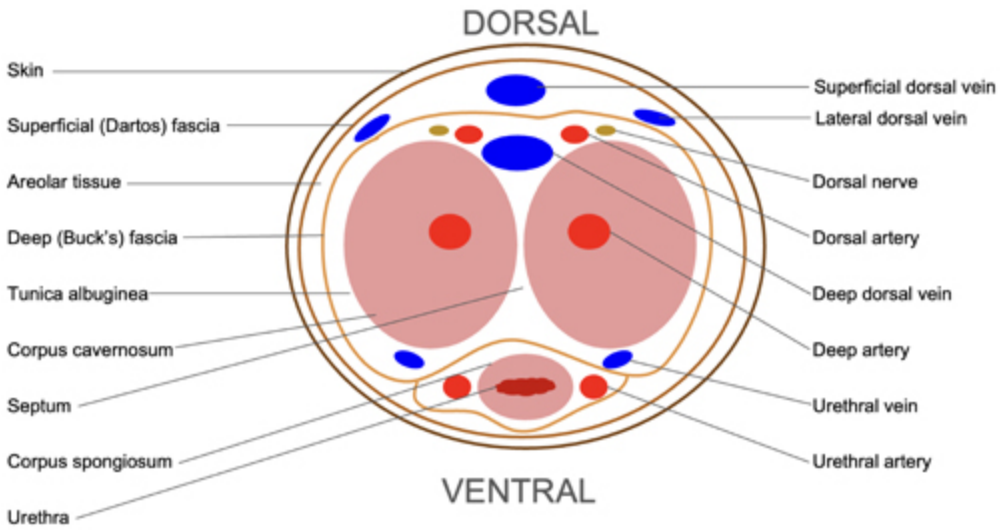


Figure 2.2 Cross section of the penis.⏎

- *Root*: The most proximal structure, located in the superficial perineal pouch of the pelvic floor.
- *Body*: Suspended from the pubic symphysis by the fundiform ligament, which descends from the linea alba to encircle the penis and combine inferiorly with the dartos (forming the scrotal septum). The body contains three cylinders of erectile tissue – two corpora cavernosa and the

corpus spongiosum. Supporting skin, connective tissue and fascia comprise the rest of the penile body.

- *Glans*: The distal extension of the corpus spongiosum. The proximal glans is termed the corona. The distal glans contains the external urethral meatus. The prepuce is the second skin layer that covers the glans and is connected to the ventral surface by the frenulum.

The root of the penis contains the two crura, bulb, ischiocavernosus and bulbospongiosus muscles. The crura of each corpora cavernosa are surrounded by ischiocavernosus muscle to assist erect function by shunting blood and compression of the deep dorsal vein to restrict venous outflow. Proximally, the crura are attached to the ischiopubic rami on each side as separate structures. The crural origins are located lateral to the midline on each side and help prevent sinking of the erect penis. The distal extension of each crus is continuous with each respective corpus cavernosa proper.

Corpus Cavernosum

There are two corpora cavernosa (CC), which are paired columns of muscle and contribute to the formation of an erection. The CC is separated by an incomplete midline septum in the distal third that allows communication and transfer of blood. The tunica albuginea is a dense fibrous sheath that surrounds each CC. The tunica albuginea consists of an inner circular layer and an outer longitudinal layer. This layer is thickened ventrally to form a groove for the corpus spongiosum and provides high tensile strength to support the cavernosal muscles but thins considerably during erections to 0.25 mm (up to 2 mm during flaccid state). There is a thin layer of areolar tissue that separates the erectile tissues of the corpora from the tunica albuginea. The CC contains sinusoidal spaces lined with endothelial cells. These spaces are separated by septa that extend from the tunica albuginea. The sinuses are supplied with blood from the helicine arteries to fill with blood during erection.

Corpus Spongiosum

Proximally, it is formed by the bulb, and distally it expands to form the glans penis. It is surrounded by a thinner layer of tunica albuginea to allow passage of ejaculate through the urethra.

Fascial Coverings

- The dartos is the superficial fascia of the penis. It lies deep to the skin of the penis, provides mobility to the skin and is continuous with Colle's fascia (superficial perineal fascia) in the perineum.
- The Buck's fascia forms a strong membranous covering over the three erectile muscles. It lies superficial to the tunica albuginea and deep to the dartos. It is continuous with the deep perineal fascia.

Arterial Supply

The superficial system arises from the external pudendal arteries (branch of the femoral arteries). Dorsolateral and ventrolateral branches form a plexus and supply the penile skin and prepuce.

The deep system arises from the internal pudendal arteries (branches of the anterior trunk of the internal iliac). The internal pudendal emerges from Alcock's canal and divides into the common penile and perineal branches. The common penile artery divides into three:

- *Dorsal artery*: Passes distally between the dorsal vein and nerve, giving circumflex branches.
- *Bulbar artery*: Penetrates Buck's fascia and supplies the spongiosum, urethra and glans.
- *Cavernosal (deep penile) artery*: Penetrates the CC at the crus. It lies within each CC to become helicine arteries. Helicine arteries supply arterial blood to sinusoids, which fill during erection.

Venous Drainage

- *Superficial*: Superficial veins are contained in the dartos fascia on the dorsolateral surface. It drains the penile skin and prepuce. These coalesce to form the superficial dorsal vein, which drains into the external pudendal vein.
- *Intermediate drainage*: Via the deep dorsal and circumflex veins. The veins lie deep to Buck's fascia and drain the glans, corpus spongiosum and distal two-thirds of the corpora. The veins ultimately drain into the peri-prostatic plexus.
- *Deep drainage*: Consists of cavernous veins, bulbar and crural veins. Blood from sinusoids via emissary veins drains into cavernous veins. Cavernous veins course laterally and drain into the internal pudendal vein.

Lymphatics

The CC drains into the internal iliac lymph nodes. Glans penis drains into the deep inguinal nodes, and the penile skin drains into the superficial inguinal nodes.

Innervation

The penis is innervated by autonomic and somatic nerves.

Sympathetic pathway: Mediates detumescence and maintenance of the penis in the non-erect state. Innervation from T10–L2 passes via white rami to sympathetic chain ganglia. Nerves pass to the inferior mesenteric and hypogastric nerves and eventually to the sympathetic trunk. Post-ganglionic fibres join the cavernous nerve.

Parasympathetic pathway: Arise from sacral spinal segments S2-4. Fibres travel with pelvic splanchnic nerves to synapse with the pelvic plexus. Postganglionic fibres leave the pelvic plexus with the cavernous nerve. This nerve enters the corpora cavernosa and is responsible for tumescence.

Somatic nerves: Originate from sacral spinal segments S2–4. Sensory innervation arises from the dorsal nerve of the penis (terminal branch of the pudendal nerve). The dorsal nerve of the penis traverses the dorsal groove between the CC with its corresponding artery and vein [8].

PHYSIOLOGY

Erection

This is a process whereby the CC engorges with blood, leading to rigidity and an increase in size. It consists of an interplay of vascular, neurological, endocrine and psychological factors. The degree of erection depends on the arterial inflow and venous outflow.

There are five phases of erection (Figure 2.3):

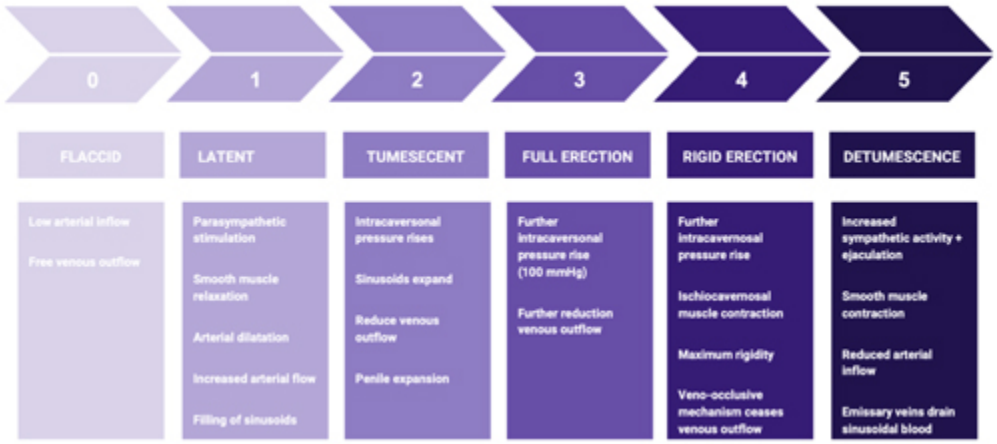


Figure 2.3 Phases of erection.⏎

- *Flaccid* (0): Low arterial inflow, free venous outflow.
- *Latent* (1): Sexual stimulus leads to parasympathetic stimulation. Smooth muscle relaxation causes arterial dilatation, increased flow and filling of sinusoids.
- *Tumescence* (2): Intracavernosal pressure rises to diastolic pressure. Sinusoids expand and reduce venous outflow, causing penile expansion.
- *Full erection* (3): Intracavernosal pressure rises to systolic pressure, with further reduction in venous outflow.
- *Rigid erection* (4): Maximal rigidity is reached following contraction of muscles. 'Veno-occlusive mechanism' ceases venous outflow.
- *Detumescence* (5): Following ejaculation, reduction in parasympathetic activity and an increase in sympathetic nerve activity result in smooth muscle contraction and reduced arterial inflow. Emissary veins then drain to allow outflow of sinusoidal blood.

Central Control of Erection

- *Hypothalamus*: Medial pre-optic area and paraventricular nucleus are the predominant supraspinal centres for erectile function. They receive cortical projections and are rich in dopaminergic and oxytocinergic neurons. They project to the autonomic spinal centres.
- *Spinal cord*: Predominant pro-erectile centre lies in the sacral spinal cord levels S2–4, from where efferent parasympathetic nerves project.

Peripheral Control of Erection

The resting/flaccid phase is mediated by sympathetic control. Noradrenaline is the predominant neurotransmitter, which causes smooth muscle cell contraction.

The stimulation/erectile phase is mediated by parasympathetic control. Nitric oxide (NO) is the predominant neurotransmitter, which leads to smooth muscle relaxation.

NO enters smooth muscle cells via a secondary messenger system (Figure 2.4). NO activates the enzyme guanylate cyclase (GC), which catalyses the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). cGMP decreases calcium to cause smooth muscle relaxation, and this leads to arterial vasodilatation and sinusoidal relaxation. cGMP is inactivated by the enzyme phosphodiesterase-5 (PDE-5). Accumulation of cGMP allows tumescence which is under the control of both GC and PDE-5. PDE-5 inhibitors (e.g., sildenafil) act on the PDE-5 enzyme where the breakdown of cGMP is reduced, which in turn decreases intracellular calcium, leading to smooth muscle relaxation and subsequent tumescence.

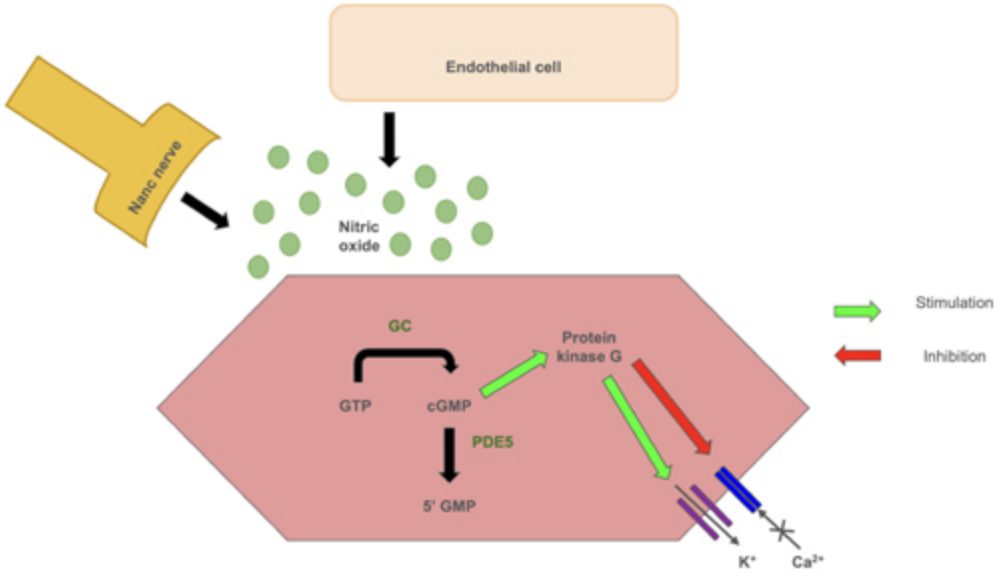


Figure 2.4 Nitric oxide control of erection.⏎

Ejaculation

The ejaculatory response consists of two phases:

- *Emission*: Secretion and expulsion of ejaculate by contractions of the vas deferens, seminal vesicles and prostate into the posterior urethra.

- *Ejection*: Occurs following emission. Closure of the internal urinary sphincter prevents retrograde flow. Rhythmic contractions of the striated bulbocavernosus, ischiocavernosus and levator ani muscles propel seminal fluid through the urethra.

Central Control of Ejaculation

Involves complex interplay between central serotonergic and dopaminergic neurons with a network of spinal and cerebral nerves.

Peripheral Control of Ejaculation

The sympathetic nervous system controls ejaculation via contraction of sphincters and muscles. Closure of the bladder neck prevents retrograde flow.

The parasympathetic nervous system mediates the secretion of seminal fluid

Hypothalamus–Pituitary–Gonadal Axis

The male reproductive function is dependent on coordinated hormone release from the hypothalamic–pituitary–gonadal axis (Figure 2.5).

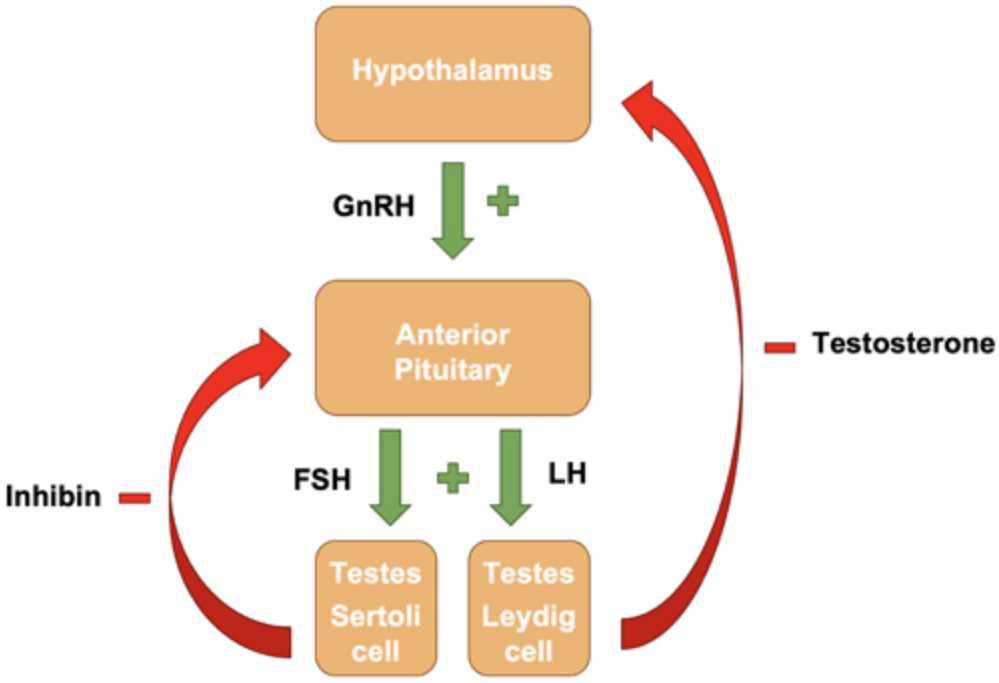


Figure 2.5 Hypothalamus–pituitary–gonadal axis.⏎

The hypothalamus is located in the lower portion of the third ventricle. It releases gonadotropin-releasing hormone (GnRH) from neuroendocrine cells in the basal hypothalamus into the pituitary portal system.

The pituitary gland is located in the hypophyseal fossa and is divided into anterior and posterior pituitary lobes. In response to GnRH, the anterior pituitary is stimulated to synthesise and secrete gonadotropins. The two peptide hormones produced are follicle-stimulating hormone (FSH) and luteinising hormone (LH).

FSH stimulates Sertoli cells in the seminiferous tubules to support spermatogenesis and LH stimulates Leydig cells to produce testosterone. Testosterone, through androgen receptors in the hypothalamus and anterior pituitary gland, provides negative feedback loop for suppression of GnRH. Stimulation of Sertoli cells will also produce inhibin, which suppresses FSH secretion by gonadotrophins [2].

Testicular–Hormonal Function

The Leydig cells are located within the testicular interstitium. They contain a round nucleus and Reinke crystals. Leydig cells provide the majority of androgen production from cholesterol via a series of P450 enzymes. Testosterone production peaks in the second and third decades. Testosterone is converted into the more potent dihydrotestosterone (DHT) in the testis by action of the 5-alpha reductase enzyme. The testis also produces oestradiol through an aromatase enzyme that converts androgens to oestrogen.

Spermatogenesis

This is a complex and specialised process of DNA reduction and germ cell metamorphosis, resulting in the development of a mature sperm cell from a primordial germ cell (Figure 2.6). Spermatogenesis occurs in the basement membrane of the seminiferous tubules and takes 64 days to complete (range 42–76 days). The primary stimulus for spermatogenesis is testosterone, which rises at puberty and is dependent on a normal hypothalamic–pituitary–gonadal axis.

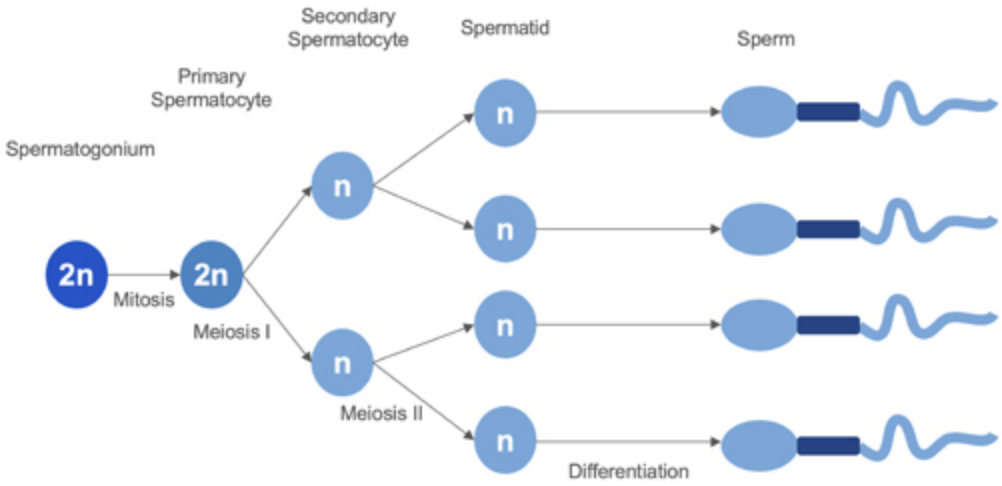


Figure 2.6 Spermatogenesis.⏎

Primordial germ cells (PGCs) originate near the yolk sac and migrate to the developing gonadal ridges, reaching the seminiferous cords between the 5th and 6th weeks of intrauterine development. Once in the testis, these cells proliferate and give rise to spermatogonia, the undifferentiated male germ cells. Spermatogonia undergo further mitotic divisions, either maintaining the stem cell pool or differentiating to enter the spermatogenic lineage. The process of expanding the spermatogonial population through successive mitotic divisions is known as spermatogoniogenesis.

Spermatogonia begin the process of spermatogenesis and are the most immature cell type in this process. Type A spermatogonia remain beyond the blood–testis barrier and multiply from puberty (stem cell renewal pathway). Men never exhaust this supply. These are diploid cells (2N) that contain the full complement of chromosomes (46 chromosome or 22 pairs). There are two subtypes of Type A spermatogonia:

- *Type Ad* (*dark*): Characterised by an ovoid nucleus containing chromatin and located adjacent to the basement membrane. At day 16, they divide by mitosis to form another Type Ad (2N) and a further Type Ap (2N) spermatogonia.
- T*ype Ap* (*pale*): These continue to divide by mitosis and are capable to self-renewal, apoptosis or further differentiation. Type Ap (pale) spermatogonia that differentiate will become Type B spermatogonia.

Type B spermatogonia (2N) migrate to the lumen of the tubule to differentiate into primary spermatocytes that are located in the adluminal compartment. Two primary spermatocytes are formed following mitotic cell divisions of Type B spermatogonia. These each undergo meiosis I to form secondary spermatocytes. Secondary spermatocyte complete meiosis II, which yields haploid spermatids (1N) connected by cytoplasmic bridges. Spermatids, which are haploid cells, lie furthest from the basement membrane and closest to the lumen of the seminiferous tubules. Here, they lose their cytoplasmic connections and differentiate into mature sperm cells – a process known as spermiogenesis).

Spermiogenesis

This is the process of sperm maturation, a series of morphological and metabolic changes with no further cell division. Round spermatids develop into a motile, flagellated cell. Sperm maturation includes acrosome development, chromatin condensation and migration of cytoplasmic organelles. Sperm motility and fertilisation capacity are androgen-dependent process. The transit time of sperm cells in the epididymis averages 12 days.

Spermatozoon Structure

The head comprises a nucleus and acrosome. The nucleus contains male genetic material, and the acrosome contains hydrolytic enzymes required for penetration of the ovum prior to fertilisation.

The midpiece contains cellular elements and centrioles with packed mitochondria for energy production.

The flagellum is a tail-like structure enabling sperm motility.

Spermiation is the process whereby a mature spermatozoa are released from the seminiferous epithelium into the lumen of the tube [9].

Semen Production and Characteristics

Semen is comprised of sperm cells and secretions of the seminal vesicles, prostate and Cowper’s glands. The semen volume is 1.5–5 ml and pH is 7.35–7.50.

The seminal vesicles contribute the majority of secretions (60%) and contain fructose, prostaglandins and ascorbic acid. The prostate provides the remainder (approximately 40%) and contains acid phosphate, citric acid and zinc. Semen also contains buffers (phosphate and bicarbonate) for the acidic vaginal environment [2].

Physiology of Fertilisation

Fertilisation is a process where a female oocyte fuses with male sperm to create a diploid cell (zygote). During intercourse, sperm cells are delivered into the vagina. Some sperms die as a result of the acidic environment of the vagina, and some will travel through the cervical mucus due to the protective effects of the seminal fluid. During transit through the female reproductive tract, sperm cell concentration decreases. Transit of sperm cells is assisted by contraction of the uterus as a result of oxytocin release centrally. Fertilisation occurs in the ampullae of the fallopian tubes.

The stages of fertilisation include:

- *Capacitation of sperm*: The female reproductive tract increases motility of sperm and destabilises the sperm membrane to promote the acrosome reaction.
- *Acrosome reaction*: Enzymatic penetration of the zona pellucida, the tough outer membrane of the ovum.
- *Sperm–ovum fusion*: Following fusion, a cortical reaction occurs, and the nucleus of the sperm is incorporated into the ovum to form a zygote [10].

References

1. Goldstein M, Schlegel P. *Surgical and Medical Management of Male Infertility*. Cambridge University Press. 2013.⏎
2. Wu W. *Male Reproductive Anatomy*. IntechOpen. 2022.⏎
3. O'Donnell L, Stanton P, de Krester D. *Endocrinology of the Male Reproductive System and Spermatogenesis*. Endotext. 2017.⏎
4. Patel A. Anatomy and physiology of chronic scrotal pain. *Translation Andrology and Urology*. 2017.⏎

5. McKay A *et al. Antony, Abdomen and Pelvis*. *Seminal Vesicle*. StatPearls. 2022.⏎
6. Singh O. Bolla S. *Anatomy*, *Abdomen and Pelvis*, Prostate. StatPearl. 2022.⏎
7. Garcia R, Sajjad H. *Anatomy*, *Abdomen and Pelvis*, *Scrotum*. StatPearls. 2022.⏎
8. Sam P, La Grange C. *Anatomy*, *Abdomen and Pelvis*, *Penis*. StatPearls. 2022.⏎
9. Gilbert S. *Developmental Biology*. 6th edition. Sunderland MA. Sinauer Associates. 2000.⏎
10. Georgadaki K *et al.* The molecular basis of fertilisation (review). *International Journal of Molecular Medicine*. 2016.⏎

3 Aetiology, Pathophysiology and Clinical Assessment of Erectile Dysfunction

Ian Eardley

DOI: 10.1201/b22940-3

Erectile dysfunction (ED) is defined as the consistent or recurrent inability of a man to attain or maintain an erection adequate for sexual intercourse. The duration of the problem should be at least 3 months. It is important to remember that ED is a symptom rather than a disease and consequently has multiple associations with underlying conditions and pathophysiological processes.

Epidemiology

Incidence and Prevalence of Erectile Dysfunction

ED is common. However, one challenge in determining its incidence and prevalence lies in the varying methods of measurement. For instance, it can be measured with a single direct question, or alternatively it can be measured by validated questionnaires, with the Erectile Function Domain (EFD) of the International Index of Erectile Function (IIEF) questionnaire being one of the commoner tools used [1]. With that caveat, there have been numerous studies and publications that have attempted to determine the prevalence of ED in a variety of different populations, while also exploring associated risk factors. These studies show a number of consistent themes [2]:

- The prevalence of ED increases with age, such that in men under the age of 50 years the prevalence is around 6%, increasing to around 16% in men 50 to 59 years, 32% in men aged 60 to 69 years, and reaching around 44% in men aged 70 to 79 years.
- ED can have varying degrees of severity, although there are varying definitions of what is mild, moderate, and severe ED. In general terms, mild ED might be considered as a difficulty in maintaining an erection that is occasionally present, while severe ED reflects the consistent inability to achieve any erection at all.
- The Massachusetts Male Aging Study (MMAS) reported a prevalence of 52% in non-institutionalised men aged 40–70 years in the Boston area. The prevalence for minimal, moderate, and complete ED was 17.2%, 25.2%, and 9.6%.
- While numerous men might have the symptom of ED, many of them are not particularly bothered by the symptom. The studies suggest that ‘bother’ appears to increase with increasing ED severity and to decrease with increasing age. This point is particularly relevant because there is evidence that treatment-seeking behaviour most closely reflects bother, rather than reflecting the presence of the symptom of ED alone.
- A few studies have attempted to measure the incidence of ED. As might be expected, the incidence depends upon the population studied, and, most importantly, the age of that population.

Natural History of Erectile Dysfunction

Few studies have attempted to ascertain the natural history of ED. However, those that have been undertaken suggest that in some men ED can be a temporary phenomenon, with 20%–50% of men improving over a 5–10 year period [2]. This likely highlights the psychological factors that often contribute significantly to the development and maintenance of ED.

Risk Factors and Underlying Conditions

Epidemiological studies regularly confirm an association with cardiovascular disease and its risk factors, including diabetes, hypertension, smoking, and hyperlipidaemia. Collectively, metabolic syndrome is a risk factor which includes obesity, hypertension, hypertriglyceridemia, low levels of HDL cholesterol and hyperglycaemia. There is a second, separate and common association with depression. In addition, other associations that have occasionally been demonstrated include lower urinary tract symptoms and prostate disease, although the underlying pathophysiology for this association is poorly understood.

Aetiology of Erectile Dysfunction

Given that penile erection is a complex neurovascular process, it is not surprising that ED can arise in conjunction with a wide range of medical conditions, and in association with a significant number of medicinal and recreational drugs. The commonest conditions that can cause ED are listed in Table 3.1, and the commonest drug-related causes of sexual dysfunction are listed in Table 3.2.

Table 3.1 Conditions Commonly Associated with the Symptoms of Erectile Dysfunction⏎

Category		Disease
Neurological	Central nervous system	Multiple sclerosis Stroke Multiple system atrophy Alzheimer's disease Temporal lobe epilepsy
	Spinal cord disease or injury	Multiple sclerosis Spinal cord injury Cauda equina compression
	Pelvic parasympathetic disease or injury	Pelvic surgery Peripheral neuropathy (e.g., alcohol, diabetes) Pelvic fracture Pelvic radiotherapy
Arteriogenic	Large vessel disease	Atherosclerosis Aorto-iliac surgery Renal transplantation Pelvic fracture/surgery Blunt perineal trauma
	Small vessel disease and endothelial dysfunction	Diabetes mellitus Hypertension Hyperlipidaemia Smoking Pelvic radiotherapy
Venogenic	Abnormal venous channel	Congenital venous abnormality Shunt surgery for priapism Penile fracture
	Impaired veno-occlusive dysfunction	Increased sympathetic neural tone Loss of penile smooth muscle (aging, post radical prostatectomy, ischaemia) Penile fibrosis, e.g., secondary to delayed treatment of priapism Genital injury

Category		Disease
Iatrogenic	Surgical damage to CNS control	Cerebral surgery Spinal surgery
	Surgical damage to pelvic parasympathetics	Radical prostatectomy Radical cystectomy Abdomino-perineal excision of the rectum Anterior resection of rectum Repair of pelvic fracture urethral distraction injury Transurethral prostatectomy
	Surgical damage to penile vasculature	Aorto-iliac surgery Renal transplantation Repair of pelvic fracture urethral distraction injury
	Surgical damage to the penis	Surgery for Peyronie's disease
	Pelvic radiotherapy	Treatment of prostate cancer Treatment of bladder cancer Treatment of rectal cancer
Anatomical		Phimosis Penile cancer Micropenis Peyronie's disease
Other causes		Chronic renal failure Chronic liver failure Hypogonadism BPH / LUTs CPP / Prostatitis Obstructive sleep apnoea

Abbreviations: BPH, benign prostate hyperplasia; CPP, chronic pelvic pain syndrome; LUTs, lower urinary tract symptoms

Table 3.2 The Main Drug-Related Causes of Sexual Dysfunction⏎

Type of Drug	Drug / Class of Drug	Sexual Dysfunction
Antidepressants	Selective serotonin reuptake inhibitors Tricyclic antidepressants Monoamine oxidase inhibitors Trazadone	Ejaculatory and orgasmic dysfunction ED and loss of libido ED and loss of libido Priapism
Major tranquillisers	Thioridazine Phenothiazines Butyrophenones	Ejaculatory dysfunction ED, loss of libido, ejaculatory dysfunction and priapism ED and painful ejaculation
Other psychotropics	Anxiolytics and hypnotics	ED, loss of libido, ejaculatory dysfunction and orgasmic dysfunction
Antihypertensives	Diuretics β-adrenoceptor blockers Centrally acting agents, e.g., α-methyl DOPA, clonidine	ED ED ED, loss of libido, ejaculatory dysfunction ED Retrograde ejaculation and priapism
Endocrine drugs	Steroidal antiandrogens, e.g., cyproterone LHRH analogues Oestrogens	ED and loss of libido ED and loss of libido ED and loss of libido
Anticholinergics	Atropine, Propantheline	ED

Type of Drug	Drug / Class of Drug	Sexual Dysfunction
Recreational drugs	Alcohol	ED, arousal disorders, ejaculatory and orgasmic dysfunction
	Marijuana	ED
	Amphetamine	Loss of libido and ejaculatory dysfunction
	Opiates	ED and loss of libido
	Cocaine	ED
	Anabolic steroids	ED and loss of libido
Others	Cimetidine	ED and loss of libido
	Spironolactone	ED
	Digoxin	ED
	Amiodarone	ED
	Disopyramide	ED and loss of libido
	Metoclopramide	ED and loss of libido
	Phenytoin, Carbamazepine	

Pathophysiology

The main pathophysiological mechanisms underlying the development of ED are listed in Table 3.3. Several are worthy of more extensive discussion.

Table 3.3 The Main Pathophysiological Causes of Erectile Dysfunction⏎

Category	Mechanism
Psychogenic	• Predisposing factors • Precipitating factors • Maintaining factors
Neurogenic	• Disruption of the cerebral control of erection • Disruption of the descending erectogenic impulses within the spinal cord • Disruption of the sacral parasympathetic outflow within the pelvis
Arterial	• Large vessels disease – Disruption of the arterial inflow to the penis secondary to atherosclerosis or trauma • Small vessel disease and endothelial dysfunction – Including diabetes, hypertension, hyperlipidaemia, smoking, and obesity
Venous	• Primary venous abnormality • Impaired cavernosal smooth muscle function (veno-occlusive dysfunction)
Endocrine	• Hypogonadism • Hyperprolactinaemia (rare) • Hyperthyroidism (very rare)

Category	Mechanism
	• Hypothyroidism (very rare)
Iatrogenic	• Drug related • Surgery related • Radiotherapy related

Psychogenic Erectile Dysfunction

Psychogenic ED is common. It can be associated with psychiatric conditions, including depression and anxiety (and from a technical perspective, such patients really should be considered to have ‘organic’ ED). However, the largest group of patients with psychogenic ED have no associated psychiatric problem. While psychogenic issues can occasionally be the sole cause of ED, they often interplay with the ‘organic’ pathophysiological mechanisms outlined in Table 3.3. Aetiological factors in psychogenic ED include:

- *Predisposing factors*: Such as a restricted upbringing, traumatic sexual experiences, poor sexual education, personality type, disturbed family relationships, and excessive viewing of pornography.
- *Precipitating factors*: Including organic disease, aging, infidelity, unrealistic expectations, depression, anxiety, and loss of a partner.
- *Maintaining factors*: Including performance anxiety, diminished attraction for one’s partner, poor communication with the partner, fear of intimacy, poor sexual education.

Diabetic Erectile Dysfunction

Generally, men with diabetes are twice as likely to suffer from ED than non-diabetic men of the same age. Diabetic ED has a multifactorial pathophysiology, with different mechanisms being relevant in different patients. Potential mechanisms include atherosclerosis, microvascular disease, endothelial dysfunction, peripheral autonomic neuropathy, and associated hypogonadism. Of these, the most important pathophysiological mechanism for most men is endothelial dysfunction.

Endothelial Dysfunction

We know that normal penile erection depends upon the release of nitric oxide (NO) within the corpora cavernosa and there are two main sources of penile NO: the parasympathetic innervation and the vascular endothelium, with both sources being important in normal penile erection. A range of conditions impair the function of the vascular endothelium, with diabetes, especially poorly controlled diabetes, having a significant and damaging effect upon the vascular endothelium of the penis, impairing the release of NO with the consequent development of ED. Other conditions that impair endothelial function include hypertension, metabolic syndrome, smoking, and physical inactivity.

Veno-occlusive Dysfunction

Normal penile erection depends upon three fundamental vascular mechanisms:

- Parasympathetic nervous stimulation results in increased arterial inflow into the penis.
- Parasympathetic nervous stimulation results in cavernosal smooth muscle relaxation with increased accumulation of blood within the dilating trabecular spaces of the corpus cavernosum.
- Associated with expansion of the corpus cavernosum within the relatively rigid tunica albuginea of the penis, there is passive compression of a sub-tunical venous plexus, resulting in reduced venous outflow and veno-occlusion.

In the 1980s and 1990s, cavernosography was able to identify abnormal veins around the penis of men with ED and the condition became known as ‘venous leakage’. It was suggested that blood was somehow leaking out of the penis through abnormal venous channels and that surgery to those veins might resolve the problem. However, it soon emerged that the results of such surgery were poor. Ultimately, it was evident that these abnormal veins were not the cause of the problem but were rather a symptom of failed cavernosal smooth muscle relaxation. When cavernosal smooth muscle fails to relax properly, the cavernosal tissue does not expand appropriately, and the sub-tunical venous plexus is not compressed, preserving blood flow through the venous channels leaving the corpora cavernosa. This is known as ‘veno-occlusive dysfunction’, and there are 3 main causes:

- Excessive sympathetic neuronal tone resulting in maintained smooth muscle contraction. This is associated with anxiety, performance-related anxiety, and excessive use of sympathomimetic agents.
- Penile smooth muscle dysfunction with impaired relaxation. This can be related to many of the mechanisms outlined above, including diabetes, hypertension, hyperlipidaemia, and ischaemia.
- Loss of penile smooth muscle; This is most commonly associated with aging and ischaemia and in following untreated ischaemic priapism. It is also likely the end-stage pathophysiology in most men who have undergone radical prostatectomy.

Erectile Dysfunction Following Radical Prostatectomy

The development of ED following radical prostatectomy initially reflects damage to the cavernosal nerves as they traverse along the side of the prostate. Nerve-sparing radical prostatectomy is designed to spare these nerves. However, even in cases where adequate nerve sparing has been achieved, early ED is common and likely indicates neuropraxia of those nerves. We know that penile erection is associated with high levels of oxygenation of the cavernosal bodies. Loss of the regular oxygenation associated with normal penile erections results in degenerative changes within the corporal bodies. In the early stages, there is smooth muscle dysfunction, and in the latter stages, there can be loss of smooth muscle with increased penile fibrosis. This ultimately leads to veno-occlusive dysfunction. Accordingly, in men who have undergone successful nerve preservation during their radical prostatectomy, the early cause of the ED reflects neuropraxia. However, if the man experiences no useful erections (with the oxygenation that accompanies those erections), then the late and permanent cause of the ED is more likely to reflect veno-occlusive dysfunction secondary to smooth muscle loss. This pathophysiology speaks to the varying attempts to institute penile rehabilitation following radical prostatectomy.

What is important to recognise is that it is the oxygenation associated with penile erection that maintains the health of the penile smooth muscle while neuropraxia resolves. Accordingly, if a phosphodiesterase-5 inhibitor (PDE5i) is used for rehabilitation, treatment will be unsuccessful unless there are good quality penile erections. A more reliable, but perhaps more invasive, approach using intra-cavernous injection therapy does result in penile erections with regular oxygenation and, theoretically at least, is more

likely to maintain healthy penile smooth muscle. Patients should also be encouraged to use vacuum erection device on a regular bases.

Clinical Assessment

It is important that all men undergo a systematic clinical assessment (Figure 3.1) when they present with ED. The purpose of this is twofold:

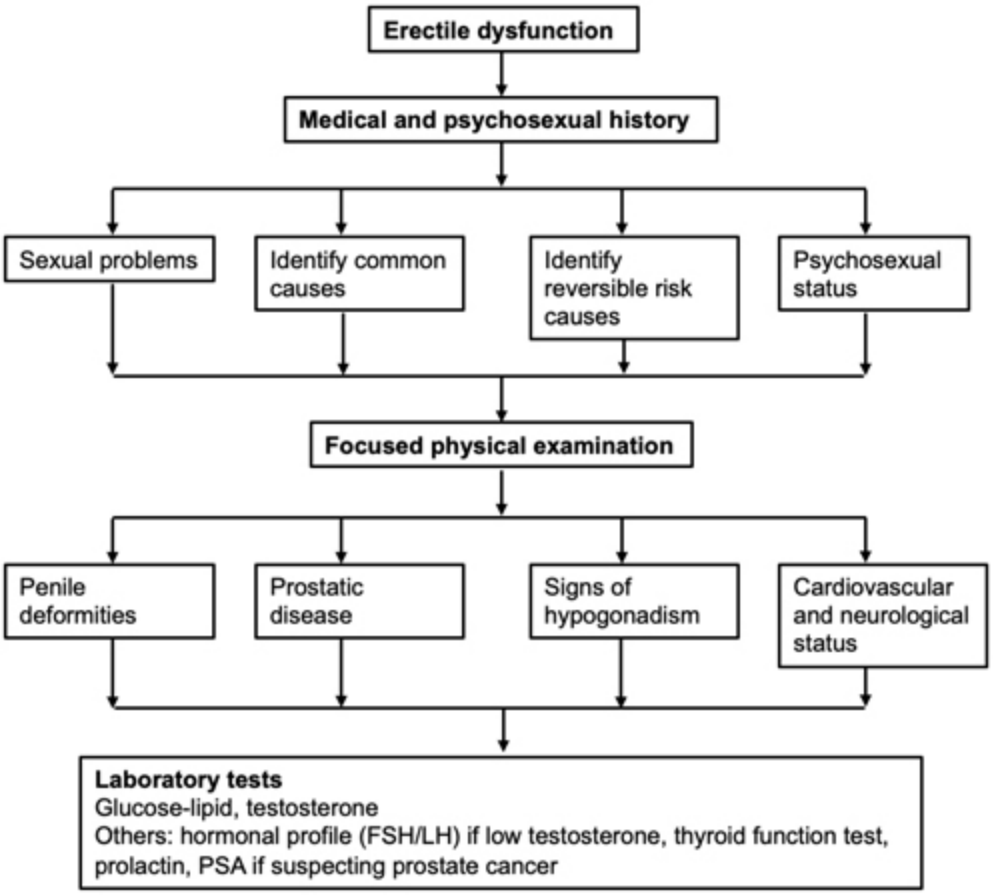


Figure 3.1 Clinical assessment of erectile dysfunction.⏎

- First, there needs to be a clear understanding of the nature, severity, and duration of the sexual problem.
- Second, and perhaps just as importantly, given that there are a multitude of potential underlying causes, it is important to identify those causes where they exist in men with ED.

This latter point is particularly true in relation to cardiovascular disease, where patients with ED are sometimes found to have previously unrecognised hypertension, hyperlipidaemia, diabetes, or hypogonadism. Identification and treatment of these risk factors not only benefits the ED but may also prevent cardiovascular problems. Indeed, it is now recognised that ED can be present some time in advance of subsequent cardiovascular events, and, particularly in young men under the age of 50 years, new onset (organic) ED is associated with a demonstrably increased cardiac risk [3].

History

The initial and essential part of clinical history taking in men with sexual dysfunction is to be absolutely clear what the patient's problem is. There are many colloquial terms used to describe the inability to attain or maintain a penile erection, and sometimes these terms are misused, such that issues of ejaculatory dysfunction or loss of libido can occasionally be confused with ED.

Following on from that, it is important to take a sexual history, a medical history, and a drug history from the patient [4].

Sexual History

In a man with erectile dysfunction, it is important to ask about the following issues:

- The mode of onset of the ED: was it sudden or gradual?
- The duration of the ED.
- Is it persistent or intermittent (situational)?
- The extent of the ED: is it difficulty in attaining or in maintaining an erection.
- Indeed, are there any erections at all?
- Are they able to engage in a penetrative sexual intercourse?
- Are there maintained nocturnal or early morning erections?
- Are there any erections associated with masturbation?
- What is the nature of the patient's interpersonal relationship(s)?
- What is the expectation of the patient in relation to treatment?
- Has the patient tried any treatments already, including black market medication?
- Are there any other associated sexual problems, including changes in sexual interest, changes in ejaculation, penile deformity or penile pain.

It is traditional to characterise ED as primarily psychogenic (where there is no demonstrable underlying organic disease) or organic (where such disease is present). However, most patients have both organic and psychogenic components. Features commonly associated with a predominantly psychogenic aetiology include the continued presence of nocturnal and early morning erections, a relatively sudden onset of ED, and intermittent or situational symptoms. Features commonly associated with predominantly organic causation include gradual onset with loss of nocturnal and early morning erections and with persistent, consistent difficulty.

Medical History

There should be an enquiry into the presence or otherwise of any associated medical conditions, and particularly those listed in Table 3.1. There should be a particular focus upon possible cardiovascular disease, previous surgical treatment, and previous radiotherapy. Similarly, a detailed drug history should be taken, with particular interest in those medications or recreational drugs listed in Table 3.2.

With the increasing recognition that hypogonadism can be associated with ED in older men, it has become increasingly common to enquire for symptoms of hypogonadism, including decreased energy, diminished libido, fatigue, and cognitive impairment.

Questionnaires

While questionnaires are not diagnostic of ED, they can provide a good assessment of the severity of ED and will likely indicate the extent of any response to treatment. The most commonly used and validated psychometric questionnaire is the IIEF, or its shortened version, IIEF-5 [1]. This has a number of domains, and in this context, recording the EFD can be used to quantify the extent of any erectile dysfunction.

Examination

It is generally accepted that a full physical examination is not necessary in all men with ED, and that the examination should be focused [4]. It is important that the following are routinely undertaken:

- Blood pressure measurement and heart rate
- Measurements of weight and ideally of waist circumference
- Assessment of secondary sexual characteristics, including checking for gynaecomastia, hair distribution, and body habitus
- A careful genital exam, assessing the size, consistency, and shape of the penis, checking for abnormalities of the prepuce and assessment of the testicle size and consistency.

In an older man with urinary symptoms, it would be reasonable to undertake a digital rectal examination to assess the prostate, although it should be recognised that prostate cancer is not a cause of ED. In a young man without any urinary symptoms, it would be difficult to justify such an examination.

Investigations

Baseline Investigations

A baseline investigation should be undertaken in all new patients with ED. This would include a fasting blood sugar, a fasting lipid screen, and an early morning (7–11 a.m.) assessment of total testosterone [4].

- A fasting blood sugar test should be performed to detect previously unrecognised diabetes. Fasting plasma glucose levels greater than 7 mmol/L are diagnostic of diabetes, as are random blood sugar levels greater than 11.1 mmol/L and HbA1c levels greater than 6.5%.
- A fasting lipid screen should assess total cholesterol, LDL cholesterol, and HDL cholesterol. As recommended by the National Institute for Health and Care Excellence (NICE) in the UK, decisions regarding treatment are made in the context of a calculated cardiac QRisk score. Current UK guidelines suggest that total cholesterol should be less than 5 mmol/L and LDL cholesterol should be less than 4 mmol/L [5].
- An early morning total testosterone level should be assessed in all men. An early morning sample is required because of the normal diurnal variation in testosterone levels, with a significant reduction in the level of testosterone towards the end of the day. A detailed discussion of hypogonadism exists elsewhere in this publication, but it is generally accepted that in a man with symptoms of hypogonadism, a total testosterone level greater than 12 nmol/L is normal and that a total testosterone level less than 8 nmol/l is abnormal. In the range 8 to 12 nmol/L, assessment of free testosterone should be undertaken. Subsequent investigation depends on the level of testosterone.
    - *Investigation of the man with a low total testosterone* (*less than 8 nmol/L*): Under these circumstances, a repeat early morning total testosterone level is measured in conjunction with serum prolactin and serum LH. The aim here is to confirm the diagnosis and to assess whether there is any coexisting pituitary disease.

- *Investigation of a man with a borderline total testosterone (8–12 nmol/L)*: Under these circumstances, a repeat early morning total testosterone is measured in conjunction with serum albumin, sex hormone binding globulin (SHBG), prolactin, and LH. The aim here is to ascertain the diagnosis. The combination of albumin, SHBG, and testosterone can be used to calculate the free testosterone, and several online calculators exist for this purpose. Free testosterone levels less than 225 pmol/L are consistent with a diagnosis of hypogonadism in a man with symptoms of hypogonadism.

Specialised Investigations

Further investigation is unnecessary in the vast majority of men with ED. However, there are occasions when additional, more specialised investigations are appropriate and necessary. The investigations that can be used are listed in Table 3.4, together with the indications for their use.

Table 3.4 Specialised Investigations and Their Indications⏎

Test	Indications	Comments
Nocturnal penile tumescence	Diagnosis of psychogenic disease	• Most commonly undertaken with a RigiScan™ device • The presence of maintained nocturnal erections in a man with ED is suggestive of psychogenic causation
Penile Duplex Doppler Assessment	Assessment of penile vasculature Patient request	• Should be undertaken following intracavernosal injection of a vasoactive agent such as alprostadil • **Peak systolic velocity (PSV):** reduced penile arterial inflow is compatible with arteriogenic ED (PSV > than 30cm/sec is normal) • **End-diastolic velocity (EDV):** < 5cm/sec is considered as normal and > 5cm/sec is indicative of veno-occlusive dysfunction • This test has become increasingly common as a means of helping to reassure a patient who is concerned about vascular disease as a cause of his ED
Selective pudendal arteriography	Assessment of penile vasculature	• Should be undertaken following intracavernosal injection of a vasoactive agent such as alprostadil • Only indicated in young men with possible arteriogenic ED, secondary to blunt perineal trauma or pelvic fracture in whom penile revascularisation is being considered (not commonly performed nowadays)
Penile MRI	Suspected Peyronie's disease Suspected penile injury Patient request	• Penile MRI has becoming increasingly useful as a means of helping to reassure a patient who is concerned about traumatic injury to the penis. • Commonly undertaken following intracavernosal injection of a vasoactive agent such as alprostadil

Test	Indications	Comments
Specialised endocrine investigation including pituitary MRI	Suspected pituitary disease	• Such investigations are typically undertaken at the same time as referral to a specialist endocrinologist

Penile cavernosometry and cavernosography were historically used quite frequently in men with ED, but their use has almost completely disappeared in recent years. As discussed above, we now know that the so-called diagnosis of venous leak does not truly exist and simply reflects veno-occlusive dysfunction, with the underlying pathophysiology being a penile smooth muscle problem.

The assessment of young men with likely psychogenic ED who are concerned that they have a significant physical problem is often challenging. Most urologists do not have access to the assessment of nocturnal penile tumescence using a RigiScan^{TM} device. It may be helpful to arrange a dynamic duplex Doppler scan where formal assessment of the penile arterial inflow can be assessed following injection of alprostadil. However, these men often have significant performance-related anxiety, with high levels of sympathetic tone, and even after an intracavernous injection of alprostadil, they may fail to achieve an erection, and there may be associated veno-occlusive dysfunction. Another test that is often used under these circumstances is penile MRI, which again will give detailed anatomical information about the penis and the surrounding structures.

Onward Referral in Men with Erectile Dysfunction

There are a few indications for onward referral to other specialists:

- In men who have clearly unrecognised, but significant psychological or psychiatric disease, referral to a psychiatrist is indicated.
- In men who have significant cardiac disease, referral to a cardiologist is indicated in order to ascertain whether the exercise involved in sexual intercourse is safe, and whether the patient’s cardiac status can be improved medically or surgically.
- In men with significant endocrine disease suggestive of pituitary disease, hyperprolactinaemia, or thyroid disease, referral to an endocrinologist is indicated.
- In men with unrecognised diabetes, referral to a diabetologist is indicated.
- In men with unrecognised hyperlipidaemia or hypertension, referral to the primary care physician or a cardiologist is indicated.

References

1. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction *Urology*, (1997) 49: 822–830.⏎
2. Eardley I. The incidence, prevalence and natural history of erectile dysfunction. *Sex Med Rev*, (2013) 1: 3–16.⏎
3. Jackson G, Boon N, Eardley I, Kirby M, Dean J, Hackett G, Montorsi P, Montorsi F. Erectile dysfunction and coronary artery disease prediction: evidence-based guidance and consensus. *International Journal of Clinical Practice*, (2010), 64; 848–857.⏎
4. European Association of Urology. Sexual and reproductive health. Available at: https://uroweb.org/guidelines/sexual-and-reproductive-health⏎
5. National Health Service. Cholesterol levels. Available at: https://www.nhs.uk/conditions/high-cholesterol/cholesterol-levels/⏎

4 The Management of Erectile Dysfunction

Ali Alrawahneh, Karl H. Pang and Hussain M. Alnajjar

DOI: 10.1201/b22940-4

Introduction

In the 1970s, erectile dysfunction (ED) treatment advanced with the increasing use of penile vacuum pumps. However, in the 1980s, a turning point came with research conducted by Dr Giles Brindley which sparked a therapeutic revolution, leading to the adoption of vasodilators and alpha-blocking agents as the preferred mode of treatment. By the 1990s, sildenafil – a heart medication – proved to be a further advancement in this sphere, with patients experiencing firmer and longer-lasting erections. Towards the end of the decade, in 1998, sildenafil, marketed by Pfizer, USA, under the name Viagra, exploded in popularity, and, a quarter of a century later, continues to be the most popular treatment for ED.

It is now established that ED can be treated with different modalities. Treatment can be tailored based on many factors, including treatment invasiveness, efficacy, safety and cost, in addition to patient preferences. Therefore, patient counselling and awareness are crucial steps in ED management. Patients should be informed about the physiological and psychological factors affecting their sexual response. Furthermore, patients' expectations and needs, along with treatment options, should be discussed clearly during consultations, and preferably involve their sexual partners [1, 2].

Identifying the underlying causes of ED helps in patient management, as there are reversible causes for ED, e.g., hormonal causes. Treating these

reversible conditions will potentially treat the ED. Also, modification of risk factors associated with ED, such as obesity, smoking, hypercholesterolaemia, hypertension, changing medications that contribute to ED, and optimising management of diabetes, will have a positive impact on treatment outcomes.

Management of Erectile Dysfunction

Cardiovascular Risk Assessment for Men with Erectile Dysfunction

Patients seeking treatment for ED should be assessed for cardiovascular risk before starting therapy, as ED is an independent risk factor and an early warning sign for cardiovascular diseases, such as coronary artery disease and stroke. Patients with ED can be stratified into low, intermediate and high-risk categories according to the Princeton Consensus Cardiac Risk Stratification [3] (Table 4.1).

Table 4.1 Cardiac Risk Stratification⏎

Low-risk Category	Intermediate-risk Category	High-risk Category
Asymptomatic, > 3 risk factors for CAD (excluding gender)	≥ risk factors for CAD (excluding sex)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (within 2-6 weeks)	Recent MI (within 2 weeks)
LVD/CHF (NYHA class I or II)	LVD/CHF (NYHA class III)	LVD/CHF (NYHA class III–IV)
Post-successful coronary revascularisation	Non-cardiac sequelae of atherosclerotic disease (e.g., stroke peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate to severe valvular disease

Source: Based on 2nd and 3rd Princeton Consensus.
Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; LVD, left ventricular dysfunction; MI, myocardial infarction; NYHA, New York Heart Association.

Based on this stratification, a treatment algorithm for patients wishing to resume sexual activity is established [4] (Figure 4.1). Alternatively, through detailed medical history and their level of exercise tolerance, a clinician can

estimate the risk of sexual activity in most patients. For example, sexual activity is equivalent to walking 1 mile on a flat surface in 20 minutes or easily climbing two flights of stairs in 20 seconds [5].

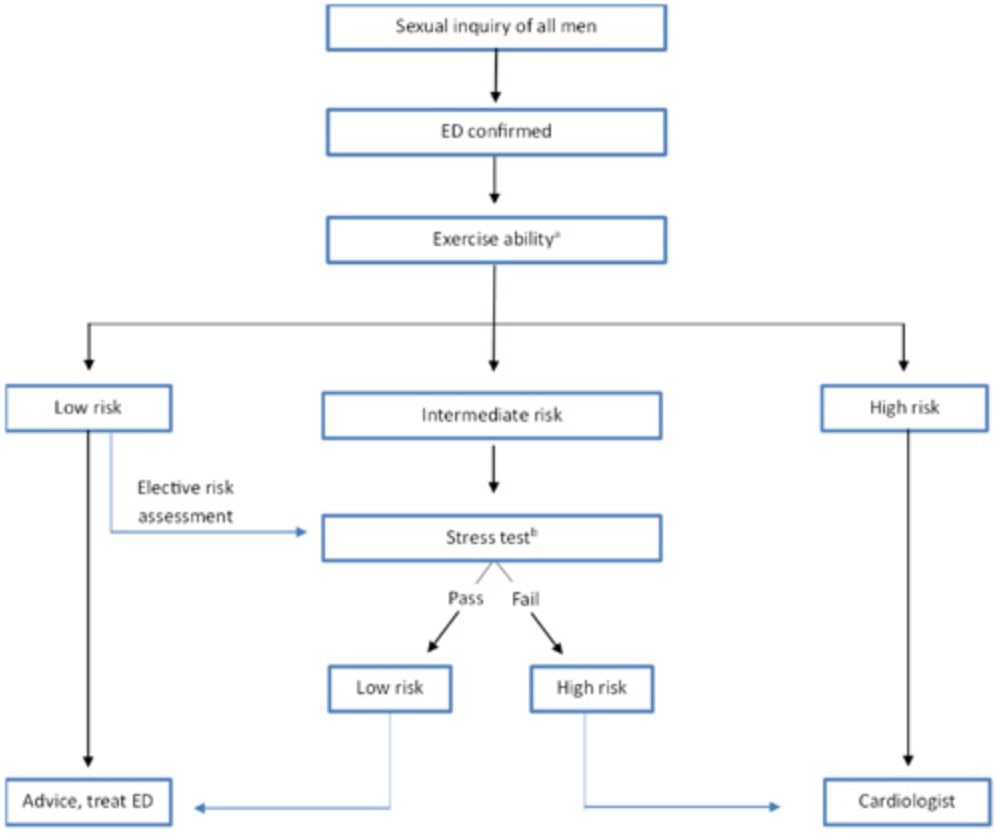


Figure 4.1 Treatment algorithm for determining level of sexual activity according to cardiac risk in erectile dysfunction. Based on 3rd Princeton Consensus.[a] Sexual activity is equivalent to walking 1 mile on the flat in 20 minutes or briskly climbing two flights of stairs in 20 seconds.[b] Sexual activity is equivalent to 4 minutes of the Bruce treadmill protocol.⏎

Treatment of Erectile Dysfunction

The European Association of Urology (EAU) developed a comprehensive algorithm for treating ED based on the efficacy and level of invasiveness of each treatment (Figure 4.2).

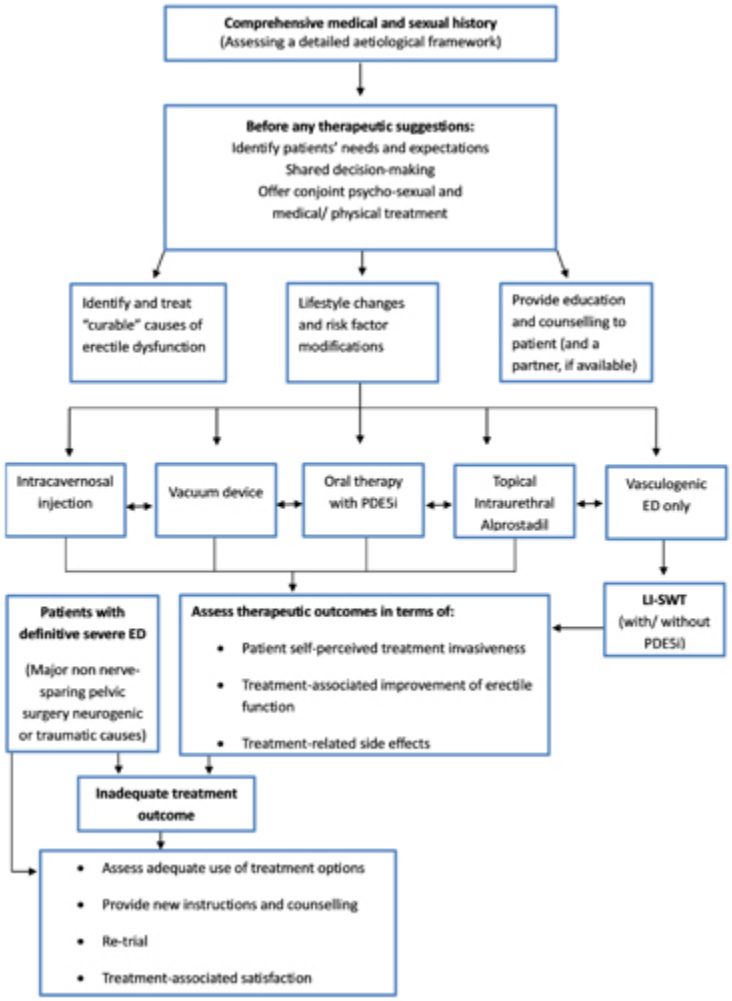


Figure 4.2 Management algorithm for erectile dysfunction, adapted from the EAU guidelines [6]. ED, erectile dysfunction; PDE5i, phosphodiesterase 5 inhibitors; LI-SWT, low-intensity shockwave therapy.⏎

Oral Pharmacotherapy

Phosphodiesterase 5 inhibitors (PDE5i) are commonly used for the treatment of ED. They are readily available and are safe. The majority of patients prefer to start ED treatment by taking PDE5i, unless contraindicated. Currently, the available medications approved by the EMA for treatment of ED are sildenafil, tadalafil, vardenafil and avanafil.

Mechanism of Action

Type 5 phosphodiesterase, which is mainly present in the cavernosal smooth muscle, promotes the hydrolysis of cyclic guanosine monophosphate (cGMP). Nitric oxide produced at parasympathetic nerve endings in response to sexual stimulation promote the conversion of guanosine triphosphate (GTP) into cGMP, which in turn promotes cavernosal smooth muscle relaxation by reducing the intracellular calcium levels. As a result, cavernosal blood flow increases leading to dilatation and expansion of cavernous sinuses, which will compress the sub-tunical emissary veins leading to erection [6] (Figure 4.3).

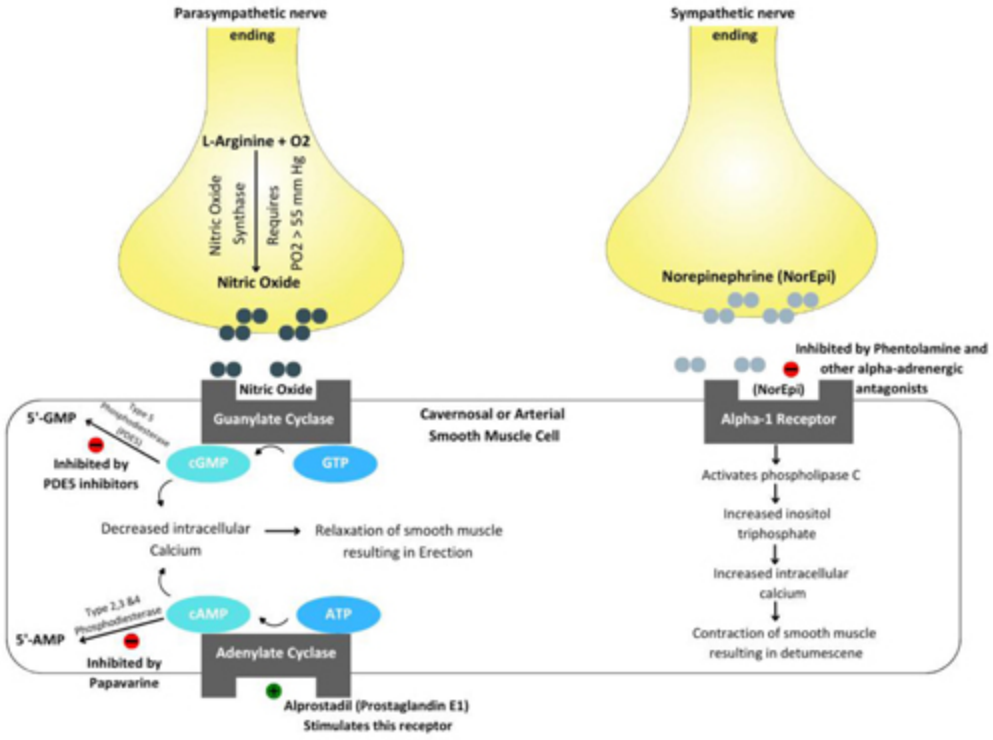


Figure 4.3 Physiology of erection. Alprostadil (prostaglandin E1) stimulates the adenylate cyclase pathway; papaverine inhibits PDE 2,3,4; PDE5 inhibitors, such as sildenafil, tadalafil, vardenafil and avanafil inhibit PDE5; phentolamine and other alpha-adrenergic antagonists inhibit the alpha-1 receptor. cAMP: cyclic adenosine monophosphate, cGMP: cyclic guanosine

monophosphate, ATP: adenosine triphosphate, GTP: guanosine triphosphate, GMP: guanosine monophosphate, AMP: adenosine monophosphate, PDE5: phosphodiesterase 5 (PDE5), NorEpi: norepinephrine.⏎

It is crucial to know that PDE5i do not initiate erections, but once erection is present these medications make the erection stronger. Therefore, sexual stimulation to initiate an erection is essential for these medications to exhibit their effect. Efficacy of PDE5i is defined as an erection with rigidity, sufficient for satisfactory sexual intercourse [7].

Dose and Pharmacokinetic

The efficacy of all PDE5i in treating ED is well established. The main differences between these agents are the onset of action, half-life, drug–food interaction and duration of action. For example, the absorption of sildenafil and vardenafil is reduced when taken after a meal, especially a high-fat meal. In contrast, tadalafil is unaffected by food, while avanafil absorption is not reduced by food but may be delayed if taken with a meal [8]. Table 4.2 summarises the pharmacokinetic and recommended starting dose for these agents.

Table 4.2 Phosphodiesterase 5 Inhibitors for Erectile Dysfunction⏎

PDE5 Inhibitor Name	Median Tmax (hours)	T ½ (hours)	Duration of Action	Fatty Food Significantly Impairs Absorption	Affinity to Other PDEs	Dose Range (mg)	Starting Dose (mg)
Sildenafil	1	4	6–8	Yes	PDE-6	25–100	50
Tadalafil	2	17.5	24–36	No	PDE-11	PRN: 5 - 20 DAILY: 2.5–5	PRN: 10 DAILY: 2.5
Vardenafil	1	4–5	6–8	Yes	PDE-6	5–20	10
Avanafil	0.5–0.75	5	6	No	Has much lower affinity for non-type 5 phosphodiesterase	50–200	100

Abbreviations: PDE, phosphodiesterase; PDE5, phosphodiesterase-5; Tmax, time to maximum serum concentration; T½, half-life; PRN, as needed.

Due to its ability to inhibit PDE-11, present in skeletal muscles, kidney, prostate and testicles, a 5mg daily dose of tadalafil is approved and licensed as monotherapy for treatment of benign prostate hyperplasia-related lower urinary tract symptoms, and will significantly improve urinary symptoms after 12 weeks of treatment [9].

Side Effects

Overall, PDE5i show a high safety profile. Headaches and hot flushes are the commonest side effect, while blurry vision, dyspepsia, lower back pain (PDE11), muscle ache, nasal congestion and impaired colour vision or presence of blue hue in the visual field (PDE6) are less common side effects. The incidence of priapism or visual loss are extremely rare when using PDE5i. Table 4.3 summarises the common side effects of PDE5i and their incidence.

Table 4.3 Common Adverse Events of the Four PDE5is Currently Approved by the EMA to Treat Erectile Dysfunction⏎

Adverse event	Sildenafil	Tadalafil	Vardenafil	Avanafil
Headache	12.8%	14.5%	16%	9.3%
Flushing	10.4%	4.1%	12%	3.7%
Dyspepsia	4.6%	12.3%	4%	Uncommon
Nasal congestion	1.1%	4.3%	10%	1.9%
Dizziness	1.2%	2.3%	2%	0.6%
Abnormal vision	1.9%**		>2%**	None
Back pain		6.5%***		>2%
Myalgia		5.7%***		>2%

Source: Adapted from EMA statements on product characteristics.
** Affinity to PDE-6 in the retina is responsible for some visual side effects, such as diplopia, blurry vision and impaired colour vision (chromatopsia).
*** Affinity to PDE-11 in the muscle, testicles, prostate and kidney is responsible for some side effects, such as back pain and myalgia.

Contraindications and Precautions for Using PDE5i

The absolute contraindication of PDE5i is the concomitant use with nitrates, nitric oxide donors and guanylate cyclase stimulators, as PDE5i potentiate the effect of these medications resulting in life-threatening hypotension [10].

PDE5i should be avoided in the following situations:

1. Patients with penile cancer, phimosis and paraphimosis
2. Patients with resting hypotension (systolic blood pressure < 90 mmHg)
3. Patients with nonarteritic ischaemic neuropathy
4. Patients with hereditary degenerative retinal disorders and retinitis pigmentosa
5. Patients with recent history of myocardial infarction or stroke

PDE5i can potentiate the hypotensive effect of alpha blockers so patients should be haemodynamically stable before commencing PDE5i treatment. Using uroselective alpha blockers, e.g., alfuzosin, doxazosin, terazosin, tamsulosin and prazosin, is recommended to reduce side effects of concomitant use with PDE5i [11].

Failure of PDE5i Treatment

The most common cause of treatment failure with PDE5i is the improper use of the medication, either due to failure of adequate sexual stimulation, inadequate dose or not allowing enough time between drug ingestion and commencing sexual intercourse [12]. Some data suggest failure can be due to the relation between genetic polymorphism of endothelial nitric oxide synthase (eNOS) and variability in response to PDE5i [13].

Adequate patient counselling and modification of ED risk factors increase treatment success rate in most patients. Additionally, the use of new formulations such as oral dispersible films, which have a faster onset of action and are easier to use, may improve efficacy. In non-responding patients, the use of combination therapy such as, adding vacuum device may improve treatment outcomes [14].

Topical/Intraurethral Treatment

Alprostadil (prostaglandin E1) activates adenylate cyclase, consequently increasing intracellular cyclic adenosine monophosphate (cAMP), which in turn decreases intracellular calcium leading to cavernosal smooth muscle relaxation (Figure 4.3).

Topical Alprostadil Cream

Alprostadil is administered through the urethral meatus as a cream formulation, which contains permeation enhancer to facilitate absorption. Some clinical studies have demonstrated that this formulation is effective in treating ED [15, 16]. The recommended dose is 300 mcg, 5–30 minutes before sexual intercourse. Due to limited systemic absorption, systemic adverse effects are very rare. Local adverse effects, including penile burning, pain and erythema, are usually resolved within two hours of application.

Intraurethral Alprostadil Formulation

Alprostadil is administered inside the urethra as a pellet (suppository). Medicated urethral system (MUSE) is a reasonable alternative to intracavernous injections (ICI) in patients who cannot tolerate ICI [17]. The recommended initial dose is 250 mcg, which may be titrated to 1,000 mcg in cases of poor response. Comparing it to topical cream MUSE is associated with a higher incidence of systemic side effects – such as dizziness and hypotension – especially in patients with significant veno-occlusive dysfunction. The most common local side effect is the burning sensation in the urethra and urethral bleeding. Penile fibrosis and priapism are very rare with MUSE. Intraurethral alprostadil treatment is contraindicated in patients with distal urethral strictures, urethritis, significant penile curvature or fibrosis, and balanitis, as well as in those with a high predisposition to priapism.

Intracavernous Injections

Direct injection into the corpus cavernosum with erectogenic drugs is the oldest pharmacological treatment for ED. The vasoactive agents used as ICI include alprostadil, vasoactive intestinal peptide (VIP), papaverine and phentolamine. Alprostadil is the only monotherapy currently approved for

treating ED [18]. It binds with a membrane receptor, activates adenylate cyclase and increases intracellular cAMP. Papaverine is a non-selective PDEi (type 2, 3 and 4). Due to its high incidence of side effects, papaverine is not licensed as monotherapy and is used only in a combination therapy. Phentolamine inhibits the alpha-adrenergic receptor (i.e., inhibits detumescence) but does not induce erection, so it is only used in combination with other agents to prolong the erection. Vasoactive intestinal peptide increases the intracavernous pressure by inducing smooth muscle relaxation leading to erection.

Before starting Alprostadil injections, clinicians should train the patient, or his partner (in case of limited manual dexterity), in how to perform the penile injection. In addition, patients should be counselled about the possibility of priapism (risk is <1%) and are advised to seek medical help in case of a prolonged erection of more than 4 hours.

Alprostadil dose is 5–40 mcg; usually the treatment should be started at a lower dose and increased based on the patient's response. Erection ensues after 5–15 minutes upon administration of the injection. The duration of erection as well as the side effects are dose dependent. The most common side effect of alprostadil is penile pain, with an incidence of around 50% in patients using this medication, which is usually self-limited after prolonged use. For those who cannot tolerate the pain at the beginning of the treatment, they can add local anaesthetic or sodium bicarbonate to the alprostadil injection to alleviate the pain. Other adverse effects include prolonged and undesired erection, priapism, penile fibrosis and mild hypotension [19]. Alternatively, Invicorp maybe used in cases of penile pain related to Alprostadil injections, with adequate efficacy.

Alprostadil ICI is contraindicated in men predisposed to priapism, severe penile angulation or fibrosis, and those who have bleeding disorders [20] (Table 4.4).

Table 4.4 Intracavernous Injection Therapy: Compounds and Characteristics⏎

Substance	Dosage	Efficacy	Adverse Events	Comment
Alprostadil	5–40 mcg/ mL	~ 70%	Penile pain, priapism, fibrosis	Easily available
Papaverine	20–80 mg	>55%	Elevation of liver enzymes, priapism, fibrosis	Abandoned as monotherapy

Substance	Dosage	Efficacy	Adverse Events	Comment
Phentolamine	0.5 mg/ ml	Poor efficacy as monotherapy	Systematic hypotension, reflex tachycardia, nasal congestion, and gastrointestinal upset	Abandoned as monotherapy
Papaverine + Phentolamine	30 mg/ ml + 0.5 mg/ ml	~ 90%	Similar to Alprostadil (less pain)	Not licensed for the treatment of ED
Papaverine + Phentolamine + Alprostadil	30 mg/ ml + 1 mg/ ml + 10 mcg/ ml	~ 92%	Similar to Alprostadil (less pain)	Not licensed for the treatment of ED
Vasoactive intestinal peptide (VIP) + Phentolamine	25 mcg + 1–2 mg	~ 80%	Similar to Alprostadil (without pain)	Easily available

Vacuum Erection Devices

Vacuum pumps are cylindrical pumps placed over the penis. When the device withdraws air from the cylinder, it leads to passive engorgement of the corpus cavernosum. Once an erection is achieved, a constrictor band is applied to the base of the penis to maintain the erection. The amount of air withdrawn from the cylinder is controlled by the vacuum limiter to prevent generating high negative pressure, which may lead to penile injury.

Patients should be counselled that the maximum duration the constricting ring can be applied is 20–30 minutes to avoid skin necrosis. Patients need to wait at least one hour before using the pump again. Side effects of vacuum pumps include penile pain and haematoma, cold penis, numb penis and inability to ejaculate. Vacuum erection devices are contraindicated in men with bleeding disorders or if on anticoagulant therapy [21]. In general, the uptake of vacuum erection devices amongst patients with ED is low, as many find them awkward and cumbersome.

Shockwave Therapy

Low-intensity Shockwave therapy (LI-SWT) has been proposed as a treatment option for vasculogenic ED. The proposed mechanism of action is to induce angiogenesis and improve blood flow in the penis, which is essential for erections. Most studies suggest improvement of erectile function in men with mild ED. Currently, there is no consensus on the type of shockwaves delivered, set-up parameters and the treatment protocol [22].

Investigational Therapies

Platelet-Rich Plasma

Platelet-rich plasma (PRP) is an investigational therapy for ED and should only be used in clinical trial settings. Platelets contain several growth factors including VEGF, EGF, IGF-1, PDGF and FGF which stimulate angiogenesis [23].

Botulinum Neurotoxin

Botulinum neurotoxin type A (BoNT-A) has been investigated as a treatment option for patients who are non-responders to other approved treatments [24]. The proposed mechanism of action is thought to be that BoNT-A inhibits the release of noradrenaline by adrenergic neurons, resulting in reduction in sympathetic tone and relaxation of cavernosal smooth muscle, which facilitates erection. Due to the lack of large clinical trials confirming the efficacy and safety of BoNT-A, this treatment is currently not recommended by the EAU.

Penile Prostheses

Despite being the most invasive treatment for ED, penile prosthesis (PP) has the highest satisfaction rate (92%–100%). Surgical implantation of a PP is recommended if other treatment modalities have failed, or are not suitable, or for patients who prefer definitive treatment. In the UK, the commonest aetiologies for ED are diabetes, prostate surgery and Peyronie's disease [25].

Penile Prosthesis Types

The current available types of PP are semi-rigid (malleable) and inflatable (three-piece). Patients who aspire for more natural erections may prefer the inflatable penile prostheses (IPP), even though semi-rigid PP are recommended for patients with limited manual dexterity, patients with waist circumference > 100 cm, and those who require PP insertion for buried penis.

Different PP models are available in the market mainly from two manufactures, Boston Scientific (USA) and Coloplast Corporation (Denmark). The three-piece IPP (AMS 700) from Boston Scientific is unique for being the only IPP on the market coated with an antibiotic layer

(Inhibizone), which is a combination of rifampicin and minocycline. This layer acts as an antibacterial barrier and consequently decreases infection associated with PP insertion [26].

There are three models of AMS 700: the standard IPP AMS 700 CX, which provides optimal penile length and girth; AMS 700 CXR, with a narrow base, ideal for patients with narrow or extensively fibrosed crura; and AMS 700 LGX, which provides 25% expansion in length and girth.

Boston Scientific manufactures two types of reservoirs: a spherical reservoir (65 ml and 100 ml) and a conceal flat reservoir (only in 100 ml). The latter is a parylene coated reservoir to increase flexibility and durability. The AMS momentary squeeze pump has a lock-out valve to resist auto-inflation and one touch button for easy deflation.

Titan Touch is the IPP manufactured by Coloplast. It has a hydrophilic coating which allows for soaking the implant with antibiotics before insertion, decreasing the risk of infection. It is crucial that the implant not be touched before it is immersed in the antibiotic solution. In addition to the standard Titan Touch Coloplast IPP, Coloplast also manufactures a narrow-base Titan Touch for narrow or fibrosed crura. The reservoir from Coloplast is called cloverleaf. It is coated with hydrophilic material and has a lock-out valve to prevent auto-inflation. There are two volumes of cloverleaf available on the market: 75 ml and 125 ml, with the former used for larger cylinders. The Coloplast pump is also coated with a hydrophilic layer and has a one-touch deflation button for easy deflation. It is important to note that the implants used for insertion through the infrapubic approach have longer tubings than the penoscrotal ones.

Both manufacturers produce semi-rigid prostheses, AMS Tactra from Boston Scientific and Genesis from Coloplast. The AMS Ambicor is the only two-piece IPP, and it is reserved for patients in whom reservoir placement should be avoided due to prior abdomino-pelvic surgery. However, the production of AMS Ambicor IPP has now been discontinued by the manufacturer.

The types of implants are demonstrated in Table 4.5. Also see Figure 4.4.

Table 4.5 Penile Prostheses Models Available on the Market⏎

Semi-rigid Prostheses	(Three-piece)
AMS Tactra™ [Boston Scientific]	Titan™ One-Touch Release [Coloplast]
AMS Spectra™ [Boston Scientific]	
Genesis™ [Coloplast]	Titan OTR NB™ (narrow base) [Coloplast]
	Titan Zero Degree™
Tube™ [Promedon]	AMS 700 CX™ [Boston Scientific]
ZSl 100™ [Zephyr]	AMS 700 LGX™ [Boston Scientific]
Virilis II™ [Subrini]	AMS 700 CXR™ [Boston Scientific]
	ZSI 475™ [Zephyr]
Rigi10™ (Rigicon™)	Infla10 Plus serie™ (Rigicon™)

Figure 4.4 Types of implants. With permission from Coloplast and Boston Scientific™.

Patient Counselling and Preparation

A detailed history and physical examination should be performed before surgery. Many factors should be considered before proceeding with implant insertion (Table 4.6).

Table 4.6 Factors That Should Be Considered Before Proceeding with Implant Insertion⏎

Factors
Presence of penile conditions and anatomy. For example, chronic or acute priapism, phimosis, etc.
Stretched penile length
Scrotal size
Spinal cord injury
History of pelvic surgery
Presence of artificial urinary sphincter
History of radiotherapy
Immunosuppression
Body habitus
Manual dexterity
Abdominal scars/presence of stoma
Diabetes mellitus
Patients' preferences
Smoking

Prosthesis infection is a devastating complication of penile implant surgery. To decrease the risk of infection, patients should have a negative urine culture, negative MRSA screening and HbA1C <9% for diabetic patients before surgery.

Insertion of a PP is an irreversible procedure which mandates adequate patient counselling before surgery. A detailed discussion with patients (and preferably with partners) regarding the types of implants, description of surgery, possible risks and appropriate post-operative expectations and follow-up is essential. Ideally, clinical nurse practitioner should demonstrate to patients the implant components, types of devices and how to cycle the device. In addition to in-person counselling, patients should be provided with detailed written information about the intention of surgery, what to expect from the surgery and possible risks of surgery (Figure 4.5) [27].

Penile Prosthesis Counselling

Name: ---------- Referring consultant:----------

Hospital No.:---------- Consultant:----------

Cause of ED & management to date:

IIEF & EDITS:

PMH incl. LUTs, abdominal scars/ Hernia &

BMI & waist circumference

Medication incl. anticoagulants:

Manual dexterity:

Implant types demonstrated:
Malleable implants and inflatable incl. Genesis & Titan Touch

Risks discussed:
Infection, erosion, bleeding, auto-inflation, glans droop, urethral injury, altered glans sensitivity. Average lifespan of inflatable devices=10yrs.

What an implant will do:
Essentially it is internal scaffolding providing rigidity and maintenance of erection.

What it won't do:
Implant WILL NOT provide extra length to penis and WILL NOT restore length lost through prolonged erectile dysfunction/ Peyronie's disease. Unlike the vacuum device and intraurethral/ intracavernosal alprostadil, a penile prosthesis WILL NOT provide engorgement to the penile tissues.

Non reversible:
Corporal tissue is damaged/ destroyed when spaces are created for placement of the cylinders/ malleable rods and therefore surgery is considered an end stage procedure.

Pre-operative requirements and post-operative care:
Must attend PAC, Must have negative MSU, LOS, time off work, pain, follow up

Added to waiting list: YES/ NO
Agreed to data collection-audit and prosthesis audit YES/ NO

Deferred for medical reasons/ patient wishes to consider options/ further OPA/ Speak to another patient
All points have been discussed today

Signature's CNP:----------Patient----------Date:----------
NB: Patient advised that all penile prosthesis cases are discussed at a dedicated meeting to confirm suitability for prosthesis surgery.

Figure 4.5 Penile prosthesis counselling proforma. Courtesy of Fiona Holden and Clare Akers. ED, erectile dysfunction; IIEF, International Index for Erectile Function; EDITS, Erectile Dysfunction Inventory of Treatment Satisfaction; PMH, past medical history; LUTS, lower urinary tract symptoms; BMI, body mass index; PAC, pre-assessment clinic; MSU, midstream specimen of urine; LOS, length of stay; OPA, outpatient appointment; CNP, clinical nurse practitioner.⏎

Surgical Technique

Penile prostheses can be inserted using a penoscrotal, infrapubic or subcoronal incision.

Infection is the main concern for PP surgery. Accordingly, all measures should be taken to minimise the risk of infection, including wearing a face mask by all staff members inside the theatre and decreasing personnel traffic to and from the operating theatre. Clear signage should be displayed on theatre doors, and laminar flow systems should be employed.

Intravenous antibiotics should be administered at anaesthesia induction. Recent data show that the addition of IV antifungal may decrease the risk of infection in diabetics.

Patient Scrubbing and Draping

A full shave of the genitalia and suprapubic area should be performed before scrubbing the surgical site. A 10-minute 4% w/v chlorhexidine-gluconate scrub or Povidone-iodine scrub followed by 2% chlorhexidine-gluconate and 70% isopropyl alcohol is recommended to eliminate skin flora and consequently minimise the risk of infection [28].

After applying surgical drapes, a traction suture is applied on the glans and is used to stretch the penis during surgery. A temporary drape is used to insert a 14fr Foley catheter. Surgeons should change their gloves after wiping the catheter with a rifampicin/gentamicin antibiotic-soaked swab and discard the temporary drape.

Application of additional skin adhesive drape (e.g., Ioban), which is known as a no-touch approach, has proved to decrease rate of infection [29].

Penoscrotal Approach

Penoscrotal approach is the technique most frequently used, and the steps are described below.

Incision and Dissection

A transverse incision is made 1cm below the penoscrotal junction. The dissection of the dartos layer should be performed with caution using diathermy to avoid urethral injury. Once the urethra is identified, dissection should proceed laterally to expose the corpora.

Corporotomies and dilatation

Once the corpora is exposed, two pairs of stay sutures with 0 Vicryl are placed as low as possible so that the exit tubings can be concealed. The corporotomy is made between the stay sutures, which should be limited to the tunica layer.

Before the dilatation with corporal dilators, tunnelling should be performed using Metzenbaum scissors, which should be inserted in both corporotomy ends while its curved tip is directed laterally away from the urethra. Brooks or Hegar dilators can be used to dilate the corpora. However, Brooks dilators have a higher risk of perforation in fibrotic corpora due to their tapered end. To avoid urethral injury, the dilatators should be directed laterally, and the urethra should be pinched and pushed to the contralateral side. The proximal extent of the crura is at the base of the penis, where they attach to the ischiopubic rami; distally, the limit is at the tips of the corpora.

The following safety check manoeuvres should be performed proximally and distally before implant insertion:

1. *Absence of crossover*: Two dilators are inserted simultaneously, and if a metal clinking sound is heard, it confirms cross-over.
2. *Goalpost sign*: Two Brooks dilators are inserted simultaneously, and the presence of a discrepancy in the level of dilators may indicate corporal perforation or under-dilation.
3. *Urethral perforation test*: The presence of leakage of antibiotic solution through the meatus during corporal flushing confirms urethral perforation.

A Furlow is a measuring instrument used to measure the corpora distally and proximally. A meeting point between distal and proximal measurements can be marked by placing an artery forceps at the corporotomy lip.

Prior to implant insertion, the device must be appropriately prepared and cycled, ensuring air in the device has been fully expelled and tubings clamped with protected (shods) Kelly clamps.

Prosthesis Insertion

Insertion of Cylinders

Cylinders are the first components to be inserted. Furlow loaded with a Keith needle is used to advance the device to the distal corpora. Once the Furlow has reached the distal corporal tip, the Keith needle is launched through the glans, using a pusher. The proximal end of the cylinders are placed into the proximal corpora by the aid of the Furlow. Once the cylinders are positioned in the correct site, the stay sutures are tied using an air tie technique to close the corporotomies.

Insertion of the Reservoir

The reservoir can be placed blindly in the retropubic space (Retzius). After emptying the bladder, the external inguinal ring is identified superior to the pubic tubercle. The fascia transversalis is incised, and a Cottle nasal speculum is inserted and opened into the retropubic space. The reservoir is then pushed into the retropubic space using a ring clamp for the Coloplast reservoir insertion or a Furlow for the AMS reservoir. The reservoir should be filled with 0.9% normal saline to check for herniation and back pressure.

Blind reservoir insertion should be avoided in patients who have had previous pelvic or abdominal surgery. In such cases, open or ectopic reservoir insertion should be utilised.

In open insertion, the reservoir is placed in the retropubic or retroperitoneal space under vision, through a separate iliac fossa incision. A skin incision is made 2cm medial and inferior to the anterior superior iliac spine. The incision is extended 3 cm inferiorly and parallel to the inguinal ligament. The external oblique fascia is incised along its fibres. Blunt dissection of the internal oblique muscle, transversus abdominis muscle and transversalis fascia is performed to reach the retroperitoneum. A space is created for the reservoir using a finger sweeping manoeuvre. After placing the reservoir in the created space, the layers should be closed with 2/0 Vicryl sutures. The reservoir should be filled with 0.9% normal saline to test for back pressure and herniation through the fascia. A Roberts clamp is used to deliver the reservoir tubing, by passing the clamp posterior to external oblique fascia and into the penoscrotal wound.

In ectopic reservoir insertion, the reservoir is placed within the anterior abdominal wall, posterior to the rectus muscle and anterior to the transversalis fascia through the external inguinal ring. The reservoir should be filled with the minimum required volume of saline to avoid the reservoir from being palpable or visible.

Placement of the Pump

The pump is placed in the most dependent part of the scrotum within the sub-dartos space between the testicles using a nasal speculum. Closure of the dartos muscle in layers is essential to secure the pump in place.

Tubing Connection and Wound Closure

The tubings are connected using the connector or assembly kit provided with the device. Care should be taken to avoid the entrance of air into the device. The device should be inflated to recognise any penile deformity and to ensure its correct positioning.

Careful haemostasis should be performed. Insertion of a 10Fr Redivac drain and keeping the device partially inflated for 24 hours are all critical steps to avoid haematoma formation [30].

The dartos should be closed using absorbable suture in a multilayer fashion to obliterate any potential space. The skin is closed in vertical mattress stitches. A ‘mummy wrap’ dressing is applied, ensuring the pump is within the dressing.

Infrapubic Approach

Although the penoscrotal approach is the most commonly used method for inserting an inflatable penile prosthesis, the infrapubic approach is the second most widely adopted technique. It offers several advantages, including the ability to cycle the device early postoperatively and the benefit of inserting the reservoir under direct vision. However, the approach is not without limitations – primarily the risk of injury to the neurovascular bundle and the limited exposure of the corpora cavernosa. These risks can be minimised through careful dissection, hydrodistension and the use of a nasal speculum to insert the pump into the scrotum. With this approach, the patient is positioned in a supine recumbent position, and the operating table

is hyperextended at the level of the pubic bone to create a flat surgical surface. After a standard 10-minute scrub and draping, an artificial erection is performed using a mixture of 30 mL normal saline and 10 mL of 0.5% Marcaine to distend the corporal tissues and reveal any penile deformities. A 2 cm incision is made one fingerbreadth above the penopubic junction and carried down to Scarpa's fascia, which is incised and bluntly dissected bilaterally along the penis to expose the corpora. Four stay sutures are placed on each side using 0 Vicryl Plus sutures and corporotomies are performed between these sutures using a sickle shaped blade. In most cases, direct corporal measurement with a Furlow is sufficient, and further dilation is unnecessary due to the prior hydrodistension. However, if further dilation is needed, Brooks dilators may be used. Once the safety checks have been completed and the implant is prepared, the reservoir is inserted under direct vision through the external inguinal ring, into the Retzius space. Cylinders are then placed using the same technique as in the penoscrotal approach. The pump is inserted using a long nasal speculum, passed adjacent to the corporal bodies down to the most dependent part of the scrotum. Proper positioning of the pump is confirmed if it remains in the most dependent location during ventrodorsal movement of the penis. Finally, all connections are made, a 10 Fr Redivac drain is inserted, and the wound is closed in layers.

Complications of Penile Prostheses

Intraoperative Complications

Corporal crossover occurs when a cylinder crosses the midline, resulting in both cylinders being positioned within the same corporal body, either distally or proximally. Crossover should be suspected if a clinking sound is heard during simultaneous dilator insertion, if there is difficulty placing the second cylinder, unequal corporal measurements or midline urethral deviation between the inflated cylinders. Crossover can be prevented by dilating the corpora in the dorsolateral direction.

Proximal or Distal Corporal Perforation

Forceful dilatation of fibrosed corpora could lead to proximal or distal perforation. The fossa navicularis is the most common distal site for perforation. Indicators of perforation include blood at the meatus, spillage of antibiotic solution through the urethral meatus and seeing the dilators through the meatus. To avoid distal perforation, the surgeon should secure the distal urethra (fossa navicularis) by compressing the glans firmly between the index finger and the thumb of the non-dominant hand. Due to the high risk of contamination and infection, penile prosthesis implantation should be abandoned if a distal urethral perforation is identified.

Bladder, Bowel or Vascular Injury

Blind insertion of the reservoir into the perivesical (retropubic) space, also known as the space of Retzius, carries an increased risk of bladder injury – particularly in patients with a history of pelvic surgery or radiotherapy. Haematuria following reservoir placement is an indicator of bladder injury.

To reduce the risk of bladder injury, the bladder should be emptied prior to reservoir insertion. Alternatively, the reservoir may be placed in an ectopic position or via an open incision into the retropubic space: either between the rectus abdominus and the transversalis fascia, or retroperitoneally under the transversalis fascia, respectively.

Although bowel and vascular injuries are extremely rare, they require immediate surgical intervention. Bowel injuries may present as bowel obstruction, peritonitis or the formation of an intestinal fistula. The iliac vessels lie approximately 3–4cm lateral to the space of Retzius, making them susceptible to injury during blind-technique reservoir placement. Significant bleeding following reservoir insertion necessitates prompt involvement of a vascular surgeon.

Postoperative Complications

1. Infection

   Prosthesis infection can be a devastating complication. However, it is uncommon in high- volume centres (1-3%). It has serious sequalae as its management necessitates implant removal. Patients with PP infection mostly present with penile pain, swelling, erythema, abscess,

and sometimes with systemic signs such as fever and leucocytosis [31].

2. Erosion

   Erosion (5%) usually occurs months to years after surgery and should be managed by explantation of all components of the device and revision surgery at a later date (≥ 6 months) [32].

3. Penile Deformity

   Penile deformity occurs mainly due to inserting cylinders of inappropriate size. Insertion of an undersized cylinder leads to glans drooping or supersonic transporter deformity, while S- shape deformity is a result of inserting oversized cylinders or unrecognised crossover [33].

4. Mechanical Failure

   Continuous improvements of device design and material decrease the incidence of mechanical failure (<5%). The device can be fully functioning for > 10 years. The most common cause of mechanical failure is leakage in the system.

Post-operative Care

The penile dressing (mummy wrap) and urinary catheter can be safely removed the next day, and the device should be deflated before removing the Redivac (suction) drain at 24–72 hours. The drain can be removed if its output is less than 50ml/24 hours following PP deflation. Patients are discharged with 7 days of oral antibiotics. A follow-up appointment with a nurse specialist after 3 weeks is arranged to start device cycling. Patients can normally resume sexual activity around 6 weeks post-operatively.

References

1. Montorsi, F., *et al.* Summary of the recommendations on sexual dysfunctions in men. *J Sex Med*, 2010; 7: 3572.⏎
2. Hatzichristou, D., *et al.* Recommendations for the clinical evaluation of men and women with sexual dysfunction. *J Sex Med*, 2010; 7: 337.⏎

3. Nehra, A., *et al.* The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. *Mayo Clin Proc*, 2012; 87: 766.⏎
4. Kostis, J.B., *et al.* Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). *Am J Cardiol*, 2005; 96: 313.⏎
5. Vlachopoulos, C., *et al.* Erectile dysfunction in the cardiovascular patient. *Eur Heart J*, 2013; 34: 2034.⏎
6. European association of urology guidelines on sexual and reproductive health 2024. https://uroweb.org/guidelines/sexual-and-reproductive-health/chapter/citation-information.⏎
7. Hatzimouratidis, K., *et al.* Pharmacotherapy for erectile dysfunction: recommendations from the fourth international consultation for sexual medicine (ICSM 2015). *J Sex Med*, 2016; 13: 465.⏎
8. Adapted from EMA statements on product characteristic.⏎
9. Roehrborn, C.G., *et al.* Erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH) combined responders to tadalafil after 12 weeks of treatment. *BJU Int*, 2016; 118: 153.⏎
10. Gur, S., *et al.* Update on drug interactions with phosphodiesterase-5 inhibitors prescribed as first-line therapy for patients with erectile dysfunction or pulmonary hypertension. *Curr Drug Metab*, 2013; 14: 265.⏎
11. Adamou, C., *et al.* The hemodynamic interactions of combination therapy with α-blockers and phosphodiesterase-5 inhibitors compared to monotherapy with α-blockers: a systematic review and meta-analysis. *Int Urol Nephrol* 2020; 52: 1407.⏎
12. Hatzichristou, D., *et al.* Sildenafil failures may be due to inadequate patient instructions and follow-up: a study on 100

non-responders. *Eur Urol*, 2005; 47: 518.⏎
13. Mostafa, T., *et al.* Effect of genetic polymorphism on the response to PDE5 inhibitors in patients with erectile dysfunction: a systematic review and a critical appraisal. *Sex Med Rev*, 2020; 8: 573.⏎
14. Hatzimouratidis, K., *et al.* Psychosocial outcomes after initial treatment of erectile dysfunction with tadalafil once daily, tadalafil on demand or sildenafil citrate on demand: results from a randomized, open-label study. *Int J Impot Res*, 2014. 26: 223.⏎
15. Anaissie, J., *et al.* Clinical use of alprostadil topical cream in patients with erectile dysfunction: a review. *Res Rep Urol*, 2016; 8: 123.⏎
16. Rooney, M., *et al.* Long-term, multi-centre study of the safety and efficacy of topical alprostadil cream in male patients with erectile dysfunction. *J Sex Med*, 2009; 6: 520.⏎
17. Costa, P., *et al.* Intraurethral alprostadil for erectile dysfunction: a review of the literature. *Drugs*, 2012; 72: 2243.⏎
18. Porst, H., *et al.* SOP conservative (medical and mechanical) treatment of erectile dysfunction. *J Sex Med*, 2013; 10: 130.⏎
19. Eardley, I., *et al.* Pharmacotherapy for erectile dysfunction. *J Sex Med*, 2010; 7: 524.⏎
20. Lakin, M.M., *et al.* Intracavernous injection therapy: analysis of results and complications. *J Urol*, 1990; 143: 1138.⏎
21. Lewis, R.W., *et al.* External vacuum therapy for erectile dysfunction: use and results. *World J Urol*, 1997; 15: 78.⏎
22. Chung, E., *et al.* Evaluation of clinical efficacy, safety and patient satisfaction rate after low-intensity extracorporeal shockwave therapy for the treatment of male erectile dysfunction: an Australian first open-label single-arm prospective clinical trial. *BJU Int*, 2015; 115 Suppl 5: 46.⏎

23. Banno, J.J., *et al.* The efficacy of platelet-rich plasma (PRP) as a supplemental therapy for the treatment of erectile dysfunction (ED): initial outcomes. *J Sex Med*, 2017; 14.⏎
24. Reddy, A.G., *et al. Application of botulinum neurotoxin in male sexual dysfunction: where are we now? Sex Med Rev*, 2021; 9: 320.⏎
25. Bajic, P., *et al.* Etiology of erectile dysfunction and duration of symptoms in patients undergoing penile prosthesis: a systematic review. *Sex Med Rev*, 2020; 8: 333.⏎
26. Atri, E., *et al.* A comparison between AMS 700 and coloplast titan: a systematic literature review. *Cureus*, 2020; 12: e11350.⏎
27. Counselling form Fiona Holden and Clare Akers. https://www.baus.org.uk/_userfiles/pages/files/patients/leaflets/Penile%20Prosthesis%20Counselling.pdf⏎
28. Yeung, L.L., Grewal, S., Bullock, A., Lai, H.H., Brandes, S.B. A comparison of Chlorhexidine -alcohol versus povidone - iodine for eliminating skin flora before genitourinary prosthetic surgery : a randomized controlled trial. *J Urol*. 2013; 189(1): 136–140.⏎
29. Eid, J.F., Wilson, S.K., Cleves, M., Salem, E.A., *Coated implants and "non touch" surgical technique decreases risk of infection in inflatable penile prosthesis implantation to 0.46%*. *Urology*, 2012; 79 (6): 1310–1315.⏎
30. Sadeghi-Nejad, H., Ilbeigi, P., Wilson, S.K., Delk, J.R., Siegel, A., Seftel, A.D., Shannon, L., Jung, H. Multi-institutional outcome study on the efficacy of closed -suction drainage of the scrotum in three – piece inflatable penile prosthesis surgery. *Int J Impot Res*, 2025; 17(^): 535–538.⏎
31. Gross, M.S., *et al.* Multicenter investigation of the micro-organisms involved in penile prosthesis infection: an analysis

5 Aetiology, Pathophysiology, Clinical Assessment and Management of Ejaculatory Disorders

Muslim Dogan Deger and Ege Can Serefoglu

DOI: 10.1201/b22940-5

Introduction

One of the most prevalent male sexual problems is ejaculatory dysfunction (EjD) [1]. EjD includes premature ejaculation, delayed ejaculation, or a complete inability to ejaculate (anejaculation). The less common forms are retrograde ejaculation, painful ejaculation, haematospermia, ejaculatory anhedonia, and the recently described post-orgasmic illness syndrome (POIS) [2, 3, 4]. This chapter will be summarizing the four most common types of EjD, namely premature ejaculation (PE), delayed ejaculation (DE), anejaculation (AE), and retrograde ejaculation (RE).

Physiology of Ejaculation

Desire, arousal, orgasm, and resolution are the four interrelated stages that make up the sexual response cycle [5]. The ejaculatory reaction, which usually ends the sexual encounter for the male, is triggered when rising levels of sexual stimulation reach a threshold that causes ejaculation. Orgasm is a separate cortical event that is experienced both cognitively and emotionally. It is caused by striated pelvic muscle spasms and subsequent seminal fluid released during expulsion, orchestrated by sensory neurons in the pelvic area [6].

Ejaculatory latency, or the period of time between the start of penile stimulation and the moment of ejaculation, varies between men and for men in different circumstances [7]. The vast majority of sexually active men appear to achieve ejaculation after 3–5 minutes of penile stimulation and are, along with their partners, content with the duration [8]. However, some men may be bothered with their ejaculation latency and seek medical help for this problem [9, 10]. Surgical operations, various medications, or neurological/hormonal disorders may disrupt the bladder neck closure mechanisms along with emission and expulsion phases of ejaculation, which results in RE or AE [3].

Various central and peripheral neurological systems function together during the ejaculatory reflex. This physiological phenomenon involves intricate interactions between central serotonergic and dopaminergic neurons, with cholinergic, adrenergic, oxytocinergic, and gamma-aminobutyric acid (GABA) neurons playing a supporting role. Synergistic stimulation of the somatic and autonomic (sympathetic and parasympathetic) nervous system regulates the peripheral processes that result in emission and expulsion phases of ejaculation. Furthermore, non-adrenergic non-cholinergic (NANC) innervation may influence ejaculation control by regulating the activity of accessory sex glands [6].

The ejaculation reflex is often split into three synchronized phases: emission, expulsion, and orgasm. The sympathetic and parasympathetic pathways are synergistically activated to modulate emission, but a cholinergic excitatory mechanism may also be present [6]. Ejection is caused by pulsatile contractions of the bulbospongiosus, ischiocavernosus, and levator ani muscles, as well as relaxation of the internal urinary sphincter, which is mediated by somatic nerves (S2 to S4) within the pudendal nerve. A sympathetic spinal cord reflex that causes the bladder neck to shut in order to stop retrograde flow is also involved in ejection. The pudendal nerve sensory stimulus caused by increased pressure in the posterior urethra, verumontanum sensory stimulus, and contraction of the urethral bulb and accessory sexual organs are processed by the brain to produce an orgasm. Several neurotransmitters play a role in the regulation of ejaculation; serotonin is inhibitory whereas dopamine facilitates seminal emission/ejaculation via D2 receptors.

Premature Ejaculation

Aetiology, Pathophysiology, and Clinical Assessment of Premature Ejaculation

Epidemiology

Observational studies of men with PE [9, 11] and community-based normative intravaginal ejaculatory latency time (IELT) research [7] showed that men with IELTs of less than 1 minute have a low prevalence of about 2.5% in the general population. However, a much higher proportion of men with normal IELT complain of PE [9, 11] as the frequency of the complaint of PE is around 19.8%–25.80% among the sexually active male population [9, 11]. Considering this discrepancy, Waldinger and Schweitzer proposed a new classification of PE, dividing it into four subgroups based on the length of the IELT, frequency of complaints, and the history of the patient. This classification includes variable PE and subjective PE, in addition to lifelong and acquired PE [12]. Men with variable PE will occasionally ejaculate early. This should be viewed as a natural variation of a man's ejaculation time rather than a problem. Yet, men who experience subjective PE claim to have an 'early ejaculation problem' while having normal or even prolonged ejaculation time [13]. This PE complaint is likely influenced by cultural and/or psychological variables. The prevalence rates for lifelong PE, acquired PE, variable PE, and subjective PE are reported to vary between 2.3%–3.2%, 3.9%–4.5%, 8.5%–11.4%, and 5.1%–6.4%, respectively [9, 11, 14].

Aetiology of Premature Ejaculation

Although the characteristics of short ejaculation time, diminished (or absent) perceived ejaculatory control, and the presence of negative personal consequences from PE appear to be shared by men with both lifelong and acquired PE [15], their aetiological factors are different from each other.

Lifelong Premature Ejaculation

The pathophysiology of lifelong PE may be influenced by neurobiological and genetic abnormalities in some men and may be sustained and aggravated by psychological and environmental factors [16, 17]. Hyposensitivity of the 5-HT2C receptors and/or hypersensitivity of the 5-HT1A receptors may be responsible for lifelong PE [18]. Penile hypersensitivity can also result in enhanced stimulation in the ejaculation reflex and cause lifelong PE [17].

Acquired Premature Ejaculation

Common causes of acquired PE include anxiety about sexual performance, psychological or interpersonal issues, erectile dysfunction (ED), prostatitis, hyperthyroidism, and drug withdrawal or detoxification from legal or illicit substances [19]. Up to 50% of people with ED also have PE [20]. In order to avoid early detumescence of a partial erection, subjects with ED may either need higher levels of stimulation or purposefully ‘rush’ intercourse, resulting in ejaculation with short latency. ED, PE, and painful ejaculation are linked to acute and chronic urogenital infections, or chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) [21]. There is no precise aetiology known for the association between chronic prostatitis, ED, and PE [21].

Pathophysiology of Premature Ejaculation

Although the exact cause of PE is unknown, several hypotheses are formulated, involving complex combinations of neurophysiological, psychosocial, and cognitive components [17, 21]. Many psychosocial factors that can cause PE include: early experience, anxiety, psychodynamic theories, sexual conditioning, and technique or/and frequency of sexual activity. Penile hypersensitivity, hyperarousability, hyperexcitable ejaculatory reflex, genetic susceptibility, endocrinopathy, and 5-HT receptor function impairment are all biogenic factors.

Clinical Assessment of Premature Ejaculation

Medical / Sexual History

Men who self-report PE should undergo a comprehensive medical and sexual history, a focused physical examination, an assessment of erectile function, and any further investigations indicated by these findings [22, 23, 24]. If possible, their partners should be included in the assessment process.

The diagnosis of PE is established by a medical/sexual history. In clinical practice, IELT should be noted based on the patient's and their partner's self-reported ejaculatory latency. It is possible to employ standardized assessment tools like validated questionnaires and patient reported outcome (PRO) measurements such as the Index of Premature Ejaculation (IPE) [25] and the Premature Ejaculation Profile (PEP) [26]. The Premature Ejaculation Diagnostic Tool (PEDT) [27], a third quick diagnostic test, is also available.

The International Index of Erectile Function (IIEF) [28] may be helpful in determining whether concomitant ED is present. In order to avoid early detumescence of a partial erection, subjects with ED may either need higher levels of stimulation or purposefully 'rush' intercourse, resulting in ejaculation with short latency. High levels of performance anxiety due to ED may make this situation worse and help to exacerbate their prematurity.

Focused Examination

In order to determine the cause of PE and treat any potential causes, a physical examination is required in men with acquired PE. All men over 40 should have a routine digital prostate examination in an andrological environment to look for any signs of prostatic inflammation or infection. However, physical examination may not always be necessary for patients with lifelong PE [24].

Investigations

Specific tests are not normally required for the diagnosis of PE. If the patient has concomitant ED blood levels of glucose, morning testosterone and lipid profile may be necessary [22]. If the patient is over 50 years of age or describes complaints suggestive of prostatic diseases, PSA levels can also be measured [22].

Management of Premature Ejaculation

There are numerous pharmacological and psychosexual therapies for PE [29] (Figure 5.1). The most effective treatment for men with lifelong PE is pharmacotherapy, either alone or in combination with psychosexual therapy. On the other hand, acquired PE patients should receive aetiology-specific treatment, psychosexual counselling, or ED medications. Psychosexual education and psychotherapy should be the main forms of treatment for men with variable PE or subjective PE (Figure 5.2).

Treatment	Advantage	Disadvantage
Behavioural therapy	• High reported initial success rate in uncontrolled studies	• Limited long-term efficacy
Topical anaesthetics (creams and sprays)	• Effective in majority of patients	• Penile and vaginal hypoesthesia • Female anorgasmia • Skin reactions
Clomipramine	Significant improvement in IELT	• Nausea • Erectile dysfunction • HSDD • Reduced vigilance • Rhythm disorders
Antidepressant SSRIs	Significant improvement in IELT	• Generally, require daily dosing • Limited data on patient-reported outcomes • SSRI withdrawal syndrome • Poorly accepted by patients and partners
PDE5 inhibitors	First line option in PE with concomitant ED	Arguable efficacy in only PE patients
Tramadol	• Significant improvement in IELT • Suitable for on-demand dosing	• Limited clinical data • Limited real-life clinical experience • Risk of addiction?

Figure 5.1 Current premature ejaculation treatments. (PE: premature ejaculation; ED: erectile dysfunction; SSRIs: selective serotonin reuptake inhibitors; PDE5i: phosphodiesterase 5 inhibitors; IELT: intravaginal ejaculatory latency time; HSDD: hypoactive sexual desire disorder.)⏎

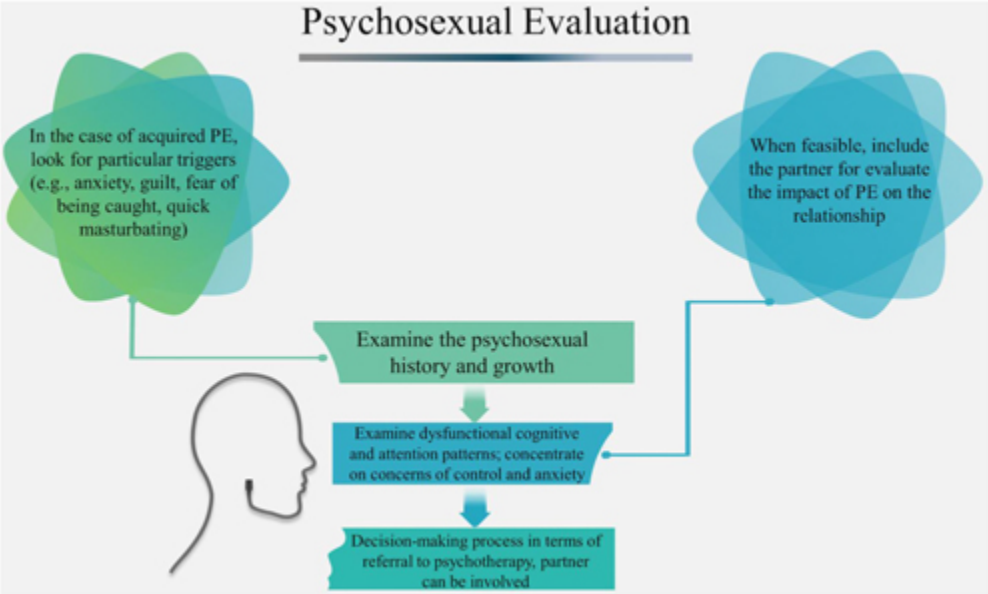


Figure 5.2 Management of premature ejaculation.⏎

Men who self-report PE should have their comprehensive medical and sexual history reviewed, undergo a focused physical examination, complete an inventory-based assessment of erectile function, and receive any investigations indicated by these findings. Where possible, their partners should be involved in the management process.

Psychosexual Therapy

All PE patients should obtain fundamental coaching or education about their sexuality [23]. In order to dispel common misconceptions about PE, this may involve sharing information about the prevalence of PE and IELT of the general population, providing advice about pleasurable sexual activities to broaden the man's and his partner's sexual options, and addressing avoidance of sexual activity or reluctance to discuss sex with his partners [23].

PE causes a significant psychological stress in men, their partners, and their relationships as a whole [30]. Men with PE exhibit feelings of shame/guilt, anxiety/depression, and fear of failure [30]. Increasing IELT is not the only goal of psychological PE therapies. The man, his partners, and their relationships are the primary targets. This occurs by assisting

men/couples to: (a) learn methods to control and/or delay ejaculation, (b) gain confidence in their sexual performance, (c) reduce performance anxiety, (d) modify rigid sexual repertoires, (e) overcome barriers to intimacy, (f) resolve interpersonal issues that precipitate and maintain the dysfunction, (g) improve communication, and (h) come to terms with feelings/thoughts that inhibit.

Psychotherapy and behavioural interventions can improve ejaculatory control [31], but the psychological–behavioural strategy has some limitations, including being time-consuming, frequently requiring significant financial resources, lacking immediate results, requiring partners' agreement, and having mixed (and less well-documented) success. Additionally, there is a paucity of evidence to establish long-term efficacy [22].

Medical Management

The earliest known pharmacological treatment for PE involved the application of topical local anaesthetics (LA), such as lidocaine, prilocaine, or benzocaine, either alone or in combination, to reduce the sensitivity of the glans penis. PE treatment was transformed by the development of selective serotonin reuptake inhibitors (SSRIs), including dapoxetine, paroxetine, sertraline, fluoxetine, citalopram, and the tricyclic antidepressant (TCA) clomipramine [29] (Figure 5.3). These medications increase 5-HT neurotransmission and stimulate post-synaptic membrane 5-HT receptors by preventing 5-HT transporters from reabsorbing serotonin from the synaptic cleft of central serotonergic neurons. Phosphodiesterase 5 inhibitors (PDE5i) and tramadol have also been used for the treatment of PE [29] (Figure 5.4).

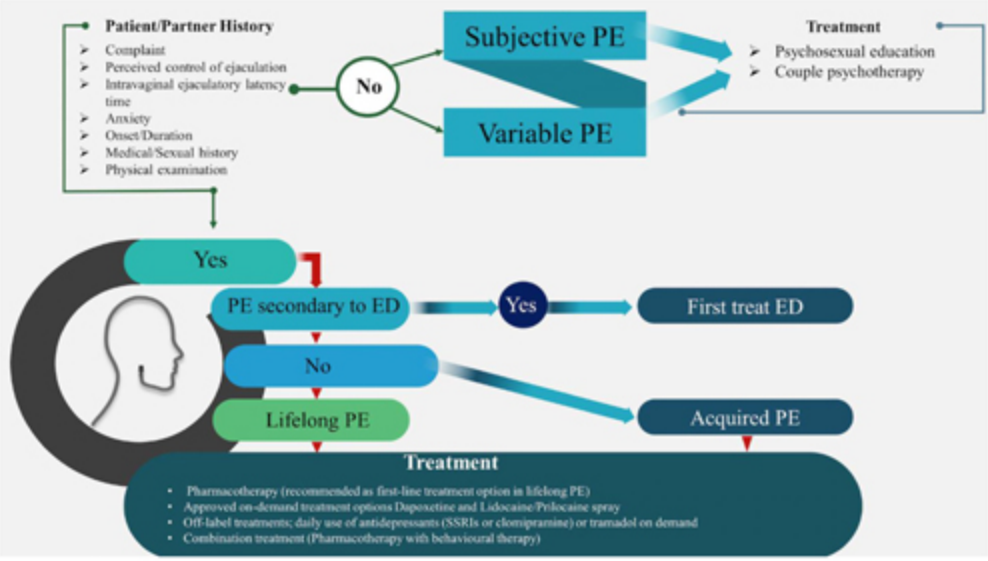


Figure 5.3 Psychosexual evaluation.⏎

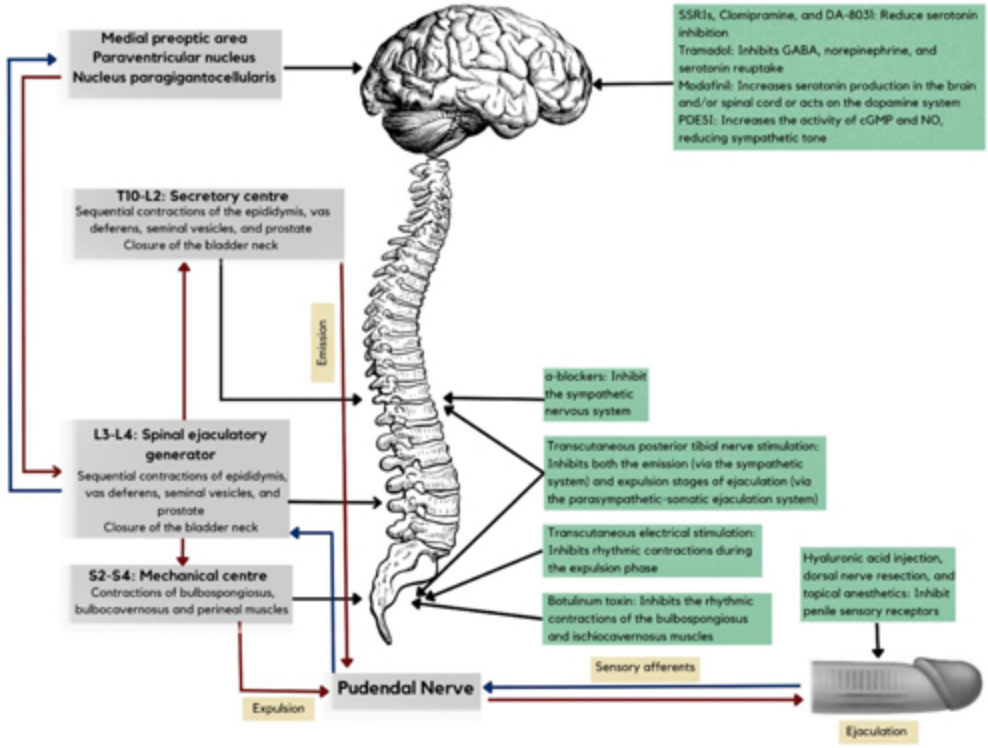


Figure 5.4 Treatments and mechanisms of action.⏎

PDE5i, phosphodiesterase 5 inhibitors; SSRIs, selective serotonin reuptake inhibitors.

Examining the psychosexual history and growth is essential. Men with PE have been found to exhibit faulty responsibility attribution processes when it comes to their sexual experiences. When possible, engage the partner in the evaluation of the impact of PE on the relationship.

Selective Serotonin Reuptake Inhibitors

SSRIs can be used to treat PE when they are taken as needed or daily. Daily doses of paroxetine, citalopram, or clomipramine can also delay ejaculation [29]. In more than 50 nations throughout the world, on-demand dapoxetine is approved for the treatment of PE. Its quick acting and short half-life pharmacokinetic profile supports its potential as an on-demand therapy for PE. Dapoxetine 30 or 60mg administered 1–2 hours before sexual activity was shown to be superior to placebo from the first dose in RCTs, increasing IELT by 2.5 and 3.0-fold, improving ejaculatory control, reducing distress, and boosting satisfaction [32]. A sudden stop to the use of dapoxetine did not appear to cause withdrawal symptoms or to increase the likelihood of suicidal thoughts or attempts. The high cessation rate for dapoxetine (87% at 12 months) was mostly brought on by the expense and lack of spontaneity involved with on-demand administration [33].

Fluoxetine 20–40 mg, sertraline 50–200 mg, paroxetine 10–40 mg, clomipramine 12.5–50 mg, and citalopram 20–40 mg are usually effective in delaying ejaculation with off-label daily treatment [29]. The decision to treat PE with daily off-label SSRI dose or on-demand dosing of dapoxetine should be based on the treating physician’s evaluation of the specific needs of each patient. Many men with PE who infrequently have sex may prefer on-demand care, but other PE patients in committed relationships may be more satisfied with the convenience of daily medicine [34].

Adverse reactions related to SSRI treatments are often mild, begin within the first week of therapy, and may gradually go away in two weeks. They consist of drowsiness, yawning, moderate nausea, diarrhoea, or sweating. About 90% of patients stop treatment before one year because of

not wanting to take an antidepressant, treatment outcomes being below expectations, and cost [35].

Topical Local Anaesthetics

When applied to the glans and shaft of the penis 5–10 minutes before sexual intercourse, topical local anaesthetics (LAs) (such as lidocaine and/or prilocaine, in cream, gel, or spray form) can delay ejaculation. Glans sensitivity reduction may prevent the spinal reflex arc that triggers ejaculation. LAs may cause substantial penile hypo-anaesthesia and result in DE or ED. Moreover, transvaginal absorption, vaginal numbness, and subsequent female anorgasmia can occur unless a condom is used, or the penis is washed before vaginal intercourse [36].

Phosphodiesterase 5 Inhibitors

On-demand or a daily dose of PDE5i is advised for the treatment of PE in men with or without ED, either alone or in combination with other PE medications. PDE5i is beneficial in increasing IELT, enhancing erectile functions, and increasing patient satisfaction [22].

On-Demand Treatment with Off-Label Tramadol

Tramadol is a centrally acting synthetic opioid analgesic with an unknown mechanism of action that includes binding of the parent and M1 metabolite to μ-opioid receptors and mild inhibition of GABA, norepinephrine, and serotonin reuptake. Although the mechanism of action is not fully understood, tramadol's efficacy may be due to anti-nociceptive and anaesthetic-like actions, as well as central nervous system regulation via suppression of serotonin and noradrenaline reuptake [37]. The International Society for Sexual Medicine (ISSM) expert group for the treatment of PE considered that tramadol could be an effective therapy choice [24]. However, given the potential for addiction and side effects, it should be explored after other therapies have failed. Nausea, vomiting, dizziness, somnolence, fatigue, and headache are the most prevalent adverse effects. It should not be used with an SSRI due to the risk of serotonin syndrome, which can be fatal.

Daily Treatment with Off-label Alpha 1-adrenoceptor Antagonists

Alpha 1-adrenoceptor antagonists are commonly used in the treatment of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). These medications can cause RE or AE. Silodosin is a highly selective alpha 1-adrenoceptor which has the potential to prolong IELT [38].

Emerging Investigational Drugs and Treatment Methods

Considering the high drop-out rates for currently available PE treatments, there are many clinical trials to develop a PE drug which will meet the expectations of PE patients [33, 35]. These experimental treatments are not currently recommended by the American Urological Association (AUA) and European Association of Urology (EAU) guidelines and must be considered as experimental treatments [22, 23].

DA-8031

DA-8031 is a fast-acting SSRI that could be used to treat PE. The monoamine transporter binding and reuptake inhibition assay shows strong affinity and selectivity for the serotonin transporter but low affinity and selectivity for the dopamine and norepinephrine transporters. DA-8031 substantially inhibited ejaculation in rat models after oral and intravenous administration, according to several pre-clinical studies [39].

Oxytocin Antagonists

Oxytocin is a nine-amino acid peptide hormone that aids sexual reproduction in animals. Plasma oxytocin levels in men increase during penile erection and orgasm. Studies showed that central administration of a selective oxytocin-receptor antagonist inhibited ejaculation in male rats [40]. Clinical data show modest increase in IELT and improvement PRO measures of men with lifelong PE [41].

Modafinil

Modafinil is a wake-promoting drug and is currently used to treat narcolepsy. D-modafinil may cause DE by increasing serotonin production

in the brain and/or spinal cord or by acting on the dopamine system. On-demand modafinil treatment can be beneficial in the treatment of PE [42].

Botulinum-A Toxin

Botulinum toxin selectively inhibits acetylcholine release at nerve endings, thereby blocking neural transmission. It can be used to delay ejaculation by inhibiting the rhythmic contractions of bulbospongiosus and ischiocavernosus muscles during the ejection phase of ejaculation [43] and one clinical trial demonstrated its efficacy in the treatment of lifelong PE [44].

Glans Penis Augmentation with Hyaluronic Acid

Injection of hyaluronic acid to the glans penis may prevent tactile sensations from reaching the sensory receptors of the glans penis, and delay ejaculation. Numerous clinical studies were conducted to assess the effectiveness of hyaluronic acid injections into the glans penis for the treatment of PE [45]. However, the general quality of these studies is jeopardized by imprecise PE definitions for patients enrolled in the trials, the lack of control groups, and the lack of regular follow-up. The most frequently reported mild adverse effects were local pain at the injection site, penile ecchymosis, and papule formation in the glans penis. Identifying the optimal PE patients, ideal bulking agents, and safe surgical procedures is critical for improving the efficacy of this surgery.

Surgical Neurotomy, Cryoablation and Neuromodulation of the Dorsal Penile Nerve

In Asian countries, selective resection of the dorsal penile nerves (SRDN) is commonly used to reduce penile sensitivity and treat PE. This surgery is reported to be the second most commonly applied treatment after SSRIs in Korea due to its efficacy in increasing IELT and improving ejaculatory control [46]. Abnormal sensation in glans, pain, and ED are the most common complications. Despite its favourable outcomes, the ISSM, EAU, and AUA guidelines do not recommend SRDN for the treatment of PE due to its invasive and irreversible nature [15, 22, 23].

Transcutaneous Neuromuscular Electrical Stimulation

Transcutaneous electrical stimulation (TES) works by causing a plateau action potential in the bulbospongiosus and ischiocavernosus muscles, which inhibits rhythmic contractions during the expulsion phase of ejaculation. As a result of this constant stimulation, the affected muscles stay in a state of subtetanic persistent contraction. Because ejaculation needs rhythmic contractions, applying TES to the bulbospongiosus and ischiocavernosus muscles during sexual activity may result in a delayed ejaculation [47]. Prolonged IELT and better ejaculatory control were obtained when a TES device was placed onto the perineum. Future head-to-head comparison trials are required, and user-friendly TES devices must be designed to avoid sexual pain.

Transcutaneous Posterior Tibial Nerve Stimulation

The emission phase of ejaculation is primarily regulated by T12-L1 stimuli, whereas the expulsion phase is primarily controlled by S2-S4 stimuli [6]. Transcutaneous posterior tibial nerve stimulation (TPTNS) may inhibit both the emission (via the sympathetic system) and expulsion stages of ejaculation (via the parasympathetic-somatic ejaculation system). Treatments with 30-minute TPTNS three times per week for 12 weeks provided an increase in IELT [48]. To validate the efficacy of TPTNS in treating PE, randomized controlled trials with larger sample sizes are required.

Delayed Ejaculation

DE is probably the most under-diagnosed, under-studied, under-reported and least understood male sexual dysfunction [49]. Nevertheless, the impact of DE is important because it can lead to a lack of sexual satisfaction for both the man and his partner. This effect is exacerbated by the couple's desire to have children.

Aetiology, Pathophysiology, and Clinical Assessment of Delayed Ejaculation

Epidemiology of Delayed Ejaculation

Historically, DE has rarely been reported in the literature, with rates exceeding 3% [1]. However, in Europe, over 40% of men aged 50 to 79 have DE at some point in their life [50]. DE prevalence appears to be linked with age, varies between races, and is also associated with LUTS, low serum testosterone levels, and hyperlipidaemia. Males with DE experience a significant level of relationship distress, sexual dissatisfaction, anxiety about their sexual performance, and overall health problems [51]. Men with DE have normal erectile function, with some men able to maintain an erection for extended periods. However, they frequently report low levels of subjective sexual desire.

DE is defined by the American Psychiatric Association (DSM-V) as a marked delay or absence of ejaculation in almost all or all (about 75%–100%) of partnered sexual activity that causes clinically significant distress in the person and without a desire for delay [52]. DE should not be the result of a non-sexual mental disorder or other significant stressors. It should also not be caused by the effects of a substance, drug, or other medical condition. DE can be lifelong or acquired, and mild, moderate, or severe. The DSM-V definition of ‘latency’ has no clear boundaries, as there is no consensus on what is a reasonable time to reach orgasm, or what is unacceptably long for most men and their sexual partners.

As diagnostic criteria do not exist, there are no clear criteria for when a man meets the conditions for DE. Given that the majority of sexually functional men ejaculate within about 4–10 minutes after vaginal penetration, it can be assumed that men whose ejaculation exceeds 25 or 30 minutes and who are distressed by this condition, or who have stopped sexual activity due to fatigue and irritation, are eligible for this diagnosis. Such symptoms are usually sufficient for a diagnosis of DE, with a man and/or his partner deciding to seek help for the problem.

Aetiology of Delayed Ejaculation

The pathogenesis of DE is complex [49]. Several causes include disorders caused by congenital and psychological factors, treatment of pelvic cancers with surgery or radiotherapy, neurological diseases (e.g., Diabetic neuropathy, multiple sclerosis, spinal cord injury, Parkinson’s disease),

hormonal disorders (e.g., hypogonadism, hypothyroidism), and medications (e.g., tranquilizers, antidepressants, anti-psychotics, alpha-blockers) [53].

Performance anxiety, marital conflict, hypoactive sexual desire, poor sexual communication, psychological conflict connected to fear of having children, and guilt that may arise from religion are all examples of psychological issues [51]. Sometimes men with DE report a certain type of masturbation that is unrelated to intercourse (idiosyncratic masturbation style) and this habit makes them not ejaculate during vaginal intercourse.

Psychological Delayed Ejaculation

DE is frequently related to sexual performance anxiety and causes the male to avoid amorous ideas that lead to arousal. Other psychodynamic hypotheses focus on psychosexual development concerns and link lifelong DE to a variety of factors, such as fear, anxiety, religious beliefs, and relationship difficulties. Masturbation methods that are idiosyncratic and violent, or an ‘automatic sexual’ orientation in which men obtain more excitement and pleasure from masturbation than from intercourse are risk factors for DE [54].

Organic Delayed Ejaculation

DE is frequently linked to hypothyroidism [55] and/or hypogonadism [51]. Any prescription or recreational substance that affects the amounts of neurotransmitters involved in central or peripheral control of ejaculation (such as serotonin, dopamine, or oxytocin) might cause DE. SSRIs are linked to a 60% increase in sexual dysfunction, most commonly DE [56].

Among the elderly male population, both DE and AE are frequently related to degeneration of penile fast-conducting afferent neurons, diabetic autonomic neuropathy, multiple sclerosis, and spinal cord injury [51]. Various cancers and their treatments may also disrupt the ejaculation reflex and cause DE. The most prevalent causes of DE include pelvic radiotherapy, colorectal surgery, and retroperitoneal lymph node dissection (RPLND) in testicular cancer.

Pathophysiology of Delayed Ejaculation

The pathophysiology of DE is typically multimodal, coming from several biological or psychogenic causes. It might be primary (lifelong) or secondary (acquired). DE pathophysiology comprises interrelated brain sensory areas, motor centres, and multiple spinal nuclei. The pathophysiology of DE is heavily influenced by biogenic, psychogenic, and environmental variables.

Clinical Assessment of Delayed Ejaculation

Medical/Sexual History

The sexual history should include an assessment of the frequency, duration, and circumstances of ejaculation. If ejaculation does not occur, the reasons for interrupting intercourse (e.g., fatigue, loss of erection, frustration, or partner desire) must be noted. If ejaculation occurs during self- or partner-assisted masturbation after intercourse, organic causes can be excluded.

It is necessary to identify the presence and extent of negative psychological repercussions, such as discomfort, distress, frustration, or avoidance of sexual interaction. The quality of the non-sexual relationship should also be investigated. Previous sickness, surgery, and drugs should be evaluated in men with acquired DE. The presence of new stressors in the patient's life may also be responsible for the acquired DE.

Focused Examination

The major purpose of the evaluation is to rule out organic disorders. A thorough genital examination must be performed. The testicles, epididymides, and vasa deferentia should be examined. Rectal examination may be useful to assess prostate size and consistency, anal sphincter function, and neuropathic reflexes [22, 23].

Investigations

The levels of testosterone and PSA can be useful in excluding hypogonadism and prostate diseases, respectively. The lack of ejaculation or low-volume orgasm indicates RE or ejaculatory duct obstruction. The presence of spermatozoa in the urine following masturbation implies RE,

but the presence of azoospermia/oligospermia, low viscosity, low fructose, and pH in semen analysis suggests ejaculatory duct obstruction. If the diagnosis is unclear, MRI and ultrasonography may be useful [22, 23].

Management of Delayed Ejaculation

Treatment should be tailored to the aetiology and may include psychosexual education and/or therapy, serotonergic or dopaminergic medications, or a combination of treatments for the patient/couple. If there is a desire for children, testicular sperm retrieval techniques may be considered. Regardless of whether there is a clear pathophysiological cause, patients may be advised to make lifestyle changes to ensure greater intimacy, such as spending more time together, limiting alcohol consumption, practising techniques that maximize penile stimulation, such as pelvic floor exercise, and making love when not tired. Since neuropathic DE is usually irreversible, the patient may be counselled to adopt alternative methods of achieving mutual sexual satisfaction with their partners. If organic factors cannot be identified, a referral to a psychosexual therapist may be helpful to analyse the causative psychological and behavioural difficulties. The therapeutic benefits of psychotherapy are determined by the severity of the DE as well as the individual's willingness to attend counselling and follow the counsellor's advice [22, 23].

Medical Management

The use of drugs to treat DE has demonstrated poor efficacy. These medications promote ejaculation by a central dopaminergic, anti-serotonergic, or oxytocinergic mechanism of action, as well as a peripheral adrenergic mode of action. However, no medications have been approved by regulatory agencies for this purpose, and the majority of the compounds found for prospective usage have poor efficacy, considerable side effects, or are still deemed experimental [22, 23].

Pre-coital use of alpha-1 adrenergic receptor agonists such as pseudoephedrine (120 mg 1–2 hours before intercourse) or the daily use of SNRI antidepressant reboxetine (4–8 mg daily) (which decrease synaptic noradrenaline reuptake) can be beneficial in decreasing ejaculatory latency, but their effectiveness is low [57]. Cabergoline, a central D2 agonist

authorized for the treatment of hyperprolactinemia, has been shown to reduce ejaculation time and make ejaculation easier [58]. It has also been used to treat men with anorgasmia. Other pharmacologic drugs, like amantadine, apomorphine, bromocriptine, bupropion, and buspirone, have been anecdotally reported as viable DE pharmacotherapy, although randomized clinical trials are missing. Intranasal oxytocin is another promising alternative; however, its efficacy has yet to be shown in large patient groups [22, 23]. Yohimbine is a selective competitive α2-adrenergic receptor blocker used for orgasmic dysfunction. One study found that 55% of men responded well to yohimbine treatment for anorgasmia and DE [59].

Anejaculation and Anorgasmia

Aetiology, Pathophysiology, Clinical Assessment

The complete lack of antegrade or retrograde ejaculation is referred to as AE [60]. It is caused by the failure of semen emission from the seminal vesicles, prostate, and ejaculatory ducts into the urethra. True anejaculation is frequently associated with central or peripheral nerve system disorders (e.g., post RPLND) or medications, and it produces a normal orgasmic sensation. It has similar aetiologic factors with DE and RE [60].

Anorgasmia is the perception of a lack of orgasm. Anorgasmia can be a lifelong or acquired disease, regardless of whether ejaculation occurs. Some non-specific psychological issues, such as substance misuse, obesity, anxiety, and fear, are thought to be risk factors for anorgasmia. It is widely acknowledged that psychological factors account for 90% of the causes of anorgasmia [61]. The patient and partner should be thoroughly examined physically and psychosexually, including determining the onset of anorgasmia, history of medication and illness, penile sensitivity, and psychological problems. Organic causes should be ruled out by checking testosterone, prolactin, and thyroid hormone levels. Patients with loss of penile sensitivity should be investigated further. The adverse effects of RPLND for residual masses following treatment of non-seminomatous malignancy are well documented. With non-nerve-sparing procedures, anejaculation occurs in the majority of patients [22, 23].

Management

Psychosexual therapy or medication for anejaculation caused by neuropathy and lymphadenectomy are not effective. The administration of a vibrator to the penis is the first-line treatment in all of these circumstances, as well as in men with spinal cord injury. If this treatment does not work, electro-ejaculation can be used. Fertility can be achieved by surgical sperm retrieval procedures [22, 23].

Treatment of anorgasmia is similar to the treatment of DE. Affected persons may be advised to change their masturbation style, increase their desire, and reduce their alcohol usage. However, it is difficult to determine success rates from the literature. Various medications are being tried, including cyproheptadine, yohimbine, buspirone, amantadine, and oxytocin. However, these reports are usually from case-cohort studies and the drugs have limited efficacy and significant side effect profiles. Therefore, the current evidence is not strong enough to recommend medication for the treatment of anorgasmia [22, 23].

Retrograde Ejaculation

Aetiology, Pathophysiology, and Clinical Assessment of Retrograde Ejaculation

Normal ejaculation necessitates a closed bladder neck during the ejection phase [6]. RE may occur as a result of surgical operations that disrupt the bladder neck closure mechanism (e.g., transurethral resection of the prostate, TURP) [3]. The reported incidence of RE following prostate resection operations ranges from 42% to 100% [62]. RE is more common in patients with diabetes mellitus. Some medications like alpha-blockers may also cause RE. The presence of spermatozoa and fructose in a post-masturbatory urine specimen distinguishes RE from failure of emission [3].

Management of Retrograde Ejaculation

Alpha-adrenergic sympathetic nerves control both bladder neck closure and emission [3]. Pharmacotherapy, which includes medications such as

pseudoephedrine, midodrine, and imipramine, has varying degrees of efficacy. The tricyclic antidepressant imipramine, which inhibits noradrenaline reuptake by the axon from the synaptic cleft, is also occasionally beneficial. Urinary sperm collection and artificial insemination with in vitro fertilization is an alternative technique for fertility in patients who do not achieve antegrade ejaculation with surgery or medication [3].

References

1. Laumann EO, Paik A, Rosen RC. *Sexual dysfunction in the United States: prevalence and predictors*. *JAMA*. 1999;281(6):537–544.⏎
2. Rowland D, McMahon CG, Abdo C, Chen J, Jannini E, Waldinger MD, *et al*. Disorders of orgasm and ejaculation in men. *J Sex Med*. 2010;7(4 Pt 2):1668–1686.⏎
3. Parnham A, Serefoglu EC. Retrograde ejaculation, painful ejaculation and hematospermia. *Transl Androl Urol*. 2016;5(4):592–601.⏎
4. Waldinger MD, Schweitzer DH. Postorgasmic illness syndrome: two cases. *J Sex Marital Ther*. 2002;28(3):251–255.⏎
5. Masters WH, Johnson VE. *Human Sexual Inadequacy*. Boston: Little Brown; 1970. pp. 92–115.⏎
6. Clement P, Giuliano F. Physiology and pharmacology of ejaculation. *Basic Clin Pharmacol Toxicol*. 2016;119 Suppl 3:18–25.⏎
7. Waldinger MD, Quinn P, Dilleen M, Mundayat R, Schweitzer DH, Boolell M. A multinational population survey of intravaginal ejaculation latency time. *J Sex Med*. 2005;2(4):492–497.⏎
8. McMahon CG, Jannini E, Waldinger M, Rowland D. Standard operating procedures in the disorders of orgasm and

ejaculation. *J Sex Med*. 2013;10(1):204–229.⏎
9. Serefoglu EC, Yaman O, Cayan S, Asci R, Orhan I, Usta MF, *et al*. Prevalence of the complaint of ejaculating prematurely and the four premature ejaculation syndromes: results from the Turkish Society of Andrology Sexual Health Survey. *J Sex Med*. 2011;8(2):540–548.⏎
10. Serefoglu EC, Cimen HI, Atmaca AF, Balbay MD. The distribution of patients who seek treatment for the complaint of ejaculating prematurely according to the four premature ejaculation syndromes. *J Sex Med*. 2010;7(2 Pt 1):810–815.⏎
11. Gao J, Zhang X, Su P, Liu J, Xia L, Yang J, *et al.* Prevalence and factors associated with the complaint of premature ejaculation and the four premature ejaculation syndromes: a large observational study in China. *J Sex Med*. 2013;10(7):1874–1881.⏎
12. Waldinger MD, Schweitzer DH. The use of old and recent DSM definitions of premature ejaculation in observational studies: a contribution to the present debate for a new classification of PE in the DSM-V. *J Sex Med*. 2008;5(5):1079–1087.⏎
13. Janssen PKC, Waldinger MD. Men with subjective premature ejaculation have a similar lognormal IELT distribution as men in the general male population and differ mathematically from males with lifelong premature ejaculation after an IELT of 1.5 minutes (Part 2). *Int J Impot Res* 2019;31(5):341–347.⏎
14. Saitz TR, Serefoglu EC. The epidemiology of premature ejaculation. *Transl Androl Urol*. 2016;5(4):409–415.⏎
15. Serefoglu EC, McMahon CG, Waldinger MD, Althof SE, Shindel A, Adaikan G, *et al*. An evidence-based unified definition of lifelong and acquired premature ejaculation: report of the second International Society for Sexual Medicine

Ad Hoc Committee for the Definition of Premature Ejaculation. *J Sex Med*. 2014;11(6):1423–1441.⏎
16. Janssen PK, Bakker SC, Rethelyi J, Zwinderman AH, Touw DJ, Olivier B, *et al.* Serotonin transporter promoter region (5-HTTLPR) polymorphism is associated with the intravaginal ejaculation latency time in Dutch men with lifelong premature ejaculation. *J Sex Med*. 2009;6(1):276–284.⏎
17. Waldinger MD. The pathophysiology of lifelong premature ejaculation. *Transl Androl Urol*. 2016;5(4):424–433.⏎
18. Waldinger MD. The neurobiological approach to premature ejaculation. *J Urol*. 2002;168(6):2359–2367.⏎
19. Culha MG, Tuken M, Gonultas S, Cakir OO, Serefoglu EC. Frequency of etiological factors among patients with acquired premature ejaculation: prospective, observational, single-center study. *Int J Impot Res* 2020;32(3):352–357.⏎
20. Jannini EA, Lombardo F, Lenzi A. Correlation between ejaculatory and erectile dysfunction. *Int J Androl*. 2005;28 Suppl 2:40–45.⏎
21. McMahon CG, Jannini EA, Serefoglu EC, Hellstrom WJ. The pathophysiology of acquired premature ejaculation. *Transl Androl Urol*. 2016;5(4):434–449.⏎
22. Salonia A, Bettocchi C, Boeri L, Capogrosso P, Carvalho J, Cilesiz NC, *et al.* European Association of urology guidelines on sexual and reproductive health-2021 update: male sexual dysfunction. *Eur Urol*. 2021;80(3):333–357.⏎
23. Shindel AW, Althof SE, Carrier S, Chou R, McMahon CG, Mulhall JP, *et al.* Disorders of ejaculation: an AUA/SMSNA guideline. *J Urol*. 2022;207(3):504–512.⏎
24. Althof SE, McMahon CG, Waldinger MD, Serefoglu EC, Shindel AW, Adaikan PG, *et al.* An update of the International Society of Sexual Medicine’s guidelines for the diagnosis and

treatment of premature ejaculation (PE). *J Sex Med*. 2014;11(6):1392–1422.⏎
25. Althof S, Rosen R, Symonds T, Mundayat R, May K, Abraham L. Development and validation of a new questionnaire to assess sexual satisfaction, control, and distress associated with premature ejaculation. *J Sex Med*. 2006;3(3):465–475.⏎
26. Althof SE, Symonds T. Patient reported outcomes used in the assessment of premature ejaculation. *Urol Clin North Am*. 2007;34(4):581–589, vii.⏎
27. Symonds T, Perelman MA, Althof S, Giuliano F, Martin M, May K, *et al*. Development and validation of a premature ejaculation diagnostic tool. *Eur Urol*. 2007;52(2):565–573.⏎
28. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*. 1997;49(6):822–830.⏎
29. Gul M, Bocu K, Serefoglu EC. Current and emerging treatment options for premature ejaculation. *Nat Rev Urol*. 2022;19(11):659–680.⏎
30. Symonds T, Roblin D, Hart K, Althof S. How does premature ejaculation impact a man s life? *J Sex Marital Ther*. 2003;29(5):361–370.⏎
31. Althof SE. Therapeutic weaving: The integration of treatment techniques. *Handbook of Clinical Sexuality for Mental Health Professionals*. New York, NY, US: Brunner-Routledge; 2003. pp. 359–376.⏎
32. McMahon CG, Althof SE, Kaufman JM, Buvat J, Levine SB, Aquilina JW, *et al*. Efficacy and safety of dapoxetine for the treatment of premature ejaculation: integrated analysis of results from five phase 3 trials. *J Sex Med*. 2011;8(2):524–539.⏎

33. Mondaini N, Fusco F, Cai T, Benemei S, Mirone V, Bartoletti R. Dapoxetine treatment in patients with lifelong premature ejaculation: the reasons of a “Waterloo”. *Urology*. 2013;82(3):620–624.⏎
34. Waldinger MD, Zwinderman AH, Olivier B, Schweitzer DH. The majority of men with lifelong premature ejaculation prefer daily drug treatment: an observation study in a consecutive group of Dutch men. *J Sex Med*. 2007;4(4 Pt 1):1028–1037.⏎
35. Salonia A, Rocchini L, Sacca A, Pellucchi F, Ferrari M, Del Carro U, *et al.* Acceptance of and discontinuation rate from paroxetine treatment in patients with lifelong premature ejaculation. *J Sex Med*. 2009;6:2868–2877.⏎
36. Martyn-St James M, Cooper K, Ren K, Kaltenthaler E, Dickinson K, Cantrell A, *et al.* Topical anaesthetics for premature ejaculation: a systematic review and meta-analysis. *Sex Health*. 2016;13(2):114–123.⏎
37. Tan H, Zhou Z, Cui Y, Feng F, Zhang Y. A systematic review and meta-analysis of randomized controlled trials of “on-demand” use of tramadol vs “on-demand” use of paroxetine in the management of patients with premature ejaculation. *Int J Clin Pract*. 2021;75(11):e14825.⏎
38. Sato Y, Otani T, Amano T, Araki T, Kondou N, Matsukawa M, *et al.* Silodosin versus naftopidil in the treatment of premature ejaculation: a prospective multicenter trial. *Int J Urol*. 2017;24(8):626–631.⏎
39. Jeon HJ, Kim HS, Lee CH, Lee YG, Choi SM, Sohn YS, *et al. Candidate molecule for premature ejaculation*, DA-8031: in vivo and in vitro characterization of DA-8031. *Urology*. 2011;77(4):1006 e17–21.⏎
40. Argiolas A, Collu M, D’Aquila P, Gessa GL, Melis MR, Serra G. Apomorphine stimulation of male copulatory behavior is prevented by the oxytocin antagonist d(CH2)5 Tyr(Me)-Orn8-

vasotocin in rats. *Pharmacol Biochem Behav*. 1989;33(1):81–83.⏎
41. McMahon C, Althof S, Rosen R, Giuliano F, Miner M, Osterloh IH, *et al.* The oxytocin antagonist cligosiban prolongs intravaginal ejaculatory latency and improves patient-reported outcomes in men with lifelong premature ejaculation: results of a randomized, double-blind, placebo-controlled proof-of-concept trial (PEPIX). *J Sex Med*. 2019;16(8):1178–1187.⏎
42. Tuken M, Kiremit MC, Serefoglu EC. On-demand modafinil improves ejaculation time and patient-reported outcomes in men with lifelong premature ejaculation. *Urology*. 2016;94:139–142.⏎
43. Serefoglu EC, Hawley WR, Lasker GF, Grissom EM, Mandava SH, Sikka SC, *et al.* Effect of botulinum-A toxin injection into bulbospongiosus muscle on ejaculation latency in male rats. *J Sex Med*. 2014;11(7):1657–1663.⏎
44. Li ZT, Li YF, Zhang Y, Luo Y, Zhu T, Li K, *et al.* Injection of botulinum-A toxin into bulbospongiosus muscle for primary premature ejaculation: a preliminary clinical study. *Zhonghua Nan Ke Xue*. 2018;24(8):713–718.⏎
45. Kosseifi F, Chebbi A, Raad N, Ndayra A, El Samad R, Achkar K, *et al.* Glans penis augmentation using hyaluronic acid for the treatment of premature ejaculation: a narrative review. *Transl Androl Urol*. 2020;9(6):2814–2820.⏎
46. Liu Q, Li S, Zhang Y, Cheng Y, Fan J, Jiang L, *et al.* Anatomic basis and clinical effect of selective dorsal neurectomy for patients with lifelong premature ejaculation: a randomized controlled trial. *J Sex Med*. 2019;16(4):522–530.⏎
47. Shechter A, Mondaini N, Serefoglu EC, Gollan T, Deutsch F, Appel B, *et al.* A novel on-demand therapy for lifelong premature ejaculation using a miniature transperineal electrical

stimulator-the vPatch: an as-treated analysis. *J Sex Med*. 2023;20(1):22–29.⏎
48. Uribe OL, Sandoval-Salinas C, Corredor HA, Martinez JM, Saffon JP. Transcutaneous electric nerve stimulation to treat patients with premature ejaculation: phase II clinical trial. *Int J Impot Res*. 2020;32(4):434–439.⏎
49. Abdel-Hamid IA, Ali OI. Delayed ejaculation: pathophysiology, diagnosis, and treatment. *World J Mens Health*. 2018;36(1):22–40.⏎
50. Rosen R, Altwein J, Boyle P, Kirby RS, Lukacs B, Meuleman E, *et al.* Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). *Eur Urol*. 2003;44(6):637–649.⏎
51. Corona G, Mannucci E, Petrone L, Fisher AD, Balercia G, De Scisciolo G, *et al.* Psychobiological correlates of delayed ejaculation in male patients with sexual dysfunctions. *J Androl*. 2006;27(3):453–458.⏎
52. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5™*: American Psychiatric Publishing, Inc.; 2013.⏎
53. Chen J. The pathophysiology of delayed ejaculation. *Transl Androl Urol*. 2016;5(4):549–562.⏎
54. Perelman MA. Reexamining the definitions of PE and DE. *J Sex Marital Ther*. 2017;43(7):633–644.⏎
55. Carani C, Isidori AM, Granata A, Carosa E, Maggi M, Lenzi A, *et al.* Multicenter study on the prevalence of sexual symptoms in male hypo- and hyperthyroid patients. *J Clin Endocrinol Metab*. 2005;90(12):6472–6479.⏎
56. Madeo B, Bettica P, Milleri S, Balestrieri A, Granata AR, Carani C, *et al.* The effects of citalopram and fluoxetine on sexual behavior in healthy men: evidence of delayed ejaculation and unaffected sexual desire. A randomized,

placebo-controlled, double-blind, double-dummy, parallel group study. *J Sex Med*. 2008;5(10):2431–2441.⏎
57. Keller Ashton A, Hamer R, Rosen RC. Serotonin reuptake inhibitor-induced sexual dysfunction and its treatment: a large-scale retrospective study of 596 psychiatric outpatients. *J Sex Marital Ther*. 1997;23(3):165–175.⏎
58. Wittstock M, Benecke R, Dressler D. Cabergoline can increase penile erections and libido. *Neurology*. 2002;58(5):831.⏎
59. Adeniyi AA, Brindley GS, Pryor JP, Ralph DJ. Yohimbine in the treatment of orgasmic dysfunction. *Asian J Androl*. 2007;9(3):403–407.⏎
60. Geboes K, Steeno O, De Moor P. Primary anejaculation: diagnosis and therapy. *Fertil Steril*. 1975;26(10):1018–1020.⏎
61. Di Sante S, Mollaioli D, Gravina GL, Ciocca G, Limoncin E, Carosa E, *et al*. Epidemiology of delayed ejaculation. *Transl Androl Urol*. 2016;5(4):541–548.⏎
62. Edwards L, Powell C. An objective comparison of transurethral resection and bladder neck incision in the treatment of prostatic hypertrophy. *J Urol*. 1982;128(2):325–327.⏎

6 Peyronie’s Disease: Aetiology, Pathophysiology and Clinical Assessment

Neil James Harvey, Xenia Sara and Ian Pearce

DOI: 10.1201/b22940-6

Peyronie’s Disease: Aetiology, Pathophysiology and Clinical Assessment

First described by Fallopius and Vesalius in 1561, Peyronie’s disease (PD) later acquired its eponym from François Gigot de la Peyronie (1678–1747), who described the condition in detail in 1743. PD is an acquired connective tissue disorder of the tunica albuginea. It is characterised by the development of fibrosis and classically presents as a palpable plaque of the penis causing curvature towards the lesion. Associated symptoms can include pain (at rest or during erection), erectile dysfunction (ED), penile shortening, palpable defects of the corpora cavernosa, waisting of the penis, distal flaccidity, buckling of the penis during intercourse, negative impact on (sexual) relationships and the mental health impact of loss of sexual function and masculine identity. ‘Second patients’ include sexual partners who may also suffer dyspareunia and similar mental health and relationship impacts.

Aetiology and Pathophysiology

PD is inherently an acquired disorder, but the exact aetiology remains unclear. The commonly accepted cause in the majority of cases is recurrent microvascular trauma, with the progressive dysfunction in healing seen

with aging being one contributing factor and surmised as the reason for the rising incidence seen in older age groups. There is an incomplete association with the fibroproliferative diseases Dupytren's contracture and Ledderhose disease, where the palmar and plantar fasciae, respectively, initially undergo myofibroblast proliferation followed by progressive deposition of type III collagen. The resultant increased ratio of type III to type I collagen as discussed below results in the clinical presentation. These associations suggest a common pathway, and the current understanding of the pathophysiology of PD would support this. At least 38 genes are implicated in this process, but contradictory data on how these contribute to the development of the disease, or its severity, render clinical application of these impossible at the present time [1].

Currently, the most widely accepted pathophysiology is of overexpression of transforming growth factor (TGF)-β1, which results in differentiation of fibroblasts into myofibroblasts, disrupting apoptosis and ultimately resulting in overaccumulation of extracellular matrix with types I, III and IV collagen. Type III collagen is particularly inelastic, the primary reason for the formation of plaques and therefore the symptoms seen.

Nevertheless, a second, smaller group of patients should be noted. Those presenting with curvature after a single significant trauma, typically a penile fracture, with subsequent fibrosis and curvature. Although the pathophysiology may not be the same, clinical management is essentially identical.

Risk factors and associated diseases are presented in Table 6.1.

Table 6.1 Risk Factors For and Diseases Associated with Peyronie's Disease⏎

Fibroproliferative Diseases	Cardiovascular Diseases	Endocrine Diseases	Other Risk Factors
Dupytren's contracture	Erectile dysfunction	Hypogonadism	Age
Ledderhose disease	Hypertension	Autoimmune diseases	Trauma
	Dyslipidaemias	Diabetes mellitus	Phenytoin use
	Ischaemic cardiopathy		Smoking
	Heart failure		Excessive alcohol consumption
			Pelvic surgery (radical prostatectomy)

Natural History

The natural history of PD is of 2 phases (Figure 6.1):

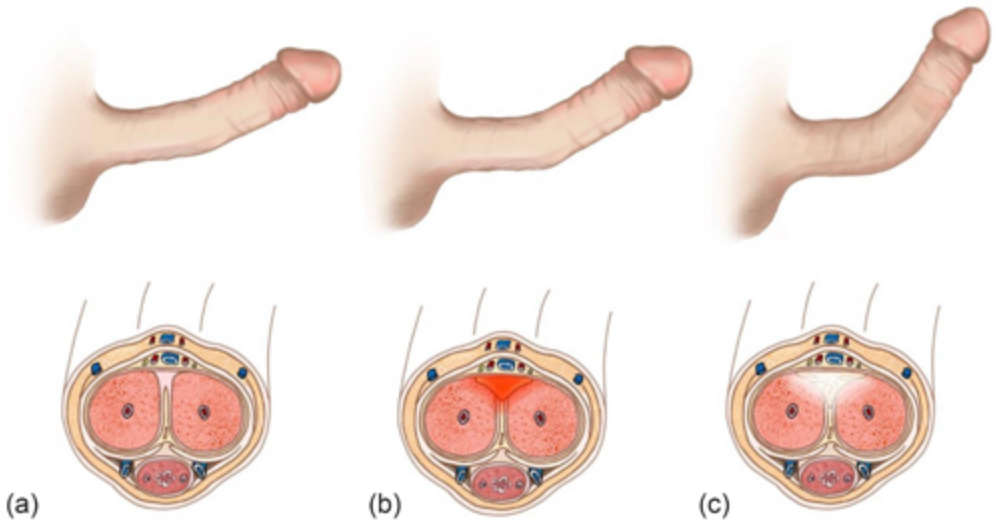


Figure 6.1 Phases of Peyronie's disease: (a) premorbid penis; (b) acute phase; (c) chronic phase.⏎

1. The acute phase, typically lasting 9–12 months, but occasionally extending to 18 months, is an inflammatory process typified by the over activation of myofibroblasts and usually presenting clinically as a painful nodule of the penis with development of a curvature in the majority of cases.
2. The chronic phase, during which the plaque fibroses, becoming hard to palpation and possibly calcifying. Ninety percent of men can expect their pain to resolve within the first 12 months [2, 3], and resolution of this pain is often used as the marker of transition into the chronic phase in which surgical correction is considered viable.

Adequate counselling of the patient presenting in the acute phase is dependent on an understanding of disease progression in this population.

Table 6.2 demonstrates reported rates of spontaneous resolution, stabilisation and progression of untreated/conservatively managed PD.

Table 6.2 Spontaneous Resolution, Disease Stabilisation and Disease Progression Rates for Conservatively Managed Peyronie's Disease

Author (Year)	Number of Patients	Spontaneous Resolution (%)	Stabilisation (%)	Disease Progression (%)
Gelbard (1990) [2]	97	13	47	40
Kadioglu (2002) [4]	307	3.2	66.7	30.2
Mulhall (2006) [3]	246	12	40	48
Berookhim (2014) [5]	176	12	67	21

It should be noted that in these studies the definition of spontaneous resolution is unclear. Stemming from this, the more significant issue with spontaneous resolution rates is the potential that these cases actually represent disease progression/second disease episodes, with progression in penile shortening and erectile dysfunction despite the curve correction, risking inappropriate discharge of patients who could be offered improvement to their sexual function.

Epidemiology

Incidence

The incidence of PD has historically been reported as 25.7 cases per 100, 000 males per year, but current data suggest this rate has decreased to 20.9 cases per 100 000 males per year [6, 7].

Worldwide, prevalence has been more thoroughly investigated. Reported rates by country are presented in Figure 6.2 [6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19]. Classically, the rate of 'clinically significant' PD reported in the general population is 3.2%, though the range varies widely from 0.29% to 7.1%, and the 3.2% quoted refers to any clinically detectable induration. Rates with angulation are lower (2.7%) [8, 9]. Rates in specific patient

groups, particularly those with ED or diabetes have inconsistently been reported to be much higher – up to 20.3%.

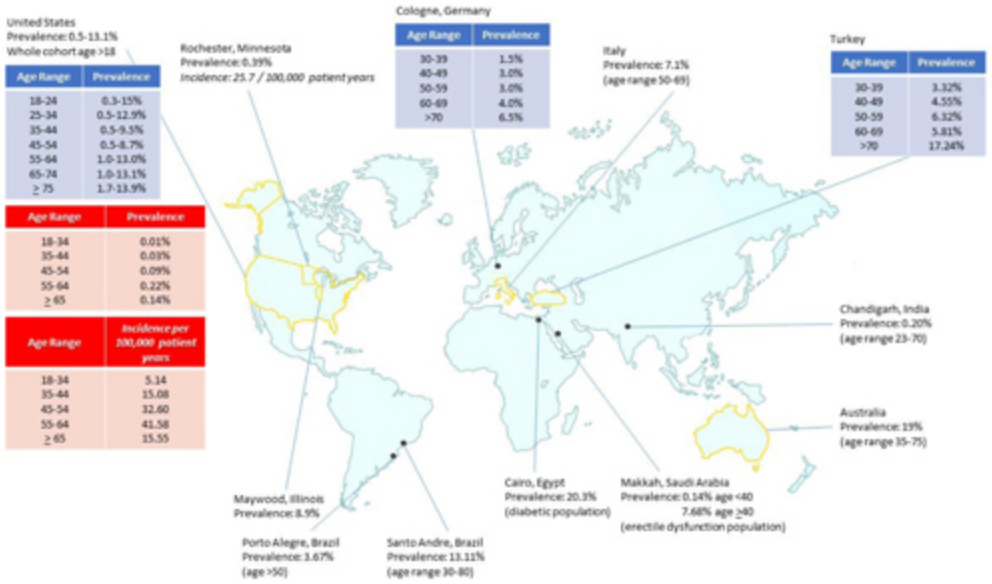


Figure 6.2 Incidence and prevalence of Peryonie's disease by geographical distribution [6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19].⏎

The more recent, survey based, assessments of prevalence of PD (0.5%–0.7% clinician diagnosed and 11.8%–13.1% symptoms of, respectively) suggest rates may be rising, with a rate of 15% reported in the 18–24 years old age bracket [15, 20]. Multiple reasons have been suggested, including true rises due to increased trauma or artefactually high reported rates due to the assessment (i.e., survey) format or rising rates of genital dysmorphia [21].

The majority of patients with PD have curvatures <30°, with reported rates of curvature <30° of 42.7%–65.5%; curvatures of >30° but <60° are reported in 19.5%–38.8%, and curvatures of >60° are reported in 18.6% [4, 10].

Despite the prevalence of both PD and ED, and the strong association between these two diseases, the combination of PD and ED severe enough to warrant insertion of a penile prosthesis remains uncommon, with a mean

of 37 implants inserted for this indication each year in the United Kingdom on national auditing [22].

Differential Diagnosis

The differential diagnosis of PD is limited.

The main diagnosis to be excluded by way of history is a congenital curvature, with upfront surgical treatment indicated in this patient group [23].

Alternative causes of the penile pain at rest over a protracted period seen in the acute phase are (thrombo)phlebitis of the superficial dorsal vein of the penis (eponymously named penile Mondor's disease) and non-venereal sclerosing lymphangitis of the penis. Both can also present as a superficial palpable cord mistaken for a plaque of the tunica albuginea.

From a referral perspective, a penile plaque may raise patient concerns regarding penile malignancy. Although extremely rare, penile sarcoma should be considered when the clinical assessment and history are not typical of PD. Magnetic resonance imaging (MRI) of the penis or ultrasonography imaging may be helpful in select cases.

Guidelines

Currently, four organisations have published guidelines on the assessment and management of PD. Most recently, the European Association of Urology in 2025 [23], with less contemporaneous guidelines available from the Canadian Urological Association in 2018 [24], the International Society of Sexual Medicine in 2016 [25] and the American Urological Association in 2015 [26].

Clinical Assessment

Prior to Review in Clinic

The patient pathway is more efficiently run when the patient is advised how to produce photographs to bring to the appointment [27], as well as having height and weight (with BMI), waist circumference and blood pressure checked on arrival. The International Index of Erectile Function, IIEF

(discussed in the erectile dysfunction chapter) and PDQ (discussed later) can also be completed prior to being seen. Questionnaires are most useful for determining pre-existing satisfaction with sexual function rather than determining severity of disease. These also then form a baseline for comparison of response to treatment at follow-up appointments.

The patient should attend with their sexual partner where possible.

History

History of Presenting Complaint

A focused andrological history, in combination with either photographs or an artificial erection test, will ultimately determine if intervention is required, and if so, which is appropriate.

The goal of any PD therapy is to return the penis to the functional (though not necessarily cosmetically straight) state, where the patient can undertake satisfactory sexual activity that is pain free to them and any partners. Expounding this to patients early in the consultation helps elucidate whether there is an opportunity to improve their situation. Similarly, it is important early in the consultation to establish the underlying reason for the presentation, which may differ from the reported presenting complaint, and will better guide management.

The history should cover:

1. Reason for presentation
    a. Curvature
        i. extent
        ii. direction
        iii. position
        iv. progression
    b. shortening of the penis
    c. pain in the penis
        i. at rest
        ii. during intercourse/erection
    d. pain (or fear of causing pain) in sexual partner
    e. erectile dysfunction
    f. fear of a palpable plaque being penile cancer

2. Onset and duration of individual symptoms (the primary discriminating feature between PD and congenital penile curvature)
    a. history of inciting trauma/event
3. Direction and number of curve(s), with degree and stability of curvature (see Figure 6.3); the most significant factors in treatment decision-making
    a. functionally or only cosmetically bothersome
    b. any associated shortening
    c. hinging (Figure 6.4a)
    d. buckling (Figure 6.4b)
    e. waisting/hourglass deformity (Figure 6.4c)
4. Pain in the penis
    a. current or previously
    b. therapies tried for this
    c. at rest or during intercourse only
5. Erectile function
    a. presence of flaccidity distal to plaque/curve
6. Other aspects of sexual function (to exclude concurrent issues and appropriately counsel patients regarding the benefits of intervention)
    a. ability to penetrate
    b. ability to ejaculate
    c. ability to orgasm
7. If a plaque has been noticed by the patient (most useful for their assistance in identifying a plaque during examination)
8. Previous andrological therapies and surgeries (including circumcision)
9. In specific scenarios (i.e., when considering incision and patch grafting), the religious beliefs of the patient will also be relevant
10. The degree of bother experienced by the patient because of their condition, and their expectations of therapy, in order to address any mismatch early
11. Assessment of any psychological impact on the patient

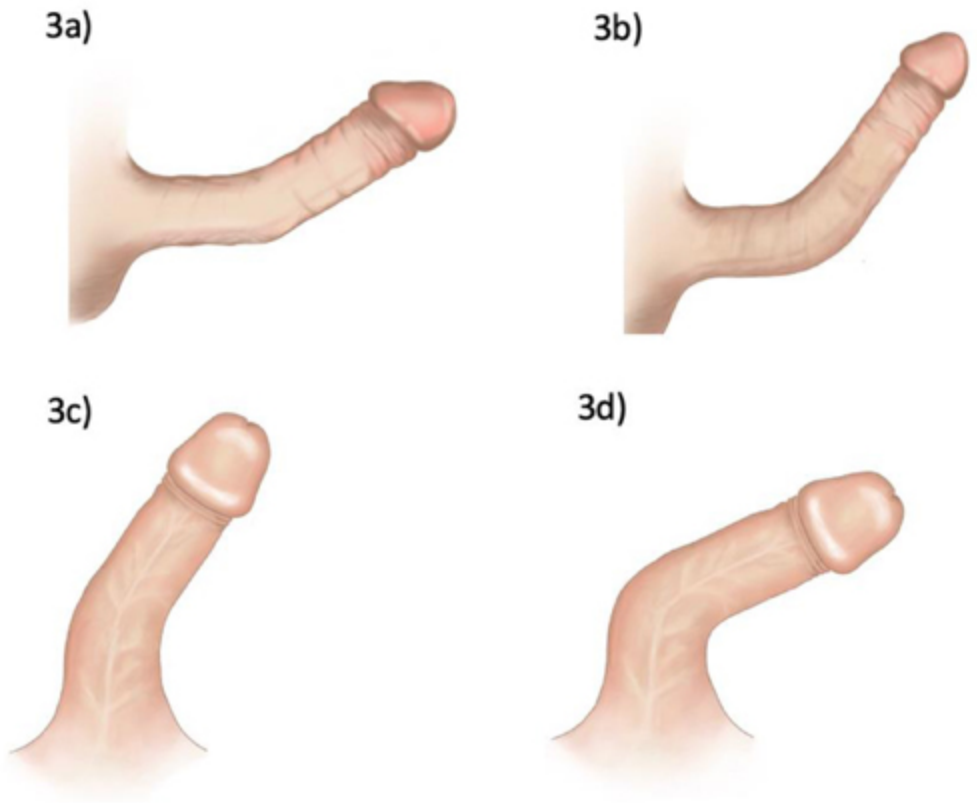


Figure 6.3 Direction and number of curves (a) 30° dorsal curvature; (b) 60° dorsal curvature; (c) 30° lateral curvature; (d) 60° lateral curvature.⏎

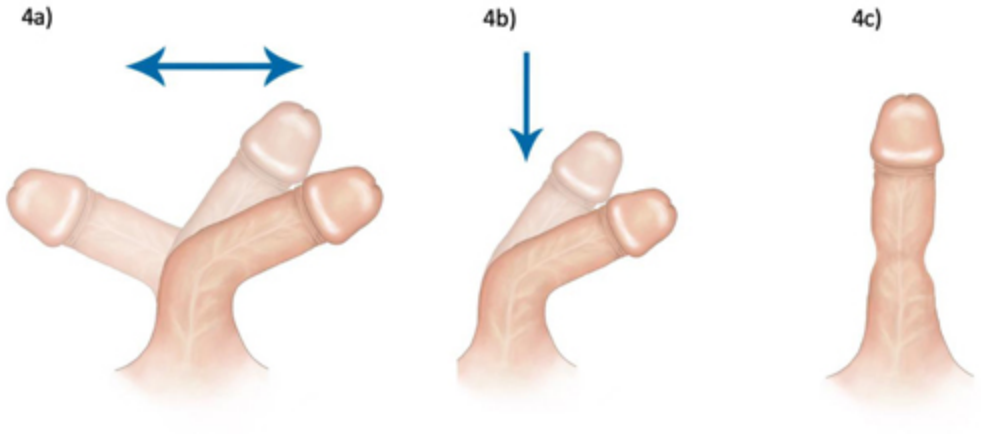


Figure 6.4 Curving of the penis (a) hinging of Peyronie's disease penis during lateral force; (b) buckling of

Peyronie's disease penis during axial force; (c) waisting/hourglass deformity in Peyronie's disease.⏎

Other Aspects of History

The important aspects of the rest of a patient's history (i.e., past medical, past surgical, drug and social) can be broadly categorised into three areas:

1. Conditions associated with PD
2. Risk factors for ED
3. Factors likely to impact surgery

The conditions associated with PD are primarily of interest only. Ultimately, if a patient presents with a subclinical PD, using the presence of risk factors to determine likelihood of PD is moot – if the disease is subclinical or has no impact on the patient or his partner, it will not require treatment. More important, and overlapping to some extent, are the risk factors of ED. Increasing numbers of risk factors for ED will change the frame of reference for discussing the surgical management options of PD and may nudge a consultation towards a penile prosthesis over an alternative form of curvature correction.

Diseases associated with PD are covered above, in the section on Aetiology, while risk factors for ED, with significant overlap, are covered in Chapter 3**.**

Again, there is some overlap with factors likely to impact surgery, but these include fitness for an anaesthetic, diabetic control and the use of anti-platelets and anticoagulants.

Counselling by Presenting Complaint

Counselling and patient education are critical steps in managing the PD patient and should be woven through the initial consultation. Early on, it should be stressed that the intended outcome of any intervention for PD is to return the patient to the functional state wherein they are able to undertake satisfactory sexual activity that is pain free to them and any partners. The primary goal of therapy should never be the pursuit of the

cosmetically straight penis, and it is paramount early in the consultation that returning the patient's penis to its pre-morbid state is impossible.

The man solely concerned about appearance should be reassured and dissuaded from corrective surgery. Psychosexual counselling may be appropriate in these cases. Similarly, the man afraid of cancer may be happy to be discharged after reassurance.

In cases of vaginal dyspareunia in female partners of a relevant age, hormonal/menopausal status is important to determine. Atrophy of the vagina is easily modifiable if the female partner wishes, and this alone may be sufficient to treat the dyspareunia.

Examination

In addition to the elements checked prior to review in clinic (height, weight, body mass index (BMI) and blood pressure), focused examination should note the presence of a prepuce (and any degree of phimosis), any palpable plaque of the penis and palpable deficits of the corpora in keeping with waisting. The stretched flaccid penile length should be demonstrated to the patient and recorded, while in cases of perceived shortening, the depth of the suprapubic fat pad should also be documented.

Investigations After First Review

In addition to the BMI, waist circumference and blood pressure checked prior to assessment, assessment of a patient's curvature during erection is mandatory and can be performed via (self) photography, assessment under a vacuum induced erection, or under a pharmacologically induced erection [23]. Questionnaire-based (self-)assessment is important in the setting of clinical trials and can provide a baseline for later comparison if a patient is subsequently dissatisfied with treatment but is not essential in routine cases. Minimum laboratory investigations focus primarily on risk factors for ED, in line with international guidelines [23].

In rare cases of diagnostic uncertainty, patients may also require imaging. The most common use of imaging is penile doppler ultrasound used as an adjunct to evaluate associated ED.

Assessment of Curvature During Erection

Though a saline artificial erection test is an option in theatre, prior to arrival at that point, the options are pharmacologically inducing an erection in clinic, or the patient taking photographs of their erect penis. Each has their benefits and drawbacks.

Pharmacologically Induced Erection Testing

Pharmacologically inducing an erection can be performed with the clinician's preferred intracavernosal therapy (see Chapter 4, The Management of Erectile Dysfunction). From a practical perspective, these patients should be brought to an appointment early in the clinic. As with any other administration of intracavernosal therapies, the risk of priapism and how to manage this should be discussed prior to the injection.

After induction of erection, erect penile length, direction, and degree of curvature (as well as number of curves, hinging and waisting if applicable) should be identified. Rigidity of erection (including distal flaccidity) should also be noted.

Also important for guiding management is ascertaining how the induced erection compares with the erections the patient has at home (i.e., does the patient have better, similar or worse erections during sexual activity?).

Overall, the strength of assessment of a pharmacologically induced erection is the immediacy and certainty of the assessment in clinic. The drawbacks are the mildly invasive nature, low but present risk of complications, and the potential to demonstrate a better-quality erection in clinic than the patient experiences at home, hence exaggerating both the erect penis's rigidity and degree of curvature (thus influencing the clinician to recommend an alternative management option when a penile prosthesis would be more appropriate).

Patient Self-photography

Patient self-photography offers an excellent alternative to pharmacologically induced erection assessment but requires a degree of patient education to ensure images of a sufficient quality, from appropriate angles, are produced.

Patients should be encouraged to take photographs in the comfort of their own home to avoid any issues stemming from trying to produce these

on hospital grounds. Photographs should be handled like any other patient information, following a pre-agreed pathway – typically by emailing them to a designated secretary or clinician for upload to the patient's medical record – in accordance with the Caldicott Principles and GDPR legislation.

Questionnaires

There is currently only one patient questionnaire specific to PD, the helpfully named Peyronie's Disease Questionnaire (PDQ) [28].

The PDQ was designed by Auxilium Pharmaceuticals Inc. as part of the protocol of the two phase 3 trials for intralesional injections of collagenase clostridium histolyticum (CCH) in 2013 (IMPRESS I and II trials). It assesses three domains scored separately, which are not equivocal (and there is therefore not an overall score for severity):

1. Psychological and physical problems associated with PD (such as concern around damaging the penis, buckling of the penis, or difficulty entering the vagina)
    - Six Likert scale questions scored 0–4
2. Penile pain (at rest, during an erection and during vaginal intercourse)
    - Three 11-point visual analogue scales
3. Symptom bother
    - Four questions of degree of bother up to extremely bothered

Strengths of the PDQ are that it is self-administered and standardised, with test–retest reliability [29], is responsive to changes in PD [30] and is validated for bother and distress [31]. It is also potentially more sensitive to the impact of PD symptoms (particularly pain) on mental health than more generic sexual relationship (e.g., Self-Esteem and Relationship Questionnaire) and mental health (e.g., Center for Epidemiologic Studies Depression Scale Questionnaire) questionnaires [32].

However, there are some criticisms. It does not assess the patient's perception of the severity of their curvature and does not therefore directly assess their subjective response to any treatment. It is heteronormative,

being designed exclusively for use in men who have had penetrative vaginal intercourse within the last three months, therefore excluding significant proportions of the population of men for whom this does not encompass the breadth of their sexual relationships. Finally, it does not consider the impact of PD on the partner, which can be the driving factor behind presentation and requires assessment with a further questionnaire (such as the female sexual function index in female partners).

Further work is being performed to develop a validated patient-related outcome measure questionnaire for use after penile curvature surgery, validated in its third iteration, but not yet disseminated in the literature [33].

Another key questionnaire – arguably even more important for decision-making in the treatment of PD – is the IIEF, or its more commonly used short form, the Sexual Health Inventory for Men (SHIM; also known as the IIEF-5), as erectile function is often the primary factor influencing the choice of a penile prosthesis over other treatment options.

Laboratory Investigations

Laboratory investigations are primarily relevant in considering concurrent risk factors for ED. HbA1c should be performed in order to exclude undiagnosed or early type 2 diabetes mellitus, or in established cases of diabetes ensure adequate control for safe surgery. HbA1c, with up-to-date lipid profile and early morning fasting testosterone assessment, represents the minimum necessary investigations for ED [23]. As discussed further in the ED chapter, in select cases prostate-specific antigen, prolactin and luteinising hormone levels should also be checked.

Imaging in Peyronie's Disease

Imaging in PD is supplementary and not necessary prior to instigation of therapy in the case of a clear clinical history with supporting photographs or clinical assessment under pharmacologically induced erection. That said, there are niche areas where ultrasound and MRI can prove useful.

Computed tomography has no role in the assessment of PD, though may incidentally identify thickened plaques, particularly if these are calcified.

Ultrasound

Ultrasound (as a diagnostic test, not to be confused with extra-corporal shockwave therapy; see PD treatment, Chapter 7) in PD is best performed with a pharmacologically induced erection, which increases the sensitivity of the test [34]. Plaques are echogenic in nature, with calcifications even more so, and easily identified if present. Since the withdrawal of collagenase clostridium histolyticum from markets outside the United States, the identification of calcifications has less impact on overall management but remains relevant to decision-making in incision and patch graft planning.

The particular value of ultrasound is in visualising involvement of adjacent structures (i.e., the dorsal neurovascular bundle) in the plaque, and any associated intracavernosal fibrosis. In most cases, however, these features are academic, and treatment is determined by the clinical picture.

Magnetic Resonance Imaging (MRI)

Again, MRI is best performed with a pharmacologically induced erection. Plaques are identified as thickening of the tunica albuginea, and with a hypointense signal on both T1 and T2 weighted images (typically better seen on T2) [35].

The presence of calcification is much harder to assess on MRI.

The use of contrast (gadolinium-diethylenetriaminepentaacetic acid) to demonstrate areas of active inflammation, and with this determine whether the PD is in the acute or chronic phase, is controversial and should not be used to guide management.

Conclusion

PD is a common condition and essentially diagnosed clinically. At a minimum, a focused history, examination and assessment of curvature during erection should be performed. Counselling should occur throughout the history-taking process, ensuring patients understand the goal of treatment is a return to satisfactory pain-free sexual activity, not a cosmetically straight penis.

References

1. Herati AS, Pastuszak AW. The Genetic Basis of Peyronie Disease: A Review. *Sex Medicine Rev* 4: 85–94.⏎
2. Gelbard MK, Dorey F, James K. The Natural History of Peyronie's Disease. *J Urology*; 144: 1376–1379.⏎
3. Mulhall JP, Schiff J, Guhring P. An Analysis of the Natural History of Peyronie's Disease. *J Urology*; 175: 2115–2118.⏎
4. Kadioglu A, Tefekli A, Erol B, *et al*. A Retrospective Review of 307 Men with Peyronie's Disease. *J Urology*; 168: 1075–1079.⏎
5. Berookhim BM, Choi J, Alex B, *et al*. Deformity Stabilization and Improvement in Men with Untreated Peyronie's Disease. *BJU Int* 2014; 113: 133–136.⏎
6. Lindsay MB, Schain DM, Grambsch P, *et al*. The Incidence of Peyronie's Disease in Rochester, Minnesota, 1950 through 1984. *J Urology*: 1007–1009.⏎
7. Moghalu OI, Das R, Horns J, *et al*. Regional Variation in the Incidence and Prevalence of Peyronie's Disease in the United States—Results from an Encounters and Claims Database. *Int J Impot Res*: 64–70.⏎
8. Sommer F, Schwarzer U, Wassmer G, *et al*. Epidemiology of Peyronie's Disease. *Int J Impot Res*: 3900863.⏎
9. Schwarzer U, Sommer F, Klotz T, *et al*. The Prevalence of Peyronie's Disease: Results of a Large Survey. *BJU Int* 2001; 88: 727–730.⏎
10. Chung E, Gillman M, Rushton D, *et al*. Prevalence of Penile Curvature: A Population-Based Cross-Sectional Study in Metropolitan and Rural Cities in Australia. *BJU Int* 2018; 122: 42–49.⏎
11. Arafa M, Eid H, El-Badry A, *et al*. The Prevalence of Peyronie's Disease in Diabetic Patients with Erectile Dysfunction. *Int J Impot Res*: 3901518.⏎

12. Pera GL, Pescatori ES, Calabrese M, *et al*. Peyronie's Disease: Prevalence and Association with Cigarette Smoking. *Eur Urol* 40: 525–530.⏎
13. Mulhall JP, Creech SD, Boorjian SA, *et al*. Subjective and Objective Analysis of the Prevalence of Peyronie's Disease in a Population of Men Presenting for Prostate Cancer Screening. *J Urology*; 171: 2350–2353.⏎
14. Segundo A, Glina S. Prevalence, Risk Factors, and Erectile Dysfunction Associated with Peyronie's Disease Among Men Seeking Urological Care. *Sex Med-Uk* 2020; 8: 230–236.⏎
15. Stuntz M, Perlaky A, Vignes F des, *et al*. The Prevalence of Peyronie's Disease in the United States: A Population-Based Study. *Plos One*; 11: e0150157.⏎
16. Kumar B, Narang T, Gupta S, *et al*. A Clinico-Aetiological and Ultrasonographic Study of Peyronie's Disease. *Sex Health* 2006; 3: 113–118.⏎
17. Kadioglu A, Dincer M, Salabas E, *et al*. *A Population-Based Study of Peyronie's Disease in Turkey: Prevalence and Related Comorbidities*. *Sex Med-Uk* 2020; 8: 679–685.⏎
18. Rhoden E, Teloken C, Ting H, *et al*. Prevalence of Peyronie's Disease in Men Over 50-y-Old from Southern Brazil. *Int J Impot Res* 13: 291–293.⏎
19. El-Sakka AI. Prevalence of Peyronie's Disease Among Patients with Erectile Dysfunction. *Eur Urol* 49: 564–569.⏎
20. DiBenedetti DB, Nguyen D, Zografos L, *et al*. A Population-Based Study of Peyronie's Disease: Prevalence and Treatment Patterns in the United States. *Adv Urology* 2011; 2011: 282503.⏎
21. Harvey N, Pearce I. At What Cost Is Collagenase Clostridium Histolyticum Viable for Treating Peyronie's Disease in a Public Healthcare System? *Andrology* 2020; 8: 1304–1311.⏎

22. Muneer A, Fowler S, Ralph DJ, *et al*. UK Practice for Penile Prosthesis Surgery: Baseline Analysis of the British Association of Urological Surgeons (BAUS) Penile Prosthesis Audit. *BJU Int* 2021; 127: 326–331.⏎
23. Salonia A, Bettocchi C, Carvalho J, *et al*. *EAU Guidelines on Sexual and Reproductive Health*. Available at https://uroweb.org/guidelines/sexual-and-reproductive-health.⏎
24. Bella AJ, Lee JC, Grober ED, *et al*. Canadian Urological Association Guideline for Peyronie's Disease and Congenital Penile Curvature. *Can Urological Assoc J*; 12. doi: 10.5489/cuaj.5255.⏎
25. Chung E, Ralph D, Kagioglu A, *et al*. Evidence-Based Management Guidelines on Peyronie's Disease. *J Sex Medicine* 2016; 13: 905–923.⏎
26. Nehra A, Alterowitz R, Culkin DJ, *et al*. Peyronie's Disease: AUA Guideline. *J Urology*; 194: 745–753.⏎
27. Micallef D, Modgil V, Pearce I. A Picture of the Penis: What Your Surgeon Wants to Know. *Trend Urol Men Heal*; 11: 13–15.⏎
28. IncAP. Peyronie's Disease Questionnaire.⏎
29. Coyne KS, Currie BM, Thompson CL, *et al*. Test–Retest *Reliability of the PDQ. J Sex Medicine* 2015; 12: 543–548.⏎
30. Coyne KS, Currie BM, Thompson CL, *et al*. Responsiveness of the Peyronie's Disease Questionnaire (PDQ). *J Sex Medicine* 2015; 12: 1072–1079.⏎
31. Hellstrom WJG, Feldman R, Rosen RC, *et al*. Bother and Distress Associated with Peyronie's Disease: Validation of the Peyronie's Disease Questionnaire. *J Urology*; 190: 627–634.⏎
32. Flores JM, Salter CA, Nascimento B, *et al*. *The Prevalence and Predictors of Penile Pain in Men with Peyronie's Disease*. *Sex Med-Uk* 2021; 9: 100398.⏎

33. Natarajan M, Akiboye D, Skrodzka M, *et al*. PD48-07 Final Validation of a Patient Reported Outcome Measure (PROM) for Penile Curvature Surgery. *J Urology*. 2021;206:e841.⏎
34. Liu Y, Zheng D, Liu X, *et al*. Ultrasound on Erect Penis Improves Plaque Identification in Patients with Peyronie's Disease. *Front Pharmacol* 2019; 10: 312.⏎
35. Bertolotto M, Pavlica P, Serafini G, *et al*. *Painful Penile Induration: Imaging Findings and Management1*. *Radiographics* 2009; 29: 477–493.⏎

7 Management of Penile Deformity

Niall Kelly and Rowland Rees

DOI: 10.1201/b22940-7

Introduction

Penile deformities can be a significant source of distress for men, though the exact incidence of this is unclear. They can lead to difficulties with sexual intercourse and sexual relationships and contribute to self-image issues for men.

Some penile deformities are congenital, others are acquired. Congenital deformities, which include hypospadias and some disorders of sexual differentiation, are not discussed in this chapter.

Peyronie's disease is a commonly known cause of penile curvature, with prevalence rates ranging from 1% to as high as 20%, depending on the population studied, and the questions asked. Certainly, there is a suggestion that it is an underdiagnosed condition. It tends to be a disease of older men, with typical onset between 50 and 60 years of age.

Penile Curvature

Aetiology

The exact cause of Peyronie's disease (PD) is unknown. It is, however, hypothesised that it is probably due to a degree of micro-trauma to the tunica albuginea of the penis. In general, the accepted pathophysiology of PD involves a localised disruption of the tunica albuginea, resulting in extracellular matrix disorganisation and cellular contraction secondary to the release of various cytokines and growth factors, with ensuing de-differentiation of fibroblasts into myofibroblasts [1]. Transforming growth

factor beta 1 (TGF-b1) and matrix metalloproteinase (MMPs) are thought to contribute to the pathogenesis of PD. The abnormal wound healing and the subsequent development of fibrotic plaques also contribute to PD. This plaque restricts corporal expansion with erections leading to a degree of penile curvature, which, if severe, can prevent sexual intercourse.

PD is associated in some cases with Dupuytren's contractures of the hand and Ledderhose contractures of the feet. This suggests a possible genetic component at least contributing to the disease process. Up to 39% of patients with PD will have concomitant Dupuytren's disease; similarly, up to 25% of patients with Dupuytren's have PD. Some genes have been identified as contributing to these disease processes, although results have ultimately been contradictory.

Risk Factors

In addition to a potential genetic component, diabetes, hypertension, dyslipidaemia, ischaemic cardiomyopathy, autoimmune disease, erectile dysfunction (ED), smoking, excessive alcohol, low testosterone, and prior pelvic surgery have all been implicated as risk factors for the development of PD.

History and Examination

Patients typically describe a disease history that mirrors the pathophysiological changes. An *acute active inflammatory* phase often leads to painful erections and the development of a palpable plaque. Curvature may also be noticed at this point. This acute phase can last for up to 12 months. A *chronic fibrotic* phase follows the acute phase, at which point the plaque can become harder due to calcification. There is a stabilisation of the degree of deformity and patients may indeed describe a decrease in the severity of their pain. The disease stabilises at this point for up to 70% of patients.

Penile deformity tends to be the primary symptom that patients report, followed by penile pain. The presence of a palpable plaque may occasionally be the initial symptom. Other concomitant symptoms may be penile shrinkage, waisting, hour-glass deformity, and erectile dysfunction.

Occasionally, men present with depression or anxiety related to the adverse functional effects of PD on sexual intercourse.

History taking should focus on obtaining as much information about the presenting symptoms and their duration. Validated questionnaires are available that can help in clinical practice and trials. One such questionnaire is the Peyronie's Disease Questionnaire [PDQ], which assesses symptoms in three domains including psychological and physical symptoms, penile pain and symptom bother [2]. This questionnaire was developed to assess patient response to collagenase clostridium histolyticum treatment but is widely used in other PD populations and has been validated in non-English languages also.

Examination should look for the presence of plaques as well as possible Dupuytren's or Ledderhose scarring. The measurement of the stretched or erect penile length is also important to document, as it may impact on treatment decisions and can be useful for comparison with post-treatment outcomes. The stretched penile length is typically measured from the pubic symphysis to the tip of the penis.

Objective assessment of severity of penile curvature with an erection is mandatory. A variety of methods have been used, including self-photography of the natural erection, the use of a vacuum erection device or intracavernosal injections (ICI) in the clinical setting. The ICI method would seem to induce an erection closest to that when a patient is sexually aroused [3], though this can be challenging to facilitate in the clinical setting. There are a number of smartphone applications available that can help with determining the degree of curvature, with a number of differing methods utilised.

Formal radiological imaging has only a limited role and would not be recommended on a routine basis. Ultrasound measurements of plaque size has limited accuracy but can be of some use if used in conjunction with assessments for ED. Magnetic resonance imaging (MRI) scanning of the penis can help identify 'waisting' of the penis, where the presence of fibrous plaques leads to a narrowing and potentially instability of the penis [4]. This can be helpful in guiding decision-making around appropriate surgical treatments.

Careful evaluation of the patient's erectile function is imperative as it can have significant implications for treatment decisions. Validated

questionnaires of erectile function, such as the IIEF, are available, though have not been specifically validated in the PD population.

How to Measure Curvature

While the administration of ICI may give the most accurate representation of the extent of curvature affecting the erect penis, it can pose some practical problems with regard to clinic time and space, not to mention patient comfort and dignity. Home photography can give a good representation of the degree of curvature, but clear instructions need to be given to the patient. Specifically, images from at least two planes are required, ideally one picture from above and one picture from the side.

It may be prudent to advise patients to disconnect the photo app from any cloud-based services when taking these pictures, in an effort to prevent misdistribution of the pictures. There are a number of smartphone apps which can automate the picture and measuring process, and some even avoid the potential problems of auto-backup, which include ‘iGrafter’ and ‘Peyronie’s Self-Assessment’. Access to these apps is geographically restricted.

Management

Spontaneous resolution of Peyronie’s disease has only been reported in 3%–13% of patients. Indeed, up to 48% of patients may identify further worsening of the disease even after the onset of the chronic phase.

Conservative Treatment

Conservative treatment of Peyronie’s disease is primarily focused on the acute stage of the disease to help alleviate pain and where possible prevent disease progression. Analgesia, specifically non-steroidal anti-inflammatories, can be beneficial for pain management. A variety of treatments including other oral medications, intralesional treatments, topical treatments, oral supplements and shockwave therapy have all been suggested. However, there are significant problems with the quality of the data supposedly supporting these treatments and thus there is no strong

recommendation for the use of any of these. Treatment with these agents may delay the use of other more efficacious medical treatments.

Penile traction devices and vacuum erection devices may help reduce the severity of penile deformity and could be used as part of a multimodal therapy approach, although outcome data from these devices are limited. A recent systematic review [5] assessed the evidence to date, which seemed to favour the use of traction devices. The paper included protocols that ranged from using the device for 30 minutes twice daily for 3 months, to using it for 6 hours per day for 6 months, with no single protocol being superior.

Medical Treatment

The use of phosphodiesterase 5 inhibitors (PDE5i) can be used to treat concomitant ED or if the deformity from Peyronie's disease results in difficulty with penetrative intercourse. Furthermore, daily low dose PDE5i in the acute phase appears to have beneficial effects on the degree of curvature [6].

Intralesional therapy with collagenase clostridium histolytica can be used in patients with stable Peyronie's disease and a dorsal or lateral curvature of more than 30 degrees who are keen to avoid surgery. This treatment was recently withdrawn from European markets but is still available in North America. There is an apparent increased risk of penile fracture with misuse.

Low-intensity extra corporal shockwave treatment (Li-SWT) has no role in improving penile curvature or reducing plaque size but has been shown to have a role in reducing severity of penile pain in the acute phase.

Surgical Treatment

The aim of surgical correction of Peyronie's disease is to correct the curvature and facilitate penetrative intercourse. It should not be offered to patients in the acute phase, and, ideally, they should have had symptoms for over 12 months, with the curvature stabilised for 3 months.

Careful documentation of the size and location of penile plaques, the degree of curvature and additional complex deformities such as a hinge penis or hourglass deformity is necessary. The penile length and in particular the presence or absence of ED is integral to disease management. The documentation can also be useful in medicolegal settings.

Specific risks and complications from surgery should be discussed in detail. These complications include penile shortening, ED, penile numbness, delayed orgasms, risks of recurrence of curvature, potential residual curvature, cosmetic dissatisfaction and the risk for penile waisting. Regardless of the surgical approach, penile shortening should be specifically mentioned in the consenting process.

The decision for the most appropriate surgical intervention depends on penile length assessment, curvature severity and erectile function status. The expectations that a patient might have from surgery should also be addressed in the preoperative setting. The main aim of surgery is for a functionally straight penis (≤20 degrees) and matching patient expectations to this is important, as this can occur following any scarring process.

The three main types of reconstructive procedures are:

1. Tunical shortening procedures
2. Tunical lengthening procedures
3. Penile prosthesis insertion

Penile degloving with associated circumcision should be considered the standard approach for all types of procedure. Circumcision is performed to prevent postoperative phimosis or foreskin overhang. Patients declining circumcision should be made aware of the risk of post-operative phimosis or overhang. Alternative non-degloving techniques have also recently been described.

How to Achieve an Artificial Erection

The artificial erection test is an important intraoperative step to ascertain the severity of curvature, help refine the choice of surgical procedure and locate the point of plication or lengthening. Surprisingly, there is little in the literature about how this procedure should be performed [7].

The authors recommend the placement of a 19-gauge butterfly needle through the glans penis into one of the corporal bodies. Correct placement can be confirmed by a flashback of venous blood. We secure that needle with a 3-0 Vicryl stay suture and attach a 50 ml Luer-lock syringe to the end of the butterfly. Pressure is applied to the corporal bodies at the level of the symphysis pubis to compress them proximally, and fluid is then instilled to

generate an erection. We recommend the use of a fluid dispensing device that is available from some companies which can be operated single-handedly, which can give the surgeon greater control over the volume of fluid instilled.

The erection can be made to detumesce by releasing the pressure on the corporal bodies.

Plication/Tunical Shortening Procedure

These procedures work by shortening the longer convex side of the penis to make it even with the contralateral affected side (Figure 7.1).

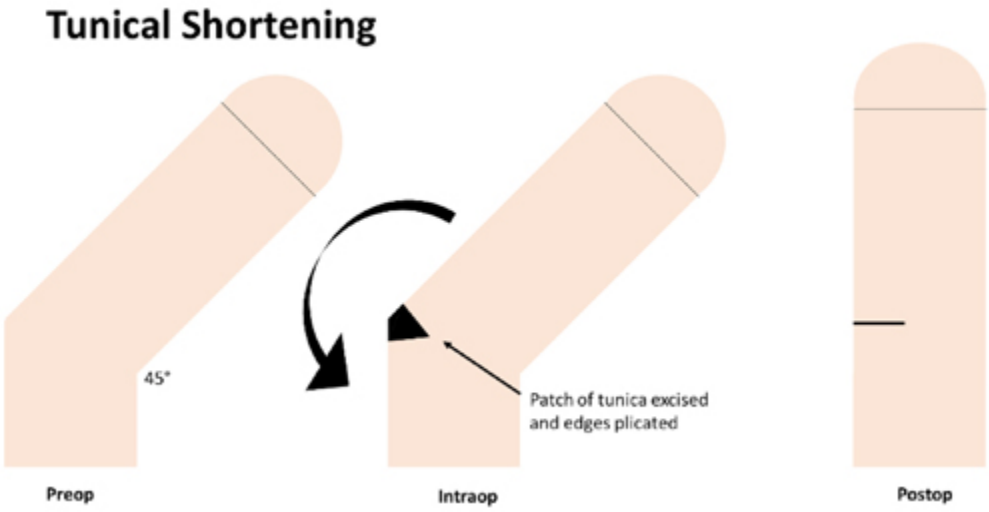


Figure 7.1 Graphic depicting a simplified version of the tunical shortening procedure.⏎

Plication procedures are ideal for men with good erectile function and with adequate penile length, without a complex deformity and without severe curvature. There are a number of different penile shortening procedures that can be adapted.

The Nesbit procedure (Figure 7.2) was described in 1965 and involves a 5 to 10 millimetre transverse elliptical excision of the tunic albuginea and subsequent closure with 0 PDS sutures. The overall short-term and long-term results of a Nesbit's operation are excellent. Complete straightening is

achieved in 48%–100% of cases, with patient satisfaction rates ranging from 58% to 96% [8].

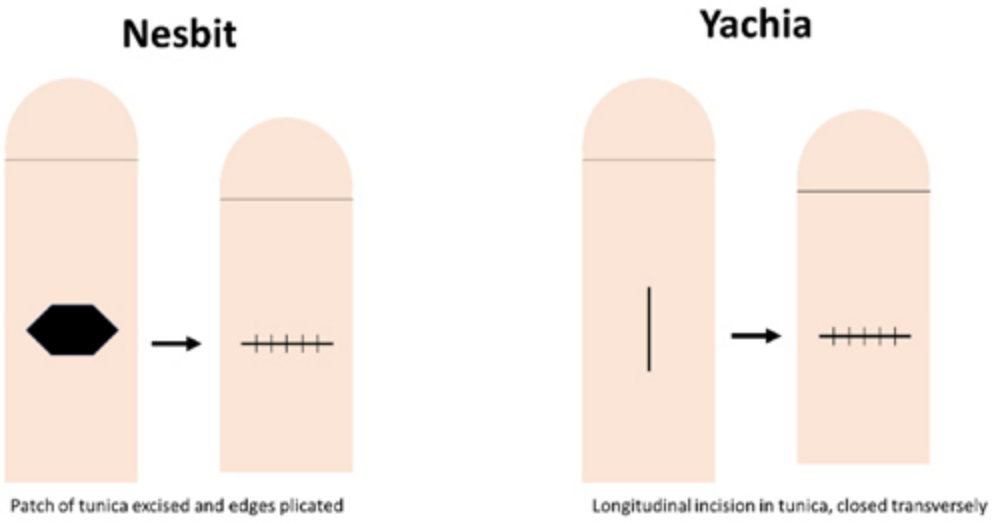


Figure 7.2 Diagram of Nesbit and Yachia procedures, showing differences between them.⏎

The Yachia procedure (Figure 7.2) is based on the Heineke–Mikulicz principle, where a longitudinal tunical incision is closed in a transverse manner leading to shortening on that side. The incision is made on the convex side.

Pure plication procedures are even simpler to perform. These include the 16 dot procedure where two pairs of parallel plications are tensioned depending on the degree of curvature.

Complete penile straightening can be achieved in over 85% of patients, with tunical shortening techniques. Recurrence of curvature is uncommon, and post operative ED is low. Shortening of 1 to 1.5 centimetres has been reported in many patients, which is rarely the cause of significant post operative sexual dysfunction. Patients should be reminded that it is only the longer side of the penis that will be shortened, to match the length of the side shortened by PD.

Plaque Incision and Grafting/Tunical Lengthening Procedures

Tunical lengthening procedures are performed on the concave side of the penis after making an incision or excision of the plaque, filling the defect with a graft.

An incision is made at the point of maximum curvature on the concave side of the penis, which creates a defect in the tunical albuginea when the penis is straightened. This defect is then filled with a graft (Figure 7.3). Excision of the plaque can be associated with higher rates of ED, with rates of postoperative ED reported in 30% to 50% of cases. Thus, this technique is contraindicated in patients with pre-operative ED (non-responsive to pharmacotherapy).

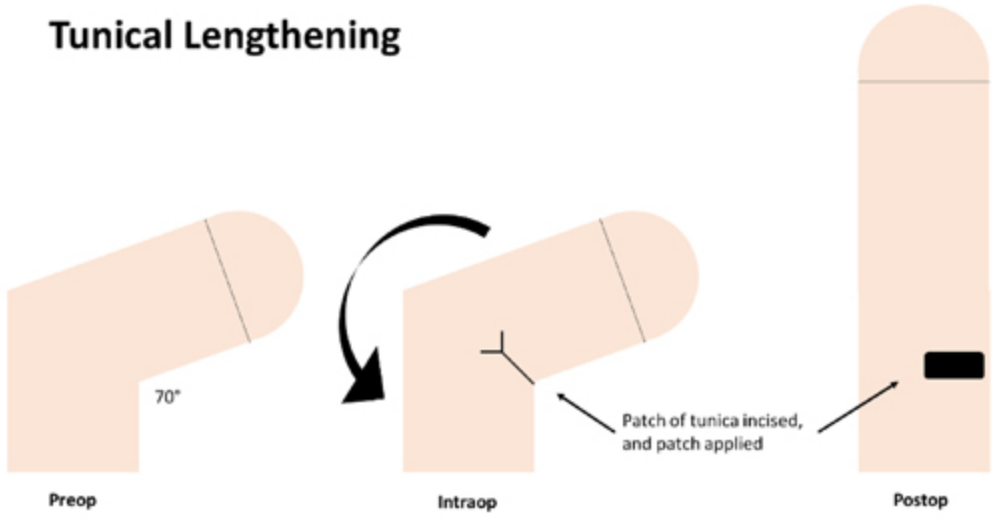


Figure 7.3 Graphic depicting a simplified version of the tunical lengthening procedure.⏎

Tunical lengthening surgery is preferable in patients with significant penile shortening, severe curvature or complex deformities but have preserved erectile function. The threshold for severe curvature and the use of tunical lengthening has been proposed to be 60 degrees, but this has not been validated.

A variety of grafting materials have been used, broadly classified into four types: autografts, allografts, xenografts and synthetic grafts. Cadaveric dura mater was previously used but has since ceased due to the potential risk of infection. It is generally recommended that synthetic grafts such as

Dacron or Gore-Tex are also avoided due to increased risks of infection. Bovine pericardium is a commonly used graft, though there are increasing reports of xenografts such as TachoSil being used.

Post-operative penile rehabilitation is recommended by many authors to improve surgical outcomes. This includes the use of a vacuum erection device and oral PDE5 inhibitors. The hypothesis involves preventing contraction around the graft and increasing blood flow though the penis to aid in graft take and maturation, but again there is no consensus on regimens.

Advanced Procedures

Patients with Peyronie's disease and associated ED not responding to usual conservative treatments are likely to have a better outcome with a penile prosthesis. The inflatable penile prosthesis is considered generally more effective, though outcome data suggest that the malleable penile prosthesis insertions have similar satisfaction rates [9]. The decision concerning the type of prosthesis should be made by the surgeon and the patient with careful counselling.

Patients with only mild to moderate curvature can expect excellent outcomes from corporal dilatation and implant cylinder insertion, which often provide enough rigidity to correct the curvature without additional procedures. Where curvature does persist after implant insertion, modelling with a prosthesis may be necessary. Modelling involves counter-flexion of the penis against the direction of curvature with the aim of disrupting any plaques present, after which the implant can prevent recurrence.

In selected cases of end-stage Peyronie's disease with ED and significant penile shortening, a lengthening procedure with simultaneous penile prosthesis implantation and penile length restoration, commonly called the sliding technique, has been advocated. However, it is not a generally recommended procedure due to its potential complications. There have been reported cases of glans necrosis after the sliding technique. Alternative and safer penile-lengthening procedures performed concurrently with penile prosthesis implantation have been described and utilised, including plaque incision and grafting, the Multiple Slit Technique (MUST), and the Multiple Incision Technique (MIST), to restore penile length and girth. However, all

of these manoeuvres are associated with a higher risk of complications and infection. Thorough and careful preoperative counselling is therefore essential [10, 11, 12].

Penile Size Abnormalities

Introduction

While penile curvature problems are the more commonly encountered complaints with regards to penile deformities, there is an increasing demand for penile enhancement surgeries, and it is prudent that urologists are aware of and educate themselves in this novel field. The European Association of Urology has recently expanded its guidelines on sexual and reproductive health[13] to include a review of some of these issues. The literature in this field behind the medical and surgical therapies offered is extremely limited and expert consensus is required. A particular challenge is that many treatments are offered by providers outside of the medical profession, yet managing the potential complications often falls to urologists.

Epidemiology and Classification

Penis size has long been taken as a marker of masculinity and as a symbol of a man's fertility and sexual performance. The subjective impression of smaller penile size can have a negative effect on a man's sexual function and their quality life and can then ultimately impact upon their sexual life. In a real life study, only 55% of men reported being satisfied with the length of their penis, with nearly half expressed a desire for a larger size. Interestingly, this contrasts with 84% of women who reported satisfaction with their male partner's penis size.

A particular challenge in the management of penile size abnormalities is the lack of consensus of the definition of a short penis, or indeed a normal penis. Studies dating back over 130 years have taken groups of men and assessed penile length across different age ranges and ethnicities in the flaccid stretched and erect states. *Stretched penile length* (SPL) is defined as the distance between the pubic symphysis and the apex of the glans, and represents the most reported measurement of the penis.

It is important to discern between:

- *A true micropenis*: Which may have anatomical or endocrinological origins and is defined as a SPL which is 2.5 standard deviation cm shorter than the average length for the age of a given population group. Epidemiological studies demonstrate between 0.015% and 0.66% male newborns have a micropenis.
- *A short penis:* Which is a subjective complaint. This can be associated with small penis anxiety syndrome, which relates to a man's excessive anxiety relating to an otherwise normal-sized penis.
- *A buried penis*: Where there is a normal-sized penis, but a significant proportion of it is concealed by surrounding adipose or lymphoedematous tissue. This may be exacerbated by excessive circumcision. Apparent loss of penile length may also occur due to denervation following pelvic or other surgery, or as a result of chronic erectile dysfunction and loss of nocturnal erections.
- *Penile dysmorphic disorder*: PDD is a variation of Body Dysmorphic Disorder (BDD) cases, characterised by exaggerated focus on the size and shape of the penis resulting in mental health impairment and considerable damage in key areas of the individual's life. BDD is a clinical diagnosis and is defined by the American Psychiatric Association as the strong distress generated by perceived defects or flaws in individuals' physical appearance. Both BDD and PDD are conceptually different from small penis anxiety or small penis syndrome, which refer to a man's excessive anxiety regarding his normal-sized penis.

Investigations and Management

A detailed medical history is required, with particular attention being paid to common causes of penile shortness, such as phimosis, priapism, hypospadias, penile trauma etc. Any past or present diagnosis of body dysmorphia should also be noted. The use of psychometric testing can also be a useful adjunct to a thorough physical examination. Penile Doppler ultrasound and penile MRI can provide additional data regarding the penile anatomy and the extent of penile burying, but there is no evidence that this additional information contributes to the physical examination enough to justify its routine use.

Non-Surgical Management

Psychotherapy may have a role in helping improve self-perception and self-esteem prior to embarking on surgical surgery and may also help with addressing any discrepancy between expected versus real penile augmentation outcomes. Penile traction therapy seems affective in

lengthening the penis both in the flaccid and stretch state with minimal side-effects. Penile traction therapy, however, does not seem to improve penile girth. Despite its widespread use in the paediatric setting, there is no evidence for testosterone administration in the role of micropenis in adults.

Surgical Management

There are a variety of surgical procedures that could be attempted depending on the aetiology of the abnormality.

Adult Acquired Buried Penis

There is a broad spectrum of surgical reconstructive procedures that can be performed for acquired buried penis, ranging in complexity. They include mobilisation of penile skin, division of the suspensory ligament, division of a peno-scrotal web, apronectomy or liposuction, insertion of a malleable penile prosthesis, and skin grafting where there is deficient or diseased penile skin.

These procedures have a low incidence of recurrence and high satisfaction rates, but there can be a significant incidence of postoperative complications.

Congenital Intrinsic Penile Shortness

The literature is quite broad in the recommendations for surgical treatment of congenital intrinsic penile shortness, ranging from less invasive procedures such as the suspensory ligament release to more complex total phallic reconstruction. Giving advice is challenging with such broad ranges. Careful patient selection is particularly important amid potential complication rates.

Acquired Penile Shortness

Approximately 72% of patients report subjective decreased penile length after the insertion of a penile prosthesis: The objective numbers can be less than 1 cm even 1 year postoperatively. Much more invasive procedures, such as penile disassembly and corporal advancing manoeuvres, have also been described but are associated with significant complications.

Penile Girth Enhancement

Like penile length, there are no precise definitions or indications for penile girth enlargement within the literature or existing guidelines. Recent surveys have reported that the diameter of the penis is more important than length for orgasm in women during penetrative intercourse.

A variety of substances can be injected to increase girth size. These include:

- autologous fat tissues
- hyaluronic acid
- silicone
- paraffin
- other synthetic substances

Satisfaction rates are high, running from 78% to 100% for hyaluronic acid injections, with low rates of side effects reported [13]. This contrasts with injections of silicone or paraffin, which have been reported to lead to the development of a chronic granulomatous inflammatory foreign body reaction called sclerosing lipogranuloma of the penis. Also referenced as paraffinoma, this leads to bulky nodular lesions that ultimately require penile reconstruction. The injection of autologous fat also seems to have high satisfaction rates, reportedly over 75% in some series.

Surgical techniques using grafting procedure for penile girth enhancement are controversial and at this point should be considered experimental. The PENUMA silicon penile implant has been approved for implantation recently and seems to have promising results in penile girth enhancement [14]. It leads to an average increase in penile circumference of between 2 and 5 cm, with low complication rate, as per reports to date, though long-term data are lacking and there are reports of significant rates of complications, requirement for explantation and penile reconstruction.

References

1. Chung E, Ralph D, Kagioglu A, *et al.* Evidence-based management guidelines on Peyronie’s disease. *J Sex Med* 2016; 13 (6):905–923.⏎

2. Hellstrom WJG, Feldman R, Rosen RC, *et al.* Bother and distress associated with peyronie's disease: Validation of the Peyronie's disease questionnaire. *J Urol* 2013; **190**.⏎
3. Ohebshalom M, Mulhall J, Guhring P, *et al.* Measurement of penile curvature in Peyronie's disease patients: comparison of three methods. *J Sex Med*; **4**.⏎
4. Hauck EW, Hackstein N, Vosshenrich R, *et al.* Diagnostic value of magnetic resonance imaging in Peyronie's disease: a comparison both with palpation and ultrasound in the evaluation of plaque formation. *Eur Urol* 2003; **43**.⏎
5. Almsaoud NA, Safar O, Alshahrani ST, *et al.* The effect of penile traction device in men with Peyronie's disease on penile curvature, penile length, and ED: a systematic review and meta-analysis. *Transl Androl Urol*; **12**: 1671685–1673685. Available at: https://tau.amegroups.org/article/view/118936/html, accessed February 26, 2024.⏎
6. Spirito L, Manfredi C, La Rocca R, Napolitano L, Di Girolamo A, Capece M, Trama F, Sciorio C, Sokolakis I, Creta M, Arcaniolo D. Daily low-dose tadalafil may reduce the penile curvature progression rate in patients with acute Peyronie's disease: a retrospective comparative analysis. *Int J Impot Res* 2024 Apr;36(2):129–134.⏎
7. Kayes O, Crisp N and McLoughlin J: Artificial erection in Peyronie's disease surgery. *Ann R Coll Surg Engl* 2011; **93**.⏎
8. Osmonov D, Ragheb A, Ward S, *et al.* ESSM position statement on surgical treatment of Peyronie's disease. *Sex Med*; **10**.⏎
9. Habous M, Tealab A, Farag M, *et al. Malleable penile implant is an effective therapeutic option in men with Peyronie's disease and ED. Sex Med 2018*; 6.⏎

10. Egydio PH, Kuehhas FE. Penile lengthening and widening without grafting according to a modified ‘sliding’ technique. *BJU Int* 2015 Dec;116(6):965–972.⏎
11. Fernández-Pascual E, Gonzalez-García FJ, Rodríguez-Monsalve M, Turo J, Martínez-Ballesteros C, Carballido J, Martínez-Salamanca JI. Surgical Technique for Complex Cases of Peyronie’s Disease With Implantation of Penile Prosthesis, Multiple Corporeal Incisions, and Grafting With Collagen Fleece. *J Sex Med* 2019 Feb;16(2):323–332.⏎
12. Egydio PH, Kuehhas FE. The Multiple-Slit Technique (MUST) for Penile Length and Girth Restoration. *J Sex Med*. 2018 Feb;15(2):261–269.⏎
13. Anon: European Association of Urology (EAU) Sexual and Reproductive Health Guidelines. In: *EAU Guidelines*. Edn. Presented at the EAU Annual Congress Milan 2023. 2023.⏎
14. Elist JJ, Valenzuela R, Hillelsohn J, *et al*. A single-surgeon retrospective and preliminary evaluation of the safety and effectiveness of the penuma silicone sleeve implant for elective cosmetic correction of the flaccid penis. *J Sex Med*; 15.⏎

8 Male Sterilisation: Clinical Assessment and Surgical Technique

Kirby F. Sebro, Karen Randhawa and C.J. Shukla

DOI: 10.1201/b22940-8

Vasectomy is the safest, most effective, and most universally used method of permanent male sterilisation [1]. Despite its success and widespread adoption, adverse outcomes, such as vasectomy failure and chronic post vasectomy pain syndrome, have resulted in vasectomies becoming a highly litigious surgical procedure [2, 3, 4].

History

A focused clinical history should include the patient's age, relationship status, capacity to give informed consent, and number of children. Past surgical history, including any inguinal or scrotal surgery (particularly orchidopexy for undescended testis) should also be included, in addition to relevant medications and current contraceptive use.

Examination

The patient should be examined in a warm room with a chaperone present. Examination should include inspection for scars from any previous inguinal or scrotal surgery, as this could result in thickening of the spermatic cord and make localising the vas difficult. Scrotal laxity should be noted and obvious pathology such as testis tumours, absent or undescended testicles, hernia, hydrocoele, epididymal cysts, and varicoceles should be documented. The absence/presence of both vasa should be assessed.

If the vas cannot be palpated or easily brought to the skin surface and fixed with the thumb and index finger without discomfort to the patient, then the patient is not suitable for vasectomy under local anaesthesia (LA). Patients who are anxious or uncomfortable during examination may be more suited to general anaesthesia (GA).

Preoperative Counselling

Ideally, the patient's partner should be a part of the decision-making process, although medico-legally this is not a prerequisite. Information on the procedure risks and complications should be provided – for example, the British Association of Urological Surgeons (BAUS) information leaflet on vasectomy [5]. The irreversibility of the procedure should be stressed. Risks, benefits, and alternative methods of contraception, including female sterilisation, hormonal, barrier methods, and abstinence should also be discussed [3, 4].

The patient should be informed of the need to continue with current methods of contraception until an azoospermic semen sample is obtained or special clearance is granted based on the finding of two consecutive sperm counts <100,000/ml with no motile sperm after a minimum of 7 months after vasectomy. BAUS recommends that at least 12 weeks should pass before submitting a semen sample, or at least 20 ejaculations [5].

The early vasectomy failure rate (1:300 due to surgical error) or late failure rate (1:2000 due to recanalization) should also be discussed [5, 6].

Complications

The most common complications of surgery are swelling and bruising (80%), infection (3%), epididymo-orchitis (10%) and haematoma requiring re-exploration (3%). Haematospermia (10%), though benign and self-limiting, can be alarming to the patient if he is not warned [5, 6].

Late complications include sperm granuloma (10%) and dissatisfaction or regret (10%). Chronic testicular pain, known as post-vasectomy pain syndrome, may also be reported (5%) [7]. Approximately 60%–80% of patients develop detectable serum levels of anti-sperm antibodies; however,

their presence does not affect fertility following vasectomy reversal and is therefore considered clinically irrelevant [5, 6].

Investigations

Pre-operative lab tests are not usually indicated unless considering a GA procedure or suggested by the patient's history.

Surgical Technique

There are two key steps in the vasectomy procedure:

1. Skin incision/vas isolation
2. Vas occlusion

Skin Incision/ Vas Isolation

There are numerous incisions and methods identified for isolating the vas; however, any method is acceptable based on surgeon preference. The patient should ideally have Emla cream applied on the scrotum approximately 30 minutes prior to LA vasectomy.

a) Bilateral scrotal incisions
b) Single midline scrotal incision
c) No-scalpel technique

a) In the authors' preferred technique, bilateral scrotal incisions of less than 1 cm are made laterally at the junction between the upper and middle thirds of the scrotum. After isolating the vas between the fingers and thumb, a needle is passed through the skin and beneath the vas, then secured with a haemostat following the administration of LA. This adjunct manoeuvre frees one hand and helps prevent slippage or movement of the vas during the procedure (Figure 8.1). The skin incision can then be made with a scalpel after the administration of LA. The vasectomy ring clamp (Figure 8.2) and vasectomy dissector are used to enable dissection of the vas and peri-vasal tissues.
b) In the second technique, a single scrotal midline incision (1.5– 3 cm) is performed at the junction between the upper and middle third of the scrotum. This is the incision of choice in difficult cases where the vas is not easily palpable. No specialised equipment

is needed as the vas can be isolated with a towel clip or Allis forceps. An advantage of this procedure is that other pathology such as hydroceles or epididymal cysts can be treated at the same time if performed under GA. Disadvantages of this method include the risk of inadvertently dividing the vas twice on the same side and the need for a larger incision compared to other techniques.

c) In the no-scalpel technique, a vas ring clamp is applied around the vas first, after the administration of LA, then a <1cm skin opening is made by piercing the skin with the vas dissector. The peri-vasal tissue is dissected, and the bare anterior wall of the vas is exposed. The bare vas is pierced with one tip of the vas dissector, and the vas dissector is then rotated to elevate the vas above the skin opening. The vas is regrasped with the vas ring clamp. The vas dissector is then used to isolate the vas, which is then dissected free from surrounding peri-vasal tissue and vessels. The advantage of this technique is that due to the small incision size, there is no need to suture the skin opening except in rare cases [8, 9, 10, 11]. Sokal et al. demonstrated in a large multi-centre randomised controlled trial (RCT) of 1,429 patients that there was a statistically significant decrease in the incidence of haematoma formation in no-scalpel versus conventional vasectomy (1.9% vs 12.2%, $p<0.01$ [10]. The disadvantage to this technique is that specialised equipment is required that may not be readily available [11, 12].

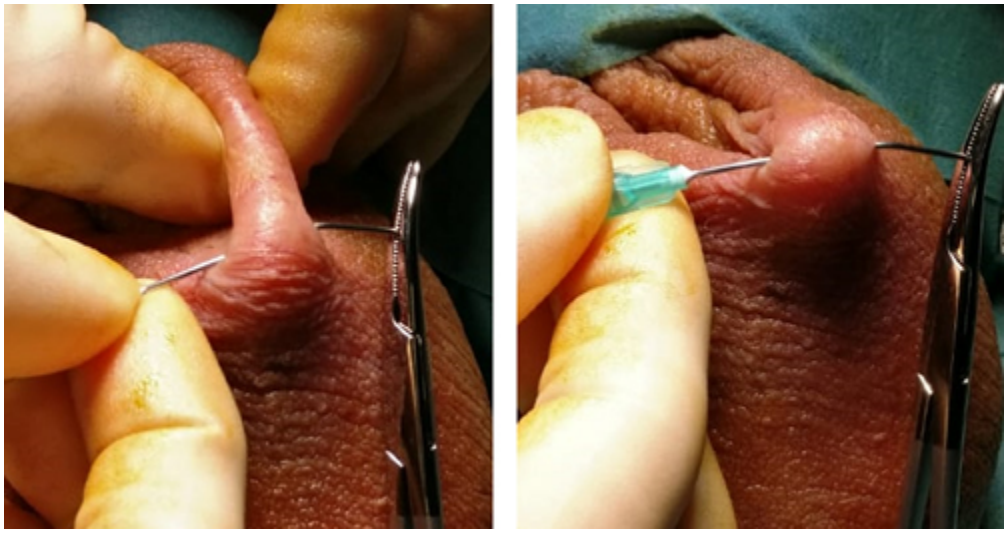


Figure 8.1 Localising the vas. After localising the vas with the non-dominant hand, a needle is passed through the scrotal skin and secured with a haemostat. This prevents slipping of the vas during the operation.⏎

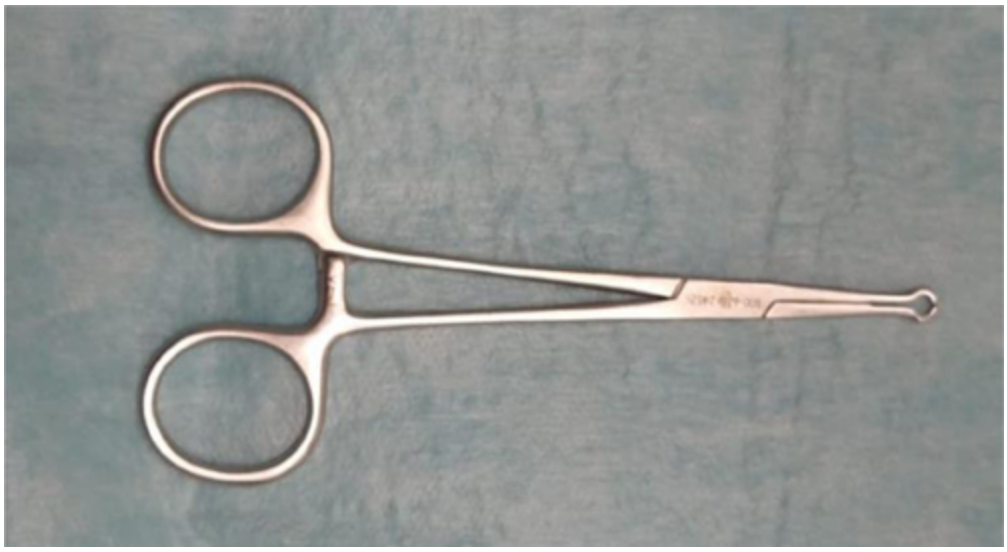


Figure 8.2 Vasectomy ring clamp.⏎

Vas Occlusion

Several techniques have been described for vasal luminal occlusion. Four are recommended [13]:

a) Mucosal cautery of both abdominal and testicular vas ends (0%–1% failure rate).
b) Mucosal cautery of both the testicular and abdominal vas ends with fascial interposition (0%–0.55% failure rate) [13, 14, 15].
c) Open ended vasectomy – leaving the testicular end of the vas open and using mucosal cautery on the abdominal end and fascial interposition (0%–0.5% failure rate).
d) The Marie Stopes International technique (0.64% failure rate) [16].

In the mucosal cautery vas occlusion method, thermal or electrical cautery is applied to the vasal mucosa of the cut ends of the vas while limiting cautery damage to the muscular layer (as seen in Figure 8.3). This creates scar tissue and occludes the vasal lumen. Limiting the muscular layer damage prevents sloughing of the cauterised vas. The authors recommend that this technique is combined with excision of a vas segment. Ligation

and fascial interposition are performed to minimise the risk of vasectomy failure [13, 14, 15].

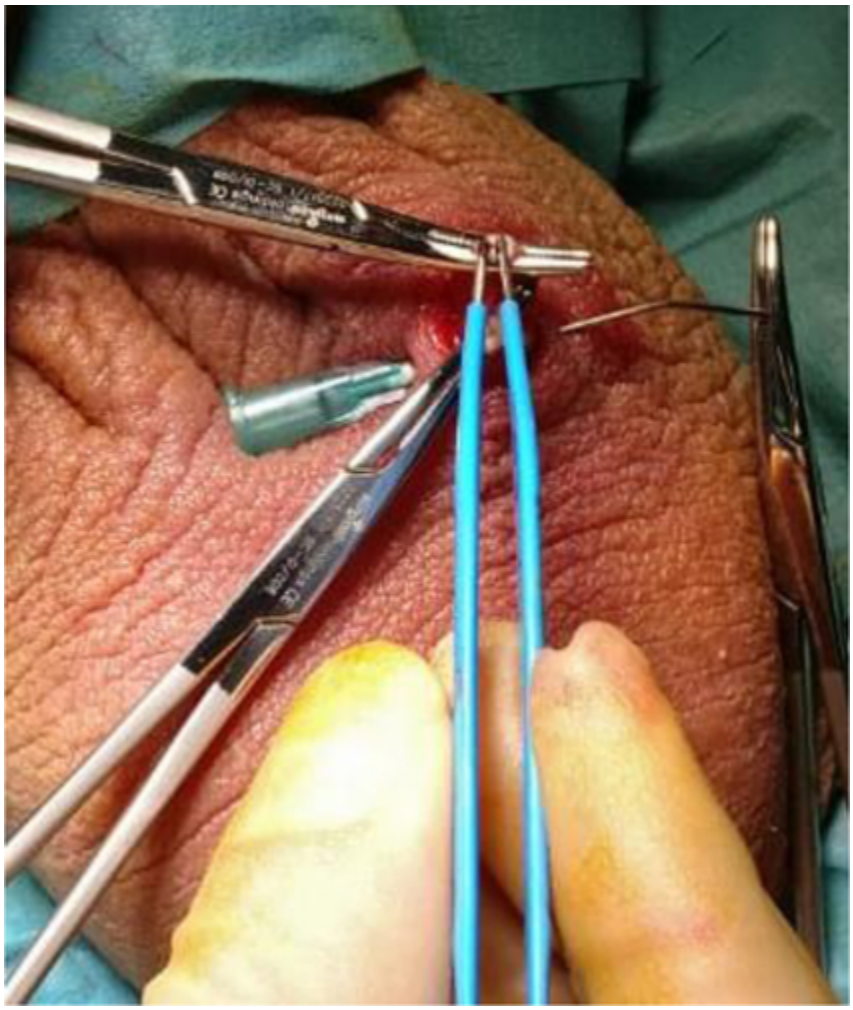


Figure 8.3 Mucosal bipolar electrocautery.⏎

Fascial interposition is the technique of placing a layer of the internal spermatic fascia between the two divided ends of the vas (Figure 8.4). It is usually combined with other techniques such as ligation and excision or mucosal cautery (Figure 8.5).

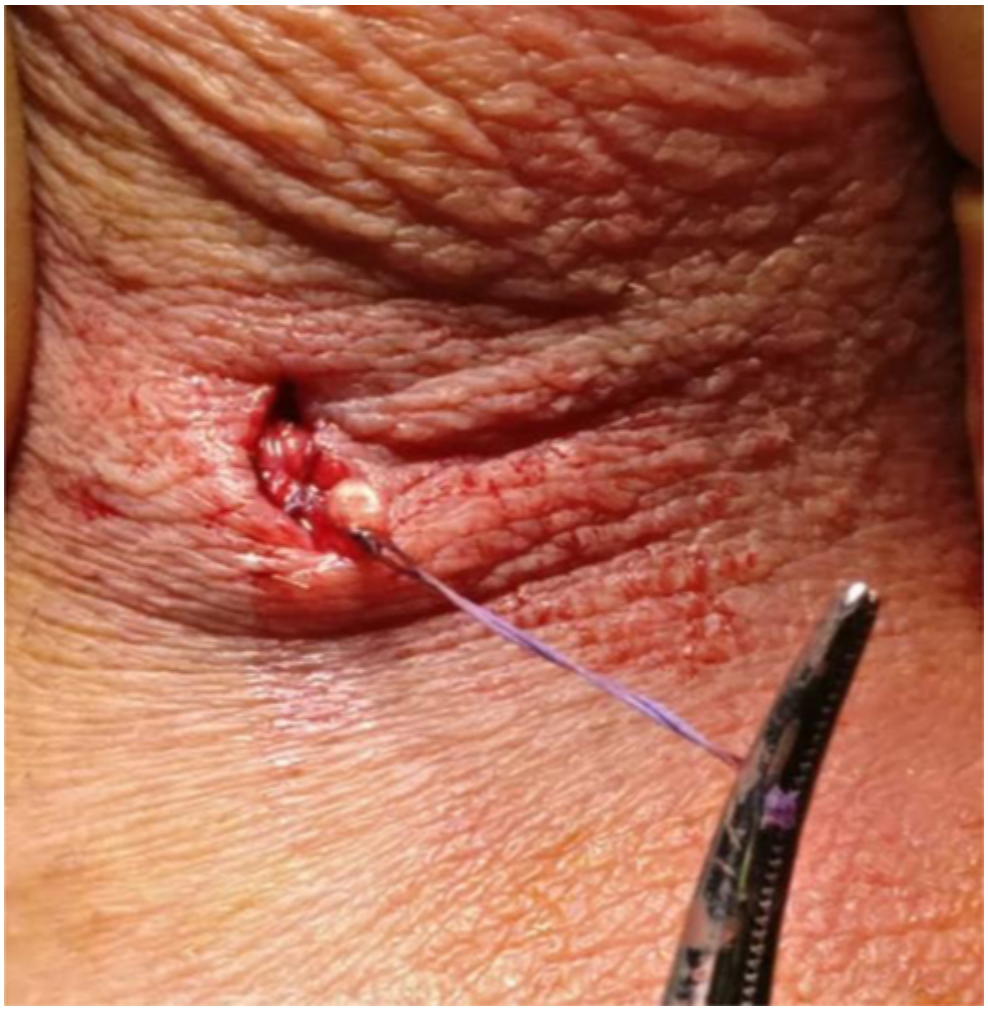


Figure 8.4 Fascial interposition of vas.⏎

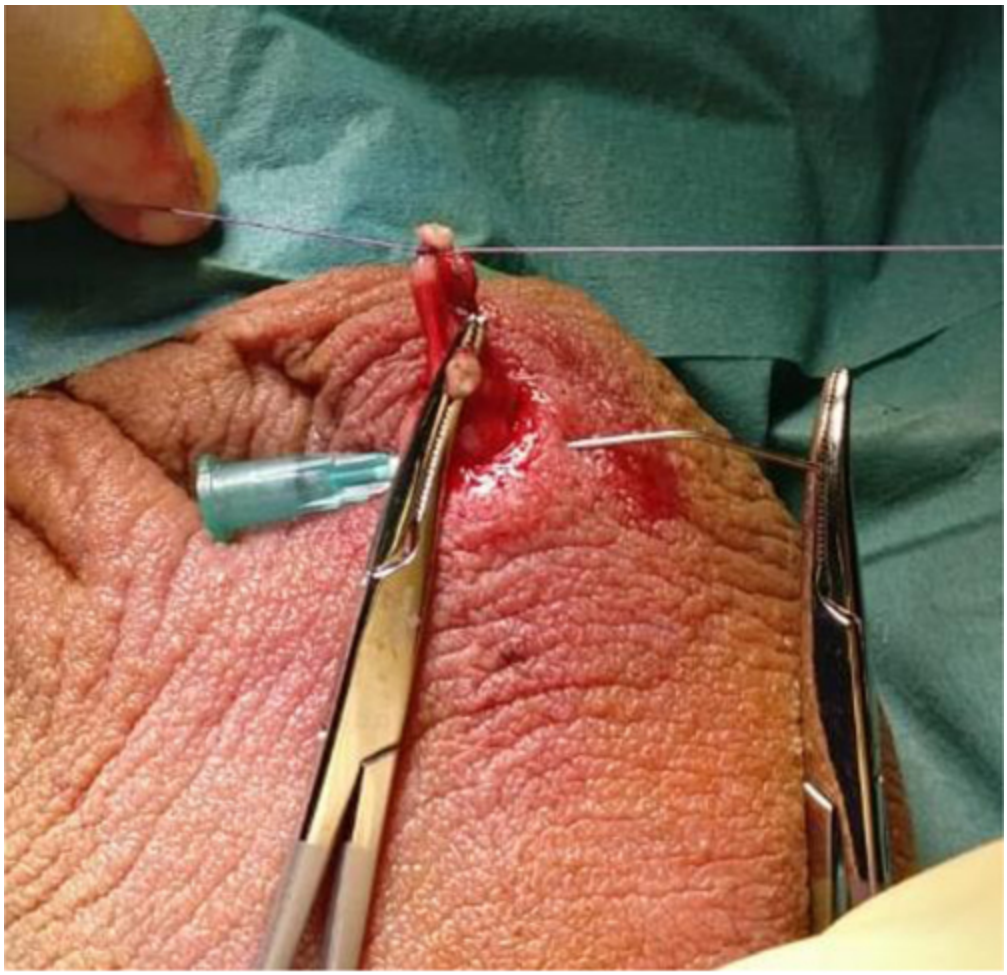


Figure 8.5 Ligation of the vas.⏎

In an open-ended vasectomy, the testicular end of the divided vas is left unoccluded, while the abdominal end is sealed. This approach is thought to reduce post-vasectomy pain by lowering back pressure on the epididymis and promoting the formation of a sperm granuloma at the transected testicular end, which may improve the likelihood of successful vasectomy reversal. Fascial interposition can be used in conjunction with this technique to further reduce the risk of recanalisation [13, 14, 16, 17].

The Marie Stopes International technique is the only non-divisional vasectomy method. It involves extended monopolar electrocautery of the full thickness of the anterior wall and partial thickness of the posterior wall of the vas over a length of 2.5–3 cm, without dividing the vas [16].

Other Techniques

Ligation and occlusion of the vas with ligatures, followed by excision or division between the occluded points – with or without fascial interposition – may also be performed. This can be achieved with sutures or surgical clips. Typically, a 1 cm segment of the vas is excised (Figure 8.5). Folding back is a technique in which each divided end of the vas is folded and sutured onto itself to prevent the cut ends from facing one another.

In a multi-centre RCT, Sokal et al. evaluated patients undergoing vasectomy who were randomised to ligation with or without fascial interposition. They found that azoospermia was achieved more rapidly in the group receiving fascial interposition. Most significantly, fascial interposition reduced the rate of vasectomy failure by 50% [14]. In a multi-centre prospective observational study, Barone et al. examined the effectiveness of cautery for vasal occlusion and found that it achieved azoospermia more quickly than techniques involving ligation and excision alone [15].

Routine histologic examination of the vas is not required.

Sample Operative Note (General Anaesthetic Vasectomy)

WHO checklist.

Supine position.

Patient is shaved pre-operatively if required.

Area cleaned and prepared

Sterile drapes applied.

Vas palpated and manipulated to the superficial scrotal skin.

21G needle passed through the skin, under the vas and secured with a haemostat clip.

Local anaesthetic (1% lidocaine and 0.5% bupivacaine in a 1:1 ratio) instilled into the skin and deeper tissues including vasal sheath proximally and distally.

1 cm scrotal incision performed over the isolated vas and vas manipulated out through the incision.

Vas sheath incised longitudinally, and denuded vas isolated using a vas ring forceps and two mosquito clips applied approximately 2 cm apart.

Short segment (1 cm) of vas excised.

Testicular and abdominal vas ends ligated with 2/0 Vicryl ties.

Vas ends occluded by intra-luminal cautery, and fascial interposition performed using 4/0 Vicryl Rapide.

Skin closure performed with interrupted 4/0 Vicryl Rapide sutures.

Procedure then repeated on opposite side.

OpSite Spray applied to wound.

Post-Procedure Considerations

The couple must be advised to continue to practise alternative forms of contraception until a single negative post-vasectomy semen analysis (PVSA) is realised (usually after 20 ejaculations or 3 months' post-vasectomy) [2]. A negative PVSA is defined as one well-mixed uncentrifuged fresh post-vasectomy semen specimen documenting either azoospermia at that time or ≤100,000 non motile sperm/ml i.e., rare non-motile spermatozoa (RNMS) [18, 19] 7 months after vasectomy. The definition of vasectomy failure is persistent motile sperm in PVSA beyond 6 months post-vasectomy and re-operation is recommended [2, 18, 19]. If PVSA continues to show >100,000 non-motile sperm/ml then either PVSA monitoring or re-operation is warranted, depending on surgeon's clinical judgement [2, 18, 19].

Conclusion

Vasectomy is a simple, safe, and effective form of permanent male sterilisation. Patient satisfaction and contraceptive success can be attained with proper patient selection, thorough pre-operative counselling, and selection of effective vas isolation and occlusion techniques. Issues that

must be addressed during pre-op counselling include the need for continued contraception immediately following vasectomy, in addition to failure and complication rates. The no-scalpel vasectomy technique for vas isolation is associated with a lower complication rate when compared to conventional techniques. Contraceptive effectiveness of vasectomy is most closely linked to the vas occlusion technique used [13, 14, 15].

References

1. Schwingl PJ, Guess HA. Safety and effectiveness of vasectomy. *Fertil Steril*. 2000;73(5):923–936.⏎
2. Goldstein M. Surgical management of male infertility. In Wein A, Kavoussi L, Partin A, Peters C eds, *Campbell-Walsh Urology*, 11th edn, Chapter 25. Philadelphia: Elsevier, 2016: 580–611.⏎
3. Kaplan AI, Rappaport JA. The law and vasectomy. *Urol Clin North Am*. 2009;36(3):347–357.⏎
4. Gingell C, Crosby D, Carroll R, Review of the complications and medicolegal implications of vasectomy. *Postgrad Med J* 2001;77:656–659.⏎
5. The British Association of Urological Surgeons. Vasectomy. Available at: https://www.baus.org.uk/_userfiles/pages/files/Patients/Leaflets/Vasectomy.pdf.⏎
6. Philp T, Guillebaud J, Budd D. Complications of vasectomy: review of 16,000 patients. *Br J Urol*. 1984 Dec;56(6):745–748.⏎
7. Hori S, Sengupta A, Shukla CJ, Ingall E, McLoughlin J. Long-term outcome of epididymectomy for the management of chronic epididymal pain. *J Urol*. 2009;182(4):1407–1412.⏎
8. Li SQ, Goldstein M, Zhu J *et al*. The no-scalpel vasectomy. *J Urol*. 1991;145:341.⏎

9. Engender Health. No-Scalpel Vasectomy an Illustrated Guide Third *Addition*. *Engender Health*; 2003.⏎
10. Sokal D, McMullen S, Gates D, Dominik R. A comparative study of the no scalpel and standard incision approaches to vasectomy in 5 countries. The Male Sterilization Investigator Team. *J Urol*. 1999;162(5):1621–1625.⏎
11. Chiles K, Feliciano M, Goldstein M. No scalpel vasectomy: 20-year outcomes utilizing combined cautery, clip and facial interposition. *Fertil Steril*. 2015;104(3,Supplement):e233.⏎
12. Cook LA, Pun A, Gallo MF, Lopez LM, Van Vliet HA. Scalpel versus no-scalpel incision for vasectomy. *Cochrane Database Syst Rev*. 2014;3:CD004112.⏎
13. Cook LA, Van Vliet HA, Lopez LM, Pun A, Gallo MF. Vasectomy occlusion techniques for male sterilization. *Cochrane Database Syst Rev*. 2014;3:CD003991.⏎
14. Sokal D, Irsula B, Chen-Mok M, Labrecque M, *Barone MA. A comparison of vas occlusion techniques: cautery more effective than ligation and excision with fascial interposition*. *BMC Urol*. 2004;4(1):12.⏎
15. Barone MA, Irsula B, Chen-Mok M, Sokal DC. Investigator study group. effectiveness of vasectomy using cautery. *BMC Urol*. 2004;4:10.⏎
16. Black T, Francome C. The evolution of the Marie Stopes electrocautery no-scalpel vasectomy procedure. *J Fam Plann Reprod Health Care*. 2002;28:137.⏎
17. Esho JO, Cass AS. Recanalization rate following methods of vasectomy using interposition of fascial sheath of vas deferens. *J Urol* 1978;120:178.⏎
18. Hancock P, Woodward BJ, Muneer A, Kirkman-Brown JC. Laboratory guidelines for postvasectomy semen analysis: Association of Biomedical Andrologists, the British Andrology

Society and the British Association of Urological Surgeons. *J Clin Pathol*. 2016;69(7):655–660.⏎
19. Korthorst RA, Consten D, van Roijen JH. Clearance after vasectomy with a single semen sample containing than 100 000 immotile sperm/mL: analysis of 1073 patients. *BJU Int* 2010;105(11):1572–1575.⏎

9 Vasectomy Reversal

Matthew J. Rewhorn and David J. Ralph

DOI: 10.1201/b22940-9

History, Examination and Investigations

In England, an average of 10,000 vasectomies are performed each year, and around 100,000 opposite-sex divorces occur annually [1, 2]. The European Association of Urology (EAU) and the British Association of Urological Surgeons (BAUS) guidelines on vasectomy state that approximately 2%–6% of men request a vasectomy reversal within 10 years of the original vasectomy procedure [3, 4].

A detailed history should be obtained from every man requesting a vasectomy or a vasectomy reversal. Men are more likely to request reversal if:

- the original operation was performed at a young age [5]
- the couple have no children
- the man is not in a relationship, has a new partner or remarries
- a couple suffers the death of a child
- the man wishes to have more children
- psychological issues were present originally, or coercion by a partner occurred
- chronic post-vasectomy pain (CPPV) persists despite medical therapy [6]

Prior to a vasectomy, patients should be counselled on alternative contraception options for both men and women.

Scrotal examination should be performed at the initial consultation, or before the procedure, to identify scars, exclude new pathologies such as testicular atrophy and to locate the vasal ends and assess the epididymis bilaterally [7].

Patients should be made aware that vasectomy reversal involves complex surgery that can achieve high postoperative patency rates, yet may

not restore fertility or ensure pregnancy or live birth. Reversal options include:

- vasovasostomy (VV)
- epididymovasostomy (EDV) in conjunction with surgical sperm retrieval (SSR):
    - percutaneous epididymal sperm aspiration (PESA)
    - testicular sperm aspiration or extraction (TESA/TESE)

SSR provides sperm for assisted reproduction techniques (ART) such as intracytoplasmic sperm injection (ICSI) and can be performed alongside reversal or independently in patients who decline reversal or who have previously failed reversal surgery.

National Institute for Health and Care Excellence (NICE) guidelines advise patients that the NHS does not routinely offer reversal. Reported success rates (the presence of motile sperm in a post-operative sample) following reversal operations vary from 40% to over 97%, with the success rate declining the longer the time interval since the vasectomy [8].

The decision to have a vasectomy reversal or to opt for assisted reproductive techniques will depend on several factors (Figures 9.1 and 9.2).

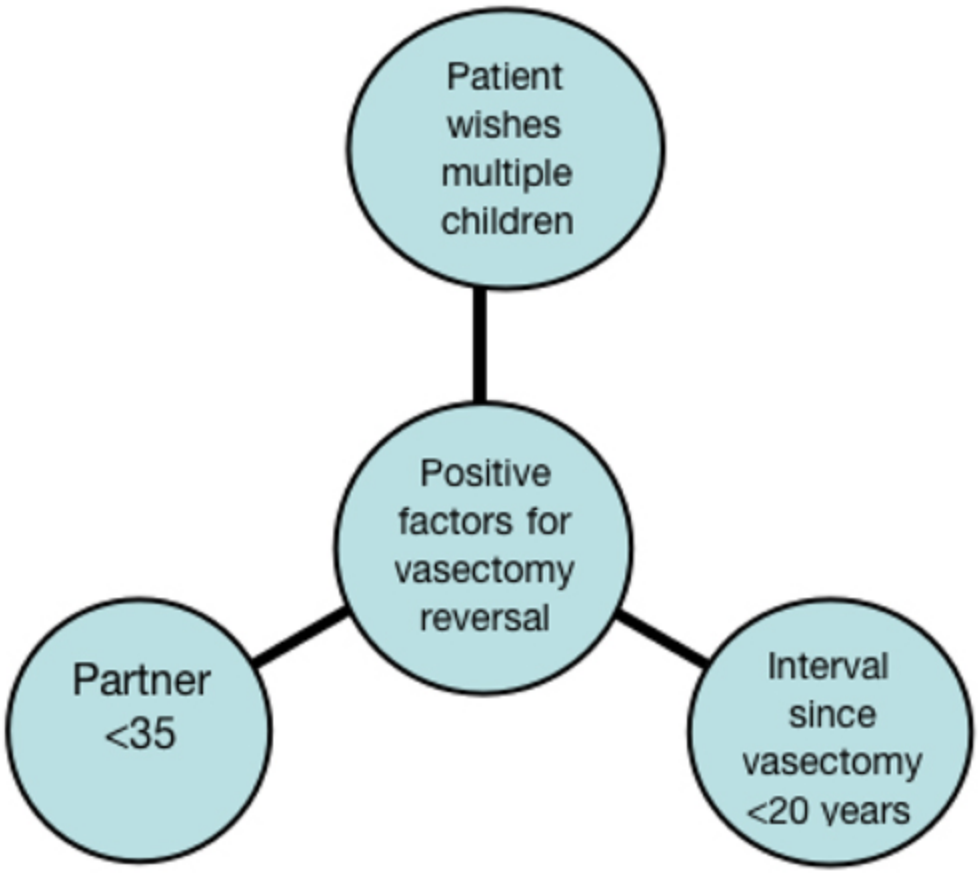


Figure 9.1 Factors for vasectomy reversal.⏎

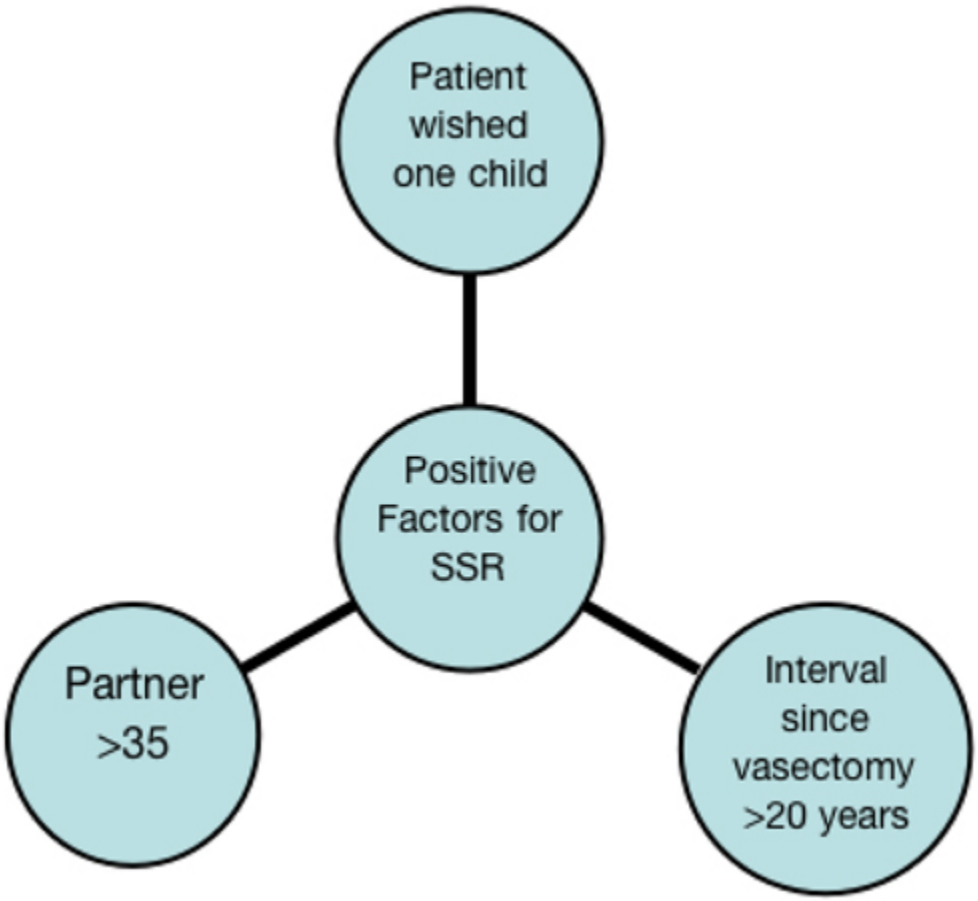


Figure 9.2 Factors for surgical sperm retrieval.⏎

- the length of time since the patient's vasectomy (Table 9.1)
- partner's age (the most important factor in progressing from patency to pregnancy) (Table 9.2).
- the number of children the couple wish to have
- the costs involved

Table 9.1 Success of Vasectomy Reversal Linked to Obstruction Interval⏎

Interval (Years)	Patency Rate (%)	Pregnancy Rate (%)
<3	97	75
3–8	88	50–55
9–14	79	40–45
15–19	70	30
>20	40	<10

Source: Belker AM, Thomas Jr AJ, Fuchs EF, *et al.* Results of 1,469 microsurgical vasectomy reversals by the Vasovasostomy Study Group. *J Urol* 145 (1991): 505.

Table 9.2 Success of Vasectomy Reversal Linked to Female Partner's Age⏎

Female Partner Age (years)	Patency Rate (%)	Pregnancy Rate (%)
20–24	90	67
25–29	89	52
30–34	90	57
35–39	86	54
>40	83	14

Source: Gerrard ER, Jr, Sandlow JI, Oster RA, Burns JR, Box LC, *et al.* Effect of female partner age on pregnancy rates after vasectomy reversal. *Fertil Steril* 87 (2007): 1340–1344.

Vasectomy Reversal

VV is a micro surgical procedure that reconnects the proximal and distal ends of the previously transected and ligated vas deferens and can thus be used to reverse vasectomy (Figures 9.3a-f). EDV is a more complex technique that joins the distal vas lumen to a single epididymal tubule that can also be undertaken to reverse vasectomy. It is more demanding due to the discrepancy of luminal size between the two structures. Typically, EDV is performed when epididymal obstruction is present (usually in the cauda epididymis), when no sperm is found on fluid aspirate or when VV has failed. The surgical tenets required, irrespective of the technique chosen, include a tension-free, watertight anastomosis with mucosal apposition and preserved blood supply.

Surgical Steps

Usually performed under general anaesthesia, particularly if EDV is anticipated.

- Palpate for vasal deficit.
- Make bilateral high vertical incisions.
- Expose the vasal deficit, excise the scarred segment with a perpendicular cut and stabilise both ends using a vas clamp (Figure 9.3a).
- Cannulate the distal (abdominal) end with a Prolene suture to confirm patency.

- Aspirate vasal fluid from the proximal (testicular) end using a syringe and soft cannula.
- Examine the vasal fluid under a microscope, assessing colour, opacity and viscosity, and evaluate for the presence and quality of sperm.
- Proceed with VV if:
    - Clear vasal fluid is present
    - Morphologically normal, motile sperm are found
    - Otherwise perform EDV.

- Anastomotic options for VV (using operating microscope)
- *Modified one layer technique*: Interrupted 9–0 Nylon sutures placed through all layers, followed by a second seromuscular suture between each full-thickness suture [9] (Figure 9.3e–f).
- *Multilayer technique*: Inner mucosal layer sutured with interrupted 10–0 Nylon, followed by a second seromuscular layer using interrupted sutures [10]. A ‘micro-dot’ technique has also been described, in which six ink dots are marked around each vasal lumen with a micro-tip marker to guide precise mucosal apposition [11].

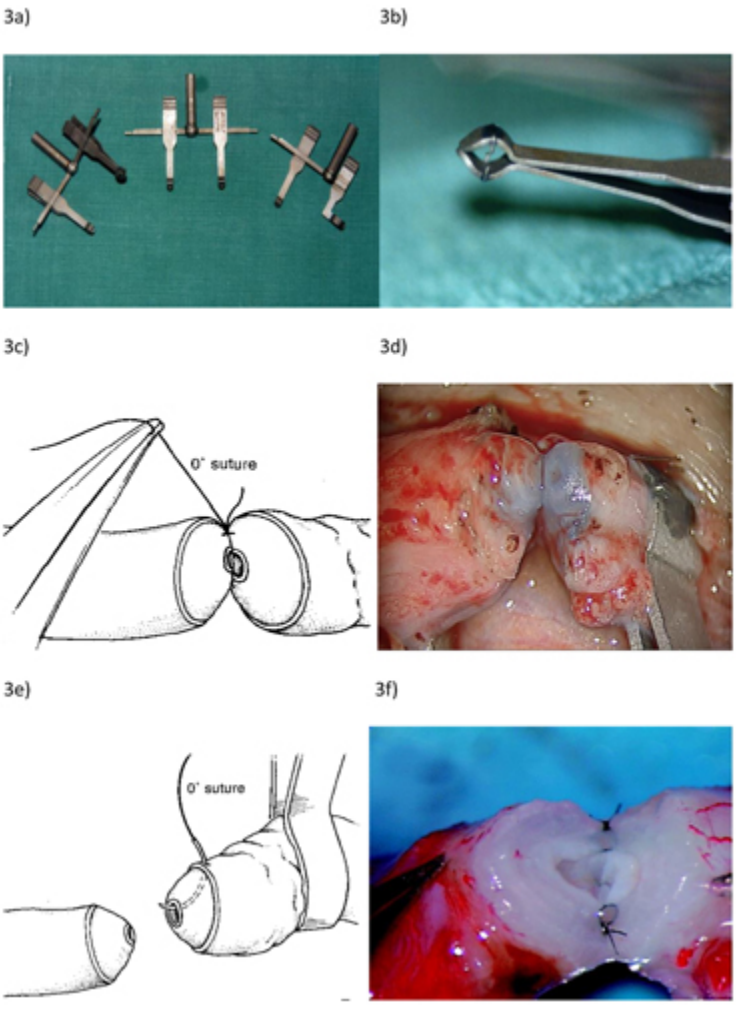


Figure 9.3 Vasectomy reversal.⏎

(a) vas reversal clamps articulate to allow optimal opposition of vassal ends; (b) vas reversal clamp; (c) diagram of anchoring suture; (d) vasal ends stained blue to allow identification of the mucosal lumen; (e) diagram of modified single-layer closure; (f) operative picture of double-layered closure with mucosal apposition.

Epididymovasostomy

- If VV is not appropriate, then proceed to identify tubules dilated to 0.1–0.2 mm in diameter, secondary to obstruction.
- Anastomotic options (using operating microscope) for EDV depend on surgeon preference.
    - *End-to-end*: This method is now seldom used due to the difficulty in differentiating the patent end of the epididymal tubule but is described in literature. Epididymis is dissected 1cm from the testis, transected, and fluid checked microscopically for the presence of sperm. Interrupted 10–0 Nylon sutures are placed on the appropriate epididymal tubule, posteriorly and anteriorly, in an outside-in fashion. This is followed by inside-out suturing through the vasal mucosa. The muscularis layer of the vas is then approximated to the tunica surrounding the epididymis [12].
    - *End-to-side*: A single epididymal loop is isolated; double-ended 10–0 Nylon is used in a triangular fashion; the anterior wall is opened and the tubule invaginated into the vasal lumen [13].
    - *Longitudinal intussusception epididymovasostomy*: Two double-armed 10-0 Nylon sutures are placed on a single tubule; needles are passed only after the defect is created, preventing decompression. Needles are brought inside-out through the vas, causing intussusception [14].

Risks and Complication (BAUS Consent)

- Swelling, discomfort and bruising of the scrotum lasting several days (10%–50%)
- No guarantee that sperm will return to semen; continued azoospermia (10%–50%)
- Even if sperm found in ejaculate, no guarantee of pregnancy (10%–50%)
- Miscarriage rate of 15%–20% (no higher than the general population) (10%–50%)
- Haematospermia (10%–50%)
- Chronic scrotal pain or sperm granuloma (5%)
- Re-stenosis of vas (5% each year)
- Bleeding requiring further surgical intervention (2%–10%)
- Epididymo-orchitis (0.4%–2%)
- Technical inability to perform reversal on one or both sides (0.4%–2%)

Post-Operative Instructions

- Scrotal support for 1 week
- Intermittent covered ice packs and analgesia for pain and swelling
- Avoid intercourse for 1 month
- Sperm may appear in ejaculate after 6 weeks for VV and up to 18 months for EDV

Outcomes

Patency and Pregnancy Rates

- Single-layer vasovasostomies (4 studies): patency 90% ± 8%; pregnancy 53% ± 10%, respectively)
- Double-layer vasovasostomies (12 studies): patency 87% ± 13%; pregnancy 52% ± 17%, respectively) [18]

The Vasovasostomy Study Group found no statistical difference between double-layer and modified single-layer anastomoses [19].

References

1. Sexual and Reproductive Health Services, *England* (Contraception) 2021; 4: Sterilisations and Vasectomies. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/sexual-and-reproductive-health-services/2021-22/sterilisations-and-vasectomies⏎
2. Office for National Statistics 2020; *Divorces in England and Wales* 2020. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/divorce/bulletins/divorcesinenglandandwales/2020#:~:text=In%202020%2C%20there%20were%20103%2C592,%2Dsex%20couples%20(98.9%25).⏎
3. Dohle GR, Diemer T, Kopa Z *et al.* European association of urology guidelines on vasectomy. *European Urology*, 61(1) (2012): 159–163.⏎
4. British Association of Urological Surgeons; *Reversal of Vasectomy Information Leaflet* 2020. Available at:

https://www.baus.org.uk/_userfiles/pages/files/Patients/Leaflets/Reversal%20of%20vasectomy.pdf.⏎
5. Potts JM, *et al.* Patient characteristics associated with vasectomy reversal. *J Urol* 161.6 (1999): 1835–1839.⏎
6. Nangia AK, Myles JL, Thomas AJ. Vasectomy reversal for the post-vasectomy pain syndrome: a clinical and histological evaluation. *J Urol* 164.6 (2000): 1939–1942.⏎
7. Patel AP, Smith RP. Vasectomy reversal: a clinical update. *Asian J Androl* 18.3 (2016): 365.⏎
8. *NICE Guidelines; Male Sterilisation* 2021.⏎
9. Willscher MK, Novicki DE. Simplified technique for microscopic vasovasostomy. *Urology* 15 (1980): 147.⏎
10. Silber SJ. Vasectomy and vasectomy reversal. *Fertil Steril* 29 (1978): 125.⏎
11. Goldstein M, Li PS, Matthews GJ. Microsurgical vasovasostomy: the microdot technique of precision suture placement. *J Urol* 159 (1998): 188.⏎
12. Silber SJ. Microscopic vasoepididymostomy: specific micro anastomosis to the epididymal tubule. *Fertil Steril* 30 (1978): 565.⏎
13. Berger RE. Triangulation end-to-side vasoepididymostomy. *J Urol* 159 (1998): 1951.⏎
14. Chan PT, Li PS, Goldstein M. Microsurgical vasoepididymostomy: a prospective randomized study of 3 intussusception techniques in rats. *J Urol* 169 (2003): 1924.⏎
15. Schroeder-Printzen I, Diemer T, Weidner W. Vasovasostomy. *Urol Int* 70 (2003): 101.
16. Weinerth JL. Long-term management of vasovasostomy patients. *Fertil Steril* 41 (1984): 625.
17. Wright GM, Cato A, Webb DR. Microsurgical vasovasostomy in military personnel. *Aust N Z J Surg* 65 (1995): 20.

18. Kim HH, Goldstein M. History of vasectomy reversal. *Urol Clin N Am* 36(3) (2009): 359. https://doi.org/10.1016/j.ucl.2009.05.001.⏎
19. Belker AM, Thomas Jr AJ, Fuchs EF, *et al.* Results of 1,469 microsurgical vasectomy reversals by the Vasovasostomy Study Group. *J Urol* 145 (1991): 505.⏎
20. Gerrard ER, Jr, Sandlow JI, Oster RA, Burns JR, Box LC, *et al.* Effect of female partner age on pregnancy rates after vasectomy reversal. *Fertil Steril* 87 (2007): 1340–1344.

10 Aetiology and Pathophysiology of Obstructive and Non-Obstructive Causes of Male Factor Infertility

Amr Elmekresh, Rozh Jalil, Selcuk Guven and Kamran Ahmed

DOI: 10.1201/b22940-10

Introduction

Infertility is defined as the inability of a couple to conceive for at least 1 year of unprotected sexual activity. Male factor infertility (MFI) accounts for about 20% of all cases of infertility, while another 30% to 40% of cases also have men as a contributing factor [1]. Men can experience infertility for several reasons, but in roughly 40% of cases, the cause is unclear. MFI can be caused by several factors, the most significant of which are: Physical causes, sexually transmitted diseases, hormonal deficiencies, environmental and lifestyle variables, and genetics [2].

MFI is caused primarily by factors encompassing: Abnormal semen parameters or function; anatomical, endocrine, genetic, functional, or immunological abnormalities of the reproductive system; chronic illness; and sexual conditions incompatible with the ability to deposit semen in the vagina.

The clinical definition of MFI is the male partner of an opposite-sex couple who is unable to conceive after a year of unprotected intercourse having abnormal semen parameters or sperm functional assays, or who is functionally unable to deliver semen into the vaginal canal. MFI is

classified by the World Health Organisation (WHO) as having one or more abnormalities in the semen analysis or having insufficient ejaculatory or sexual function [3].

A rising number of couples have been affected by infertility in recent years. Although there are no accurate statistics on the prevalence of infertility worldwide, estimations indicate that over 72.4 million couples face reproduction issues. According to estimates from the WHO, 60–80 million couples worldwide are struggling with infertility problems right now. It varies across the globe and is thought to affect 8%–12% of couples globally. In fact, infertility is more prevalent in areas where fertility rates are high, a phenomenon called 'barrenness amid plenty' [5, 6].

The National Centre for Health Statistics reports that from 4.56 million in 1982 to 7.26 million in 2002, the absolute number of women with impaired infertility increased by roughly 2.7 million women. From 2006 to 2010, this figure significantly decreased to 6.71 million. Additionally, the fertility rate of men under 30 has declined by 15% globally [4]. A comprehensive overview of MFI, and obstructive and non-obstructive causes of MFI, will be covered in this chapter, shedding light on their underlying mechanisms and contributory factors.

Male Factor Infertility

Male infertility is the inability of an adult male to successfully induce pregnancy in a fertile female. A change in sperm concentration, motility, or morphology is considered a sign of 'male factor' infertility in at least one sample of two sperm analyses, taken 3 months apart. It affects about 7% of all men in humans and causes 40%–50% of infertility. Semen quality is utilized as an indirect measure of male fertility since defects in the semen are frequently the cause of male infertility [7]. MFI is diagnosed when sperm parameters are below the WHO-recommended levels. The three most significant diagnoses for MFI are as follows:

1. Absence of sperm (azoospermia) or low sperm concentration (oligospermia)
2. Poor sperm motility (asthenospermia), and
3. Aberrant sperm morphology (teratospermia)

Semen volume and other seminal markers of epididymal, prostatic, and seminal vesicle activity are other parameters less well linked to infertility. Up to 90% of issues with MFI are related to count, and aberrant semen characteristics have a favourable correlation with sperm count. Pre-testicular, testicular, and post-testicular variables are all involved in the disordered regulation mechanism that results in problems with sperm count, motility, and morphology [8].

Azoospermia can be categorized as obstructive azoospermia (OA) or non-obstructive azoospermia (NOA). Understanding the aetiology and pathophysiology of these conditions is crucial for accurate diagnosis, appropriate treatment, and potential interventions to improve fertility outcomes. NOA results from spermatogenesis dysfunction, whereas OA is brought on by obstruction of the testicular and genital ductular systems.

Obstructive Causes of MFI

The absence of spermatozoa in the ejaculate despite adequate spermatogenesis is known as obstructive azoospermia (OA). The prevalence of OA, a prevalent urological condition, ranges from 6.1% to 13.6% among people seeking fertility examinations. Vasectomy is a common cause of OA; however, other aetiologies account for 19% to 69% of patients having surgical investigation for OA [9].

Obstructive causes of MFI refer to conditions where the blockage or absence of the ductal system impairs the transport of spermatozoa. The main obstructive causes include the following (Figure 10.1):

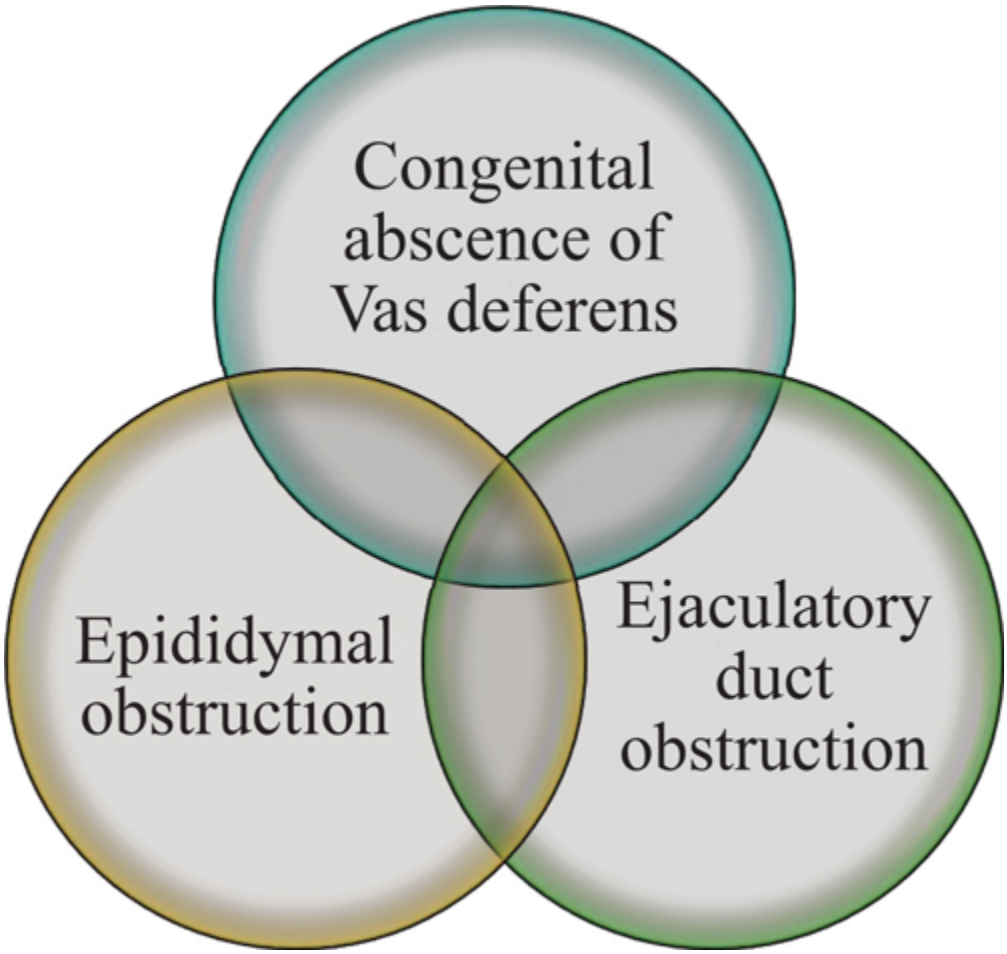


Figure 10.1 Three major reasons for obstructive type of male factor infertility.⏎

1. Congenital bilateral absence of the vas deferens (CBAVD)
2. Epididymal obstruction
3. Ejaculatory duct obstruction (EDO)

These conditions can result from genetic abnormalities, infections, or prior surgeries. The blockage prevents sperm from being ejaculated or reaching the site of fertilization, thereby causing infertility. Various diagnostic methods – such as physical examination, semen analysis, hormonal analysis, imaging techniques, and genetic testing – aid in identifying obstructive causes.

Congenital Bilateral Absence of the Vas Deferens

MFI may be exacerbated by the CBAVD. The underlying pathophysiology involves disrupted fluid secretion and altered epididymal function, leading to infertility. Five morphological manifestations of CBAVD may now be distinguished based on the numerous clinical findings that have occurred since: three for bilateral absences (CBAVD) and two for unilateral absences (CUAVD) (Figure 10.2) [10]. Since there are so many different phenotypes, it is challenging to understand the aetiopathogenic pathways, especially given that morphological defects that affect the kidney and the seminal vesicle (SV), two other organs, may or may not be linked to CBAVDs. CBAVD is present in 1.3% of all infertile men and CUAVD has been estimated to affect up to 1% of all men. Men who have a single functional testis due to CUAVD may be more susceptible to infertility.

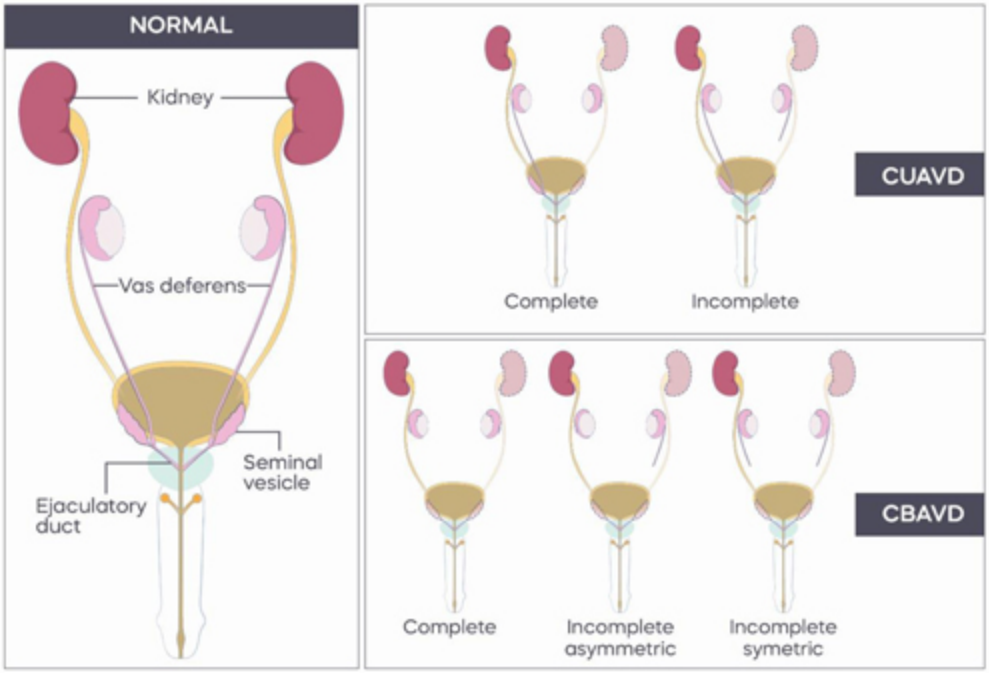


Figure 10.2 Descriptions of the morphological abnormalities associated with congenital bilateral absence of the vas deferens (CBAVD) and congenital unilateral absence of the vas deferens (CUAVD).⏎

Depending on the absences reported by imaging of the vas deferens alone (shown in red), the three forms of CBAVD

and two forms of CUAVD are physically distinguishable. Organs with dotted lines signify potential absence of the kidney and/or one or both seminal vesicles. The ejaculatory ducts, the ampulla of the vas deferens, and other potentially related anomalies missing from the body and/or tail of the epididymis are not considered.*Source*: Images adapted and modified from Bieth, E., Hamdi, S.M., Mieusset, R. Genetics of the congenital absence of the vas deferens. *Hum Genet* 140, 59–76 (2021). https://doi.org/10.1007/s00439-020-02122-w); Harris ID, Fronczak C, Roth L, Meacham RB. Fertility and the aging male. *Rev Urol.* 2011; 13: e184–e190. *Abbreviations*: E, epididymis; T, testicles; K, kidney; U, urethra.

Variable frequencies of SV size anomalies (hypotrophy, atrophy, dilation) or SV absence have been recorded; this is likely because different detection methods were utilized in each case. Bilateral SV abnormalities are primarily described in CUAVD (80%), where they are typically ipsilateral, and appear to be twice as common in CBAVD (50% vs 25%). These CUAVD statistics, however, mostly apply to azoospermic men.

On the other hand, the relationship between CAVDs and renal problems has been the subject of greater research. Reverdin et al. in the 1870s described a typical case of a man with CUAVD, ipsilateral SV absence, and unilateral renal absence (URA). Numerous investigations since then have established that URA is detected with CAVDs at a high rate of 5%–40%, although the prevalence of URA at birth is around 1,000 times lower. It is crucial to remember that individuals with CUAVD experience URA two to three times more frequently than those with CBAVD [11, 12].

Additionally, CAVDs are commonly associated with cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations and are characterized by the absence of the vas deferens that transports sperm from the testes to the urethra [13].

Developmental abnormalities are known to cause CAVD and related abnormalities of the epididymis. CFTR gene mutations lead to impaired ion

transport, affecting the maturation and function of the vas deferens. It has been suggested that aberrant CFTR action may play a role in the abnormal development of the Wolffian (mesonephric) duct. However, it is unclear how the CFTR gene affects the growth of these Wolffian ducts [10].

Assisted reproductive techniques (ART) combined with surgical sperm retrieval are often utilized to overcome infertility in CBAVD cases [11]. Figure 10.3 elaborates on the management of CBAVD.

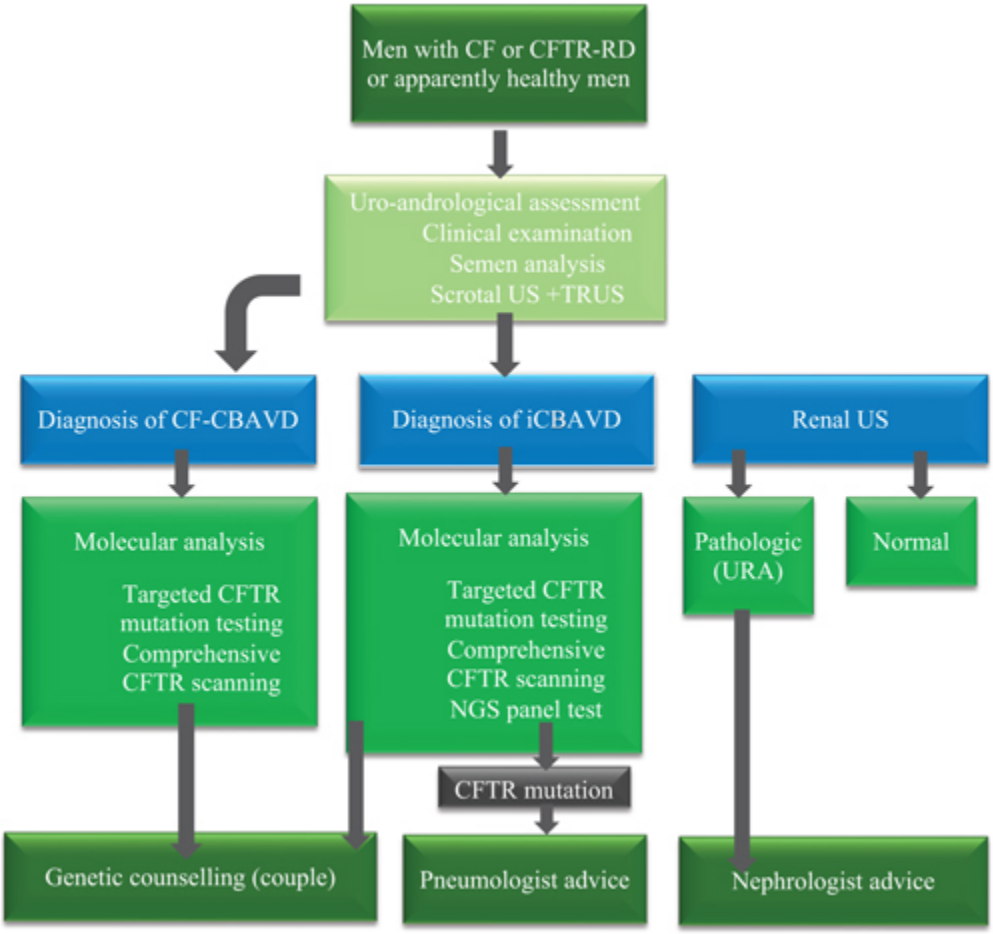


Figure 10.3 Management of men with congenital bilateral absence of the vas deferens (CBAVD). *Abbreviations*: CFTR, cystic fibrosis conductance regulator gene; iCBAVD, incomplete congenital bilateral absence of vas; US, ultrasound; TRUS, transrectal ultrasound of prostate; NGS: next-generation sequencing.⏎

This assessment is mandatory to confirm and characterize any suspicious CBAVD [10].

Epididymal Obstruction

An infectious aetiology should always be taken into consideration in men with the diagnosis of epididymitis, a common genitourinary illness. Epididymitis has been linked to a number of conditions, including gonorrhoea, chlamydia, trichomoniasis, brucellosis, BCG, ureaplasma, mycoplasma, coliforms bacteria, adenovirus, and enterovirus. Epididymitis can result in a severe inflammatory response regardless of the aetiology, which can induce subsequent scarring and obstruction of the epididymis.

Epididymal obstruction refers to the blockage of the epididymal duct, which hampers the transit of spermatozoa from the testes to the vas deferens. The obstruction disrupts the maturation and storage of sperm, leading to impaired sperm quality and motility. Figure 10.4 explains the aetiopathogenesis of MFI due to epididymal obstruction.

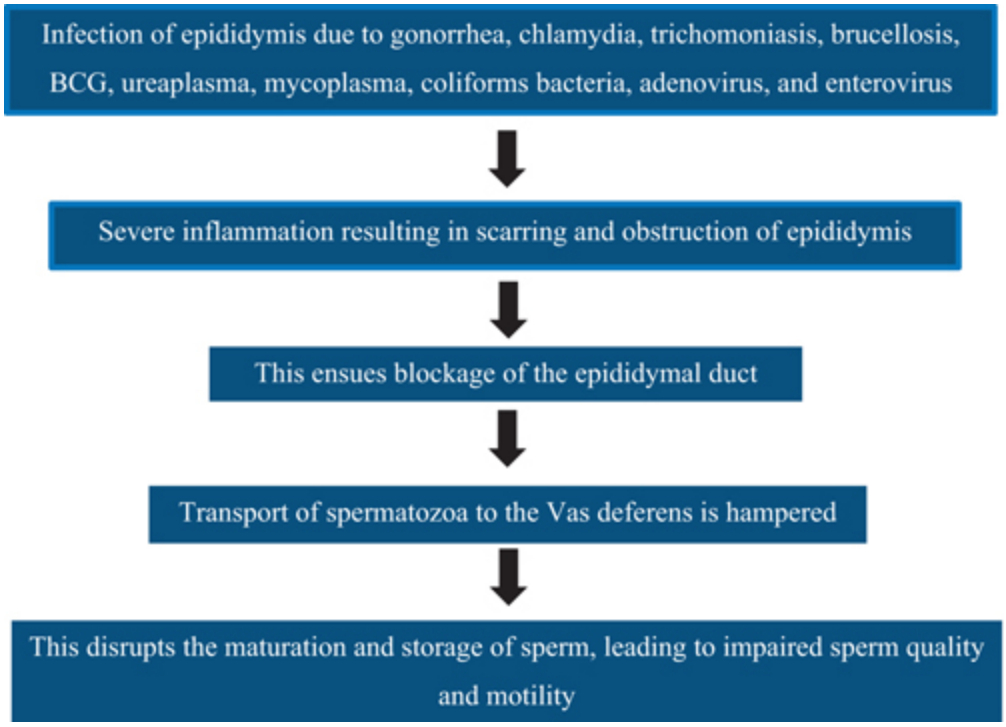


Figure 10.4 Aetiopathogenesis of male factor infertility due to epididymal obstruction.⏎

In 8%–46% of patients having vasal reconstruction in multiple large series, infection was put forth as the possible cause of OA. The post-infectious epididymal blockage is assumed to be uncommon in developed countries due to modern healthcare systems and avoidance of delays in treatments, but it may be a significant contributor in underdeveloped nations. An obstruction location may be indicated by a transition point and/or swollen or indurated epididymides found during a physical examination [14].

White cells are not always found in the urine or ejaculate outside of the acute infection period, and semen volumes are usually normal. When tuberculosis affects the prostate and seminal vesicles, the vas deferens may become nodular and swollen, and a low-volume ejaculate may be present.

An effective treatment for post-infectious epididymal blockage is scrotal exploration and microsurgical repair. Surgical procedures like microsurgical epididymal sperm aspiration (MESA) or percutaneous epididymal sperm aspiration (PESA) can retrieve sperm for use in ART, allowing infertile couples to achieve pregnancy [15].

Ejaculatory Duct Obstruction

About 1% of patients presenting with male infertility have EDO, an uncommon cause of OA. EDO occurs when there is a blockage in the ejaculatory duct, which carries sperm from the vas deferens to the urethra. It can result from congenital malformations, infections, or post-inflammatory scarring. The obstruction prevents the release of seminal fluid, impairing fertility.

When a patient has low-volume, acidic, sperm-free semen, the diagnosis of total EDO should be considered. Fructose is present in the secretions from the seminal vesicles; hence, the absence of fructose in the semen confirms the diagnosis. It is occasionally stated that ejaculation causes pain. The rectal examination is generally normal, but physical examination may show enlarged epididymis or a midline lump in the prostate.

Typically, in such patients, the vasa deferentia are present and the testicular volume is normal. Normal levels of gonadotropin and testosterone will be confirmed by laboratory tests. Nevertheless, by looking for sperm in the post-ejaculatory urine, retrograde ejaculation should be ruled out.

Transrectal ultrasound, MRI, seminal vesiculography, and cystoscopy are commonly employed to diagnose ejaculatory duct obstruction [4].

The prostate and other accessory sex organs can be seen clearly with an endocavitary ultrasound probe that operates at a frequency of 7–10 MHz. A diagnosis of EDO is made when the seminal vesicles are more than 1.5 cm dilated in the anteroposterior axis, and when the seminal vesicle aspirate contains 10 or more sperm per high-powered field. The patient should be told to ejaculate within the last 24 hours in order to help with the diagnosis. Additionally, sonography can show ejaculatory duct dilatation, calcifications inside the ejaculatory ducts, or a midline prostatic cyst, utricle, or Müllerian duct that may obstruct the ejaculatory ducts [16].

Surgical interventions, such as transurethral resection of the ejaculatory ducts (TURED) or transurethral incision of the ejaculatory ducts (TUIED), are performed to relieve the obstruction and restore fertility. This operation should ideally be performed in conjunction with a radiologist, where real-time TRUS images can be obtained to assess the depth of the cyst/resection. According to recent research, people with EDO may also benefit from vesiculoscopy combined with ejaculatory duct dilatation and/or calculi removal [16].

Non-obstructive Causes of MFI

Non-obstructive causes of MFI involve abnormalities in spermatogenesis, where the production of viable sperm is compromised. These causes encompass a range of conditions, including hormonal imbalances, genetic disorders, testicular dysfunction, and environmental factors. One in 100 men is predicted to be affected by NOA.

MFI due to NOA is typically regarded as an incurable condition, and up to 10% of all infertile men fall into this category. A number of these men have been successful in becoming parents using surgically harvested sperms from their testis, thanks to the development of IVF employing intracytoplasmic sperm injection (ICSI) as a routine treatment technique. However, the difficulty is to enhance their spermatogenic function and enable sperm to appear in their ejaculate or to increase the likelihood of a successful testicular retrieval for ICSI [17].

The initial assessment seeks to address the following problems:

1. Confirming azoospermia
2. Distinguishing obstructive from non-obstructive aetiology
3. Determining whether reversible variables are present
4. Determining whether any genetic abnormalities are present

Lack of typical spermatogenesis by testicular histology in the presence of azoospermia or an increased follicle-stimulating hormone (FSH) level is commonly accepted as sufficient proof of NOA. The most frequent reversible causes that have to be ruled out include recently administered exogenous hormones, having a severe febrile illness, receiving chemotherapy or radiation, or frequent use of antibiotics [18].

The cornerstone of the assessment and management of NOA includes hormone analysis by performing two crucial tasks (Table 10.1). The first is to identify a specific subset of men who have hypogonadotropism (low FSH), in which azoospermia is caused by insufficient gonadotropin activation of the testis. The treatment and outcome of infertility in these men vary from all other categories, and the innate spermatogenic ability of the testis may be partially recoverable. The second purpose is to forecast whether medicinal therapy and surgical sperm retrieval will be effective [18].

Table 10.1 Two Broad Categories of non-obstructive azoospermia (NOA) as a Result of Hormonal Imbalance⏎

Hypogonadotropic Hypogonadism	Hypergonadotropic Hypogonadism/Eugonadism
• Low FSH, Low LH, Low testosterone	• High/normal FSH, Normal/high LH, Normal/low testosterone
	• Congenital: Genetic abnormalities (Chromosomal)
• Congenital: Kallmann syndrome (hypothalamic GnRH deficiency)	• Acquired: Varicocele, orchitis, gonadotoxins (chemotherapy/radiation), trauma/torsion
• Acquired: Pituitary tumours	• Idiopathic

The two major classifications, hypogonadotropic hypogonadism (HH) and hypergonadotropic hypogonadism, or eugonadism, are based on these preliminary hormone tests. Men who do not have hypogonadotropism show significant overlap in their hormonal profiles, with related aetiologies causing a range of hormonal alterations.

As the initial hormonal evaluation, the American Urological Association suggests estimating serum FSH and testosterone levels [19]. Less than 3% of all occurrences of male infertility are caused by endocrine disorders, a rare cause. In accordance with the possibility of their abnormality and its management implications, additional hormone analysis, such as luteinizing hormone (LH), estradiol, and prolactin evaluations, is carried out [20].

Another conventional classification of NOA is based on the aetiology, i.e., pre-testicular or testicular origin (Figure 10.5). Pre-testicular NOA, also known as secondary hypogonadism, is a hormonal condition that prevents a physically normal testis from being efficiently stimulated to create sperm. It typically develops as a result of hypothalamic-pituitary abnormalities. Testicular azoospermia, also known as primary hypogonadism, refers to a testicular abnormality that impairs spermatogenesis [21].

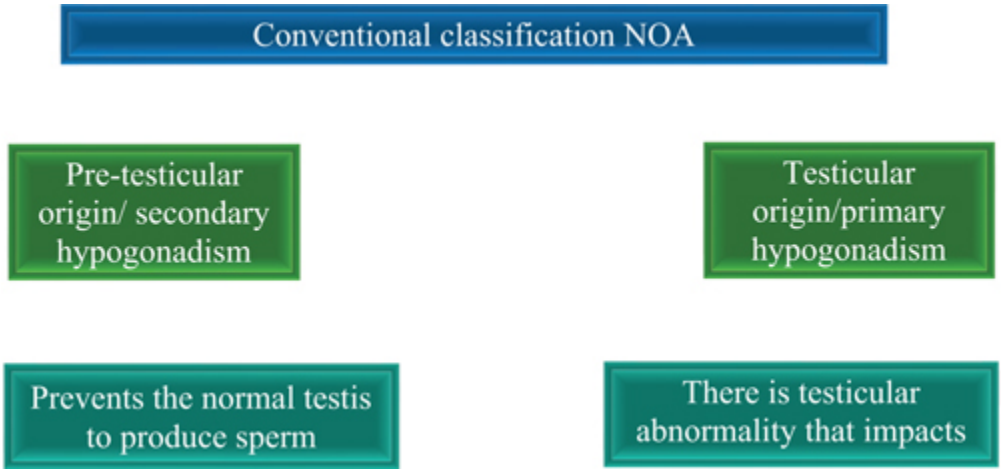


Figure 10.5 Classification of non-obstructive azoospermia (NOA) based on the origin.⏎

Figure 10.6 summarizes the pre-testicular and testicular causes of NOA and the hormonal profiles of men presenting with this form of MFI.

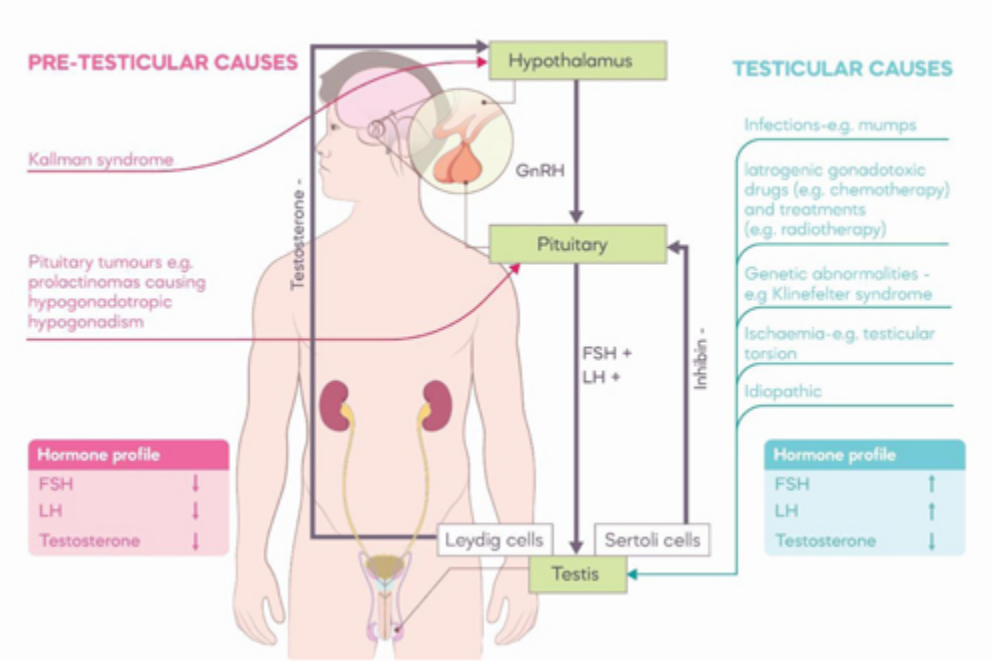


Figure 10.6 Causes of non-obstructive azoospermia (NOA) and the male reproductive hormone profiles of the affected men.⏎

(Image adapted from Tharakan T, Luo R, Jayasena CN, Minhas S. Non-obstructive azoospermia: current and future perspectives. *Fac Rev*. 2021 Jan 26; 10: 7) [21].

The histological characteristics of NOA are divided into the following types:

1. Sertoli-cell only (SCO)
2. Maturation arrest
3. Hypospermatogenesis

All stages of germ cell development in spermatogenesis are present in hypospermatogenesis, but in reduced numbers. When spermatogenesis is prevented due to maturation arrest, it stops at either the primary spermatocyte, secondary spermatocyte, or spermatid stage. Consequently, mature spermatozoa are typically lacking. A total loss of the germinal

epithelium results and it is a defining feature of SCO syndrome. It is important to recognize that diverse histological findings are typical in men with NOA.

Detection of Genetic Abnormalities in Men with NOA

Primary testicular failure characterizes the majority of NOA patients. When counselling and treating affected couples, genetic testing is recommended to assess for transmissible and health-relevant genetic lesions. Approximately 5% of men with NOA undergo cytogenetic analysis by karyotyping, with non-mosaic Klinefelter syndrome (47, XXY) being the most commonly identified abnormality. In addition to having a significant impact on sperm retrieval treatment choices, the diagnosis of Klinefelter syndrome puts affected men at higher risk for a variety of health issues, including osteoporosis, metabolic syndrome, type 2 diabetes, breast cancer, and extragonadal germ-cell tumours. Robertsonian translocations, reciprocal translocations, and chromosomal inversions have also been identified in azoospermic men [22].

Men who have NOA and primary testicular failure should also be tested for Y chromosome microdeletions. This testing is essential not only to counsel affected men about the risk of infertility in male offspring, but also to avoid unnecessary surgery in those with a very low likelihood of successful sperm retrieval. Men with NOA have more severe Y-chromosome microdeletions involving the complete AZFa and AZFb regions, which are associated with a very poor prognosis for sperm retrieval; therefore, they should not undergo unnecessary surgical sperm retrieval (SSR). However, men with AZFc microdeletions have transferable azoospermia, which may be passed on to their male offspring conceived through ART [23]. Hence, genetic testing and counselling are paramount.

In order to educate patients about the risks of HH in their offspring, genetic testing should also be considered in cases of NOA associated with congenital forms of HH. Numerous genes, notably those in the Kallman syndrome family – implicated in anosmic congenital hypogonadism – have been found to carry mutations. In one-third of cases, genetic lesions with

varied inheritance patterns can be identified. Preimplantation genetic testing for aneuploidy (PGT-A), which allows screening for unaffected embryos, offers clinicians the opportunity to counsel patients on the risks of HH in their children [24].

Management of NOA

Hormonal Optimization for Primary NOA

The pathogenesis of NOA may be influenced by low intratesticular testosterone levels and an altered testosterone-to-oestrogen ratio. It is therefore reasonable to consider that treatment aimed at improving the hormonal milieu for spermatogenesis may be beneficial. Men with NOA treated with the aromatase inhibitor letrozole have been reported to ejaculate sperm. A small number of non-randomized studies have suggested that such hormonal optimization may be effective. However, despite these indications in the literature, the available evidence – both in quantity and quality – is insufficient to support the routine use of hormonal optimisation therapy in clinical practice. [25].

Non-steroidal anti-oestrogens such as clomiphene citrate are well-established and generally safe agents that may be used empirically in the treatment of NOA [26]. By blocking the negative feedback of oestrogen at the hypothalamus and anterior pituitary, clomiphene citrate, a selective oestrogen receptor modulator, raises serum levels of LH, promoting spermatogenesis, and enhancing testosterone synthesis. According to a recent meta-analysis, anti-oestrogens can improve spermatogenesis in men with NOA [27]. Although anti-oestrogen therapy is sometimes referred to as an ‘empirical’ therapy, anti-oestrogen treatment requires careful monitoring of hormonal parameters, as individual responses in testosterone levels, spermatogenic activity, and duration of effect can vary significantly. While typically safe, anti-oestrogen therapy may occasionally produce negative effects. For example, elevated red blood cell counts may be seen, particularly in patients with supraphysiological serum testosterone levels (greater than 28–31 nmol/L).

NOA Associated with Hypogonadotropic Hypogonadism

The age at presentation and underlying aetiology are important considerations when developing therapeutic strategies for HH. Regardless of its aetiology, HH is one of the most medically treatable forms of NOA. In individuals with hypothalamic dysfunction but intact pituitary function, gonadotropin-releasing hormone (GnRH) therapy is as effective as gonadotropin therapy in inducing spermatogenesis and achieving pregnancy. Pulsatile administration of GnRH via a portable infusion pump – delivering 5–20 µg every two hours – is more commonly used than intravenous or intranasal delivery, due to improved convenience and patient adherence. Approximately 77% of initially azoospermic men treated with this regimen for 12 to 24 months achieved spermatogenesis. Men who were showing signs of puberty when GnRH medication was started often showed recovery within six months [28].

Recombinant FSH pretreatment enhances the effectiveness of GnRH therapy and may serve as an alternative to GnRH monotherapy. In current practice, pulsatile GnRH is probably used less frequently than gonadotropin therapy, owing to its inconvenience and limited efficacy in men with panhypopituitarism. Sperm production can begin following gonadotropin therapy with hCG, with or without FSH (recombinant, menopausal, or purified), typically within 3–6 months. To achieve a eugonadal state, a dose of 1,000–3,000 IU of hCG is administered two to three times per week.

Recombinant or highly purified FSH is typically initiated at 75 IU, administered two to three times per week, and may be increased by an additional 75 IU per dose after several months if spermatogenesis induction is insufficient. If spermatogenesis is not achieved after six months and sperm does not return to the ejaculate, this dosing schedule may be continued for longer.

In some men with congenital or acquired HH who might not have the pituitary function, an FSH injection is necessary to complete spermatogenesis. Men with idiopathic HH may also benefit from clomiphene citrate treatment. This inexpensive therapy requires an intact pituitary gland to be effective. Although evidence for clomiphene citrate use

has only been the subject of a single, short retrospective study, it should still be considered a potential alternative to the other treatments described above [25].

All existing studies are observational; there are no randomized controlled trials comparing gonadotropin treatment plans. A recent meta-analysis of men with HH and azoospermia examined the time to sperm production and the factors influencing response to gonadotropin and GnRH therapy. Medical treatment led to the appearance of at least one spermatozoon in the ejaculate in 75% of cases: 69%–81% for gonadotropins and 60%–85% for GnRH. Two predictors of better response to gonadotropin therapy included a postpubertal onset of HH and use of combination FSH/hCG therapy over hCG monotherapy [29].

Assisted Reproductive Technology (ART)

ART should be considered for men with HH who do not respond well enough to medical therapy to conceive naturally. Intrauterine insemination may be an option for some, while ejaculated sperm can be used for IVF or ICSI where available. If sperm is still absent from the ejaculate, sperm retrieval treatments should be considered. Although evidence is limited, a minimum of 6 months of hormonal therapy, coupled with increasing testicular volume and normalization of hormone levels, may be regarded as the therapeutic goals prior to attempting sperm retrieval.

Varicocele Management

Varicocele, which is seen in 4.3%–13.3% of men with significantly reduced spermatogenesis or azoospermia, continues to be the most prevalent form of male-factor infertility that can be corrected. A recent investigation of varicocele repair outcomes following microsurgical ligation or embolization in men with NOA revealed that 44% (151/344) of treated men had ejaculated sperm. Patients who have histological evidence of hypospermatogenesis will benefit the most from this treatment. Patients with NOA who have Sertoli cell-only syndrome or maturation arrest may respond less favourably to varicocele therapy. Varicocele grade, testicular

volume, and pretreatment FSH levels have all been found to be unreliable predictors of reproductive outcomes [30].

Conclusion

In about 20% of cases of infertility, the man is solely responsible, while in another 30%–40%, the man is a contributing factor. Overall, in around 50% of all cases of infertility, male factors significantly contribute. The causes of male factor infertility (MFI) include idiopathic cases – where semen parameters appear normal – in 10%–20% of men, and primary testicular defects – characterized by abnormal sperm parameters without an identifiable cause – in 65%–80%. Endocrine disorders (typically due to hypogonadism) are estimated to account for 2%–5% of MFI cases. Additional contributing factors may include age, medications, infections, cryptorchidism, prior surgical procedures, environmental exposure to chemicals, genetic abnormalities, and systemic illnesses.

When there are no associated female infertility problems, OA can often be successfully managed with microsurgical reconstruction of the reproductive tract, which is generally preferred over sperm retrieval and IVF/ICSI. However, when female partners have a rapidly declining ovarian reserve, coexisting infertility factors requiring IVF, or when secondary male infertility is also present, sperm retrieval (SSR) with IVF/ICSI is typically the most appropriate treatment for OA.

Currently, the primary strategy for achieving pregnancy in men presenting with NOA is through SSR followed by ART. Over the past decade, various attempts to extract spermatozoa more effectively have been made. It is now widely acknowledged that administering gonadotropins to NOA patients, aside from those with HH, is ineffective, especially in those with elevated plasma gonadotropin levels.

Although the precise mechanisms and potential outcomes of hormonal optimisation remain unclear, some cases of NOA may benefit from such treatment. One proposed mechanism is that exogenous gonadotropins increase intratesticular testosterone, thereby stimulating spermatogonia and promoting DNA synthesis and spermiogenesis in patients with residual

spermatogenic activity. Accordingly, early referral to a uroandrologist is essential to address the potentially treatable causes of NOA.

References

1. Hull MG, Glazener CM, Kelly NJ, Conway DI, Foster PA, Hinton RA, Coulson C, Lambert PA, Watt EM, Desai KM. Population study of causes, treatment, and outcome of infertility. *Br Med J (Clin Res Ed)*. 1985 Dec 14; 291(6510): 1693–1697.⏎
2. Krausz C, Riera-Escamilla A. Genetics of male infertility. *Nat Rev Urol*. 2018; 15(6): 369–384.⏎
3. Rowe PJ, Comhaire FH, Hargreave TB, *et al. WHO Manual for the Standardized Investigation and Diagnosis of the Infertile Male*. Cambridge, UK: Cambridge University Press; 2000.⏎
4. Kumar N, Singh AK. Trends of male factor infertility, an important cause of infertility: A review of literature. *J Hum Reprod Sci* 2015 Oct–Dec; 8(4): 191–196.⏎
5. Mascarenhas MN, Cheung H, Mathers CD, Stevens GA. Measuring infertility in populations: Constructing a standard definition for use with demographic and reproductive health surveys. *Popul Health Metr*. 2012; 10: 17.⏎
6. Calverton M. USA: ORC Macro and the World Health Organization. World Health Organization. Infecundity, Infertility, and Childlessness in Developing Countries. DHS Comparative Reports. 2004; 9. Available at: https://www.who.int/publications/m/item/infecundity-infertility-and-childlessness-in-developing-countries---dhs-comparative-reports-no.-9.⏎
7. Harris ID, Fronczak C, Roth L, Meacham RB. Fertility and the aging male. *Rev Urol*. 2011; 13: e184–e190.⏎

8. Wamoto TI, Nozawa S, Yoshiike M. Semen quality of Asian men. *Reprod Med Biol*. 2007; 6: 185–193.⏎
9. Baker K, Sabanegh Jr E. Obstructive azoospermia: reconstructive techniques and results. *Clinics*. 2013 Jan 1; 68: 61–73.⏎
10. Bieth E, Hamdi SM, Mieusset R. Genetics of the congenital absence of the vas deferens. *Human Genetics*. 2021 Jan; 140: 59–76.⏎
11. Schukfeh N, Kuebler JF, Schirg E, Petersen C, Ure BM, Glüer S. Dysplastic kidney and not renal agenesis is the commonly associated anomaly in infants with seminal vesicle cyst. *BJU Int.* 2009 Mar; 103(6): 816–819.⏎
12. Schlegel PN, Shin D, Goldstein M. Urogenital anomalies in men with congenital absence of the vas deferens. *J Urol*. 1996 May 1; 155(5): 1644–1648.⏎
13. Mieusset R, Bieth E, Daudin M, Isus F, Delaunay B, Bujan L, *et al.* Male partners of infertile couples with congenital unilateral absence of the vas deferens are mainly non-azoospermic. *Andrology* 2020; 8(3): 645–653.⏎
14. Schiff J, Chan P, Li PS, Finkelberg S, Goldstein M. Outcome and late failures compared in 4 techniques of microsurgical vasoepididymostomy in 153 consecutive men. *J Urol*. 2005; 174(2): 651–655.⏎
15. Ho KL, Wong MH, Tam PC. Microsurgical vasoepididymostomy for obstructive azoospermia. Hong Kong Med J. 2009; 15(6): 452–457.⏎
16. Wang H, Ye H, Xu C, Liu Z, Gao X, Hou J, *et al.* Transurethral seminal vesiculoscopy using a 6F vesiculoscope for ejaculatory duct obstruction. *J Androl*. 2012; 33(4): 637–643.⏎
17. Kumar R. *Medical management of non-obstructive azoospermia*. *Clinics*. 2013; 68: 75–79.⏎

18. Chiba K, Enatsu N, Fujisawa M. Management of non-obstructive azoospermia. *Reprod Med Biol*. 2016 Jan 18; 15(3): 165–173.⏎
19. American Urological Association. The optimal evaluation of the infertile male. Accessed February 22, 2012. Available from: http://www.auanet.org/content/media/optimalevaluation2010.pdf.⏎
20. Schoor RA, Elhanbly S, Niederberger CS, Ross LS. The role of testicular biopsy in the modern management of male infertility. *J Urol*. 2002; 167(1): 197–200.⏎
21. Tharakan T, Luo R, Jayasena CN, Minhas S. Non-obstructive azoospermia: current and future perspectives. *Fac Rev*. 2021 Jan 26; 10: 7.⏎
22. Martin R.H. Cytogenetic determinants of male fertility. *Hum Reprod Update*. 2008; 14: 379–390.⏎
23. Stahl PJ, Masson P, Mielnik A, Marean MB, Schlegel PN, Paduch DA. A decade of experience emphasizes that testing for Y microdeletions is essential in American men with azoospermia and severe oligozoospermia. *Fertil Steril*. 2010 Oct 1; 94(5): 1753–1756.⏎
24. Young J. Approach to the male patient with congenital hypogonadotropic hypogonadism. *J Clin Endocrinol Metab*. 2012; 97: 707–718.⏎
25. Practice Committee of the American Society for Reproductive Medicine. Management of nonobstructive azoospermia: a committee opinion. *Fertil Steril*. 2018 Dec 1; 110(7): 1239–1245.⏎
26. Hussein A, Ozgok Y, Ross L, Rao P, Niederberger C. Optimization of spermatogenesis-regulating hormones in patients with non-obstructive azoospermia and its impact on

sperm retrieval: a multicentre study. *BJU Int.* 2013; 111: 110–114.⏎
27. Chua ME, Escusa KG, Luna S, Tapia LC, Dofitas B, Morales M. Revisiting oestrogen antagonists (clomiphene or tamoxifen) as medical empiric therapy for idiopathic male infertility: a meta-analysis. *Andrology* 2013; 1: 749–757.⏎
28. Pitteloud N, Hayes FJ, Dwyer A, Boepple PA, Lee H, Crowley Jr WF. Predictors of outcome of long-term GnRH therapy in men with idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab*. 2002; 87: 4128–4136.⏎
29. Rastrelli G, Corona G, Mannucci E, Maggi M. Factors affecting spermatogenesis upon gonadotropin-replacement therapy: a meta-analytic study. *Andrology* 2014; 2: 794–808.⏎
30. Esteves S.C, Miyaoka R, Roque M, Agarwal A. Outcome of varicocele repair in men with nonobstructive azoospermia: systematic review and meta-analysis. *Asian J Androl*. 2016; 18: 246–253.⏎

11 Clinical Assessment of Male Factor Infertility

Chloe Mount and Philippa Sangster

DOI: 10.1201/b22940-11

Introduction

One in seven heterosexual couples experiences infertility [1]. This is defined as involuntary childlessness after 1 year of regular unprotected vaginal intercourse. In 30% of these couples, the cause will be male factor infertility (MFI) [1], although MFI will contribute to the couple's childlessness in 50% of cases, due to a mixture of male and female factors [2, 3].

It is important that the couple are investigated together, taking in to account the female partner's age and ovarian reserve. If a male factor is identified, this should be investigated by a specialist service. While in 30%–40% of cases no cause will be identified for impairment in semen parameters [2], impaired parameters can be a sign of poor male health and therefore any reversible factors need to be investigated and managed [2, 3]. Identifying the cause of infertility can help tailor management, aid counselling for couples about their chances of success and identify potential issues for any offspring for the couple.

The main aims of investigating and treating MFI are to identify any treatable underlying cause, counsel the couple about their chances of spontaneous pregnancy, downgrade the need for assisted reproductive techniques (ART) and improve the chances if ART is required.

Men who are referred to andrology services typically fall into three categories:

1. Abnormal semen parameters
2. Azoospermia (obstructive vs non-obstructive)
3. Normal semen parameters with unexplained infertility

Where a single semen analysis has shown poor parameters, it must always be repeated [1]. Semen parameters can be affected by systemic illness (including infection with SARS-CoV-2), urinary tract infections and environmental factors [4].

There is emerging evidence that male fertility declines with age, and this should be taken in to account when investigating the couple [5].

Clinical History

Taking a thorough history from the couple helps to identify areas that need further thought and investigation. This can broadly be divided into the following categories: Information about the couple, past medical history of the male partner and lifestyle factors.

Information About the Couple

How long have the couple been trying to conceive?

It is important to establish how long the couple have been trying to conceive and any investigation or treatment they have received to date. The clinician should ascertain that there is a basic understanding from the couple on when ovulation occurs and that sexual intercourse is being carried out correctly to achieve fertilisation.

How old is the female partner?

The most pertinent piece of information is the age of the female partner. This will have implications for managing the couple's fertility. If the female partner is younger, then it is more likely that there is time for prolonged investigation and treatment. However, the male investigation should be synchronously carried out with the female and the gynaecology team to investigate her ovarian reserve for a better indication of time urgency.

Each intervention will take time to have an effect on semen parameters (the lifespan of a sperm is 72 days) [6], and if the female partner is older, then moving forward with ART might be in the couple's best interest [7].

Have they been referred for in vitro fertilization?

The couple should seek referral for in vitro fertilization (IVF) at an early stage. This process can be time consuming, lead to delay in treatment and should not be left until investigation of male factors have been completed.

Do they have other children?

Has either of the couple had children previously. This gives information about fertility potential, as well as having an impact on NHS funding.

Past Medical History

Are there any significant medical problems which could impact fertility?

Many medical conditions can have an effect on the hypothalamic–pituitary–gonadal (HPG) axis and therefore impact spermatogenesis. Examples of this include prolactinomas, renal failure, hypothyroidism and systemic illness such as coeliac disease, rheumatoid arthritis and systemic lupus erythematosus. Spermatogenesis is a reflection of male health and therefore can be affected by any systemic illness [8]. Recurrent chest infections may raise the possibility of the male being a carrier of a cystic fibrosis transmembrane conductance regulator (CFTR) gene mutation. Neurological diseases can affect erectile function and ejaculation.

Have any medications been administered that might have a deleterious effect on spermatogenesis?

Drugs can affect fertility through a number of mechanisms [9]:

- Impact on HPG axis
- Direct effect on spermatogenesis
- Interfere with erectile function

- Cause ejaculatory dysfunction

In most cases, the impact of medication on spermatogenesis is reversible and the clinician should consider if it is safe to stop the medication, or if there is an alternative medication available. This may mean involving other specialists for advice. If a medication is going to be started that is known to have serious long term negative effects on spermatogenesis (for example, chemotherapy), cryopreservation should be considered prior to starting treatment.

Table 11.1 provides a few examples of medications that can impact fertility.

Table 11.1 Examples of medications that impact fertility ⏎

Drug Type	Examples	Impact
Immunosuppression	MTOR inhibitor (sirolimus)	Impact on spermatogenesis (all semen parameters) and downregulation of HPG axis
Opiates	Morphine, cocaine	Impact on spermatogenesis (all semen parameters) and downregulation of HPG axis
Exogenous testosterone, including anabolic steroids	Testogel, Nebido	Downregulation of HPG axis
5-alpha-reducatase inhibitors	Finasteride	Decreased ejaculated volume, decreased sperm count
Alpha blockers	Tamsulosin	Impact on spermatogenesis (all parameters), retrograde ejaculation
SSRI	Fluoxetine, paroxetine	Impact on spermatogenesis (all parameters), increased DNA fragmentation
Valproate (antiepileptic)	Sodium valproate	Impact on spermatogenesis (all parameters), increase androgen level
Alprostadil	Caverject	Crosses into semen

Source: Semet M, Paci M, Saias-Magnan J, Metzler-Guillemain C, Boissier R, Lejeune H & Perrin J. The impact of drugs on male fertility: a review. *Andrology*. 2017. 5(4):640–663.

Is there any history of testicular problems?

It is important to establish if there is any congenital or acquired testicular problems that would impact fertility. These can cause decreased spermatogenesis, obstruction or anti-sperm antibodies that can impact on fertility:

Cryptorchidism: Boys who have unilateral cryptorchidism have an almost normal fertility potential. However, for those with bilateral undescended testes, oligospermia can be found in 31% and azoospermia in

42% of cases, with the paternity rate falling from 93.7% in normal men to 35%–53% [2, 10].

- Testicular tumours
- Significant testicular injury (e.g., testicular torsion)
- Previous operations within the groin or scrotum (examples include orchidopexy for torsion, hydrocele repairs or removal of epididymal cysts or hernia operations)
- Infections (it is important to ask about mumps, sexually transmitted infections and episodes of epididymo-orchitis)

Are there any problems with the urinary tract indicating a potential issue?

Enquiring about urinary tract symptoms is important to establish if there is a reversible cause of infertility:

- Signs of bladder outflow obstruction
- Infection (acute infection, recurrent infections, prostatitis, epididymo-orchitis)
- Previous surgical treatment of the urinary tract or medications (such as tamsulosin)

Is sexual function normal?

Erectile dysfunction can occur as a result of hypogonadism, as a sign of poor male health or as a result of stress due to problems conceiving. If underlying causes have been ruled out, a phosphodiesterase 5 inhibitor can be prescribed to aid erectile function.

- Problems with ejaculation: This can occur secondary to spinal problems, retroperitoneal surgery, nerve injury or a result of medication.
- Volume of ejaculation: If the ejaculated volume is low, they should be asked about their post-ejaculatory urine to determine if there is evidence of retrograde ejaculation.

Social Factors

What is the occupation of the male partner?

Occupation has an impact on lifestyle (how active they are on a daily basis), heat exposure and exposure to environmental toxins. It may also have an impact on compliance with investigation and management should the need arise [11].

Is the male partner a smoker?

There is a clear negative association between smoking and sperm parameters [12]. Therefore, it is important to establish whether the male partner is a smoker, and if they have quit, how long ago this happened. Smoking may also have an impact on eligibility for NHS-funded IVF as it is often included in the local criteria. Men should be referred to smoking cessation services if appropriate.

Based on the current available evidence, it is very likely that the use of e-cigarette vaping has a deleterious effect on sperm production. Further studies are ongoing to definitively answer this question [13].

Is alcohol drunk to excess?

It is thought that moderate alcohol intake does not negatively impact semen parameters [14]. However, heavy long term ethanol consumption can cause hypogonadism, which can impede spermatogenesis [15]. This is reversible through alcohol cessation, and the male partner should be counselled to keep alcohol consumption within recommended Department of Health limits [15].

Are any illicit drugs being used?

Many illicit drugs can have an impact on fertility – for example, cannabis [16] and opiates (see Table 11.1). Some men use anabolic steroids to help build muscle when visiting the gym. It is important to ask about this directly, as otherwise it is unlikely to be disclosed.

Are gym supplements being used?

Gym supplements in the form of protein powders are largely unregulated. A portion of them contain anabolic steroids. They may also contain other products that can have a detrimental effect on spermatogenesis [17].

Is there heat exposure to the testicles?

Enquiries should be made about heat exposure to the testicles. This can include heated car seats, laptops placed on the lap and repeated hot baths or

saunas. Increased temperatures can cause oxidative stress and DNA damage. NICE guidelines support informing men that elevated scrotal temperature can reduce sperm quality [2, 18].

Is the male partner overweight?

Obesity can cause secondary hypogonadism and therefore impact on male fertility. It is important for the general health of the male partner to encourage a healthy lifestyle, including regular exercise, a healthy diet and maintaining a healthy weight [1, 2]. Regular moderate to high intensity physical activity can result in better semen parameters and improve hormonal profile [19]. BMI should be calculated, as NICE guidelines suggest that men with a BMI of >30 should be informed that they may have impaired fertility [1]. The consultation can be used as an opportunity to encourage overall healthy living for both partners.

Examination

Once the pertinent points of history have been explored, the consultation should continue with an examination to elicit further areas for investigation. This can be considered in 2 parts: a general examination of the patient and a focused urological and genital examination.

General Examination

Weight and body habitus

Secondary sexual characteristics

The male partner should be examined for pubic hair, voice changes and muscle distribution (this should also take into account penile and testicular size). Men should also be checked for gynecomastia. If there is a deficit of secondary sexual characteristics, particularly in the presence of gynecomastia, then it raises the possibility of Klinefelter's syndrome or other causes of hypogonadism.

Genital Examination

Testicles

Testicular size can be estimated clinically, measured with a Prader's orchidometer or measured on ultrasound scan. The mean volume in the general population using Prader's orchidometer is 20.0ml ± 5.0ml [2]. If there is any concern about the texture or the presence of abnormal lumps within the testicles, an urgent ultrasound scan should be arranged.

Epididymides

The epididymis should be examined to determine if it feels full and congested. This may be unilateral or bilateral. Nodules may be palpated in the epididymis or vas deferens.

Causes of obstruction include intra-testicular obstruction, CBAVD, other causes of congenital epididymal obstruction (Young's syndrome), acquired epididymal obstruction (secondary to epididymitis), trauma, surgical intervention (e.g., vasectomy, hernia repair), ejaculatory duct obstruction (cyst, calculi, post inflammatory) or functional obstruction of the distal seminal ducts.

Vasa Deferentia

The vas deferens should be palpated bilaterally. It can be confused clinically with blood vessels and therefore, if there is any doubt, an ultrasound scan should be obtained. Congenital unilateral absence of the vas deferens (CUAVD) can be associated with ipsilateral seminal duct anomalies or renal agenesis. If there is absence of the vas deferens bilaterally then congenital bilateral absence of the vas deferens (CBAVD) should be diagnosed. Patients should be investigated with a scrotal ultrasound scan, a transrectal ultrasound scan, and screened for mutations in the CFTR gene.

Approximately 2,000 mutations of the CFTR gene have been identified. Alterations in this gene can lead to CBAVD (while patients with homozygous mutations exhibit cystic fibrosis) [20]. It is not possible to test for all the mutations. Therefore, tests are carried out for the common mutations (which can vary based on ethnicity). This means that some patients with CBAVD will have negative CFTR screens but may still be carriers of rare mutations [2].

Varicocele

Varicoceles are present in approximately 15% of the normal male population, in 25% of men with abnormal semen analysis and in 35%–40% of men presenting with infertility [2]. Men should be examined lying and standing in a warm room. A Valsalva manoeuvre should be performed to determine if there is augmentation with an increase in intra-abdominal pressure. The grade of the varicocele should be documented:

Subclinical: not palpable or visible at rest or during Valsalva, but can be seen on ultrasound scan

Grade 1: Palpable during Valsalva
Grade 2: Palpable at rest
Grade 3: Visible and palpable at rest

Penis

Abnormalities of the penis may contribute to sexual dysfunction (e.g., phimosis or tight frenulum, Peyronie's disease) or may give clues about underlying conditions (hypospadias is associated with testicular dysgenesis syndrome (TDS) or epispadias associated with obstruction). The size of the penis should be taken into account when considering secondary sexual characteristics.

Investigation

The need for further investigation will be indicated by findings from the history and examination. Investigations include semen analysis, semen and urine cultures, hormone profiles, genetic blood tests and imaging (usually in the form of ultrasound scan).

Semen Analysis

Have there been two abnormal samples 3 months apart?

NICE guidelines suggest a confirmatory test 3 months after the initial analysis if the initial semen analysis is abnormal [1].

It is important to ensure that the sample is collected in the correct manner, with a short period of abstinence (2–3 days) and delivered to the lab within 1 hour of collection. The sample should be kept in a pocket close to patient's body during transport to the laboratory. Any spillages should be reported. The sample should be analysed as per the WHO *Laboratory Manual for the Examination and Processing of Human Semen* (6th edition) and the WHO reference ranges for lower reference limit should be used [8].

How should the semen analysis be interpreted?

Volume: A low semen volume (<1.4 ml) [8] may be an indication of distal obstruction or retrograde ejaculation. It is important to clarify whether any of the sample was spilled. If there is a possibility of retrograde ejaculation, the patient should be asked if there is any evidence of semen in their immediate post ejaculation void (i.e., cloudy urine) and a post-ejaculation urine analysis should be performed.

pH: Obstruction may result in a low pH (<7.2) [8]. If the pH is low then the fructose level (reference range ≥13) [8] may give clues about the level of obstruction. A low fructose can indicate obstruction at the level of the ejaculatory duct. There may be an indication for a TRUS biopsy with these findings.

Concentration and total sperm number: The sperm concentration should be >16x10^6/mL [8] and the total sperm number should be >39 ×10^6 [8]. If these numbers are low then the male partner is said to have oligozoospermia. If the sperm concentration is below 5×10^6/mL then this is considered to be severe oligozoospermia [2].

Motility: Sperm motility can be described either as progressive or non-progressive. The progressive motility of the sperm in the sample should be >30% [8] and the total motility (combining progressive and non-progressive motility) should be >42% [8]. If the motility falls below this level, then the patient is said to have asthenozoospermia.

Morphology: Abnormal appearance of the sperm is often due to head defects or tail defects. If <4% [8] of the sperm have normal forms then the patient is said to have teratozoospermia.

Should we measure sperm DNA fragmentation?

There are various methods available to measure DNA fragmentation of semen samples. This is an accumulation of single-strand and double-strand DNA breaks. It is thought that high levels of DNA fragmentation correlate to worse outcomes with ART [21]. However, further evidence is needed. DNA fragmentation is thought to be increased by several factors, including varicoceles, infection, hormonal abnormalities and lifestyle factors [2]. As these can be identified and treated, and there is no direct treatment for DNA fragmentation, in most centres this test is not offered on the NHS.

Semen and Urine Culture

Should semen and urine culture be routinely tested?

Urine and semen culture should only be performed if there is a clinical indication. This will be elicited during the history or the examination. The other indication for performing cultures is a peroxidase-positive leukocyte level of $>1.0\times10^6$ [2].

Urethritis, prostatitis, orchitis and epididymitis are potentially curable causes of male infertility.

A screen for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* should be performed if there are risk factors.

Male partners should only be treated for infection with antibiotics if this is proven on culture. There is no current evidence for empirical treatment of inflammation seen on semen analysis [1, 22].

Blood Tests

Hormones

Hormonal blood tests are useful in the diagnosis of primary or secondary hypogonadism, as well as differentiation between obstructive or non-obstructive azoospermia.

Hormone blood tests should be taken in all male partners with concerns about fertility. A fasted serum testosterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH) should be taken before 11 a.m. [2].

Hormone levels fluctuate throughout the day, with testosterone at its highest in the morning.

The lab reference range for normal total testosterone varies depending on the laboratory but is normally set at around 8 nmol/L.

If the testosterone level is low, especially in the context of hypogonadotropic hypogonadism, then a serum prolactin should be requested to rule out a prolactinoma.

FSH is often high when spermatogonia are absent or markedly diminished; however, FSH does not reliably predict the presence of spermatogenesis for patients undergoing surgical sperm retrieval [23].

Hormone levels can give an indication as to the cause of male infertility as indicated in Figure 11.1. In patients with obstruction, the hormone profile is likely to be normal.

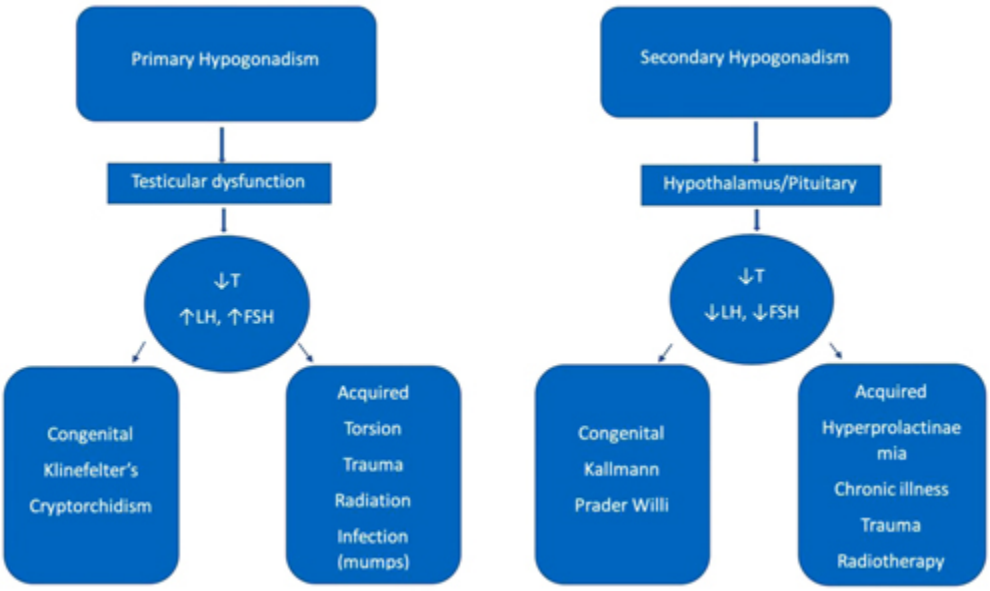


Figure 11.1 Hormone profile in hypogonadism.⏎

Genetic Tests

The current EAU recommendations are that a threshold sperm concentration of $<10x10^6$/mL should be used to indicate the need for further genetic evaluation [24]. However, this is thought to have a low

sensitivity and specificity [2]. Therefore, many centres adopt a cut-off of $<5 \times 10^6$/mL as this is thought to be more cost effective. There is emerging evidence that a lower cut-off is unlikely to miss a significant number of abnormalities and save money for the couple by performing fewer tests; however, further evidence is needed before this is reflected in the guidelines. Sperm concentrations of more than 1×10^6/ml are unlikely to reflect any genetic abnormality [25].

Genetic screening is currently used to prevent passing on genetic abnormalities to the next generation:

- *Karyotyping to detect chromosomal abnormalities* (*numerical or structural*):
- Chromosomal abnormalities can either be numerical (e.g., trisomy) or structural (e.g., inversions or translocations). The most common (and clinically relevant) sex chromosome abnormality that is detected is Klinefelter syndrome and its variants (47, XXY or 46, XY/47, XX mosaicism) [2]. These patients often have impaired Leydig cell function and may present with hypogonadism [26].
- Ongoing follow-up is required with a specialist service trained in the care of Klinefelter syndrome, as there are implications for ongoing health (e.g., metabolic disease, cardiovascular disease and increased risk of venous thromboembolism) [27]. Sperm can be retrieved in a portion of these patients and can be used for ART. There is no difference in prevalence of aneuploidy in offspring of these patients compared to the general population [2].
- *Screening for common mutations of the CFTR gene*: Carriers of CFTR gene mutations can pass these on to their offspring. The female partner must be screened, and if she is a carrier the couple should be informed that there is a 50% chance of their offspring having cystic fibrosis or CBAVD (depending on the mutation present) [2]. In vitro fertilisation and pre-implantation genetic testing can be used in these couples to decrease the risk.
- *Screening for microdeletions of the Y chromosome azoospermia factor* (*AZF*) *regions* (*AZFa, AZFb and AZFc*): The AZF region is found on the long arm of the Y chromosome [28]; this region contains genes involved in the regulation of spermatogenesis [29]. It is not possible to determine the impact of each gene and therefore regions are defined where partial or complete deletion en-block has a clinical implication. Deletion of the AZFa region is associated with Sertoli cell only syndrome and deletion of the AZFb region is associated with spermatogenic arrest. In both these cases no sperm will be found during surgical sperm retrieval, and this should not be offered [2, 30]. Deletions of AZFc have a variable phenotype ranging from oligozoospermia to azoospermia [2]. Sperm can be found in approximately 50%–75% of men with AZFc microdeletions [2, 31]. They should be informed that their male offspring will have the same microdeletion.

Genetic counselling should be offered whenever there is a genetic condition that will have an implication for any potential offspring. As outlined above,

this includes patients with Klinefelter syndrome, cystic fibrosis carriers and patients with AZF microdeletions. Other genetic conditions may also trigger a referral to a genetic counselling service, especially if pre-implantation diagnosis is important (Figure 11.2).

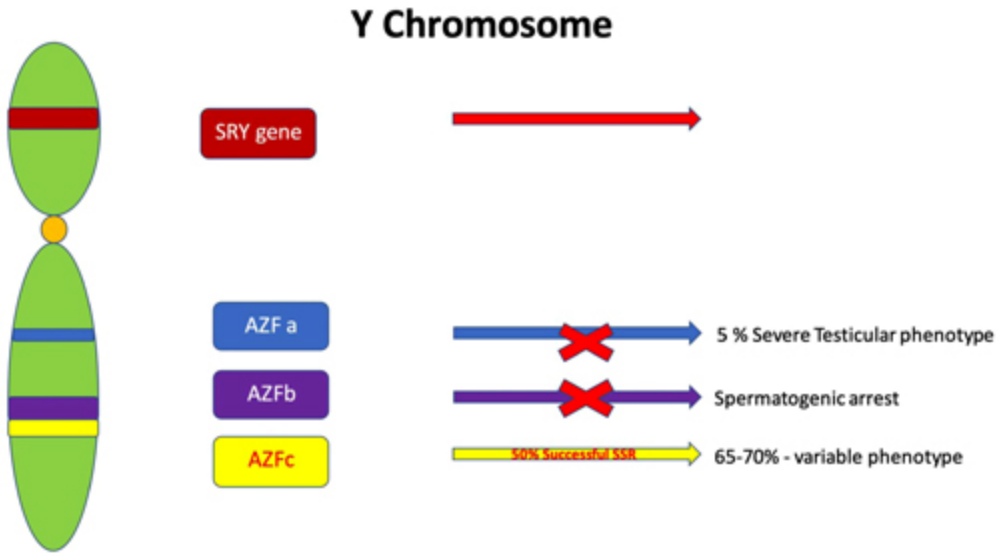


Figure 11.2 Summary of genetic investigation.⏎

Virology

Hepatitis B, hepatitis C and HIV should be tested for in an accredited laboratory if there is a possibility of cryopreservation. Most laboratories do not offer storage of sperm for men with positive virology, as samples need to be stored separately to avoid cross-contamination. However, there are specialised laboratories that offer this facility, and readers should make themselves aware of their local centre.

Imaging

When should an ultrasound scan of the scrotum be considered?

An ultrasound of the scrotum may be indicated if the clinical examination is inconclusive or an abnormality is detected. It can be useful in measuring testicular volume, assessing anatomy and detecting signs of testicular

dysgenesis. Ultrasound can be used to assess for reflux in clinical varicoceles and to monitor response to treatment.

EAU guidelines suggest performing scrotal ultrasound in patients with infertility as there is a higher risk of testis cancer [2]. Finding a testicular lesion will have implications for sperm retrieval; for example, an onco-TESE may need to be performed.

When should a transrectal ultrasound scan be considered?

Transrectal ultrasound scan is indicated if there is a suggestion of partial or complete obstruction [2]. The suggestive findings of this are: absent vas deferens, low volume, low fructose, acidic semen and normal hormone blood tests.

Are any other imaging modalities used?

The need for further imaging might be suggested from the history, examination or from abnormalities detected through investigation. These may include flow rate and post void residual, US kidneys, ureter and bladder, CT urogram or MRI scans.

Conclusion

A thorough history and examination will lead to a tailored approach of investigation. The couple should be counselled throughout about the implications of the findings. Early referral for ART is recommended, especially if the female partner is more than 35 years old. It is important to start early discussions about alternatives, such as donor sperm and adoption, as these may be viable alternatives for some couples.

References

1. National Institute for Health and Care Excellence. Fertility problems: assessment and treatment [CG156]. 2017. https://www.nice.org.uk/guidance/cg156 [accessed 27th August 2022].⏎

2. European Association of Urology. EAU Guidelines on Sexual and Reproductive Health. 2022. https://uroweb.org/guidelines/sexual-and-reproductive-health [accessed 27th August 2022].⏎
3. WHO, *WHO Manual for the Standardized Investigation and Diagnosis of the Infertile Couple*. 2000, Cambridge University Press: Cambridge.⏎
4. Nassau DN, Best JC, Kresch E, Gonzalez AC, Khodamoradi K & Ramasay R. Impact of the SARS-CoV-2 virus on male reproductive health. *BJU Int*. 2021. 129(2):143–150.⏎
5. Brandt JS, Cruzithier MA, Rosen T & Ashkinadze E. *Advanced paternal age, infertility, and reproductive risks: A review of the literature*. *Prenat Diagn*. 2019. 39(2):81–87.⏎
6. *Amann RP. The cycle of the seminiferous epithelium in humans: a needs to revisit? J Androl*. 2008. 29(5):469–487.⏎
7. Heffner LJ. Advanced maternal age: How old is too old. *N Engl J Med*. 2004. 351(19):1927–1929.⏎
8. WHO. WHO laboratory manual for the examination and processing of human semen Sixth edition. 2021. https://www.who.int/publications/i/item/9789240030787 [accessed 27th August 2022].⏎
9. Semet M, Paci M, Saias-Magnan J, Metzler-Guillemain C, Boissier R, Lejeune H & Perrin J. The impact of drugs on male fertility: a review. *Andrology*. 2017. 5(4):640–663.⏎
10. Lee PA, O'Leary LA, Songer NJ, Coughlin MT, Bellinger MF & LaPorte RE. Paternity after bilateral cryptorchidism. A controlled study. *Arch Pediatr Adolesc Med*. 1997. 151(3):260–263.⏎
11. Thonneau P, Bujan L, Multigner L & Mieusset R. Occupational heat exposure and male infertility: a review. *Human Reprod*. 1998. 13(8):2122–2125.⏎

12. Sharma R, Harlev A, Agarwal A & Esteves SC. Cigarette smoking and semen quality: a new meta-analysis examining the effect of the 2010 world health organization laboratory methods for the examination of human semen. *Eur Urol*. 2016. 70(4):635–645.⏎
13. Szumilas K, Szumilas P, Grzywacz A & Wilk A. The effects of E-cigarette vapor components on the morphology and function of the male and female reproductive systems: a systematic review. *Int J Environ Res Public Health*. 2020. 17(17):6152.⏎
14. Ricci E, Al Beitawi S, Cipriani S, Candiani M, Chiaffarino F, Vigano P, Noli S & Parazzini F. *Semen quality and alcohol intake: a systematic review and meta-analysis*. *Reprod Biomed Online*. 2017. 34(1):38–47.⏎
15. Muthusami KR & Chinnaswamy P. Effect of chronic alcoholism on male fertility hormones and semen quality. *Fertil Steril*. 2005. 84(4):919–924.⏎
16. Payne KS, Mazur DJ, Hotaling JM & Pastuszak AW. Cannabis and male fertility: a systematic review. *J Urol*. 2019. 202(4):674–681.⏎
17. Ketheeswaran S, Haahr T, Povlsen B, Laursen R, Alsbjerg B, Elback H, Esteves SC & Humaidan P. Protein supplementation intake for bodybuilding and resistance training may impact sperm quality of subfertile men undergoing fertility treatment: a pilot study. *Asian J Andrology*. 2019. 21(2):208–211.⏎
18. Durairajanayagam D, Agarwal A & Ong C. Causes, effects and molecular mechanism of testicular heat stress. *Reprod Biomed Online*. 2015. 30(1):14–27.⏎
19. Ibanez-Perez J, Santos-Zorrozua B, Lopez-Lopez E, Matorras R & Garcia-Orad A. An update on the implication of physical activity on semen quality: a systematic review and meta-analysis. *Arch Gynecol Obstet*. 2019. 299(4):901–921.⏎

20. Schlegel PN, Shin D & Goldstein M. Urogenital anomalies in men with congenital absence of the vas deferens. *J Urol*. 1996. 155(5):1644–1648.⏎
21. Simon L, Emery B & Carrel DT. Sperm DNA Fragmentation: Consequences for Reproduction. *Adv Exp Med Biol*. 2019. 1166:87–105.⏎
22. Jung JH, Ha Kim M, Kim J, Baik SK, Koh S-B, Park HJ & Seo JT. Treatment of leukocytospermia in male infertility: a systematic review. *World J Mens Health*. 2016. 34(3):165–172.⏎
23. Martin-du-Pan RC & Bischof P. *Increased follicle stimulating hormone in infertile men. Is increased plasma FSH always due to damaged germinal epithelium? Hum Reprod.* 1995. 10(8):1940–1945.⏎
24. Vincent MC, Daudin M, Philippe De M, Massat G, Mieusset R, Pontonnier F, Calvas P, Bujan L & Borrouillout G. Cytogenetic investigations of infertile men with low sperm counts: a 25-year experience. *J Androl*. 2002. 23(1):18–22.⏎
25. Johnson M, Raheem A, De Luca F, Hallerstrom M, Zainal Y, Poselay S, Mohammadi B, Moubasher A, Johnson TF, Muneer A, Sangster P & Ralph D. An analysis of the frequency of Y-chromosome microdeletions and the determination of a threshold sperm concentration for genetic testing in infertile men. *BJU Int*. 2019. 123(2):367–372.⏎
26. Pozzi E, Boeri L, Capogrosso P, Palmisano F, Preto M, Sibona M, *et al*. Rates of hypogonadism forms in Klinefelter patients undergoing testicular sperm extraction: A multicenter cross-sectional study. *Andrology*. 2020. 8(6):1705–1711.⏎
27. Calogero AE, Giagulli VA, Mongioi LM, Triggiani V, Radicioni AF, Jannini EA, Pasquali D & Klinefelter ItaliaN Group (KING). Klinefelter syndrome: cardiovascular

abnormalities and metabolic disorders. *J Endocrinol Invest*. 2017. 40(7):705–712.⏎
28. Skaletsky H, Kuroda-Kawaguchi T, Minx PJ, Cordum HS, Hillier L, Brown LG, *et al*. The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. *Nature*. 2003. 423(6942):825–837.⏎
29. Vogt PH, Edelmann A, Kirsch S, Henegariu O, Kirschmann P, Kieswetter F, *et al*. Human Y chromosome azoospermia factors (AZF) mapped to different subregions in Yq11. *Hum Mol Genet*. 1996. 5(7):933–943.⏎
30. Hopps CV, Mielnik A, Goldstein M, Palermo GD, Rosenwaks Z & Schlegel PN. Detection of sperm in men with Y chromosome microdeletions of the AZFa, AZFb and AZFc regions. *Hum Reprod*. 2003. 18(8):1660–1665.⏎
31. Abur U, Gunes S, Asci R, Altundag E, Akar OS, Ayas B, Alpaslan MK & Ogur G. Chromosomal and Y-chromosome microdeletion analysis in 1,300 infertile males and the fertility outcome of patients with AZFc microdeletions. *Andrologia*. 2019. 51(11):e13402.⏎

12 Management of Male Factor Infertility

Ankit Desai and Suks Minhas

DOI: 10.1201/b22940-12

Categorising Male Factor Infertility

Male factor infertility (MFI) can be broadly divided into cases with genetic, acquired, or an idiopathic aetiology. To help direct management, a pragmatic approach is to categorise infertile men into non-azoospermic and azoospermic, with the latter being further classified into non-obstructive or obstructive. Of those cases that are not idiopathic, the aetiology can be categorised into pre-testicular, testicular, and post-testicular causes.

Treating Non-Azoospermic Men

Male factor infertility in non-azoospermic men can range from a normal semen analysis to cryptozoospermia or severe oligozoospermia. It also encompasses those with ejaculatory dysfunction, as this can be a functional or mechanical dysfunction of semen transit.

- **Pre-testicular Causes**

Pre-testicular causes are largely due to deficient hormonal stimulation of the testes. A hormone profile will differentiate between hypergonadotropic hypogonadism (primary testicular failure) and hypogonadotropic hypogonadism (secondary testicular failure), with the latter representing a pre-testicular cause. This can be due to a number of factors:

1. ↓Gonadotropin releasing hormone (GnRH)

- *Genetic*: Deficient GnRH secretion with anosmia and delayed puberty (Kallmann Syndrome)
- *Acquired*: Cerebrovascular accident, head trauma, encephalitis, cerebral neoplasm affecting the hypothalamus

2. ↓ Gonadotropins (follicle-stimulating hormone (FSH) and/or luteinising hormone (LH))
    - *Pituitary disease*: E.g., acquired causes above
    - *Testosterone replacement therapy* (*TRT*): Oestrogens or anabolic steroids
3. Hyperprolactinaemia (↑prolactin suppresses GnRH, gonadotropin and testosterone release)
    - *Drug-induced*: E.g., risperidone, olanzapine, fluoxetine (anti-psychotics/antidepressants), cimetidine, ranitidine (H2-receptor antagonists) and verapamil
    - *Prolactinoma*: The most common pituitary tumour

GnRH or LH/FSH Deficiency

Among the acquired causes, some may respond to treating the underlying pathology (e.g., infection or excision of tumour); however, successful recovery of gonadotropin release is variable. Hence, the treatment of choice in such cases is administration of either GnRH via an external stimulator/pump, or exogenous FSH (recombinant FSH) and human chorionic gonadotropin (HCG – an analogue of LH). The latter regimen is often favoured, as GnRH pumps are expensive and rely on an intact pituitary, which the underlying aetiology may preclude.

Guideline Tip

EAU guidelines (2024)

1. Strong recommendation for treating hypogonadotropic hypogonadism with rFSH + HCG or GnRH pump
2. However, use of GnRH therapy is more expensive and does not offer any advantages compared to gonadotropins

Hypogonadotropic Hypogonadism from TRT or Anabolic Steroids

Anabolic steroids and TRT induce a hypogonadotropic hypogonadism through inhibiting GnRH, FSH, and LH release, thereby ultimately suppressing spermatogenesis. Generally, cessation of TRT should result in recovery of spermatogenesis; however, the duration of this recovery (referred to as the 'washout' period) is variable. Typically, a washout period of 4–6 months after cessation of TRT is advised, though this can vary significantly depending on:

1. Baseline fertility/testicular function prior to TRT
2. Duration of TRT (the longer the course of treatment the longer the washout period)
3. Age at cessation (the older the patient, the lower the prospects of recovery)

A typical scenario where this may be encountered is a Klinefelter syndrome patient who has been on TRT for hypogonadism but now desires fertility. Although these patients start off as having primary testicular failure (↑FSH + LH and ↓T), after TRT they may have suppressed gonadotropin levels, giving a biochemical profile more suggestive of secondary testicular failure (↓FSH + LH). As these patients may be placed on long-term TRT, often at a young age, this would confer a lengthy washout period if/when they desire fertility. In some cases, recovery of spermatogenesis may not occur on cessation of TRT alone. These patients may require additional stimulation with hormonal agents such as HCG ± rFSH or selective oestrogen receptor modulators (SERMS) (see below). However, the use of such agents is off-label, and success rates are variable, with a highly heterogeneous and weak evidence base [1]. Hence a potential strategy is to offer such patients sperm banking prior to initiating TRT if they are non-azoospermic at the time.

Natural recovery of spermatogenesis from anabolic steroid abuse is even more difficult to predict, given the unmonitored strength and frequency of dosage.

Hyperprolactinaemia

Prolactin should be measured in cases where there is gynaecomastia, low T, new-onset visual disturbance, or low libido. However, it is important to note

that prolactin can be raised in men after venepuncture due to a stress response. In cases of persistently elevated prolactin or visual disturbance (e.g., bitemporal hemianopia from local pressure effects on the optic chiasm), an MRI of the pituitary should be arranged to exclude a pituitary neoplasm.

Medical Management

Drug-induced hyperprolactinaemia may resolve by discontinuing or replacing the offending drug. Other cases may require medical therapy with dopamine agonists such bromocriptine or cabergoline to inhibit prolactin secretion.

Surgical Management

Where a prolactinoma is confirmed with radiological or clinical features of pressure effects on the optic chiasm (visual field defect), referral to a neurosurgeon is indicated for consideration of trans-sphenoidal excision.

Testicular Causes

These cases are commonly characterised by primary testicular failure (hypergonadotropic hypogonadism), of which there are a plethora of causes (Figure 12.1). While it is difficult to pinpoint the source of idiopathic MFI, for simplicity, it is considered under the ‘testicular’ category.

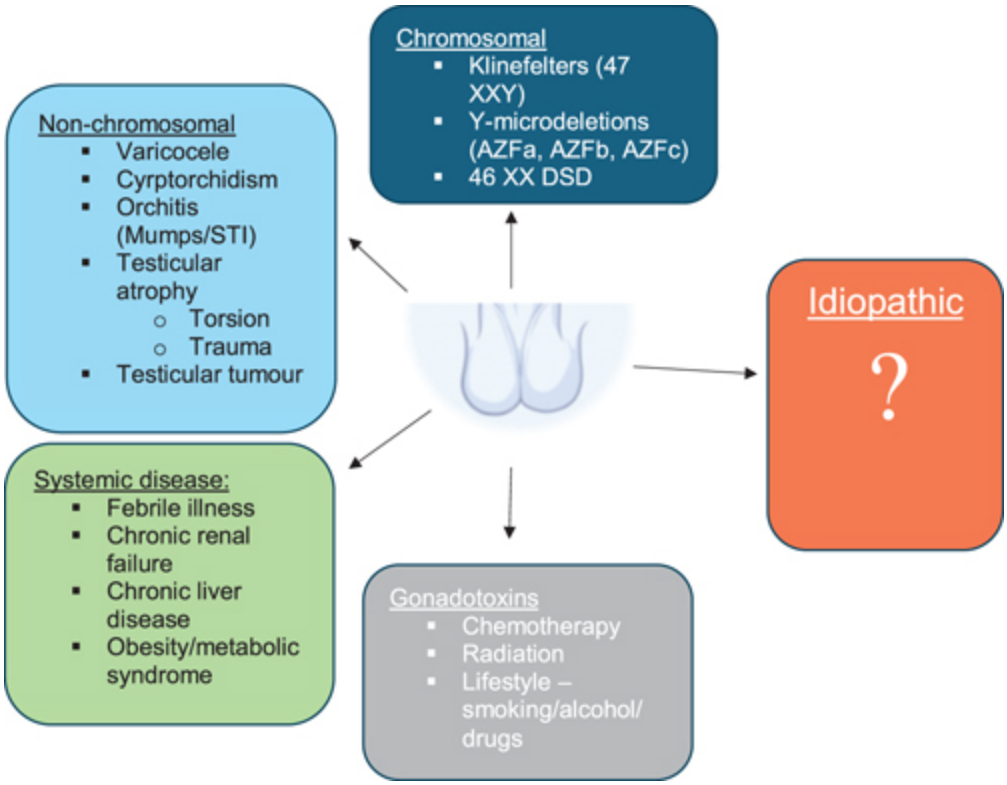


Figure 12.1 Different testicular causes of male infertility, with a substantial proportion attributable to an idiopathic aetiology (30%–50%).⏎

Resolution of any acquired/transient causes which are treatable (e.g., orchitis or systemic febrile illness) may alone improve fertility, but a semen analysis should be repeated at least 3 months following resolution of the pathology to ensure it accurately reflects the next spermatogenic cycle (post-treatment cycle).

Primary Hypogonadism

Many of the above causes can result in primary testicular failure/hypogonadism, characterised by ↓T and ↑FSH+LH. It poses an interesting challenge and has notoriously been mismanaged in the past. It is well-established that exogenous testosterone (or anabolic steroids) impairs spermatogenesis and should not be administered in men desiring fertility. The key to understanding the rationale is appreciating that it is the

intratesticular testosterone which is essential for sperm maturation. Exogenous testosterone suppresses testicular testosterone release from Leydig cells by exerting negative feedback inhibition on the hypothalamus and pituitary. This abolishes pulsatile GnRH release and suppresses LH release, the principal hormone driving testosterone release from Leydig cells.

Postgraduate Urology Examination Tip

1. In the viva you may be asked to take an examiner through the hypothalamo–pituitary–gonadal (HPG) axis to explain the hormonal control of spermatogenesis. Be prepared to draw it!
2. If presented with a hypogonadal man (low T) with infertility, do not say you will give testosterone!

Medical Management

For many of the testicular causes, management is centred around treating the underlying pathology where possible or removing the causative agent. Indeed, many of them will not have correctable causes, which make testicular aetiologies most challenging to treat, especially the idiopathic category which can account for 30%–50% of MFI.

Use of hormonal agents to increase intratesticular testosterone for idiopathic MFI is considered off-label/empirical. While there is a theoretical basis for their use in hypogonadal patients (persistently low T), there is a scarcity of strong evidence supporting their use in idiopathic MFI [1, 2]. The EAU guidelines do not conclusively recommend the use of such agents in idiopathic MFI [3].

Such agents include:

SERMs (e.g., clomiphene or tamoxifen), which attenuate the negative feedback inhibition of circulating oestrogens on the hypothalamus or anterior pituitary, thereby stimulating further gonadotropin release.

Aromatase inhibitors (e.g., anastrozole), which prevent the peripheral conversion of testosterone to oestrogen (Figure 12.2).

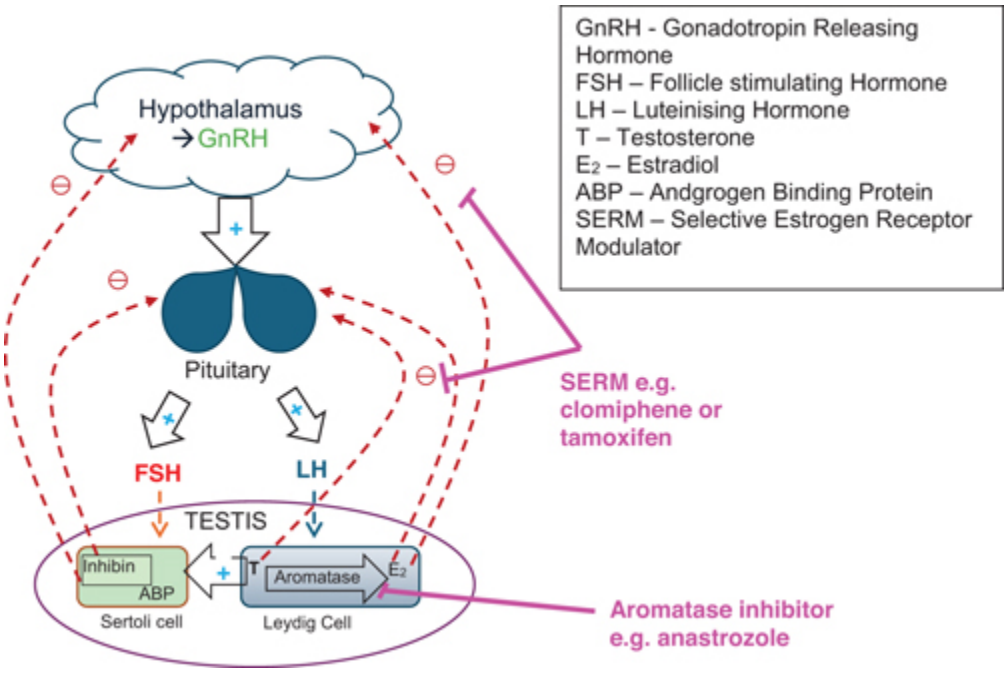


Figure 12.2 Hypothalamic–pituitary–gonadal axis.*Source*: Adapted from Dorota J. Hawksworth, Burnett AL. Other hormonal therapies and men's health. In: *Effects of Lifestyle on Men's Health*, Elsevier. 2019; 253–268; Diegidio, P., Jhaveri, J.K., Ghannam, S., Pinkhasov, R., Shabsigh, R. and Fisch, H. (2011), Review of current varicocelectomy techniques and their outcomes. *BJU Int*. 2011;108:1157–1172.⏎

Where such agents are being trialled in hypogonadal men with oligozoospermia, a reasonable duration may be 4–6 months, with regular monitoring of the hormone profile every 6–8 weeks and semen analysis at 3 months. It must be reiterated to the couple that while it is possible to augment T and sperm parameters, it may fail, and ART may ultimately still be required.

Postgraduate Urology Examination Tip

1. Treatment with such hormonal agents is empirical and off-label, and many urologists may not have experience in prescribing or monitoring

such regimens . If asked how you would manage or monitor such treatment, it is reasonable to state you would refer to an endocrinologist with an interest in reproductive medicine.

Varicoceles

Up to 15% of healthy men in the general population have varicoceles, which can be associated with infertility. Despite being the most common correctable finding in infertility investigations (up to 40% of infertile men are found to have a varicocele), a substantial proportion of men with a varicocele will not encounter difficulty fathering a child.

The main indications for treating varicoceles include:

1. *Symptomatic cases*: Cosmetic dissatisfaction/persistent dull ache with no other attributable cause
2. *Documented serial reduction in volume/size*: of ipsilateral testis and/or *hypogoandism*
3. *Infertility*: Clinically discernible or significant varicocele (grade I–III)

Traditionally, deciding to treat varicoceles in the context of infertility has been based on:

1. Abnormal semen parameters (oligo, astheno-, teratozoospermia)
2. Clinically discernible varicocele (grade 1 or higher)
3. Female partner’s age (ideally <37 years)

However, other important factors favouring treatment include:

1. Multiple miscarriages or failed IVF rounds with no female-factor identified
2. Raised oxidative stress in semen sample (measured using DNA fragmentation index; currently only available privately, not NHS-commissioned)

Consensus

Clinically discernible varicoceles (grade 1 or higher) associated with MFI should be considered for treatment [3, 4]. Nevertheless, debate surrounds the topic of treating varicoceles for infertility due to a systematic review by Evers et al. [5], which found no improvement in pregnancy rates after varicocele treatment compared with no treatment. Criticisms include inclusion of subclinical varicoceles and men with normal sperm parameters, potentially diluting treatment effects and underpowered subgroup analysis for clinical varicoceles.

Subsequent to this, other systematic reviews have analysed only those with clinically palpable/visible varicoceles and abnormal sperm parameters. These have favoured treating the varicocele, with improved pregnancy rates [6, 7].

Guideline Tip

3.EAU (2024): Strong recommendation for treating clinically palpable/visible varicoceles in men with unexplained infertility or abnormal sperm parameters (where female partner has good ovarian reserve).

Postgraduate Urology Examination Tip

Key publications on varicocele treatment in MFI

1. Evers and Collins meta-analysis (2003): No pregnancy rate improvement but included subclinical varicoceles/normal semen parameters. Underpowered subgroup analysis [5].
2. Kroese et al. (Cochrane, 2012): Marginal but statistically significant improvement in pregnancy rates after treating clinical varicoceles [6].
3. Kim et al. meta-analysis (2013): Like Evers and Collins, no improvement in pregnancy rates with surgical varicocele repair when including men with subclinical varicoceles and normal semen parameters. However, sub-group analysis of three studies with clinical varicoceles and abnormal semen parameters did find significant improvement in pregnancy rates after varicocele repair (OR >4) [7].

Following treatment of the varicocele it can take 3–4 months before any improvement in semen parameters or fertility outcomes can be appreciated [8], hence it is important to be aware of the female partner's age and ovarian reserve. In addition to this, it is important to establish expectations. Not only may treating the varicocele fail to improve fertility, but if there is any improvement, this may not be manifest as natural conception. Instead, it may improve chances of success with ART (see below) and appears to be related to the positive effects on sperm DNA fragmentation.

Treatment Modality

1) Radiological Embolisation

1. Percutaneous puncture of femoral vein (groin) or internal jugular vein (neck)
2. Access to the internal spermatic vein (target)
3. Deployment of embolisation coils or sclerosing agents

2) Surgical Ligation (Laparoscopic/Open)

Open technique can be microsurgical or non-microsurgical:

- Historically performed with a suprainguinal incision and 'high-tie' of the gonadal vein/pedicle (Palomo technique), but this failed to spare the lymphatics, hence gave high post-operative rate of hydrocele (lymphocele) (up to 20%).
- More contemporary approaches are with an inguinal incision and opening the canal with selective ligation of the testicular vein at the level of the internal ring (Ivanissevich), or subinguinal incision with isolation of the cord and selective ligation of the distended veins with the aid of an operating microscope (Marmar - subinguinal microsurgical approach) (Figure 12.3).

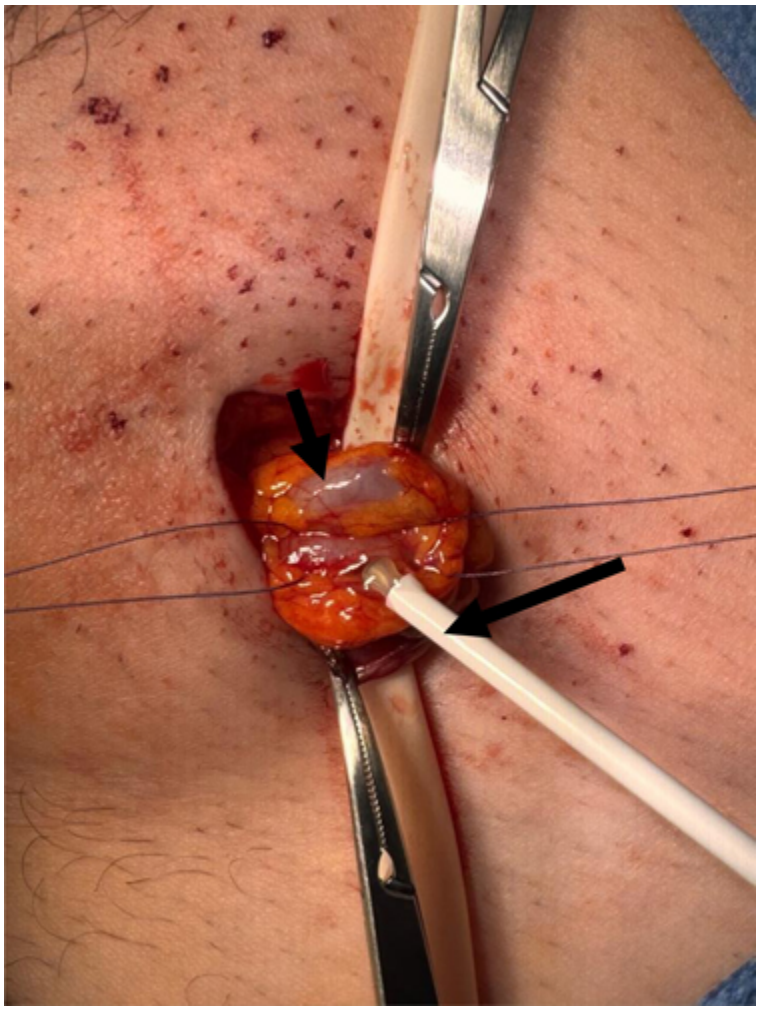


Figure 12.3 Subinguinal microsurgical varicocelectomy. Long arrow: 20 MHz Doppler probe; short arrow: Varicocele vein. Courtesy of Mr Hussain Alnajjar, UCLH.⏎

A microsurgical varicocele ligation employing the Marmar technique is now considered the gold standard and involves:

1. A subinguinal/high scrotal incision directly overlying the spermatic cord.
2. Dissection down to the cremasteric/fascial coverings of the cord.
3. Isolating the cord by placing a Penrose drain directly under it.
4. Docking the operating microscope.

5. Opening the cremasteric fascial layers to expose the dilated testicular veins.
6. Differentiating the testicular veins from the arteries can be facilitated by irrigation with 1% papaverine to make the arteries momentarily dilate and appear more prominent, making them easier to identify and avoid. Alternatively, an intra-operative 20 MHz micro-Doppler ultrasound probe can be used, if available, to detect the arterial pulsation.
7. Isolation and preservation of testicular artery, vas and lymphatics.
8. Ligation of engorged veins with 4/5–0 Vicryl suture.

Outcomes: Embolisation vs Microsurgical/Laparoscopic Ligation

To date, no head-to-head randomised controlled trial has compared the available surgical options either against each other or against a sham control. These procedures require laparoscopic or microsurgical expertise, and both outcomes and complication rates are highly dependent on surgeon experience. Nevertheless, among the surgical approaches, microsurgical ligation has emerged as the most effective in improving sperm concentration, and it is associated with the lowest rates of complications, hospital stay, and recurrence, according to recent meta-analyses and systematic reviews [9].

Microsurgical ligation confers:

1. >95% success at eradicating the varicocele.
2. <1% chance of recurrence.
3. 2%–5% risk of chronic scrotal or inguinal pain/paraesthesia.
4. ≤1% risk of testicular atrophy, vas injury or hydrocele.
5. ~40% pregnancy rate in previously infertile men has been reported within 12 months after surgical repair [10, 11, 12].

Radiological embolisation confers:

1. ~80% success rate at eradicating the varicocele.
2. ~32% improvement in pregnancy rate has been reported [12].

3. Pain and bruising at the puncture site and/or lower back can occur in 10%.
4. Recurrence rate of up to 10%.

There is a small risk of bleeding either from the puncture site or internally during the procedure, potentially resulting in a retroperitoneal haematoma in 1%–2% of cases. Bleeding at the puncture site usually responds to manual pressure, while retroperitoneal haematomas are often self-limiting but may require surgical intervention in fewer than 1% of cases.

The main advantage of embolisation is that it is less invasive than surgery and does not require a general anaesthetic.

Post-testicular Causes

In non-azoospermic men, these typically involve partial/unilateral obstruction or ejaculatory dysfunction (retrograde/anejaculation).

Unilateral/Partial Vasal Obstruction

1. May be congenital or acquired.
    - *Congenital*: Congenital unilateral absence of vas deferens (CUAVD).
        - Should be evaluated with a **renal ultrasound scan** to check for **concurrent unilateral renal agenesis**, which occurs in approximately 25% of CUAVD cases.
    - *Acquired*:
2. *Non-iatrogenic*: Trauma to the pelvis/groin.
3. *Iatrogenic*: Vasal injury from previous inguinal surgery, such as hernia repair.

Impact on fertility.

1. May reduce overall sperm concentration or affect other semen parameters.

- Fertility may be preserved if the contralateral testis and vas deferens are functional.
- Features suggestive of vasal injury from previous surgery.
- History of inguinal surgery (e.g., herniorrhaphy).
- Oligozoospermia or azoospermia with an engorged epididymis on the affected side, with normal testicular size.
- Hormone profile may be normal.
- Further investigation may include a **vasogram** to assess the site and extent of the injury.
- Reconstruction may be considered **if thought likely to improve sperm count and fertility.**

Although complex reconstruction (other than vasectomy reversal) is probably outside the remit of postgraduate exams, if vasography reveals a defect which is amenable to reconstruction, this should be referred to an andrologist with experience in vasal reconstruction. The help of a general surgeon would also be enlisted if a previous hernia repair/mesh is likely to be encountered.

Ejaculatory Dysfunction

Accounts for <2% of MFI. Suspected if low-volume/absent (‘dry’) ejaculate.

Retrograde Ejaculation

1. Confirmed by the detection of sperm (>10 per high power field) or fructose (seminal secretion) in a post-orgasmic urine sample.
2. May be from pharmacotherapy with alpha adrenoreceptor blockers, in which case cessation should revert to normal ejaculatory function.
3. Otherwise, can be from an autonomic neuropathy (e.g., as a consequence of diabetes).

    - Impaired co-ordinated contraction of internal urethral sphincter and bladder neck during ejaculation.
    - Although optimisation of glycaemic control is advised, the neurological deficit may be irreversible.

4. A surgical cause is previous bladder outflow obstruction surgery; however, this is less commonly encountered in young men presenting with infertility.
5. Other causes may be structural, inflammatory, or neoplastic in nature (e.g.,

    - prostatic or urethral lesions impeding emission or ejection of semen).
    - Should be investigated in a young man presenting with retrograde or anejaculation with no obvious neuropathic cause.

Anejaculation

Lesions affecting the sympathetic outflow (sympathetic chain or hypogastric nerve) to the genital tract can cause anejaculation. This is most commonly encountered following:

1. Spinal cord injury (SCI).
2. Retroperitoneal lymph node dissection (RPLND). The risk may be reduced by using modified templates for RPLND.

Non-surgical Treatments for Retrograde Ejaculation

Medical treatment is with sympathomimetics.

1. Examples include ephedrine, synephrine and pseudoephedrine.

- Their mechanism is by augmenting sympathetic neurotransmission to the genital tract largely by promoting release of noradrenaline vesicles at the pre-synaptic terminal and direct action on alpha adreno-receptors (Figure 12.4). This mediates contraction of the internal urethral sphincter and closure of the bladder neck during ejaculation (Figure 12.5). Quoted success rates in establishing antegrade ejaculation are ~25%–30% [13].
- Pseudoephedrine is usually prescribed at 60 mg QDS starting the day before, and an additional 120 mg dose 2–3 hours prior to intercourse.

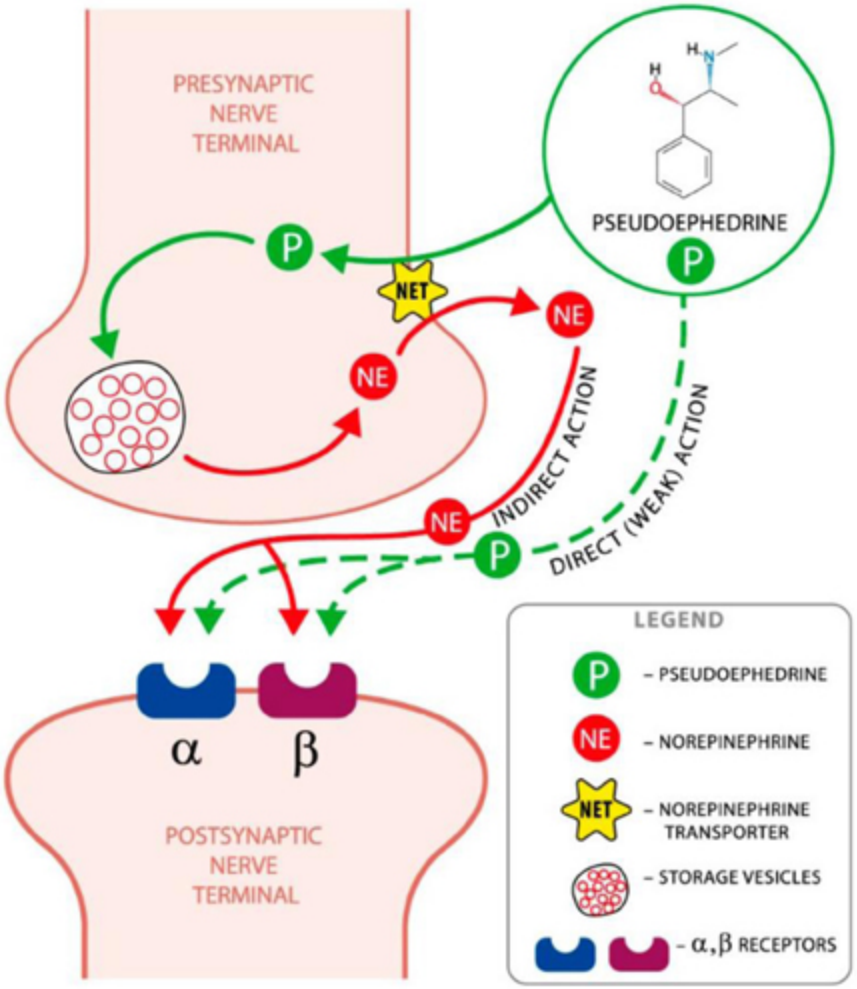


Figure 12.4 Direct and indirect mechanisms of action of pseudoephedrine in augmentation of sympathetic neurotransmission. *Source*: Used with permission from MDPI open access journals. Głowacka K, Wiela-Hojeńska A. Pseudoephedrine-Benefits and Risks. *Int J Mol Sci*. 2021;22(10):5146.⏎

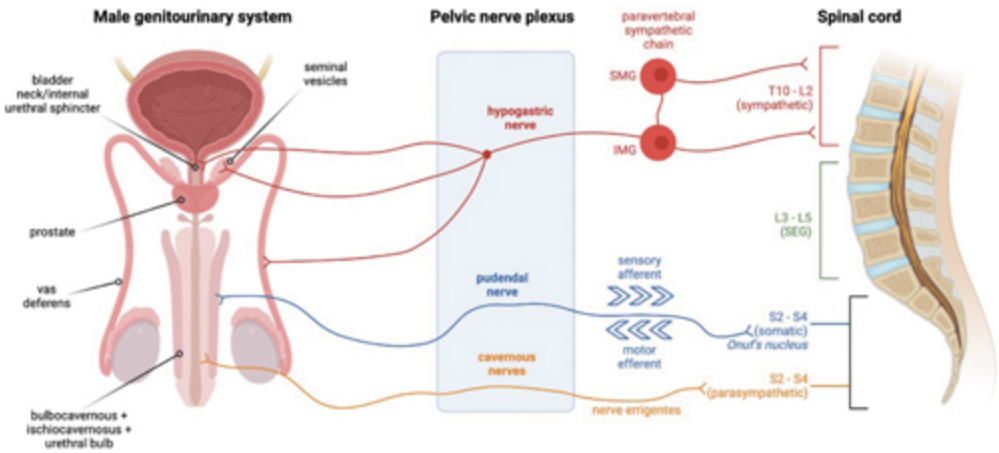


Figure 12.5 Important neural pathways governing ejaculation. *Source*: Taken from Desai et al. Understanding and managing ejaculatory dysfunction in diabetes mellitus. *Andrology* (2022).⏎

Alternative forms of pharmacotherapy include tricyclic antidepressants such as imipramine, which has anticholinergic properties and may attenuate parasympathetically mediated relaxation and opening of the bladder neck. However, these agents demonstrate relatively low efficacy (approximately 20%) [13]. Both are considered off-label treatments for this indication.

Where medical therapy has failed, sperm may be retrieved from a post-orgasmic urine sample for use in assisted reproductive technology (ART). As urine is naturally acidic and toxic to spermatozoa, it must be alkalinised prior to collection. This is typically achieved by instructing the patient to take oral sodium bicarbonate the evening before the planned collection. Following ejaculation, the voided, alkalinised urine specimen is centrifuged and examined for viable spermatozoa. A meta-analysis examining the use of sperm retrieved in this way for ART reported pregnancy rates of approximately 15% [13]. If no suitable sperm are identified for intracytoplasmic sperm injection (ICSI), surgical sperm retrieval – such as testicular sperm extraction (TESE) – may be considered.

Non-surgical Treatments for Anejaculation

A major component of the ejaculatory process is sympathetic outflow from the thoracolumbar spinal cord (T10–L2), which governs the emission of semen into the bulbar urethra. Preganglionic sympathetic efferent fibres originating from T10–L2 travel to the inferior and superior mesenteric ganglia. From there, postganglionic sympathetic fibres combine to form the hypogastric nerve, which innervates the epididymis, vas deferens, seminal vesicles, and internal urethral sphincter, producing coordinated contractions that result in semen emission. The reflex is triggered by tactile stimuli, transmitted via sensory afferents in the pudendal nerve to the thoracolumbar cord, along with visual and cognitive input from higher cerebral centres. Thus, the ejaculatory reflex arc comprises an afferent somatosensory limb (via the pudendal nerve) and an efferent sympathetic motor limb (via the hypogastric nerve), with central processing in the thoracolumbar cord (T10–L2 and L3–L5), commonly referred to as the spinal ejaculatory generator (SEG). In spinal cord injury, the level and completeness of the lesion determine the degree of ejaculatory dysfunction. Patients with upper motor neurone lesions are less likely to ejaculate naturally than those with lower motor neurone lesions. In men unable to achieve ejaculation, vibratory or electrostimulation may be used to induce it.

Vibrostimulation involves placing vibration pads at the glans to mechanically stimulate penile afferent sensory fibres travelling in the pudendal nerve, which, in turn, induce reflex sympathetic outflow from the thoracolumbar cord. Hence this technique requires an intact ejaculatory reflex arc. Electrostimulation involves a current directly stimulating the peripheral postganglionic sympathetic nerves innervating the genital tract (bulbospongiosus and ischiocavernosus muscles) to induce emission via a rectal probe. Important points to note for each technique are:

1. Vibrostimulation can be used in SCI patients with lesions above T10, as it requires an intact reflex arc.
2. Those with lesions below T10 will likely require electrostimulation.
3. Complexities of the reflex arc and not knowing the exact level/completeness of the injury can make predicting the likely outcome of vibro- and electrostimulation difficult.

4. Patients with lesions at the level of T10 can be trialled with vibrostimulation and successful ejaculation has been reported in these [14]. However, failure and the need for electrostimulation must be anticipated.
5. Penile vibrostimulation is much simpler, cheaper, and less invasive than electrostimulation.
6. Vibrostimulation can achieve successful ejaculation in up to 85% of those with an injury at T10 or above and has also been used successfully in some with incomplete injuries below this level [14]. Hence it is reasonable to trial this before electrostimulation.

Surgical Treatment

Where the above non-surgical methods are unavailable or have failed to produce any anterograde ejaculate or viable sperm, surgical sperm retrieval (SSR) in the form of percutaneous epididymal sperm aspiration (PESA) or testicular sperm extraction (TESE) can be performed.

Treating Azoospermic Men

Azoospermia is the complete absence of sperm in the ejaculate and occurs in 1% of men and 10%–15% of men presenting with infertility. It can be due to failed sperm production (maturation arrest or Sertoli cell-only syndrome [SCOS]) or obstruction to sperm release into the genital tract. Approximately 60% are non-obstructive (NOA), and 40% are obstructive (OA).

Non-obstructive Azoospermia

This is attributable to testicular and pre-testicular causes. While pre-testicular causes (e.g., hormonal deficiency) are more likely correctable, most NOA cases require TESE.

Pre-testicular Causes of NOA

The leading cause is deficient gonadotropin (FSH/LH) stimulation. In these scenarios hormonal stimulant agents may improve the chances of sperm retrieval at TESE, though evidence is weak for hypergonadotropic men (↑FSH/LH) [15].

Hormonal stimulation with gonadotropins or SERMs is usually implemented for 4–6 months pre-TESE, with hormone monitoring every 6–8 weeks to check the T level has responded/been adequately augmented. It would be prudent to check a semen analysis two weeks prior to TESE to ensure NOA has not been converted to sperm in the ejaculate, which would obviate the need for TESE.

Testicular Causes of NOA

This is an intrinsic deficiency of spermatogenesis within the testes and the causes are the same as outlined in Figure 12.1, with the majority being idiopathic. Varicoceles can also be associated with NOA; however, their contributory role in azoospermia is debatable. Hypogonadal men such as those with Klinefelter's, and those with varicocele, probably constitute a limited group of cases with a testicular cause in which a potentially treatable pathology exists.

Varicoceles in NOA

The role of varicocele treatment in NOA is controversial. While previous studies have reported sperm in the ejaculate after varicocele repair in NOA patients, this has been low-level evidence, with data from retrospective series. However, a recent meta-analysis has shown treating a clinical varicocele in NOA may improve the rate of successful sperm retrieval at TESE [16].

Nevertheless, it remains important to counsel azoospermic men that they may remain azoospermic after treatment of the varicocele and hence still require subsequent TESE. It is possible in such a scenario that treating the varicocele may improve the sperm retrieval rate at TESE; however, this cannot be guaranteed. The decision to treat a clinical varicocele in these couples must also heavily factor in the female partner's age and ovarian reserve.

Surgical Management of NOA: Testicular Sperm Extraction

TESE is considered the gold standard treatment for NOA. It may be performed as either conventional TESE (cTESE) or microdissection TESE (mTESE). Conventional TESE does not involve the use of a microscope and requires multiple incisions in the tunica albuginea to obtain biopsies from different regions of the testis. In contrast, mTESE employs an operating microscope with ×20–25 magnification to identify and selectively extract the most distended seminiferous tubules, which are more likely to contain mature spermatozoa. These tubules appear more dilated and opaque under magnification (Figure 12.6).

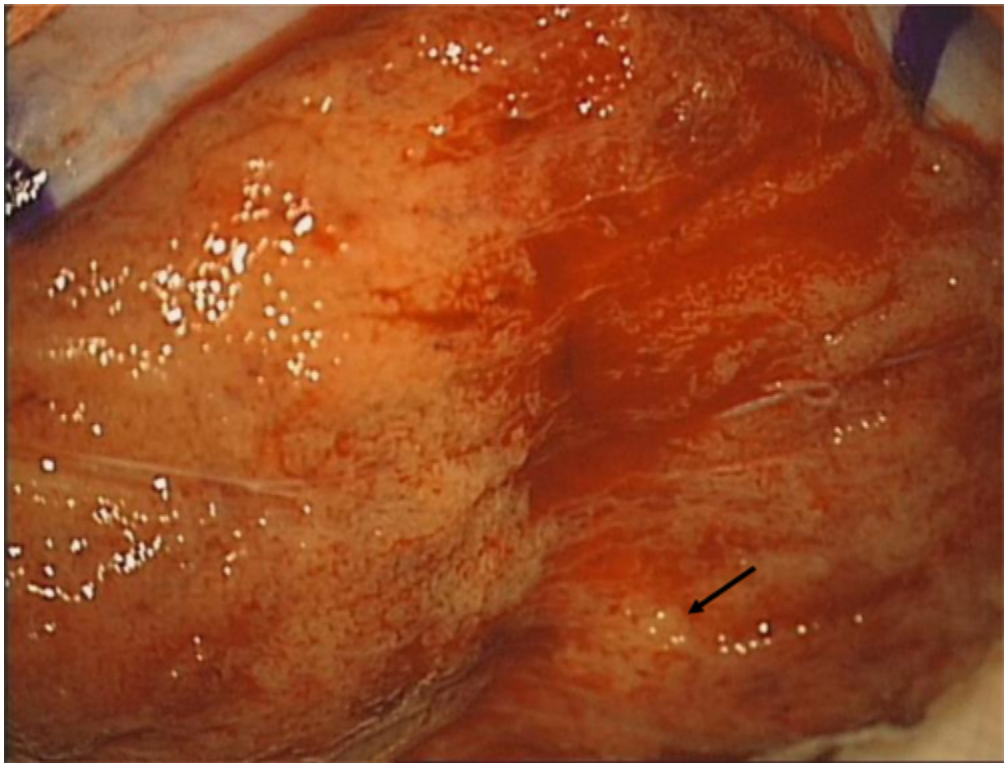


Figure 12.6 Microdissection testicular sperm extraction (mTESE). Surgical sperm retrieval by harvesting of thick and dilated seminiferous tubules (arrow) under surgical microscope. Courtesy of Mr Hussain Alnajjar, UCLH.⏎

Although meta-analyses have produced conflicting data regarding whether mTESE offers superior sperm retrieval rates compared to cTESE

[17, 18], mTESE has been shown to remove less testicular tissue. This is associated with reduced bleeding and a lower incidence (<5%) of postoperative complications such as scrotal haematoma, testicular atrophy, and hypogonadism. All sperm retrieval procedures should be performed in the presence of an embryologist in theatre to confirm the presence of viable sperm in the sampled specimen.

TESA has been used in the past for NOA; however, it yields lower sperm retrieval rates than cTESE or mTESE. As a result, the EAU guidelines recommend against TESA in men with NOA [6].

The key operative steps of mTESE include:

1. Midline scrotal raphe incision.
2. Dissection down to tunica vaginalis and opening the sac to deliver testis (start off with larger testis if there is any discrepancy in size).
3. Dock the operating microscope.
4. Equatorial incision in tunica albuginea.
5. Bivalve the testis to provide good exposure of seminiferous tubules.
6. Systematically search for most dilated tubules to sample tissue.
7. Sampled tissue is passed to embryologist in petri dish with sperm-wash medium to examine.
8. Take additional sample for histopathology to get formal report of extent of spermatogenesis (Johnsen score), as well as to exclude germ cell neoplasia in situ (GCNIS). Send in Bouin's solution.
9. If adequate amount of viable sperm found (immotile sperm can still be used for ICSI), there is no need to explore contralateral testis. If no sperm from first testis found, second testis must be sampled.
10. Judicious and precise haemostasis with bipolar diathermy, to avoided excess cautery of testicular stroma (increases risk of

atrophy and hypogonadism post-op). This is aided with use of a microscope.
11. Closure of tunica albuginea with 4 or 5/0 Vicryl.
12. Replace testis into sac and close sac with 3/0 Vicryl (do not evert sac like with Jaboulay's repair).
13. Cord block can be administered at this stage before replacing testis into hemiscrotum.
14. Closure dependent on need for contralateral testis exploration.

The extracted samples are carefully examined under a microscope by the embryologist in theatre. Regardless of whether sperm are seen in theatre, the samples are sent to the lab for further centrifuge analysis. The rate of successful sperm retrieval with mTESE is quoted at 50% across all cases of NOA; however, case-specific success rates can vary (e.g., Klinefelter's [~ 30%] and AZFc microdeletion [50%–60%]). Remember that if a patient with NOA has an aZFa or b microdeletion then mTESE should not be performed, as sperm will not be found at the time of surgery. The complications of mTESE are summarised in Table 12.1.

Table 12.1 Complications of mTESE⏎

Complications		
Immediate	**Early**	**Late**
Bleeding (very rarely uncontrollable necessitating need for orchidectomy <1%)	Pain from inflammatory/healing process (common)	Testicular atrophy (<5%)
Failure to retrieve sperm from either testes (50%)	Scrotal haematoma (2%)	Hypogonadism (persistently low T >12 months after surgery, requiring TRT) <5%
	Wound dehiscence/infection (5%)	Chronic scrotal pain (<2%)
	Epididymo-orchitis (<5%)	

Guideline Tip

1. NOA patients planned for mTESE must have genetic testing for y-microdeletions. This is not only to identify the risk of anomalies being inherited by any potential offspring (and thus

to prompt genetic counselling), but also to determine the suitability of TESE. AZFa (Sertoli cell only) or AZFb (maturation arrest) deletions confer a zero chance of successful sperm retrieval, hence TESE should not be attempted in such cases.

EAU Guidelines (2024): Recommendations

1. Those with sperm concentration of <10 million/ml should have karyotype testing.
2. Those with sperm concentration of <5 million/ml can be offered Y-microdeletion testing, but this is mandatory in those with <1 million/ml.
3. Do not attempt surgical sperm retrieval in those with AZFa and AZFb Y-microdeletions.

Post-operatively, the patient is informed of whether sperm was found on the day of surgery. The patient is subsequently reviewed in clinic 4 weeks post-op to inform them of the final centrifuge and histology result of the testis biopsy. Some histopathologists will give a Johnsen score (out of 10) on the extent of spermatogenesis (Table 12.2). A Johnsen score of 8 or above is required for ART (IVF/ICSI). If no mature spermatozoa are seen (Johnsen score <8) this would indicate maturation arrest or SCOS, in which case the options for the couple would be donor sperm or adoption.

Table 12.2 Johnsen Score⏎

10	Full spermatogenesis seen
9	Slightly impaired spermatogenesis: spermatozoa and lates spermatids seen but disorganised epithelium
8	<5 spermatozoa per tubule, few late spermatids
7	No spermatozoa, no late spermatids, many early spermatids
6	No spermatozoa, no late spermatids, few early spermatids
5	No spermatids, many spermatocytes
4	No spermatids, few spermatocytes
3	Spermatogonia only
2	No germ cells, Sertoli cells only

10	Full spermatogenesis seen
1	No seminiferous epithelium seen

Postgraduate Urology Examination Tip

1. You may be asked what the Johnsen scoring system is. It is a 10-point histopathological scoring system to grade the extent of spermatogenesis seen on testis biopsy (Table 12.2).

Surgical Sperm Retrieval In Testis Cancer (OncoTESE)

Subfertility is not only a risk factor for testis cancer, but also a possible sequalae of it. Increasingly, men presenting with testis tumours are found to be either oligozoospermic or azoospermic, with the latter constituting between 6% and 24% of testis cancer patients in the literature [19]. Non-obstructive azoospermia in those presenting with a testis tumour or the inability to ejaculate due to a pre-pubertal diagnosis are the prime indications for oncoTESE. It involves:

1. Attempted sperm retrieval from the tumour-bearing testis (hence approached transinguinally).
2. Aid of microscope.
3. A segment of the testis which is clear of tumour is explored by incising the tunica albuginea.
4. Can be performed in vivo (with the cord clamped) or ex vivo, on the bench, after the testis and cord have been excised.
5. The contralateral (tumour-free) testis can also be explored if no sperm is found in the tumour-bearing testis (as for mTESE).

- Also allows biopsy of contralateral testis to exclude GCNIS.

Obstructive Azoospermia

While this may be considered a post-testicular form of azoospermia, obstruction to sperm transit can also result from intra-testicular scarring,

particularly at the rete testis, due to trauma, infection, or fibrosis. This is referred to as intra-testicular obstruction.

Extratesticular sites of obstruction may include the epididymis, vas deferens, or ejaculatory ducts. Among these, epididymal obstruction accounts for the majority of OA cases and may be either acquired or congenital, with acquired causes being more common.

1. Acquired causes of OA

    - Most often due to:
    - Prior surgery (e.g., hernia repair, vasectomy)
    - Epididymo-orchitis
    - Sexually transmitted infections (STIs)

2. Congenital causes of OA

    - Congenital bilateral absence of the vas deferens (CBAVD) is the most common congenital cause.
    - All patients with CBAVD should undergo cystic fibrosis transmembrane conductance regulator (CFTR) gene testing.
    - The **ΔF508** mutation is the most frequently identified.
    - If the male is found to be a CFTR mutation carrier, the female partner should also be tested to facilitate genetic counselling.
    - If both partners are carriers of a recognised CFTR gene mutation, there is a 25% chance that offspring will be affected by cystic fibrosis.

3. Youngs’ syndrome/sinopulmonary-infertility syndrome

    - A rare condition associated with recurrent respiratory infections and infertility, thought to result from functional failure of sperm transport due to immotile cilia in the genital tract (epididymis and vas deferens).

When considering acquired forms of OA alone, vasectomy remains the most common aetiology.

Ejaculatory duct obstruction (EDO) accounts for <5% of OA cases and can be categorised into cystic (largely congenital) and non-cystic (largely acquired)

- *Congenital*: From a Müllerian duct cyst/remnant
- *Acquired*: From a prostatic/urethral lesion or inflammation and scarring causing stricture and obstruction of the ejaculatory ducts

Treatment of Obstructive Azoospermia

There is no real medical management of OA. The mainstay of treatment is surgical. All forms of OA can be managed with SSR via PESA/TESE; however, this would only permit conception via ART. For patients with young female partners, with good ovarian reserve, who demand natural conception/multiple children, the two main surgical treatments to know for the postgraduate urology examinations are vasectomy reversal and transurethral resection of the ejaculatory ducts (TURED).

Vasectomy Reversal

Important considerations can be divided into *pre*- and *intra*-operative factors, which will predict the chances of success. Success is gauged by patency rate (return of sperm in ejaculate) and pregnancy rate.

Pre-operative Factors

1. Time since the vasectomy (termed the ‘obstructive interval’).
    - Most important pre-operative factor determining patency rate.
    - Belker et al. showed from over 1,400 vasectomy reversals undertaken across a 9-year period over five centres that patency and pregnancy rates correlated negatively with the time since vasectomy [20] (see Table 12.3).

Table 12.3 Patency and Pregnancy Rates Following Vasectomy Reversal⏎

Time Since Vasectomy (Obstructive Interval)	Indices of Vasectomy Reversal Success	
	Patency rates (Sperm In Post-op Ejaculate)	Pregnancy Rates
0–3 years	97%	76%
3–8 years	88%	53%
9–14 years	79%	44%
>15 years	71%	30%

Source: Belker AM, Thomas AJ Jr, Fuchs EF, Konnak JW, Sharlip ID. Results of 1,469 microsurgical vasectomy reversals by the Vasovasostomy Study Group. *J Urol*. 1991;145(3):505–511. doi:10.1016/s0022-5347(17)38381-7.

2. Female partner’s age/ovarian reserve.

- Vital to inform couple that while vasectomy reversal aims to permit natural conception, it can take up to 12 months for return of viable sperm in the ejaculate following vasectomy reversal.
- Can take even longer if a more complex reconstruction (vasoepididymostomy -VE) is undertaken. Hence the female partner's age is important.
- Nevertheless, successful vasectomy reversal is considered more cost-efficient than ART.

3. Surgeon's experience in vasectomy reversal.

Intra-operative Factors

- Nature of vasal fluid emerging from the proximal (testicular) end of the vas.

Good prognostic features include:

- Clear vasal fluid.
- Motile sperm or sperm parts in vasal fluid seen by embryologist.
- Presence of sperm granuloma.

Poor prognostic factors which would favour a VE or SSR are:

- Thick and pale 'toothpaste-like' fluid from testicular end of vas.
- No fluid or sperm seen even after copious lavage of testicular end of vas.
- Very short testicular end of vas (<2.5 cm).

The pregnancy rates will be a function of both the quality of sperm returning to the ejaculate and the female partner's age and fertility status.

Vasectomy reversal is performed with an operating microscope and can be done via a vasovasostomy (VV) or a vasoepididymostomy (VE), with the latter being the more complex reconstruction, with a higher chance of failure. An important step in the counselling process is to consent for concomitant SSR (mTESE) for ART in the event the vasectomy reversal fails.

Salient operative steps of a vasectomy reversal:

1. Once the vas and vasectomy defect have been identified, a high scrotal incision is made to deliver the proximal (testicular) and distal (abdominal) ends of the cut vas.

2. Both ligated ends of the vas and adventitial layers are fashioned to reveal healthy open bleeding ends.
3. The vasal fluid from the testicular end is inspected for the aforementioned features.
4. Saline flush is used as lavage to promote sperm out of the testicular end of the vas.
5. A 1-0 Prolene suture is gently passed through both the distal and proximal ends of the vas to assess distal patency and to estimate the available length of the proximal vas originating from the epididymis.
6. If after inspection of the vasal fluid and mobilisation of both ends a VV is deemed feasible, both ends of the vas are placed in a vas-holding clamp to prepare for the anastomosis.
7. End-to-end anastomosis is undertaken in two layers (inner mucosa-to-mucosa approximation followed by anastomosis of the outer seromuscular layer) or single layer (modified technique full thickness) with interrupted 9/0 nylon suture. Principles are a water-tight, tension-free, and well vascularised anastomosis.
8. mTESE may also be undertaken as a contingency step for potential use in ART.

If unfavourable quality of vasal fluid or lack of sperm on both sides are found, and VE is being considered, the tunica vaginalis is opened and the epididymis is inspected for dilated tubules. The patency rates of the VE are lower than for VV and are highly dependent on surgical experience in the procedure. The complications of vasectomy reversal are summarised in Table 12.4. The first semen sample is usually assessed at 6 weeks post-op to check for patency. Even if patent, a low sperm count/poor quality sperm would be expected initially. Subsequent semen samples would be expected to show better sperm counts/quality.

Table 12.4 Vasectomy Reversal Complications⏎

Immediate	Early	Late
Bleeding (very rarely uncontrollable necessitating need for orchidectomy <1%)	Transient scrotal pain, bruising, swelling (10%–50%)	Testicular atrophy (<2%)
Failure to perform VV or VE on one or both sides (e.g., vasal defect too long, other technical reasons [<2%]). In this case, surgical sperm retrieval with PESA/TESE is done	Scrotal haematoma needing surgical evacuation (1%–2%)	Chronic scrotal pain or painful sperm granuloma at vasectomy reversal site (5%)
	Blood in semen for first few ejaculations (up to 50%)	Even with sperm returning to ejaculate, may still need ART using ejaculated sperm (dependent on sperm quality and female factors)
	Epididymo-orchitis (<2%)	
	Failure of sperm to return to ejaculate (dependent on time since vasectomy, intra-operative findings, and experience of surgeon) Belker et al. data.	Recurrent obstruction/blockage at vasectomy reversal/anastomosis (azoospermia despite initial return of sperm to ejaculate [5%])

Transurethral Resection of Ejaculatory Ducts

TURED is the surgical treatment of choice for EDO where natural conception is desired. It can be from multiple aetiologies (e.g. inflammatory process/scarring occluding ejaculatory ducts, midline prostatic cyst, or Müllerian duct cyst). The diagnosis would be suggested by low volume, low pH ejaculate, which may also be deficient in seminal fructose. Hormone profile is typically normal and transrectal ultrasound (TRUS) may reveal features such as a midline prostatic cyst, dilatation of the seminal vesicles (A–P diameter >15 mm) and/or the ejaculatory ducts (width >2.3 mm). The procedure involves transurethrally incising or de-roofing the cyst or blocked ejaculatory duct at the verumontanum using a cautery loop. Success rates are better for cystic EDO versus non-cystic EDO. Sixty cases of EDO treated with TURED reported return/improvement of sperm in ejaculate in 85% and pregnancy rates of 26% [21]. A more recent series has corroborated these findings [22].

Steps of the procedure include:

1. In lithotomy position, TRUS-guided injection of methylene blue into the seminal vesicles (SV). SVs can also be aspirated

first to assess for any sperm (can be cryopreserved if sperm present in aspirate).
2. Transurethral resection of veru with loop until efflux of methylene blue is seen from duct opening.
3. The procedure can be done with TRUS probe in place or access for regular digital rectal examination to further guide depth of resection (risk of rectal injury).
4. Precise resection to avoid urethral sphincter and bladder neck injury is crucial.
5. Once ejaculatory duct uncapped/de-roofed a vesiculogram can be performed to ensure patency (ejaculatory duct cannulated with ureteric catheter /pollock and diluted iodine-based contrast instilled, with image intensifier in theatre).
6. Haemostasis with judicious and pinpoint electrocautery to minimise scarring.
7. Three-way catheter inserted for overnight irrigation and usually removed next day.

Semen analysis can be checked at 6 weeks. Complications include haematuria, haematospermia, re-stricture, epididymo-orchitis, acute urinary retention, and rectal injury (Table 12.5).

Table 12.5 Complications of TURED⏎

Complications		
Immediate	**Early**	**Late**
Bleeding (haematuria)	Retrograde ejaculation	Urethral stricture
Rectal injury (<1%)	Reflux of urine into prostatic/ejaculatory ducts (can cause prostatitis/epididymitis; can affect sperm quality)	Recurrent obstruction/blockage of ejaculatory ducts (azoospermia despite initial return of sperm to ejaculate [5%])
Resection of external urethral sphincter (1%)	Watery ejaculate initially (up to 50%)	Even with sperm returning to ejaculate, may still need ART using ejaculated sperm (dependent on sperm quality and female factors)
	Epididymo-orchitis (up to 10%)	
Acute urinary retention	Blood in semen temporarily	Urinary incontinence (1%)

Percutaneous/Microscopic Epididymal Sperm Aspiration

This is the default option in cases of OA where reconstructive surgery is not desired or feasible. Sperm can be retrieved in almost all cases of OA by PESA. Where there is focal epididymal obstruction from previous inflammation, microscopic epididymal sperm aspiration (MESA) may be necessary as PESA may not obtain sperm. MESA may also be performed at the time of VE. This requires scrotal exploration to expose the epididymis and a magnified view of the most dilated epididymal tubules for targeted aspiration of sperm. In CBAVD, PESA can achieve successful SSR, but MESA may be required if PESA fails. Where sperm aspiration from the epididymis is not possible (e.g., in epididymal atresia/obstruction or intratesticular obstruction at rete testis), mTESE is performed. Hence all patients undergoing PESA/MESA under GA are consented to concurrent mTESE should the PESA/MESA fail to retrieve viable sperm.

PESA can be performed under local/regional anaesthesia with a cord block. It is a simple and quick procedure, but, as with TESE, should be done with an embryologist present. Typically, 25G (orange) hypodermic needles connected to 2 ml syringes are used, which are only partly pre-filled with sperm medium. The salient steps are:

1. Epididymis on each side is palpated (typically feels bulky and engorged in OA).
2. A cord block is placed with 15 ml of LA.
3. The epididymal head is stabilised in one hand between the grasping thumb and index/middle finger.
4. With the opposite hand the prepared 2 ml syringes with 25G hypodermic needle is inserted into the epididymal head, with the plunger of the syringe pulled back to provide constant negative pressure.
5. Multiple passes of the needle are made while ensuring the bevel of the needle is not withdrawn from the epididymis.
6. Once multiple passes are made, the needle is withdrawn from the epididymal head immediately while the syringe is under

negative pressure. If sperm is present there will often be a slight cloudy appearance of the sperm-wash solution in the syringe, but this is confirmed by the examining embryologist in theatre.

References

Desai A, *et al. Understanding and managing the suppression of spermatogenesis caused by testosterone replacement therapy (TRT) and anabolic androgenic steroids (AAS)*.⏎

Rambhatla A, Mills JN, Rajfer J. The Role of Estrogen Modulators in Male Hypogonadism and Infertility. *Rev Urol*. 2016;18(2):66–72. doi:10.3909/riu0711.⏎

EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2022. ISBN 978-94-92671-16-5.⏎

Jensen CFS, Østergren P, Dupree JM, Ohl DA, Sønksen J, Fode M. Varicocele and male infertility. *Nat Rev Urol*. 2017;14(9):523–533. doi:10.1038/nrurol.2017.98.⏎

Evers JL, Collins JA. Assessment of efficacy of varicocele repair for male subfertility: a systematic review. *Lancet*. 2003;361(9372):1849–1852. doi:10.1016/S0140-6736(03)13503-9.⏎

Kroese AC, de Lange NM, Collins J, Evers JL. Surgery or embolization for varicoceles in subfertile men. *Cochrane Database Syst Rev*. 2012;10:CD000479. doi:10.1002/14651858.CD000479.pub5.⏎

Kim KH, Lee JY, Kang DH, Lee H, Seo JT, Cho KS. Impact of surgical varicocele repair on pregnancy rate in subfertile men with clinical varicocele and impaired semen quality: a meta-analysis of randomized clinical trials. *Korean J Urol*. 2013;54(10):703–709. doi:10.4111/kju.2013.54.10.703.⏎

Machen GL, Johnson D, Nissen MA, Naber E, Sandlow JI. Time to improvement of semen parameters after microscopic varicocelectomy: When it occurs and its effects on fertility. *Andrologia*. 2020;52(2):e13500. doi:10.1111/and.13500.⏎

Wang H, Ji ZG. Microsurgery versus laparoscopic surgery for varicocele: a meta-analysis and systematic review of randomized controlled trials.

J Invest Surg. 2020;33(1):40–48. doi:10.1080/08941939.2018.1474979.⏎
Peng J, Zhang Z, Cui W, *et al.* Spontaneous pregnancy rates in Chinese men undergoing microsurgical subinguinal varicocelectomy and possible preoperative factors affecting the outcomes. *Fertil Steril*. 2015;103(3):635–639. doi:10.1016/j.fertnstert.2014.12.091.⏎
Bryniarski P, Taborowski P, Rajwa P, Kaletka Z, Życzkowski M, Paradysz A. The comparison of laparoscopic and microsurgical varicocoelectomy in infertile men with varicocoele on paternity rate 12 months after surgery: a prospective randomized controlled trial. *Andrology*. 2017;5(3):445–450. doi:10.1111/andr.12343.⏎
Diegidio, P., Jhaveri, J.K., Ghannam, S., Pinkhasov, R., Shabsigh, R. and Fisch, H. (2011), Review of current varicocelectomy techniques and their outcomes. *BJU Int* 2011;108:1157–1172.⏎
Jefferys A, Siassakos D, Wardle P. The management of retrograde ejaculation: a systematic review and update. *Fertil Steril*. 2012;97(2):306–312. doi:10.1016/j.fertnstert.2011.11.019.⏎
Ibrahim E, Brackett NL, Lynne CM. Penile vibratory stimulation for semen retrieval in men with spinal cord injury: patient perspectives. *Res Rep Urol*. 2022;14:149–157. doi:10.2147/RRU.S278797.⏎
Tharakan T, Corona G, Foran D, *et al.* Does hormonal therapy improve sperm retrieval rates in men with non-obstructive azoospermia: a systematic review and meta-analysis. *Hum Reprod Update*. 2022;28(5):609–628. doi:10.1093/humupd/dmac016.⏎
Esteves SC, Miyaoka R, Roque M, Agarwal A. Outcome of varicocele repair in men with nonobstructive azoospermia: systematic review and meta-analysis. *Asian J Androl*. 2016;18(2):246–253. doi:10.4103/1008-682X.169562.⏎
Bernie AM, Mata DA, Ramasamy R, Schlegel PN. Comparison of microdissection testicular sperm extraction, conventional testicular sperm extraction, and testicular sperm aspiration for nonobstructive azoospermia: a systematic review and meta-analysis. *Fertil Steril*. 2015;104(5):1099–103.e1033. doi:10.1016/j.fertnstert.2015.07.1136.⏎
Corona G, Minhas S, Giwercman A, *et al.* Sperm recovery and ICSI outcomes in men with non-obstructive azoospermia: a systematic

13 Aetiology, Pathophysiology, Clinical Assessment, and Management of Primary Hypogonadism

Nipun Lakshitha de Silva, Jas Kalsi and Channa N. Jayasena

DOI: 10.1201/b22940-13

Epidemiology

Prevalence

The exact community prevalence of primary hypogonadism among adult men is unknown due to variation in aetiologies and cut-off values in the diagnosis.

Klinefelter syndrome is reported in 1:660 men [1]. Approximately 8% of the male childhood cancer survivors have been found to have primary hypogonadism [2].

Ageing is associated with an increased prevalence of primary hypogonadism. Once people with diagnosed testicular failure are excluded, the community prevalence of primary hypogonadism among men aged 40–79 years is approximately 2% [3]. Similarly, 2% of men evaluated for infertility were found to have primary hypogonadism [4].

Natural History

While primary hypogonadism due to functional causes recover on correcting the underlying aetiology, organic causes lead to permanent hypogonadism needing life-long treatment.

Aetiology

Causes of primary hypogonadism may be either congenital or acquired, with some acquired ones being functional (Table 13.1). Primary hypogonadism is more commonly due to classic organic causes. Functional hypogonadism, also termed late-onset or adult-onset male hypogonadism, is mostly secondary, though primary hypogonadism is recognised in some [5]. Some of the conditions cause combined primary and secondary hypogonadism. Common causes of primary hypogonadism are outlined below.

Table 13.1 Aetiology of Primary Hypogonadism in Men

Congenital	**Acquired**	
	Organic	**Functional**
Klinefelter syndrome (47, XXY) and variants Myotonic dystrophy Cryptorchidism (mainly uncorrected, bilateral) Noonan syndrome Bilateral congenital anorchia (vanishing testes syndrome) Autoimmune polyglandular syndrome type 1 Testosterone biosynthetic enzyme defects LH receptor mutations	Bilateral testicular trauma and torsion Bilateral orchidectomy Ionising radiation to the pelvis Aging[a] Orchitis (e.g., Mumps orchitis) Autoimmune polyglandular syndrome type 2 Chemotherapy (e.g., alkylating agents, procarbazine) Sickle cell disease Malignancy (testicular, Hodgkin lymphoma) Vasculitis Human Immunodeficiency syndrome[a] Hemochromatosis[a]	Chronic systemic diseases, starvation, malnutrition[a] Organ failure[a] (e.g., chronic kidney disease, cirrhosis) Drugs (e.g., ketoconazole, glucocorticoids[a]) Heavy smoking Heavy alcohol use

[a] Combined primary and secondary hypogonadism.

Klinefelter Syndrome

Klinefelter syndrome (47, XXY) and its subclasses, including higher grade aneuploidies (48, XXXY, 49, XXXXY, and 48, XXYY) and mosaicisms, constitute the commonest chromosomal disorder among men, despite its under-diagnosis [6]. In infancy, some men can present with a micropenis and cryptorchidism. At puberty, the testes might grow initially and then shrink with the lack of secondary sexual characteristics. Characteristic features in adults include primary hypogonadism, severe oligospermia/azoospermia, and small bilateral testes. Additionally, long legs, behavioural and psychological issues, and gynaecomastia are observed. There is increased fat mass, reduced lean mass, and increased tendency to develop metabolic disorders and cardiovascular disease. However, there is a spectrum of manifestations and men with milder features can be easily missed.

Cryptorchidism

Cryptorchidism (undescended testes) can be unilateral or bilateral. This could be isolated or due to another cause of primary or secondary hypogonadism. When isolated, impaired spermatogenesis and risk of testicular cancer are the main concerns, even after surgical correction. Leydig cell dysfunction, though rare, can occur in bilateral uncorrected cryptorchidism [7].

Bilateral anorchia

This is also termed vanishing testes syndrome. Since there is male internal genitalia, functioning testicular tissue had been present during the first trimester of pregnancy. With bilateral anorchia, the patient has a micropenis, absence of pubertal changes, and severe hypogonadism.

Myotonic Dystrophy

This autosomal dominantly inherited disorder has myotonia, cataract, cardiac defects, learning disability, and hypogonadism. While impaired spermatogenesis is commoner, some can have androgen deficiency as well.

Orchitis

Orchitis is a recognised complication of viral infections, most notably mumps, and typically occurs in pubertal boys or adult men. When bilateral, it carries a risk of impaired spermatogenesis, and in severe cases, may lead to androgen deficiency. However, this is now rare due to widespread vaccination [8]. Men recovering from SARS-CoV-2 (COVID-19) infection have also been reported to exhibit impaired spermatogenesis and reduced testosterone levels. While a non-specific inflammatory response appears to be the most plausible pathogenic mechanism, there have been documented cases of orchitis associated with COVID-19. However, long-term data on its reproductive consequences are still lacking [9].

Testicular Trauma

Blunt trauma or torsion leading to ischaemia can damage the testes. Correction of testicular torsion within 6 hours usually preserves the viability of testes. If not, there is a risk of atrophy. However, patients with testicular torsion are likely to have a developmental anomaly or reperfusion injury that predisposes them to testicular dysfunction including hypogonadism and low semen parameters [10, 11].

Iatrogenic Causes

Bilateral orchidectomy leads to permanent, profound hypogonadism. Chemotherapy with alkylating agents and ionising radiation can result in irreversible hypogonadism. Germ cells are sensitive, leading to the suppression of spermatogenesis. However, with higher doses, testosterone deficiency also can occur. Medications like ketoconazole reversibly inhibit testosterone synthesis, producing functional primary hypogonadism.

Autoimmune Polyglandular Syndrome

There are 2 main types. Type 1 (autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy) is an autosomal recessively inherited condition due to mutation in the AIRE gene. The main features include

mucocutaneous candidiasis, primary adrenal insufficiency, and hypoparathyroidism. Type 2 is a polygenic syndrome mainly associated with adrenal insufficiency, autoimmune thyroid disease, and Type 1 diabetes. Primary hypogonadism is more frequent in women than in men.

Aging

Functional hypogonadism associated with ageing – also termed adult-onset or late-onset hypogonadism – is generally secondary and linked to obesity and comorbidities that suppress gonadotropins and testosterone [5]. This is a potentially reversible. However, a minority of ageing men develop elevated gonadotropins while maintaining testosterone in the normal range (termed compensated hypogonadism), which may progress to true primary hypogonadism in some [3].

Chronic Systemic Diseases

Chronic systemic diseases such as cirrhosis, chronic kidney disease, heart failure, and chronic infections can cause low testosterone. Correlation with the symptoms is complex since there is an overlap of symptoms with the underlying illness. The pathophysiology is also complex, with mixed primary and secondary hypogonadism. Measurement of gonadotropin levels guides recognising the predominant component in the individual patient.

Pathophysiology

The normal hypothalamo–pituitary–testicular axis and functions of the hormones are summarised in Figure 13.1a. Pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates luteinising hormone (LH) and follicle-stimulating hormone (FSH) production from the pituitary. Leydig cells in the testes produce testosterone under the stimulation of LH. Sertoli cells and seminiferous tubules produce spermatozoa under the stimulation of FSH and high levels of intra-testicular testosterone. Sertoli cells produce Inhibin B under the stimulation of FSH, which exerts a negative feedback inhibition on the pituitary FSH production. Only 1%-2% of testosterone circulates freely, while the rest is bound to albumin (40%–50%, loosely bound and bioavailable) and sex-hormone-binding globulin (SHBG, 50%–60% and tightly bound) [12].

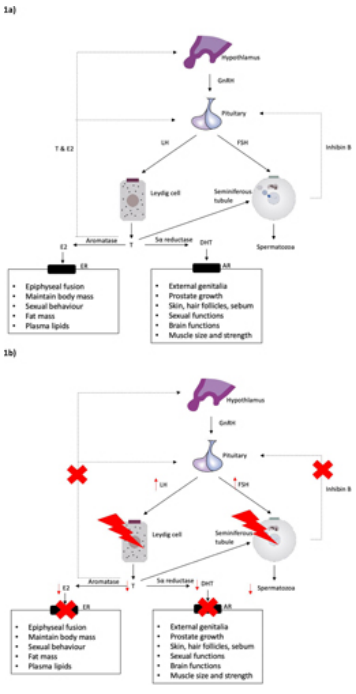


Figure 13.1a–b Hypothalamo–pituitary–testicular axis, its hormonal effects and alterations in primary hypogonadism. In a normal male (1A), hypothalamic gonadotropin-releasing hormone (GnRH) stimulates luteinising hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. LH stimulates testosterone production from the Leydig cells, and FSH and testosterone stimulate spermatogenesis. Testosterone is converted to more potent androgen dihydrotestosterone (DHT) and oestradiol (E2) which bind to androgen and oestrogen receptors, respectively. They exert different clinical effects on the end organs. Testosterone and oestradiol inhibit GnRH synthesis from the hypothalamus and LH and FSH synthesis from the pituitary. Inhibin-B produced from Sertoli cells under the stimulation of FSH inhibits FSH synthesis from the pituitary. In a male with primary hypogonadism (1B), testosterone synthesis from Leydig cells and spermatozoa and Inhibin B production from the Sertoli cells and seminiferous tubules are impaired. The lack of DHT and oestradiol produces clinical manifestations of hypogonadism; impaired feedback inhibition leads to increased levels of FSH and LH.AR- androgen receptor, DHT- dihydrotestosterone, E2- oestradiol, ER- oestrogen receptor, FSH- follicle-stimulating hormone, GnRH- Gondaotropin releasing hormone, LH- luteinising hormone, T- testosterone⏎

Testosterone is converted to more potent dihydrotestosterone (DHT) by 5-α reductase and oestradiol (E_2) by aromatase. In men, androgens and E_2 exert different effects in the body including negative feedback inhibition of the hypothalamus and pituitary [13]. During foetal life, androgens play a vital role in male internal and external genitalia differentiation and development. Activation of this axis plays a key role in puberty to produce secondary sexual characteristics, indicating the absence of pubertal development in males with the prepubertal onset of hypogonadism.

In primary hypogonadism, impaired testicular functions lead to failure of spermatogenesis and androgen synthesis resulting in a lack of effects of both androgens and oestrogen in the body systems (Figure 13.1b). Lack of negative feedback inhibition causes increased FSH and LH levels. The degree of androgen deficiency and impairment of spermatogenesis differ between individuals, but in most conditions, including Klinefelter syndrome, impairment of spermatogenesis is greater. The degree of elevation of FSH and LH levels varies depending on the impairment of Sertoli and Leydig cell functions, respectively. For example, there is greater elevation of FSH in Klinefelter syndrome.

Clinical Assessment

Clinical features of male hypogonadism vary according to the stage of onset (Table 13.2) [14, 15]. Reduced libido, absent spontaneous erections, incomplete or absent secondary sexual characteristics, lack of male type body hair and very small testes are specific features of hypogonadism [5, 8, 16]. In contrast, low mood, neurocognitive symptoms, reduced muscle mass and strength, and increased body fat are not specific, though frequently seen among men with hypogonadism. These non-specific features might be due to underlying comorbid conditions confounding the diagnosis of hypogonadism.

Table 13.2 Clinical Features of Primary Hypogonadism⏎

Stage of Onset of Hypogonadism	Clinical Features
Foetal life	Ambiguous genitalia
	Female genitalia
	Microphallus
	Bifid scrotum
	Cryptorchidism
	Hypospadias
Pre-pubertal (features described under the adult onset disease will also manifest in the adult life)	Delayed puberty

Stage of Onset of Hypogonadism	Clinical Features
Adult life (skeletal proportions, penile length, and voice are normal)	Eunuchoid body proportions (arm span greater than height at least 5 cm, symphysis-floor greater than crown-symphysis at least 5 cm)
	Infantile genitalia with small penis and testes, with poorly developed scrotum lacking rugae and pigmentation
	High-pitched voice
	Sexual dysfunction (erectile, ejaculatory, libido)
	Gynaecomastia
	Infertility
	Loss of male type hair distribution
	Decreased muscle mass
	Height loss or minimal trauma fractures
	Hot flushes (not observed in prepubertal disease)

Clinical assessment includes focused history, examination, and laboratory investigations to diagnose hypogonadism and then differentiate primary and secondary hypogonadism. Once primary hypogonadism is diagnosed, identifying the aetiology, comorbidities, and suitability for testosterone treatment should be performed.

A diagnosis of hypogonadism should only be made in the presence of clinical features of hypogonadism together with consistently and unequivocally low testosterone levels [16].

Focused History

- Symptoms of hypogonadism (Table 13.2).
- Potential causes of hypogonadism (Table 13.1 and causes of secondary hypogonadism).
- Factors that can affect testosterone level assessment
    - Recent acute illness
    - Conditions causing alteration of sex-hormone-binding globulin
        - *Increase*: Aging, thyrotoxicosis, cirrhosis, HIV, anticonvulsant use, oestrogen use
        - *Decrease*: Obesity, diabetes mellitus, hypothyroidism, glucocorticoid use, androgen use, nephrotic syndrome, acromegaly
    - *Medicines*: Androgens, anti-androgens, cannabinoids, glucocorticoids

Focused Examination

- Signs of hypogonadism (Table 13.2).
- Signs of underlying chronic illnesses that can cause hypogonadism or confound the diagnosis.

Investigations

- Fasting, morning (before 11 a.m.) total testosterone level using a validated assay.
    - Repeat if low before confirming the diagnosis
    - Reasonably excludes if normal
- Calculate free testosterone or measure using equilibrium dialysis.
    - Men with total testosterone close to the lower limit (8–12 nmol/L)
    - Men with conditions that can affect sex-hormone-binding globulin levels (see above)
- Gonadotropin levels (FSH, LH) to differentiate primary and secondary hypogonadism.
- When primary hypogonadism is confirmed.
    - Karyotyping to diagnose Klinefelter syndrome if no other obvious alternative diagnosis and small testicular volume (<14 ml)
    - Semen analysis if there is infertility or plans to have children
    - Fracture risk assessment (e.g., FRAX score) ± bone densitometry (if the history of fragility fractures or high-risk)

The proposed algorithm to evaluate for primary hypogonadism is shown in Figure 13.2.

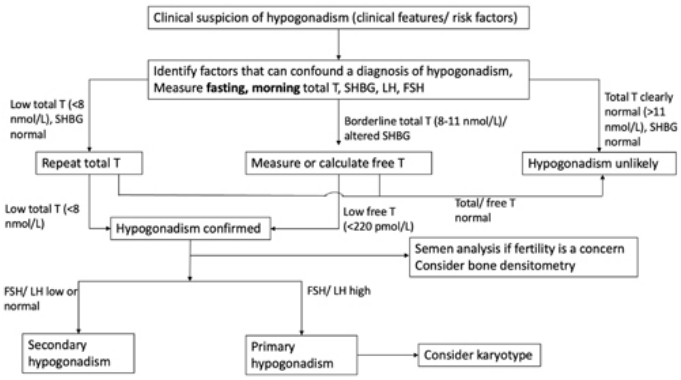


Figure 13.2 A suggested algorithm for the diagnosis and evaluation of primary hypogonadism in men with clinical suspicion of hypogonadism. Perform morning fasting total testosterone test. Repeat and confirm if total testosterone is unequivocally low. If total testosterone is borderline or there are conditions likely to affect sex-hormone-binding globulin, calculate or measure free testosterone. If total testosterone and/or free testosterone are normal, hypogonadism is unlikely. Once hypogonadism is confirmed, test gonadotropin levels to differentiate primary and secondary hypogonadism. In primary hypogonadism, perform karyotype if no other alternative causes, especially if the testicular volume is low. FSH- follicle-stimulating hormone, LH- luteinising hormone, SHBG- sex-hormone binding globulin, T- testosterone⏎

Management

Testosterone remains the gold-standard treatment for men with primary hypogonadism. Alternative treatment options, such as selective oestrogen receptor modulators and aromatase inhibitors are likely beneficial mostly in secondary hypogonadism due to their ability to increase gonadotropin levels by blocking the negative feedback inhibition exerted by oestrogen. However, in partial testicular failure, it could potentially increase gonadotropin levels further to compensate for the inadequate testicular function and increase androgen production.

Correction of the underlying risk factors is a critical component in managing functional hypogonadism, which is potentially reversible.

Testosterone Treatment

Goals of Therapy

The goals of testosterone treatment include alleviating symptoms related to hypogonadism and prevention of complications of long-term hypogonadism. Benefits of optimal testosterone treatment include [8]:

- Development/maintenance of male secondary sexual characteristics (facial and body hair growth, penile enlargement, scrotum pigmentation, and voice deepening)
- Improvement in sexual functions including libido and erectile function
- Improvement in muscle mass and strength
- Maintenance of bone strength and prevention of osteoporosis
- Prevention of anaemia

However, there is less robust evidence on improvement in mood, well-being, and cognitive functions. Some of the evidence on the effects of testosterone are from older men with functional hypogonadism rather than men with classic organic hypogonadism [17]. Therefore, benefits in men with organic primary hypogonadism are likely to be more pronounced.

Adverse Effects

- *Erythrocytosis*: The risk is higher with higher doses of testosterone and in older men. Haematocrit >54% might be a risk factor for arterial and venous thrombosis, but the evidence is lacking.
- *Effects on the prostate*: In men with hypogonadism, the prostate is small. Testosterone treatment can increase the size and prostate-specific antigen (PSA) levels. There is a potential risk of growth of small, dormant prostate tumours with testosterone. But there is no evidence that testosterone increases the risk of prostate cancer [18, 19].
- *Cardiovascular effects*: Concerns over cardiovascular safety of testosterone therapy have been raised based on some data from middle aged and older men with low testosterone rather than men with primary hypogonadism. Even in this population, recent data suggest medium-term cardiovascular safety of testosterone [20, 21].
- *Impairment of spermatogenesis and fertility*: In partial primary hypogonadism, if there is some degree of spermatogenesis, this can be suppressed by exogenous testosterone treatment by inhibiting gonadotropin levels.
- *Skin changes*: Acne, oily skin.
- Gynaecomastia.
- Worsening of obstructive sleep apnoea (OSA): Data not convincing.
- Slight reduction in HDL cholesterol.

Contraindications

- Untreated prostate and breast cancer.
- *Polycythaemia*: Cut-off haematocrit is not clearly defined. Need to be cautious even at a value of >48% since testosterone can further increase the haematocrit.
- *Severe heart failure*: NYHA class III or IV.
- *Major cardiovascular event*: Myocardial infarction/stroke within past 6 months.
- Severe lower urinary tract symptoms due to benign prostatic hyperplasia.
- PSA >4 ng/mL or prostate abnormality on digital rectal examination without further urological evaluation.
- Untreated severe sleep apnoea.

Pretreatment Evaluation

- Cardiovascular disease.
- Features of obstructive sleep apnoea.
- Lower urinary tract symptoms.
- Haematocrit.
- Prostate cancer screening- in men >50 years or >40 years if high risk (first degree relative with prostate cancer/African ethnicity) using PSA ± digital rectal examination after shared decision with the patient. Not considered mandatory since benefits are not well established.

Testosterone Preparations

Different formulations available in the market for testosterone replacement are summarised in Table 13.3. Transdermal gels and long-acting intramuscular injections are most commonly used in the UK. The most suitable preparation for the individual patient should be selected considering the pharmacokinetics, side effects, patient preference, cost, and availability. Shorter-acting agents are preferred initially to allow withdrawal in case of adverse effects. When replacing testosterone for adult men with primary hypogonadism, the dose indicated in Table 13.3 can be initiated with subsequent titration according to the clinical and biochemical response. In adolescents who have not undergone puberty, treatment should start with low doses and be escalated gradually to replicate normal pubertal progression and avoid premature epiphyseal closure. A similar cautious approach is advised for adult men with absent puberty, avoiding abrupt changes in sexual features and mood.

Table 13.3 Preparations Available for Testosterone Treatment⏎

Route	Preparation	Administration (Dose and Frequency)	Advantages	Preparation Specific Adverse Effects	Disadvantages

Route	Preparation	Administration (Dose and Frequency)	Advantages	Preparation Specific Adverse Effects	Disadvantages					
Intramuscular	Testosterone enanthate/cypionate	150–200 mg IM every 2–4 weeks or 75–100 mg IM every week	Low cost, extensive experience	Erythrocytosis commoner than transdermal, injection by a health care worker	Pain due to IM injection, fluctuations in testosterone concentrations and symptoms	Testosterone undecanoate	1 g repeated in 6–8 weeks, then every 10–14 weeks IM	Less frequent administration, fewer fluctuations	Potential of pulmonary oil microembolism, erythrocytosis commoner than transdermal, injection by a health care worker	Pain due to large volume (4 mL) of IM injection, prolonged effect if adverse effects
Subcutaneous	Testosterone pellets	600–1,200 mg (3–6 pellets) Inserted every 4–6 months	Sustained response up to 6 months	Infection and scarring at the site of insertion	Painful surgical procedure, risk of extrusion					
	Testosterone enanthate/cypionate	50–100 mg every 7–10 days	Self-injection		Frequent injections					
Transdermal	Testosterone patch	4–8 mg (using 1–2 patches) daily	Convenience, fewer fluctuations, mimics circadian rhythm when applied at night	Skin irritation	Poor adherence due to irritation and sweating					
	Testosterone-in-adhesive matrix patch	4.8 mg (two patches) applied every 2 days	Convenience, fewer fluctuations, lasts 2 days	Some skin irritation						
	Testosterone gel	5–10 gm of 1% gel (50–100 mg), 1.62% gel delivering 20.25–81 mg, or 2% gel delivering 40–70 mg, applied once daily via sachets, pumps, or tubes	Easy application, skin tolerability, fewer fluctuations, flexibility of dosing	Skin irritation in some, supraphysiological DHT concentrations	odour Skin–skin transfer to female partner/children, variable absorption, stickiness, slow drying, body					
	Testosterone axillary solution	60 mg applied daily		Good skin tolerability		Skin–skin transfer to female partner/children, variable absorption				
Buccal	Testosterone buccal preparation	30 mg buccal tablets applied twice daily		Convenience	Irritation of gums	Alteration in taste, 2 times daily administration, no dose flexibility				
Nasal	Testosterone nasal gel	11 mg 3 times daily		Rhinorrhoea, epistaxis, nasal discomfort, nasal congestion, parosmia	3 times daily administration, variable absorption, no nose blowing/sniffing					
Oral	Testosterone undecanoate	1–3 capsules (40–120 mg) 2–3 times daily with meals	Convenience of oral route	Liver toxicity	Variable bioavailability, need fatty meals for absorption					

Follow-up During Testosterone Treatment

Follow-up during testosterone treatment should assess for patient adherence, efficacy, and safety [16]. The patient is assessed at 3–12 months from initiation of treatment and then annually. Important components during follow-up are summarised in Table 13.4. The timing of testosterone concentration depends on the formulation, but the target is to maintain the mid-normal range. Monitoring for prostate cancer needs to consider patient preference since there is no clear evidence of benefit of screening. Standard recommendations for the general public can be followed.

Table 13.4 Monitoring of Men During Testosterone Treatment

Domain	Components	Timing	Remarks
Clinical features of hypogonadism	Libido, sexual functions, activity, energy and mood Body hair growth, muscle mass and strength	3 and 12 months, then annually	Symptom improvement usually by 3–6 months
Bone health	Bone densitometry	1–2 years	If high risk for fractures
Serum testosterone	Short-acting injections: Midway between 2 injections/trough levels just before the next injection Patch: 8–10 hours after the application of the patch previous night Gel/solution: Any time after application	Short-acting injections: 3–6 months, and every 6–12 months thereafter Long-acting injections: Before the third dose and annually thereafter Patch: 3–4 weeks Gel/solution: 2 weeks Monitor early if dose-adjusted	Adjust dose according to the concentration and symptoms. If trough levels are low, increase the frequency of injections.
Clinical features of adverse effects	History and focused examination for adverse effects of testosterone treatment and formulation specific adverse effects outlined above	3–6 months, 12 months, annually thereafter	Consider specific measures for adverse effects (e.g., local measures for acne, CPAP for sleep apnoea), dose reduction and slow up-titration (e.g., behavioural changes) or even temporary discontinuation (recent cardiovascular event) accordingly. For formulation specific adverse effects, consider switching formulations or specific measures (e.g., corticosteroid application for skin irritation)
Prostate	PSA ± digital rectal examination	3–12 months, then depending on local guidelines for prostate cancer screening	Only in patients eligible and consenting for prostate cancer screening as outlined under pretreatment evaluation
Erythrocytosis	Haematocrit	3–6 months, annually thereafter	If >54% discontinue and restart at a lower dose or reduce the dose. Consider evaluating for additional risk factors like chronic lung diseases or OSA

Fertility Management

Impaired spermatogenesis is usually observed in men with primary hypogonadism due to concomitant dysfunction of both Leydig and Sertoli cells. Therefore, gonadotropin therapy is not effective, unlike in secondary hypogonadism. However, semen analysis should be performed at baseline if fertility is a concern. If there is normospermia or oligospermia, cryopreservation before testosterone treatment ± assisted reproductive technologies (intrauterine insemination/in vitro fertilisation) is an option and should be discussed with the patient [6]. In men with azoospermia, microdissection testicular sperm extraction (mTESE) is the gold standard treatment to recover sperm, which can then be used for intra-cytoplasmic sperm insemination (ICSI) [22].

Genetic counselling and pre-implantation genetic testing are important for men with inherited syndromes such as Klinefelter syndrome (risk of aneuploidy) and myotonic dystrophy (risk of transmission). Donor sperm or adoption are alternatives when all interventions fail.

Other Aspects of Management

Management of primary hypogonadism should be holistic, addressing not only androgen replacement and fertility but also wider physical and psychological health challenges.

Bone health

Testosterone therapy improves bone mineral density in men with hypogonadism [23]. However, no evidence demonstrates a reduction in fracture risk. Men with hypogonadism and osteoporosis should receive standard osteoporosis care in addition to testosterone.

Sexual Dysfunction

Some sexual symptoms, such as ejaculatory and erectile dysfunction, may persist despite adequate testosterone replacement. The addition of phosphodiesterase 5 inhibitors (PDE5i) can be effective for erectile dysfunction. If the response is suboptimal, further evaluation and management should be undertaken.

Gynaecomastia

Recent-onset gynaecomastia often regresses with testosterone therapy. However, some men, particularly adolescents and adults starting treatment, develop new or worsening pain due to gynaecomastia [24]. Recent-onset cases may be treated with selective estrogen receptor modulators (SERMs) such as tamoxifen or

clomiphene citrate. Long-standing fibrotic gynaecomastia is unresponsive to medical therapy; surgery is an option if symptoms persist.

Metabolic Abnormalities

The relationship between hypogonadism and metabolic syndrome is bidirectional. While obesity and metabolic syndrome often cause secondary functional hypogonadism, hypogonadism itself can adversely affect fat distribution, insulin sensitivity, and metabolic health [25]. Men with hypogonadism are at increased risk of metabolic syndrome and related conditions. Low testosterone consistently correlates with cardiovascular disease, although a causal link remains unproven [25]. Therefore, regular screening, lifestyle interventions, and appropriate treatment of metabolic risk factors are essential.

References

1. Gravholt CH, Chang S, Wallentin M, Fedder J, Moore P, Skakkebæk A. Klinefelter syndrome: integrating genetics, neuropsychology, and endocrinology. *Endocrine Reviews*. 2018;39(4):389–423.⏎
2. Brignardello E, Felicetti F, Castiglione A, Nervo A, Biasin E, Ciccone G, et al. Gonadal status in long-term male survivors of childhood cancer. *Journal of Cancer Research and Clinical Oncology*. 2016;142(5):1127–1132.⏎
3. Tajar A, Forti G, O'Neill TW, Lee DM, Silman AJ, Finn JD, et al. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. *The Journal of Clinical Endocrinology & Metabolism*. 2010;95(4):1810–1818.⏎
4. Ventimiglia E, Ippolito S, Capogrosso P, Pederzoli F, Cazzaniga W, Boeri L, et al. Primary, secondary and compensated hypogonadism: a novel risk stratification for infertile men. *Andrology*. 2017;5(3):505–510.⏎
5. Corona G, Goulis DG, Huhtaniemi I, Zitzmann M, Toppari J, Forti G, et al. European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males: Endorsing organization: European Society of Endocrinology. *Andrology*. 2020;8(5):970–987.⏎
6. Zitzmann M, Aksglaede L. *European academy of andrology guidelines on Klinefelter Syndrome Endorsing Organization: European Society of Endocrinology*. 2021;9(1):145–167.⏎
7. Rohayem J, Luberto A, Nieschlag E, Zitzmann M, Kliesch S. Delayed treatment of undescended testes may promote hypogonadism and infertility. *Endocrine*. 2017;55(3):914–924.⏎
8. Jayasena CN, Anderson RA, Llahana S, Barth JH, MacKenzie F, Wilkes S, et al. Society for Endocrinology guidelines for testosterone replacement therapy in male hypogonadism. *Clinical Endocrinology*. 2022;96(2):200–219⏎
9. Sengupta P, Leisegang K, Agarwal A. The impact of COVID-19 on the male reproductive tract and fertility: A systematic review. *Arab Journal of Urology*. 2021;19(3):423–436.⏎
10. Aggarwal D, Parmar K, Sharma AP, Tyagi S, Kumar S, Singh SK, et al. Long-term impact of testicular torsion and its salvage on semen parameters and gonadal function. *Indian Journal of Urology: IJU: Journal of the Urological Society of India*. 2022;38(2):135.⏎
11. Jacobsen FM, Rudlang TM, Fode M, Østergren PB, Sønksen J, Ohl DA, et al. The impact of testicular torsion on testicular function. *The World Journal of Men's Health*. 2020;38(3):298.⏎
12. Dandona P, Rosenberg MT. A practical guide to male hypogonadism in the primary care setting. *International Journal of Clinical Practice*. 2010;64(6):682–696.⏎

13. Corradi PF, Corradi RB, *Greene LW. Physiology of the hypothalamic pituitary gonadal axis in the male*. *Urologic Clinics*. 2016;43(2):151–162.⏎
14. Basaria S. Male hypogonadism. *The Lancet*. 2014;383(9924):1250–1263.⏎
15. Dohle G, Arver S, Bettocchi C, Jones T, Kliesch S. *EAU guidelines on male hypogonadism*. *European Association of Urology*. 2018.⏎
16. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*. 2018;103(5):1715–1744.⏎
17. Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, et al. Lessons from the testosterone trials. *Endocrine Reviews*. 2018;39(3):369–386.⏎
18. Lenfant L, Leon P, Cancel-Tassin G, Audouin M, Staerman F, Rouprêt M, et al., editors. Testosterone replacement therapy (TRT) and prostate cancer: An updated systematic review with a focus on previous or active localized prostate cancer. *Urologic Oncology: Seminars and Original Investigations*; 2020: Elsevier.⏎
19. Bhasin S, Travison TG, Pencina KM, O'Leary M, Cunningham GR, Lincoff AM, Nissen SE, Lucia MS, Preston MA, Khera M, Khan N. Prostate safety events during testosterone replacement therapy in men with hypogonadism: *JAMA Network Open*. 2023 1;6(12):e2348692.⏎
20. Lincoff AM, Bhasin S, Flevaris P, Mitchell LM, Basaria WE, Cunningham GR, Granger CB, Khera M, Thompson Jr IM, Wang Q. Cardiovascular safety of testosterone-replacement therapy. *New England Journal of Medicine*. 2023 Jul 13; 389(2):107–117.⏎
21. Hudson J, Cruickshank M, Quinton R, Aucott L, Aceves-Martins M, Gillies K, Bhasin S, Snyder PJ, Ellenberg SS, Grossmann M, Travison TG. Adverse cardiovascular events and mortality in men during testosterone treatment: an individual patient and aggregate data meta-analysis. *The Lancet Healthy Longevity*. 2022 Jun 1;3(6):e381-93.⏎
22. Kalsi JS, Shah P, Thum Y, Muneer A, Ralph DJ, Minhas S. *Salvage micro-dissection testicular sperm extraction; outcome in men with non-obstructive azoospermia with previous failed sperm retrievals*. *BJU International*. 2015;116(3):460–465.⏎
23. Golds G, Houdek D, Arnason T. Male hypogonadism and osteoporosis: the effects, clinical consequences, and treatment of testosterone deficiency in bone health. *International Journal of Endocrinology*. 2017;4602129⏎
24. Narula HS, Carlson HE. Gynaecomastia: pathophysiology, diagnosis and treatment. *Nature Reviews Endocrinology*. 2014;10(11):684–698.⏎
25. de Silva NL, Grant B, Minhas S. Jayasena CN, Cardiovascular disease and testosterone therapy in male hypogonadism. *Annals of the New York Academy of Sciences*. 2024;1540(1):121–132.⏎

14 Urethral Stricture

Hermione Tsoi, Hannah Pendegast and Nadir I. Osman

DOI: 10.1201/b22940-14

Introduction

Urethral stricture is a circumferential narrowing of the urethra secondary to ischaemic spongiofibrosis. This causes patients to experience obstructive lower urinary tract symptoms and has a major impact on their quality of life. There are different aetiologies, including infective, inflammatory, traumatic and iatrogenic. A thorough assessment including identification of stricture characteristics (which can be established through specialist investigations), associated risk factors for stricture disease and patient comorbidities are required prior to deciding on the type and modality of treatment.

With the advancement of technology and skills, there are a number of ways to manage urethral stricture disease. Reconstructive surgeons are required to be familiar with the different techniques available and select the most appropriate treatment option for patients based on the characteristics of each stricture.

Anatomy

The male urethra is formed by the prostatic urethra, membranous urethra, bulbar urethra, and penile urethra. The former two segments form the posterior urethra, and the latter forms the anterior urethra. An adult male urethra measure about 18–20 cm in length [1].

The posterior urethra measures about 4 cm in length and consists of the membranous urethra (surrounded by the urethral sphincter). The internal

sphincter is located at the bladder neck. The prostatic urethra is relatively immobile as it is attached to the anterior pubic arch by the puboprostatic ligament. This segment ends at the perineal membrane [2].

The anterior urethra begins distal to the perineal membrane and extends to the fossa navicularis. It is surrounded by the corpora spongiosum. Urethral stricture is due to ischaemic fibrosis of spongy tissue (ischaemic spongiofibrosis) and is thus a disease of the anterior urethra. As the posterior urethra is not surrounded by spongiosis tissue, a narrowing in the posterior segment is referred to as posterior stenosis.

Blood supply

The internal pudendal arteries become the bulbar arteries as they pass through the urogenital diaphragm. The bulbar arteries travel through the perineal membrane to supply the bulb of the corpus spongiosum. The dorsal penile artery also supplies the corpus spongiosum through a retrograde flow, following its anastomosis with the bulbar arteries in the glans penis. This dual supply means that the blood flow of the corpus spongiosum can still be maintained if the antegrade supply is lost, such as when the urethra is transected [2].

Epidemiology

Urethral stricture affects about 0.6% of the population, with an associated prevalence of 229–627 per 100,000 men. Elderly men are more at risk of this condition, and it is noted that there is a significant increase after the age of 55. There are data suggesting that Black Americans have a higher risk of urethral stricture compared to white Americans [3].

The most commonly affected site is the bulbar urethra (46.9%). Studies have shown that the mean stricture length is 4 cm [4].

Aetiology

1. *Sexually transmitted infection* (*STI*): Gonorrhoea is the main cause of urethral strictures amongst all STIs. However, prompt antimicrobial

treatments for infective urethritis are thought to be helpful in reducing the risk. Thus, in developed world countries, STI as a cause of urethral stricture is largely a historical problem.

2. *Inflammation*: Lichen sclerosus is the most common cause of pan-urethral stricture (accounts for 48.6%). Risk factors for this includes uncircumcised men, obesity, diabetes mellitus, coronary artery disease, smoking and hypertension.
3. *External urethral trauma*: This is usually a result of blunt trauma to the perineum secondary to motor vehicle accidents, pelvic fracture, sporting injuries, sexual intercourse and penile fracture. The bulbar urethral is most vulnerable to this type of injury.
4. *Iatrogenic urethral injury*: Likely secondary to cystoscopies, surgery for benign prostate hyperplasia (BPH) or prostate cancer, radiotherapy and repeated catheterisation or traumatic catheterisation. It is worth noting that non-coated latex catheters are associated with higher risk of urethral stricture.

a. *Catheterisation* (*indwelling/ intermittent self-catheterisation*): False passage formation and inflation of balloon within the urethra can cause urethral injury and subsequent urethral stricture, most commonly at the bulbar and posterior urethra.
b. *Transurethral prostate surgery*: This is the most common cause of iatrogenic urethral stricture (accounts for 41%) and most commonly affecting the bulbomembranous urethra. Several operative risk factors have been identified to increase the risk of urethral stricture such as operative time >60 minutes, urethral mucosa rupture, prostatic inflammation, larger-sized endoscopic sheath and post-operative infection.
c. *Prostate radiation therapy*: Strictures post radiotherapy usually occurs in the bulbomembranous urethra. The combination of external beam radiation therapy and brachytherapy is a significant predictor for urethral stricture. Stricture rate also increase with time post radiotherapy.
d. *Post high-intensity focused ultrasound* (*HIFU*) *or cryotherapy for localised prostate cancer*: The incidence of urethral stricture following HIFU is between 1.9% and 40.3% [5].

5. *Congenital*: Congenital strictures are usually diagnosed at the early age of life. These strictures are typically short and affects the bulbar urethra.
6. *Idiopathic.* [6,7]

Pathophysiology

The urethra is lined by stratified columnar epithelium (proximal two-thirds) and stratified squamous epithelium (distal one-third). Metaplasia can occur following infection or increased voiding pressure, changing columnar epithelium to squamous epithelium. Squamous epithelium lacks elasticity and, therefore, this mucosal layer is susceptible to rupture following any form of insult such as infection, inflammation, trauma or iatrogenic injury, etc.

When mucosal breakdown happens, there will be an area of ulceration and urine can extravasate locally. During the process of healing, fibrosis takes place in the subepithelial layer within the corpus spongiosum. Vascularity to this area may be damaged and lost, leading to the formation of fibrotic plaques. These fibrotic plaques act as a layer of support to the overlying epithelium and therefore the next mucosal breakdown will happen in the adjacent areas.

Over time, more fibrotic plaques will be formed and accumulate. When these scarred tissue merge together, they form a constricting ring around the urethra resulting in a urethral stricture [8].

Assessment

History

Patients with urethral stricture disease will often present with undifferentiated voiding lower urinary tract symptoms. A thorough history and examination are essential to elicit the hallmark features that implicate urethral stricture as a differential diagnosis and to allow more focused investigations to both confirm the diagnosis and plan for its management [1, 7].

Symptoms associated with urethral stricture disease exist on a spectrum. Some patients may have a urethral stricture with no symptoms at all due to the degree of stricture not yet impeding the flow of urine. In some patients there may also be the development of compensatory mechanisms (e.g., bladder hypertrophy), which subsequently delays the onset of voiding symptoms associated with urethral stricture disease. Nevertheless, the symptoms most commonly associated with urethral stricture disease include intermittency, straining, poor urinary stream and prolonged duration of voiding. Hesitancy and incomplete emptying may also be present. The spraying of urine is very specifically related to meatal stenosis or stricture. The symptoms experienced can broadly be attributed to a degree of urinary outflow obstruction. Patients may also present with haematuria, epididymitis, prostatitis and recurrent urinary tract infections, which demonstrate development of sequalae. Differential diagnoses from the history in addition to urethral stricture disease also include prostate- and bladder-related pathology [1, 7, 9].

The complete history should also include assessment of the patient's past medical and surgical history. Specifically, within this it is important to establish previous episodes of instrumentation of the urinary tract (including catheters and the ease of their insertion), previous urological procedures or investigations, past history of urethral strictures and subsequent treatments received and any history of pelvic fractures or perineal trauma (e.g., saddle/stride injuries). Previous history of hypospadias repair is an important risk factor to identify particularly in the younger population. In the older population enquiry about history of prostatectomy and pelvic radiotherapy are also important as these can represent risk factors for development of urethral stricture disease.

Relevant non-urological history includes diabetes and the degree of glycaemic control as this can contribute to the development of lichen sclerosus and is an independent risk factor for recurrent urinary tract infections. Establishing the patient's general fitness and comorbidities is important to assess fitness and appropriateness for surgical interventions. In the social history, previous sexually transmitted infections, non-iatrogenic urethral instrumentation and trauma are important to establish [1, 10, 12].

Examination

Examination of the patient should include an examination of the abdomen and be completed with examination of the external genitalia. This should include an assessment of the presence of and quality of prepuce (as this can occasionally be considered a donor graft site) and also palpation along the length of the urethra to detect for presence of fibrosis. Examination of the scrotum should assess for previous surgical scars and evidence of sequalae (e.g., orchitis and fistula disease). A digital rectal examination of the prostate may also be performed. Examination of the patient may elicit findings that support the diagnosis of urethral stricture disease or indicate an alternative diagnosis. The presence of lichen sclerosus is important as this can be associated with some types of urethral stricture disease, and it is an important factor in determining the type and possible outcomes from treatment. It is worth noting that BPH and urethral stricture disease can exist concomitantly, particularly in those who have performed ISC, had an indwelling urethral catheter or undergone multiple instrumentations in relation to their BPH. Worsening symptoms on a background of previously stable prostate disease should raise a suspicion of this [1, 9, 10].

Investigations

Simple initial investigations should be performed. This includes a urinalysis to exclude urinary tract infection, a urinary flow rate to assess the voiding pattern and a post-void residual bladder scan to exclude urinary retention. Urethral stricture disease has a pathognomonic pattern of voiding (Figure 14.1) identifiable on the urinary flow test. There is short rise to maximal flow (Qmax), which is reduced compared to expected value for age with an early plateau at the Qmax and prolonged voiding time. This produces a flattened curve shape. Urinary retention may or may not be present depending on the degree of obstruction present from the urethral stricture and can be assessed by examination of the abdomen for a palpable bladder and bedside post-void bladder volume measurement (bladder scan) [1, 7, 9].

Figure 14.1 Urinary flow rate suggestive of a urethral stricture.⏎

Once simple investigations have been completed, if necessary, more invasive investigations may be considered. The role of flexible urethrocystoscopy in the evaluation of urethral stricture disease is limited; however, it is an essential investigation in patients presenting with haematuria to exclude a malignant underlying process. Patients undergoing this investigation for the indication of haematuria may have a stricture identified during the process. The information that can be gained by this investigation is limited to the location of the stricture, its visual appearance and its ability to be navigated with the cystoscope. Where the stricture is non-navigable the operator is unable to assess the length of the stricture or the presence of further proximal stricture. As a result of the limitations of urethrocystoscopy further imaging is almost always required. The combination of a retrograde urethrogram and voiding cystourethrogram provide a comprehensive image of the urethra. These two investigations allow the assessment of the number and length of urethral strictures present in addition to the location of the urethral stricture(s) (Figure 14.2). This comprehensive assessment ultimately allows consideration and planning of management options [1, 7, 9, 11].

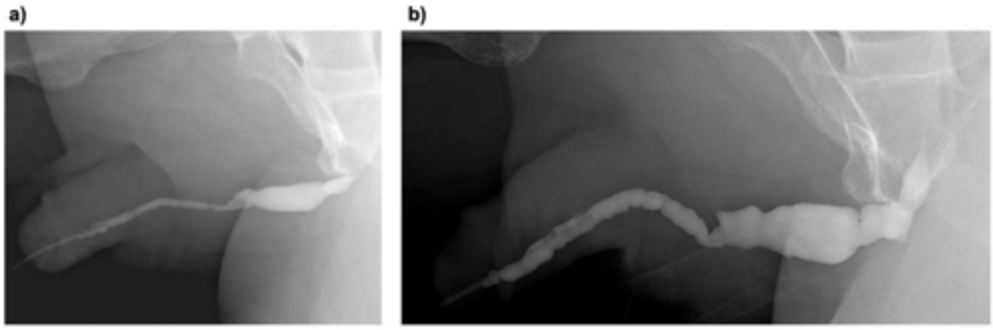


Figure 14.2a–b Ascending urethrogram.⏎

(a) Demonstrates a full-length penile urethral stricture; (b) Demonstrates a penile urethral stricture with some stricturing of the bulbar urethra.

The role of other additional adjunct investigations for urethral stricture disease is variable in clinical practice. Urethral ultrasound has been shown to be accurate in the assessment of surrounding spongiofibrosis and precise measurement of urethral stricture length. This is an investigation that can be utilised both pre- and intra-operatively, but this is not currently widely established in routine clinical practice. The role of MRI in routine practice for anterior urethral stricture disease is also controversial but MRI is increasingly used in planning posterior urethral reconstruction [1, 9, 12].

Management

The management of urethral stricture disease can be divided into conservative and operative approaches. Operative management can be further divided into endoscopic procedures and open reconstructive procedures. Prior to counselling the patient regarding possible management approaches, it is important to consider if the patient has primary or recurrent urethral stricture disease, the patient's overall fitness and the patient's outcome goals. It should also be made clear if the treatments offered are with curative or palliative intent in order to manage the patient's expectations. In addition to the above, number, location and length of

urethral strictures present will also determine the type of operative intervention offered.

A patient may wish to consider a conservative approach to treatment if they have high anaesthetic risks or high risk of operative treatment failure (particularly if they have previously undergone operative management with poor outcome) and where their symptoms can adequately be managed in the outpatient setting. It is for this reason that establishing the patient's goals and expectations with respect to their urethral stricture is important so that they can be properly counselled.

Urethral Dilatation and Direct Vision Internal Urethrotomy

Urethral dilatation involves the use of instruments to progressively stretch the urethral calibre to a larger diameter. The mechanism for this is disruption of the scar tissue. Urethral dilatation should not be performed in the presence of active urinary tract infection. Recognised side effects include urinary tract infection, development of urinary sepsis and urethral haemorrhage. The nature of the development of new scar tissue also explains the risk of recurrence of urethral stricture associated with this treatment [1, 9].

Direct vision internal urethrotomy (DIVU) is an endoscopic procedure during which the surgeon performs a longitudinal incision along the entire length of the urethral stricture and into surrounding healthy tissue. This creates a gap between the wound edges which is eventually re-epithelialized and heals by secondary intention with the result of increasing the urethral calibre. Traditionally, this procedure has been performed with a 'cold knife'; however, there are developing techniques for performing this procedure with laser, though this does not appear to hold any significant advantage [1, 7, 9]. Recognised side effects include urinary tract infection, development of urinary sepsis, urethral haemorrhage and extravasation of urine into the surrounding tissues. Erectile dysfunction can also occur if DVIU is used in the penile urethra as a result of iatrogenic fistula formation between the corpus spongiosum and corpus cavernosa.

Urethral dilatation and DIVU are most likely to be successful in primary single, short bulbar urethral strictures (<2cm in length). Longer stricture length carries higher risk of recurrence and risk of recurrence is highest in

the first 12 months after the procedure. Risk of recurrence also increases with subsequent procedures and as healthy tissue is affected the length of recurrent strictures is ultimately longer with worse outcomes. The stricture-free rate after three or more DIVU in one study was 0% with downward trending success after first (12.1%) and second procedures (7.9%) [13]. Urethral dilatation and DIVU can be considered equal in terms of success in this context, with similar risk of complications. Use of DIVU for urethral strictures in the penile and membranous urethra should be discouraged as it carries a higher risk of complications and recurrence. There is no strong evidence to support the use of intermittent self-dilatation or indwelling urinary catheter after urethral dilatation or DIVU procedures and both are associated with reduced quality of life [1, 7, 9].

Adjuncts have been explored in addition to the above interventions. Mitomycin C has anti-fibrotic properties and its role in reducing recurrence after injection into freshly incised urethral tissue has been demonstrated in randomised controlled trials (RCTs); however, concerns about consequences of its extravasation into surrounding tissues has stalled its introduction into routine clinical practice. Overall, one meta-analysis concluded that the use of Mitomycin C could significantly reduce the recurrence rate of urethral strictures (risk ratio 0.42, $p=0.0002$); however, it noted that the overall quality of available studies is low and higher quality studies are required before this can be routinely adopted into clinical practice [14].

The use of temporary and permanent endoluminal urethral stents has also been explored; however, high complication rates, including stent migration, obstruction, encrustation, infection and pain have led to their use being largely abandoned and the removal of several products from the market [9, 12].

Recently, a drug-coated balloon device has been investigated, with promising results. The Robust III trial is a multi-centre, single-blind RCT of Optilume drug-coated balloon (coated with paclitaxel) against standard care, which included DVIU, serial dilatation or use of a non-drug-coated balloon, in patients with recurrent anterior urethral strictures. Paclitaxel functions similarly to mitomycin C, inhibiting fibroblast proliferation and scar formation. The trial primarily enrolled patients with bulbar urethral strictures and found that the stricture-free rate at 6 months was significantly

higher in the drug-coated balloon group compared to the standard care group (74.6% vs 26.8%; absolute difference 44.4%, 95% CI 27.6–61.1; p< 0.0001). No difference was observed in primary safety endpoints at 3 months post-procedure; however, haematuria and dysuria were more frequently reported in the drug-coated balloon group (11.4% vs 0.1%). Further investigation is needed to determine its long-term viability and cost effectiveness [15].

Bulbar Urethroplasty

Urethroplasty is the most definitive management for anterior urethral stricture [16, 17]. There are a variety of techniques reconstruction surgeons can use when performing urethroplasty. Depending on the stricture length, location and aetiology, the surgeon will determine which technique is the most appropriate in a case by case basis.

Anastomotic Urethroplasty

In this technique, the surgeon excises the section of stricture and joins the two ends of the healthy urethral tissue. This technique can be used in short bulbar stricture (up to 3 cm). The technique carries the risk of penile curvature and shortening of penile length; therefore, it should not be used in stricture located in the penile urethra. Studies have shown that anastomotic urethroplasty carries a success rate as high as 90%. The median recurrence time is reported to be between 3.5 and 13 months.

Regarding the complication rate, there is a randomised controlled trial in 2022 which evaluated the penile complications of excision and primary anastomosis urethroplasty versus buccal mucosal graft urethroplasty. At 3 months follow-up, there were significantly more patients who received primary anastomotic urethroplasty that experienced worsened ejaculation (26%), reduced glans filling (26%), penile shortening (16%) and penile chordee (10%). Even at 12 months follow-up, there were still significantly more patients in the primary anastomosis group who reported to have reduced glans filling (19%) and penile shortening (26%). These complications are thought to be caused by the disruption of the antegrade blood flow of the urethra and corpus spongiosum at the level of the stricture, where the corpus spongiosum was transected.

Augmentation Urethroplasty

This is typically done as a one-stage procedure, usually used in bulbourethral stricture that is >2cm.

There are 3 ways to perform a one-stage procedure:

1. *Onlay augmentation urethroplasty*: This can be performed by a ventral, dorsal or lateral approach. Ventral and dorsal approaches have both shown similar success rates. There is, however, limited literature on lateral approach onlay augmentation (Figure 14.3).

a. *Ventral approach*: Easier to access, less mobilisation of the urethra

b. *Dorsal approach*: Less bleeding during dissection, less contracture during healing

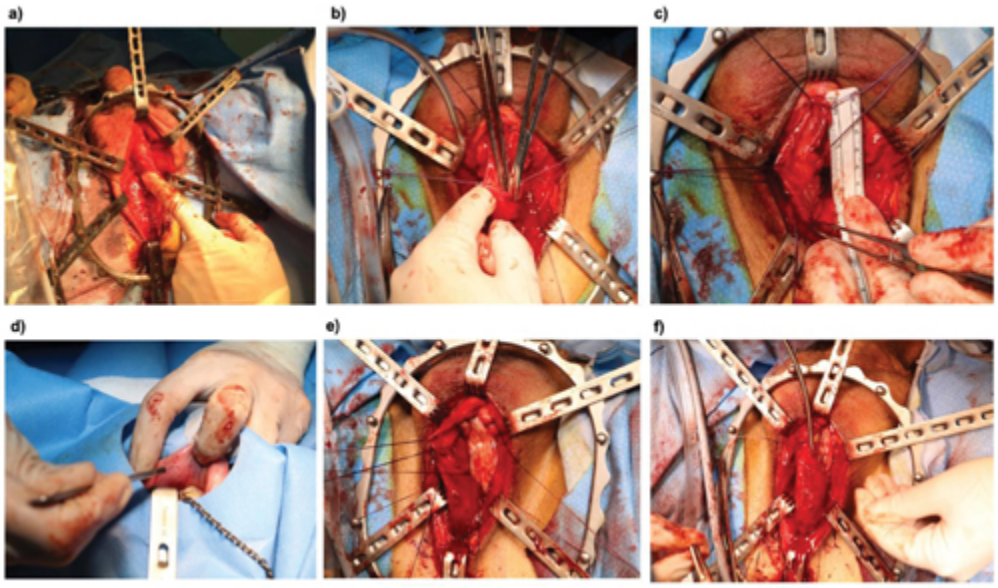


Figure 14.3 Intraoperative images of onlay augmentation urethroplasty. a) Urethral identification; b) Opening of the urethral stricture; c) Measurement of the urethral plate; d) Harvesting of the buccal mucosa graft; e) Dorsal onlay augmentation; f) Closure of the urethra.⏎

Free graft urethroplasty has a patency rate of 88%–91% up to 40 months follow-up. A randomised control study in 2016 reported 40% of patient who

underwent bulbar urethroplasty experience worsened ejaculation post-operatively using the non-bulbospongiosus muscle-sparing technique [18]. Another prospective randomised study in 2018 reported a similar ejaculatory dysfunction rate in patients who underwent non-bulbospongiosus muscle sparing technique. Approximately 36% of the same patient group also experienced post-void dribbling, and 12% developed a recurrent stricture that required further intervention [19].

2. *Augmented anastomotic urethroplasty*: Following the excision of the stricture segment, the roof strip of the native urethra is anastomosed either ventrally or dorsally and augmented by an onlay patch. This technique yields up to 91.9% patency rate.
3. *Flap urethroplasty*: Usually using penile skin flaps, rarely used in the contemporary era to due to higher morbidity compared to oral mucosal grafting.

Two-staged Urethroplasty

Staged urethroplasty is usually used in penile stricture [17]. It should be considered when a patient has pre-existing disease in the anterior urethra, such as false passage, fistula, cancer or previous failed surgical treatment.

The first stage involves the excision of the stricture and formation for the roof strip. The graft is usually laid open for healing (Figure 14.4). It is worth noting that following the first stage urethroplasty, up to 19% required revision surgery. The main complications leading to revision surgery include recurrence of lichen sclerosus in graft (8.8%), graft contracture (6.6%) and stomal stenosis (3.3%). When the graft has successfully healed, the second stage tubularisation then takes place; this usually happens 4–6 months following the first procedure. A urethral catheter is usually left in situ for 10 days to facilitate the initial phase of healing.

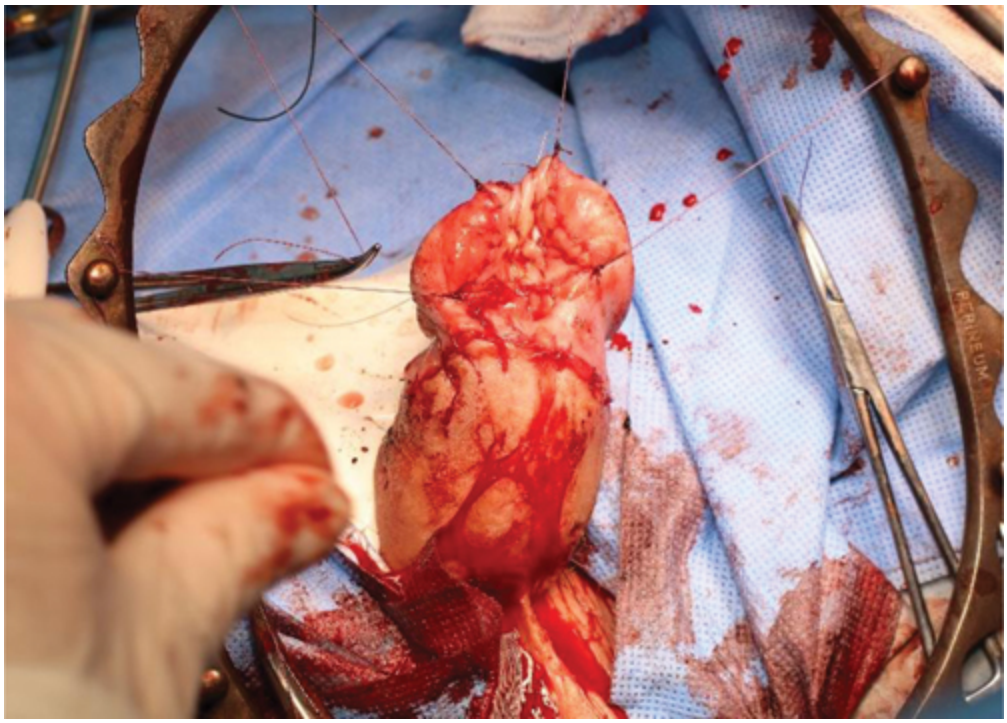


Figure 14.4 First-stage penile urethroplasty.⏎

The staged urethroplasty technique has a success rate of 73%–98% at up to 56 months follow-up. Following second urethroplasty, complications such as penile curvature (up to 9%), erectile dysfunction (up to 4%) and urethral diverticulum (1%) have been observed.

Kulkarni Technique Urethroplasty

The Kulkarni technique is a one-stage procedure for patients with panurethral stricture [20]. This procedure takes a perineal approach with invagination of the penis (Figure 14.5). The Kulkarni technique limits the dissection to only one side of the urethra, thus preserving the neurovascular supply to the urethra. In a retrospective review of 117 patients with a mean stricture length of 14 cm, this technique is reported to have an 83.7% patency rate at a median follow-up of 59 months.

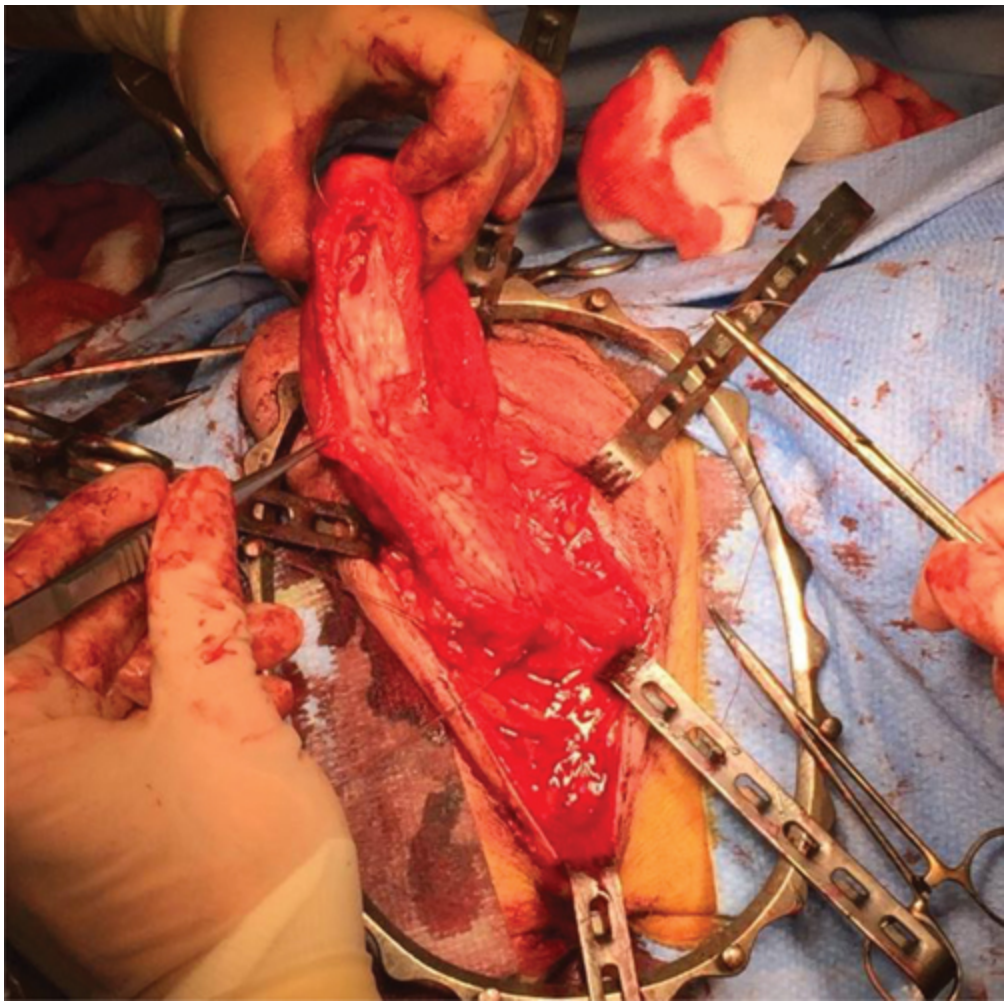


Figure 14.5 Kulkarni urethroplasty technique.⏎

Types of Grafts

Multiple different grafts have been used in literature for urethroplasty. These include oral mucosa, extragenital skin, scrotal skin, bladder and colonic mucosa. In current practice, oral mucosa (from cheek, lip or tongue) is the most commonly used.

Oral mucosa is considered as a superior option as it is used to being in a moist environment and is more resilient against skin conditions such as lichen sclerosis. The risk when harvesting an oral mucosal graft includes damage to the salivary ducts, altered sensation of the cheek and restricted mouth opening post-operatively. The risk of donor site compilation is higher in smokers, tobacco chewers and patients with poor oral hygiene.

The OPEN Trial

A patient-randomized trial published in 2020 compared the effectiveness of urethrotomy versus open urethroplasty. These patients were followed up for over 24 months. The outcome of this study showed that both procedures are similar in improving patient's urinary symptoms without significant risks, although urethroplasty led to less risk of recurrence [21].

Acknowledgement

Figures 14.3–5 are kindly provided by Mr Richard Inman (Consultant Urologist, Sheffield).

References

1. Verla W, Oosterlinck W, Spinoit AF, Waterloos M. A comprehensive review emphasizing anatomy, etiology, diagnosis, and treatment of male urethral stricture disease. *Biomed Res Int.* 2019 Apr 18;2019:9046430. doi: 10.1155/2019/9046430. PMID: 31139658; PMCID: PMC6500724.⏎
2. Gomez RG, Scarberry K. Anatomy and techniques in posterior urethroplasty. *Transl Androl Urol*. 2018 Aug;7(4):567–579. doi: 10.21037/tau.2018.03.05. PMID: 30211047; PMCID: PMC6127558.⏎
3. Alwaal A, Blaschko SD, McAninch JW, Breyer BN. Epidemiology of urethral strictures. *Transl Androl Urol*. 2014 Jun;3(2):209–213. doi: 10.3978/j.issn.2223-4683.2014.04.07. PMID: 26813256; PMCID: PMC4708169.⏎
4. Palminteri E, Berdondini E, Verze P, De Nunzio C, Vitarelli A, Carmignani L. Contemporary urethral stricture characteristics in the developed world. *Urology*. 2013 Jan;81(1):191–196. doi:

10.1016/j.urology.2012.08.062. Epub 2012 Nov 13. PMID: 23153951.⏎
5. David W. Barham, John Barnard, Joel Gelman, *Urethral stricture/stenosis as a complication of High Intensity Focused Ultrasound of the Prostate (HIFU): What is the overall patient experience?*, *Urology*, 2022;167:211–217.⏎
6. *EAU Guidelines*. Edn. presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6.⏎
7. Tritschler S, Roosen A, Füllhase C, Stief CG, Rübben H. Urethral stricture: etiology, investigation and treatments. *Dtsch Arztebl Int*. 2013 Mar;110(13):220–226. doi: 10.3238/arztebl.2013.0220. Epub 2013 Mar 29. PMID: 23596502; PMCID: PMC3627163.⏎
8. Chambers RM, Baitera B. The anatomy of the urethral stricture. *Br J Urol*. 1977;49(6):545–551. doi:10.1111/j.1464-410x.1977.tb04203.x⏎
9. Hampson LA, McAninch JW, Breyer BN. Male urethral strictures and their management. *Nat Rev Urol*. 2014 Jan;11(1):43–50. doi: 10.1038/nrurol.2013.275. Epub 2013 Dec 17. PMID: 24346008; PMCID: PMC4123447.⏎
10. Fuehner C, Dahlem R, Fisch M, Vetterlein MW. Update on managing anterior urethral strictures. *Indian J Urol*. 2019 Apr–Jun;35(2):94–100. doi: 10.4103/iju.IJU_52_19. PMID: 31000913; PMCID: PMC6458800.⏎
11. Gelman J, Furr J. Urethral stricture disease: evaluation of the male urethra. *J Endourol*. 2020 May;34(S1):S2–S6. doi: 10.1089/end.2018.0316. PMID: 32459152; PMCID: PMC7249476.⏎
12. Hillary CJ, Osman NI, Chapple CR. Current trends in urethral stricture management. *Asian J Urol*. 2014 Oct;1(1):46–54. doi: 10.1016/j.ajur.2015.04.005. Epub 2015 Apr 16. PMID: 29511637; PMCID: PMC5832879.⏎

13. Al Taweel W, Seyam R. *Visual internal urethrotomy for adult male urethral stricture has poor long-term results*. *Adv Urol*. 2015;2015:656459. doi: 10.1155/2015/656459. Epub 2015 Oct 1. PMID: 26494995; PMCID: PMC4606400.⏎
14. Xu C, Zhu Z, Lin L, Lv T, Cai T, Lin J. Efficacy of mitomycin C combined with direct vision internal urethrotomy for urethral strictures: a systematic review and meta-analysis. *Urol Int.* 2023;107(4):344–357. doi: 10.1159/000518977. Epub 2021 Oct 20. PMID: 34670219.⏎
15. Elliott SP, Coutinho K, Robertson KJ, D'Anna R, Chevli K, Carrier S, Aube-Peterkin M, Cantrill CH, Ehlert MJ, Te AE, Dann J, DeLong JM, Brandes SB, Hagedorn JC, Levin R, Schlaifer A, DeSouza E, DiMarco D, Erickson BA, Natale R, Husmann DA, Morey A, Olsson C, Virasoro R. One-year results for the ROBUST III randomized controlled trial evaluating the Optilume® drug-coated balloon for anterior urethral strictures. *J Urol.* 2022 Apr;207(4):866–875.⏎
16. Mangera A, Chapple C. Management of anterior urethral stricture: an evidence-based approach. *Curr Opin Urol*. 2010 Nov;20(6):453–458. doi: 10.1097/MOU.0b013e32833ee8d5. PMID: 20827208.⏎
17. Mangera A, Patterson JM, Chapple CR. A systematic review of graft augmentation urethroplasty techniques for the treatment of anterior urethral strictures. *Eur Urol*. 2011 May;59(5):797–814. doi: 10.1016/j.eururo.2011.02.010. Epub 2011 Feb 24. PMID: 21353379.⏎
18. Fredrick A, Erickson BA, Stensland K, Vanni AJ. Functional effects of bulbospongiosus muscle sparing on ejaculatory function and post-void dribbling after bulbar urethroplasty. *J Urol.* 2017 Mar;197(3 Pt 1):738–743. doi: 10.1016/j.juro.2016.09.083. Epub 2016 Sep 28. PMID: 27686691.⏎

19. Elkady E, Dawod T, Teleb M, Shabana W. Bulbospongiosus muscle sparing urethroplasty versus standard urethroplasty: a comparative study. *Urology*. 2019 Apr;126:217–221. doi: 10.1016/j.urology.2018.12.028. Epub 2018 Dec 31. PMID: 30605695.⏎
20. Kulkarni SB, Joshi PM, Venkatesan K. Management of panurethral stricture disease in India. *J Urol*. 2012 Sep;188(3):824–830. doi: 10.1016/j.juro.2012.05.020. Epub 2012 Jul 19. PMID: 22818345.⏎
21. Stephenson R, Carnell S, Johnson N, Brown R, Wilkinson J, Mundy A, Payne S, Watkin N, N'Dow J, Sinclair A, Rees R, Barclay S, Cook JA, Goulao B, MacLennan G, McPherson G, Jackson M, Rapley T, Shen J, Vale L, Norrie J, McColl E, Pickard R. Open urethroplasty versus endoscopic urethrotomy--clarifying the management of men with recurrent urethral stricture (the OPEN trial): study protocol for a randomised controlled trial. *Trials*. 2015 Dec 30;16:600. doi: 10.1186/s13063-015-1120-4. PMID: 26718754; PMCID: PMC4697334.⏎

15 Aetiology, Pathophysiology, Clinical Assessment and Management of Penile Cancer

Sachin Yallapa, Karl H. Pang, Asif Muneer and Hussain M. Alnajjar

DOI: 10.1201/b22940-15

Introduction

Penile cancer (PC) is a rare disease with an incidence of around 37,700 cases worldwide and 6,000 cases in Europe, according to GLOBOCAN 2022 data [1]. In the UK, there are over 700 new cases diagnosed each year and more than two-thirds of these are squamous cell carcinomas (SCC). The mortality rate is around 150–200 per year, according to GLOBOCAN 2022 and Cancer Research UK (2017–19) data [1]. Typical age for diagnosis is between 50 and 70 years [2]. Penile cancer significantly impacts quality of life (QoL); therefore, assessment and management should emphasise the importance of addressing physical, social, and psychological aspects through a multidisciplinary approach.

Aetiology

Several risk factors for PC have been identified, such as smoking, chronic inflammatory conditions, phimosis, human papilloma virus (HPV) infection, obesity, multiple sexual partners, low socio-economic income, previous ultraviolet photo-chemotherapy (PUVA), and HIV infection.

Cigarette smokers are 3–4.5 times more likely to develop PC. Phimosis is considered a significant risk factor for the development of invasive PC;

this is attributed to associated chronic infections and inflammation. Although neonatal circumcision does reduce the risk of PC; it is noted that the risk of Penile Intraepithelial Neoplasia (PeIN) is not reduced [3].

Lichen sclerosus (LS) is a persistent inflammatory condition; presence of oxidative stress leading to DNA damage and mutations occurring in genes have been noted in this condition [4]. In a descriptive study, Barbagli et al. concluded that 8.4% displayed either pre-malignant or malignant alterations. The average duration between the initial presentation of LS symptoms and the diagnosis of PC was found to be around 12 years [5].

HPV infection is one of the key risk factors, with HPV prevalence in PC being ~50.8%. Frequently noted strains are 16, 18, 31, 33, 45, 56 and 65 with HPV 16 genotype being the most common in ~68.3% [6].

Pathology

HPV-associated carcinogenesis is imputed to approximately 30%–50% of the PC [6]. It is understood that basal cells migrate upwards to differentiate. These cells can get infected by HPV without detection from the immune system. During this migration process, the virus invades the DNA of the host cell [7]. E6/E7 genes of the virus are recognised as oncogenic promoters and interact with the Rb and p53 genes. The p53 gene plays a crucial role in safeguarding the genome by inducing apoptosis in damaged cells, while the Rb gene is responsible for halting cell cycle progression if the DNA is compromised [8]. The binding of the virus to these genes impairs their ability to repair DNA, potentially leading to cancer.

The P16-INK4A or P16 tumour suppressor gene is deregulated under the presence of HPV. P16 overexpression in squamous cells has been widely used to provide significant power in diagnosis of HPV-related pathology [7].

Over 95% of PC are SCC. Depending on their association with HPV and the histological subtypes, they are classified according to the 2020 WHO Classification (Table 15.1).

Table 15.1 Histological Subtypes According to the 2022 WHO Classification⏎

HPV-independent SCC		HPV-associated SCC		Others	
Subtype	**Frequency(% of cases)**	**Subtype**	**Frequency(% of cases)**	**Subtype**	**Frequency(% of cases)**
Usual	45–75	Basaloid	4–10	Adeno-squamous	1–2
Mixed	10–19	Warty	5–10	Mucoepidermoid	Unknown
Papillary	2–15	Mixed	4–10	SCC NOS (not otherwise specified)	Unknown
Sarcomatoid	1–7	Clear cell	<1		
Cuniculatum	<1	Lymphoepithelioma-like	<1		
Pseudoglandular	<1				
Pseudohyperplastic	<1				

PeIN is noted to be the precursor abnormality in penile SCC and is also classified based on HPV association (Table 15.2).

Table 15.2 Penile Intraepithelial Neoplasia (PeIN) Classification⏎

HPV-independent	HPV-associated PeIN
Differentiated PeIN (e.g., lichen sclerosus)	Common patterns: basaloid (undifferentiated), warty (condylomatous) and mixed other (less frequent) patterns: pagetoid, clear cell and spindle cell histology

Clinical and Pathological Classification

Penile cancer is staged according to the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) 8th edition (Table 15.3).

Table 15.3 Clinical and Pathological Classification of Penile Cancer⏎

Clinical Classification
T- Primary Tumour
TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in situ (Penile Intraepithelial Neoplasia, PeIN)
Ta Non-invasive localise squamous cell carcinoma[a]
T1 Tumour invades subepithelial connective tissue
T1a Tumour invades subepithelial connective tissue without lymphovascular invasion or perineural invasion and is not poorly differentiated

Clinical Classification
T1b Tumour invades subepithelial connective tissue with lymphovascular invasion or perineural invasion or is poorly differentiated
T2 Tumour invades corpus spongiosum with or without invasion of the urethra
T3 Tumour invades corpus cavernosum with or without invasion of the urethra
T4 Tumour invades other adjacent structures
N - Regional Lymph Nodes
cNX Regional lymph nodes cannot be assessed
cN0 No palpable or visibly enlarged inguinal lymph nodes
cN1 Palpable mobile unilateral inguinal lymph node
cN2 Palpable mobile multiple or bilateral inguinal lymph nodes
cN3 Fixed inguinal nodal mass *or* pelvic lymphadenopathy, unilateral or bilateral
M - Distant Metastasis
cM0 No distant metastasis
cM1 Distant metastasis
Pathological classification
The pT categories correspond to the clinical T categories
The pN categories are based upon biopsy or surgical excision
pN - Regional Lymph Nodes
pNX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Metastasis in one or two inguinal lymph nodes
pN2 Metastasis in more than two unilateral inguinal nodes or bilateral inguinal lymph nodes
pN3 Metastasis in pelvic lymph node(s), unilateral *or* bilateral or extranodal extension of regional lymph node metastasis
pM - Distant Metastasis
pM1 Distant metastasis microscopically confirmed
Histopathological Grading
GX Grade of differentiation cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

[a] Including verrucous carcinoma.

Clinical Assessment and Staging

The clinical assessment of PC includes assessment of the primary lesion and lymph nodes (LNs). Tumour-staging and LN involvement is crucial for determining the appropriate management approach.

Primary lesion examination involves thorough inspection and palpation of the entire penis to identify any potential skip lesions, including those that may be hidden beneath the foreskin in cases of phimosis (Figure 15.1). Assessment should include the lesion's dimensions, anatomical location, extent of local invasion, and stretched penile length [9].

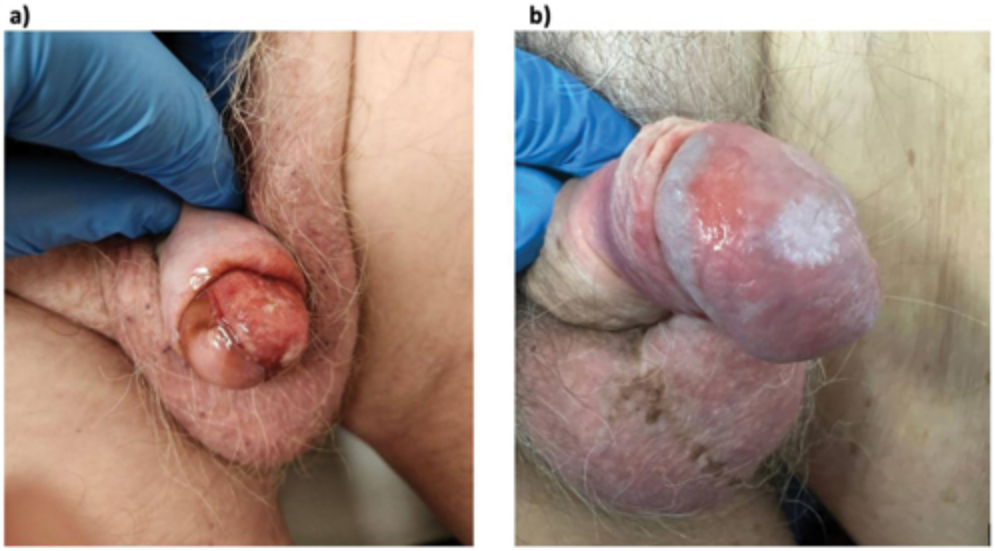


Figure 15.1a–b Images of penile lesions.⏎

(a) glans lesion; (b) undifferentiated penile intraepithelial neoplasia (PeIN).

Biopsy of the penile tumour or lesion is usually required to confirm the histological diagnosis. As per the current European Association of Urology (EAU) guidelines and recommendations, pretreatment biopsy of the primary lesion is indicated when malignancy is not clinically obvious, or when non-surgical treatment of the primary lesion is planned with topical agents, radiotherapy (RT) or laser surgery [9].

Physical examination reliably estimates penile tumour size and clinical T-stage [9]. Compared with magnetic resonance imaging (MRI) and ultrasound (US), physical examination accurately determined tumour size and detected most cases of cavernosal invasion without any false positives [10]. Hence, for distinguishing T1 from T2 disease, MRI does not outperform physical examination. However, MRI scan is useful when there is uncertainty about the cavernosal involvement by the tumour (cT3), and in planning for organ-sparing treatment options, such as glansectomy [11] (Figure 15.2). Ultrasound can be considered if MRI is not available. In one of study of 200 patients, MRI showed a sensitivity and specificity of 74% and 98.5%, and US 97% and 96% for cavernosal involvement when correlated with operative histology [12]. The accuracy in determining the

local stage remained comparable when utilising MRI whether with or without inducing an artificial erection [13]. MRI can be a useful modality to rule out skip lesions along the corpora. Computed tomography (CT) scan of chest, abdomen and pelvis is indicated to check for distant metastasis.

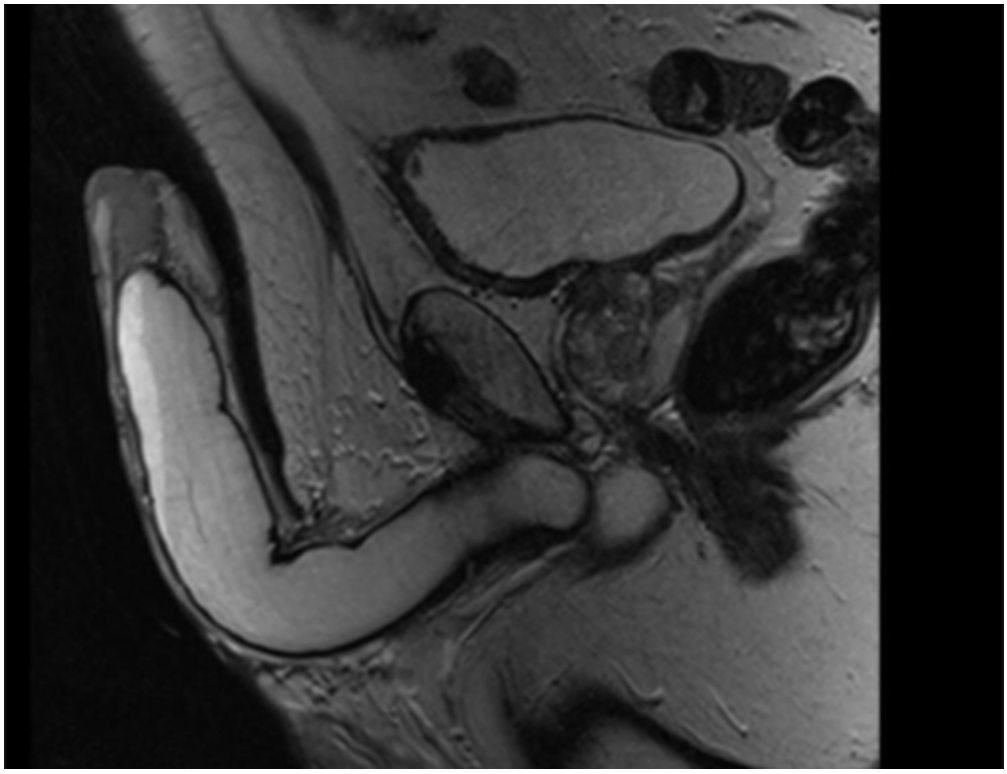


Figure 15.2 MRI penis.⏎

The T2-weighted image demonstrates a glans tumour involving the urethra (cT2 disease).

Lymph node examination is a part of initial PC patient assessment and involves thorough examination of both groins for enlarged or abnormal LNs, noting the number, location and size of LNs and if they are fixed or mobile [14]. PC disseminates in a stepwise manner, first to the inguinal LNs, then to the pelvic nodes and finally to distant nodes. The primary goal of initial LN staging is to identify metastatic disease in the inguinal LNs [15].

Based on physical examination of finding any abnormal LNs, patients can be divided into clinically node-negative (cN0) and clinically node-positive (cN+). In clinically node-negative patients, 20%–25% may still harbour occult metastases, so additional staging is warranted with US of the groins ± fine needle aspiration (FNA)[15]. In clinical node-positive patients, further imaging is recommended to assess distant metastasis, in addition to US groins + FNA.

Cancer-involved LNs tend to be round, lack a fatty hilum, and may have irregular borders or areas of fluid necrosis [16]. Lymph nodes may be imaged and assessed by various imaging techniques, namely US, MRI, CT and 18F-fluoro-2-deoxy-D-glucose positron emission tomography (18FDG-PET). However, there is no convincing evidence to show imaging modalities can detect micro-metastases [14].

Ultrasound with FNA of LNs is helpful in patients with abnormal LNs noted either clinically or on imaging. FNA-positive cohort would require formal inguinal node dissection and thus can avoid dynamic sentinel node biopsy (DSNB) in 10%–13% of patients. Fine-needle aspiration is also useful in diagnosing large-volume metastasis, particularly when LNs fail to reliably uptake the radioactive technetium used for inguinal node metastasis localisation, thereby reducing the risk of false-negative DSNB results [17].

As imaging techniques are not reliable enough to detect micro metastatic disease, surgical staging or radical inguinal lymph node dissection (rILND) remain the most appropriate approach to identify micro-metastasis [17]. However, surgical staging by rILND is considered to be overtreatment as only 20%–25% of all clinically node-negative patients have occult metastasis and it is associated with high complication rates [15]. DSNB was developed to avoid formal rILND and to reduce associated morbidity (Figure 15.3).

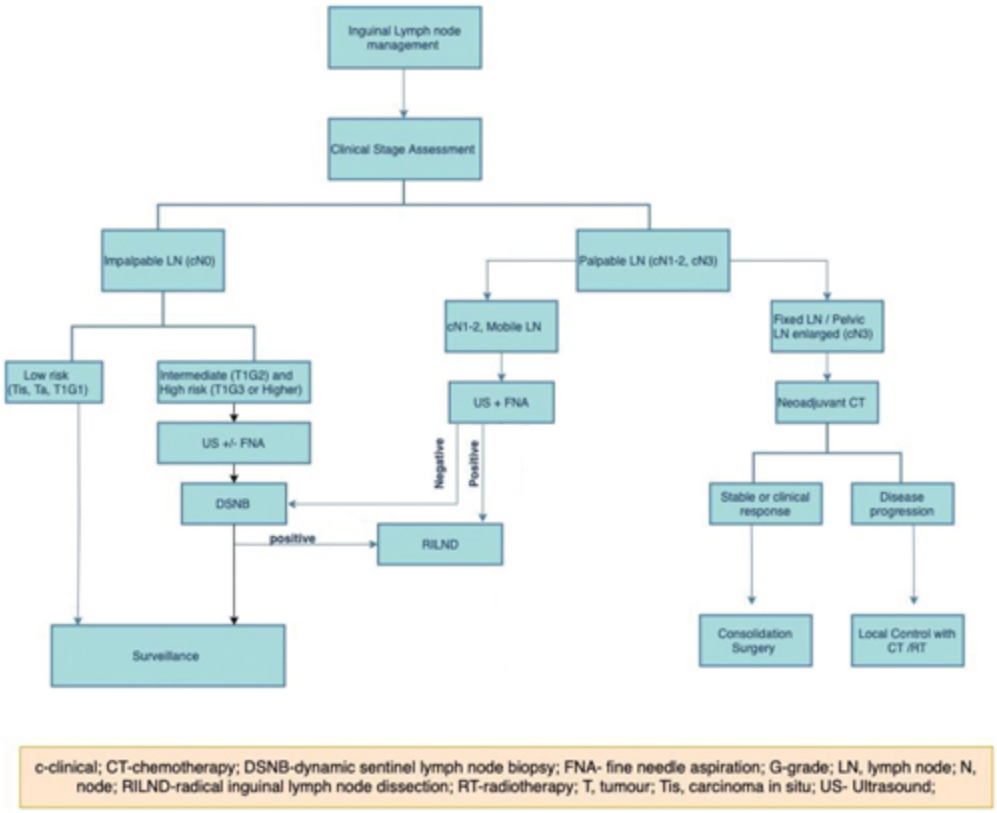


Figure 15.3 Staging and management of inguinal lymph nodes.⏎

The EAU guidelines recommend selecting patients for surgical staging based on risk categories, which include tumour T-stage, grade of differentiation and the presence of lymphovascular or perineural invasion. Tumours classified as G1, pTa, pTis or pT1a (without lymphovascular or perineural invasion) are considered low-risk, as the likelihood of metastasis is very low; thus, surgical staging of inguinal LNs is not recommended. Tumours with G2 and pT1a characteristics are intermediate-risk, carrying a 6%–8% risk of metastatic LN disease. Tumours classified as pT1b G2 or higher have a 22%–30% risk of metastasis and are therefore considered high-risk, warranting surgical staging [18].

Surgical staging of the inguinal LNs is recommended in all high-risk tumours (T1b, G3 and T2–T4, with any grade). In intermediate-risk tumours (pT1a G2), surgical staging is recommended considering each case individually to reduce the morbidity.

Management of Penile Cancer

The initial assessment and management of PC is summarised in Figure 15.4 and in Table 15.4.

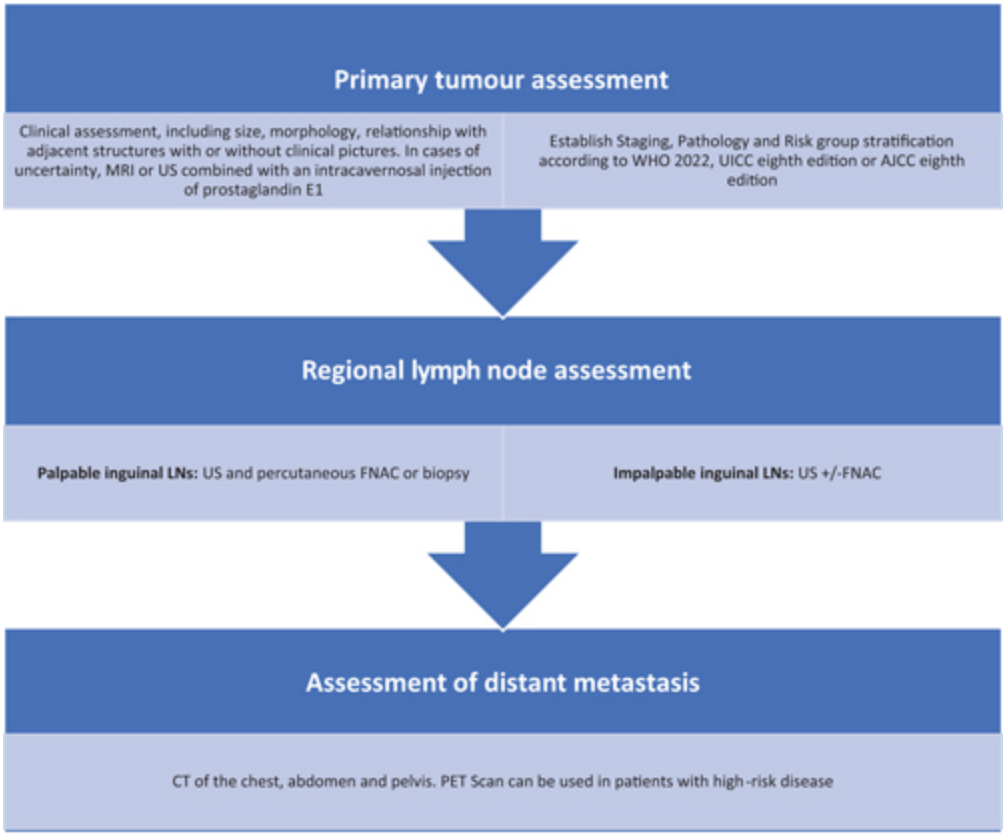


Figure 15.4 The assessment of penile cancer.⏎

Abbreviations: FNAC, fine needle aspiration cytology; LN, lymph node; US, ultrasound scan.

Table 15.4 Treatment Options of the Primary Tumour According to the T-stage⏎

Tis or Ta	• Circumcision ± WLE • Topical ChT or immunotherapy • Laser therapy • Partial/total glans resurfacing with STSG
T1 -T2	• Circumcision and WLE • Laser therapy • Partial/total glans resurfacing with STSG (for T1a lesions) • Partial/total glansectomy + STSG ± distal urethrectomy
T3-T4	• Glansectomy with distal corporectomy • Partial penectomy ± STSG • Subtotal or total penectomy with perineal urethrostomy

Abbreviations: STSG, split-thickness skin graft; WLE, wide local excision; ChT, chemotherapy; EBRT, external beam radiotherapy; T, tumour; Tis, carcinoma in situ; WLE, wide local excision.

Treatment of the Primary Tumour

Treatment in selected cases should be aimed with curative intent. Both surgical resection or RT, which includes brachytherapy and/or external beam RT (EBRT), have been employed in the treatment of PC. RT is suitable in very few selected cases of distal PC and only when patients decline a surgical option. The main objective of surgical treatment of the primary tumour is to achieve complete tumour removal with adequate margin and as much organ preservation as possible to ensure reasonable sexual function, urinary function and QoL. The surgical procedures required to achieve these would depend on the location and extent of the tumour in relation to its adjacent tissues.

Treatment of Superficial Non-invasive Disease (PeIN, Ta)

The location of PeIN lesions is mostly noted on the mucosal surfaces of the glans or prepuce.

There are multiple options for treating superficial non-invasive disease, including topical chemotherapeutic agents such as 5-fluorouracil (5-FU)/imiquimod or ablative therapies

(Nd:YAG or CO2 laser/cryotherapy). Surgical options include circumcision or glans resurfacing with a split-thickness skin graft (STSG) (Figure 15.5).

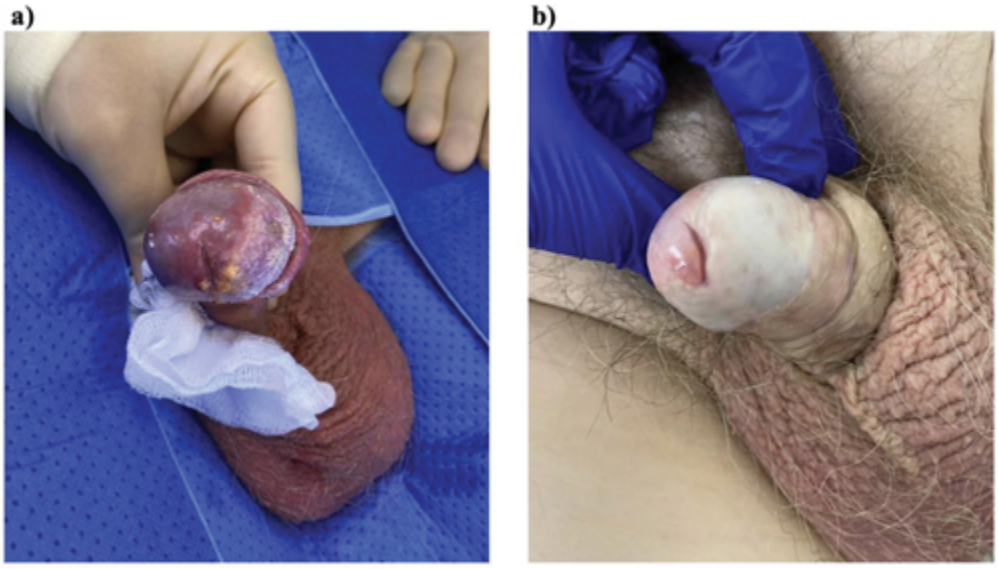


Figure –b 15.5a Intraoperative and postoperative images of glans resurfacing.⏎

(a) Squamous cell carcinoma of the glans penis; (b) Partial glans resurfacing with a split-thickness skin graft (Images courtesy of Hussain Alnajjar, UCLH).

Topical and ablative therapies are increasingly being considered as non-invasive first-line treatment options. There is not much comparative data available for optimal treatment schedules with these therapies. One study recommended application of topical chemotherapy on alternate days for 4 weeks. They reported a complete response rate of 57% [19]**.** The response and recurrence rates after topical and ablative therapies are shown in Table 15.5.

Table 15.5 Response and Recurrence Rates After Topical and Ablative Therapies⏎

	Response	Recurrence
5-fluorouracil (5-FU)	48%–74%	11%
Imiquimod	40%–100%	20%
Nd:YAG or CO2 laser	52%–100%,	7%–48%

Surgical treatment offers the benefit of complete histopathological staging and can reveal areas of invasion, which have been reported in up to 20% of cases. In selected patients, circumcision may serve as the primary surgical intervention, as keratinisation of the glans mucosa can lead to gradual resolution of PeIN. However, PeIN may progress to invasive disease in 2.6%–13% of patients despite treatment and may ultimately require wide local excision or glans resurfacing. Ongoing surveillance is therefore essential [20]. For lesions confined to the glans that spare the coronal ridge and sulcus, coronal-sparing glans resurfacing has been described. This technique preserves both sensation and sexual function and offers superior cosmetic results [21].

Treatment of Invasive Disease Confined to the Glans (cT1/ T2)

In tumours staged as T1 or T2 on the glans, glansectomy is indicated. With the recent shift towards an organ-preserving approach, either partial or total glansectomy with a STSG could be undertaken to achieve negative margins (Figure 15.6). Partial glansectomy is suggested if the tumour is small or involves less than half of the glans, depending on the location to avoid remaining glans deformity or deviation of the meatus [22]. In addition, total or partial glans resurfacing has been reported to be performed for superficially invasive lesions combined with deeper resection at the site of invasion (EAU guidelines 2025).

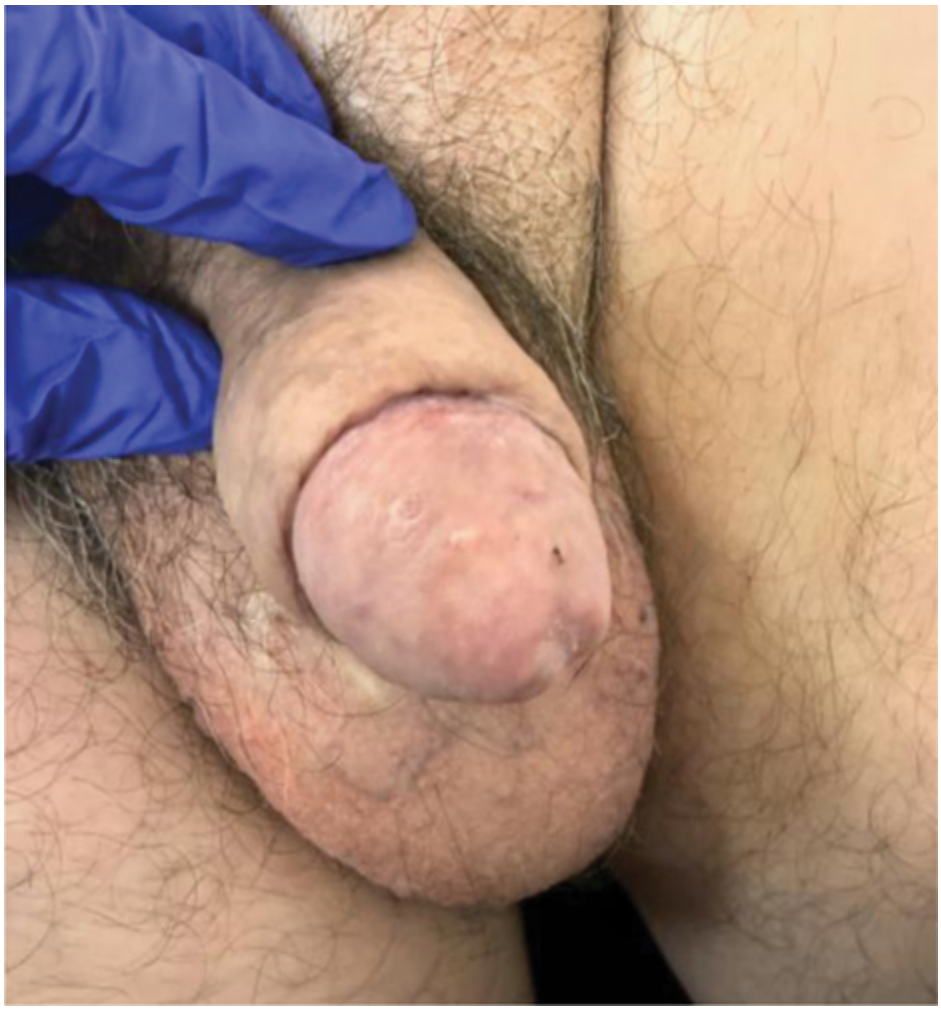


Figure 15.6 Postoperative image of a glansectomy with neoglans formation using a split-thickness skin graft (image courtesy of Hussain Alnajjar, UCLH).⏎

Treatment of Locally Advanced Disease (T3–T4)

In tumours with involvement of the corpora cavernosa partial, subtotal or radical penectomy is indicated depending on the extent of involvement of the proximal shaft to achieve negative margins and a functional penile stump for urinary and sexual function. Subtotal penectomy involves removal of corporal bodies at the level of the pubic bone and diversion of the urethra to the perineum. Radical penectomy will involve excision of the crura down to the ischio-pubic rami and formation of a perineal

urethrostomy. Intraoperative frozen sections study is a helpful tool in cases of doubtful clinical negative margin. However, routine use is not recommended. Current EAU guidelines recommend a risk-adapted strategy. Negative surgical margin more than 1 mm has been recommended as being adequate for low-risk tumours; however, for bulky and high-grade tumours, a wide margin may be required as local recurrence may impact survival [9].

Outcomes of Penile Cancer Treatment/Procedures

Following primary procedures for PC, patients generally have a good postoperative recovery. The possible complications noted are a degree of erectile dysfunction, spraying of urine, shortening of penile length, failure of the skin graft to take, requiring further treatment, urethral meatal stenosis and local recurrence.

Laser therapy for Tis/Ta lesions has a high 5-year local recurrence rate of around 50%, which emphasises the importance of close clinical follow-up [23]. Recent data reported a recurrence rate of 15.4% in patients treated with circumcision for tumour localised to the foreskin and wide local excision for lesion on the glans. In PeIN or T1a, the local recurrence rate following glans resurfacing has been reported to be up to 4.5% and positive surgical margins in 48% with repeat surgery in 28% [24].

Glansectomy has a local recurrence of 2.6%–16.7% and positive surgical margin rates of 2.9%–22.6%. Split-thickness skin graft used to reconstruct a neoglans has a graft loss rate of 1.5%–23.5%. The incidence of meatal stenosis is 2.8%–14.3% [25, 26].

Regional Lymph Node Management

LN invasion is considered one of the most important prognostic factors in patients with PC. The 5-year cancer specific survival (CSS) is noted to be 85%–100% in pN0, 79%–89% in pN1, 17%–60% in pN2 and 0%–17% in pN3 disease [27].

Current EAU guidelines suggest a risk-adapted approach for inguinal LNs management as ILND is associated with considerable morbidity and represents overtreatment in majority of the patients [16]. Complications of

ILND include wound infection, flap necrosis, wound dehiscence, bleeding/haematoma, major vascular injury, seroma, lymphoedema, deep vein thrombosis, thigh numbness. The recommendations for different clinical or pathological LN status include:

1. Patients with clinically impalpable inguinal LNs (cN0) with primary tumour of low grade or stage such as Ta, Tis, T1a are recommended surveillance. However, in patients with high-risk factors such as T1b and higher stage, poorly or undifferentiated grade, lymphovascular invasion, bilateral DSNB is recommended. In cases where DSNB is positive for metastasis, further rILND (Figure 15.7) on the side of metastasis, is recommended.
2. In patients who have abnormal inguinal LN, either clinically palpable or noted on imaging, and have positive metastasis diagnosed after image-guided FNA, a rILND on the side of metastatic disease is recommended. If the FNA shows negative result, then an excision biopsy (i.e., in bulky node/s) or DSNB is recommended depending on the clinical suspicion.
3. In patients with cN1 and cN2 (bilateral), unilateral and bilateral rILND is recommended, respectively.
4. In cN3 patients, neoadjuvant chemotherapy to downstage the mass followed by rILND is recommended, if the mass is not resectable.
5. Pelvic LND is also recommended in patients with pN2 or pN3, on a case by case basis.

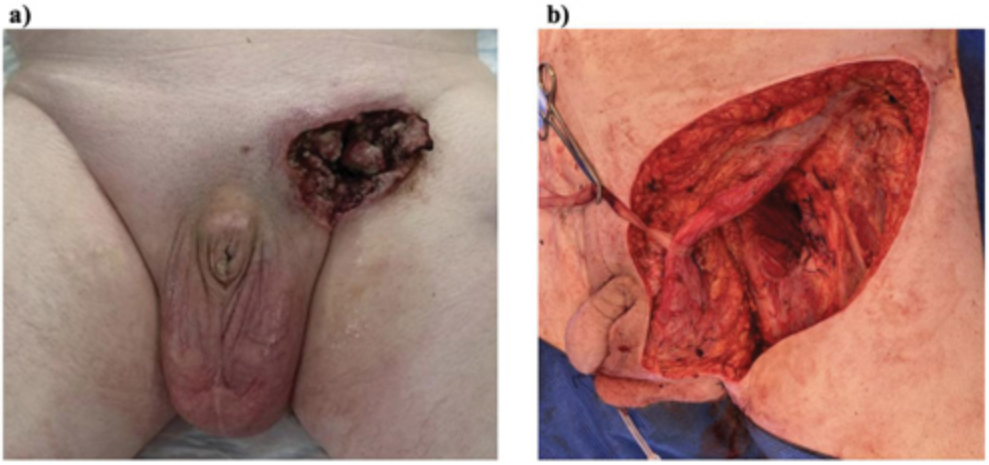


Figure –b 15.7a Intraoperative images of radical inguinal lymph node dissection (images courtesy of Hussain Alnajjar, UCLH).⏎

a) Fungating tumour involving the left groin; (b) Extensive left inguinal groin dissection. The groin dissection margins are the inguinal ligament, the medial border of the sartorius muscle and the lateral border of the adductor longus muscle.

Systemic and Palliative Therapies for Advanced Disease

Neoadjuvant chemotherapy (NAC) is the first-line treatment recommended by the National Comprehensive Cancer Network (NCCN) and EAU guidelines for patients with advanced nonresectable primary lesion and bulky nodal disease.

The most common regimens currently used for advanced disease are platinum-based regimens.

Current EAU guidelines recommend offering induction chemotherapy as multimodal treatment for nonresectable advanced primary lesion followed by surgery to responders and chemoradiotherapy to patients who do not respond or refuse surgical management.

Further EAU guidelines recommend offering:

- NAC as an alternative approach to upfront surgery to selected patients with bulky mobile inguinal LNs or bilateral disease (cN2).
- NAC in preference to upfront surgery to patients with extensive inguinal involvement (cN3) or with pelvic LNs; further offer surgery to patients who have responded to NAC and resection is feasible.
- Discussion with patients on risks and benefits of adjuvant treatment with pathological pelvic LNs (pN3) noted after surgical resection [28].
- Radiotherapy is suggested in treating patients with pN2/pN3 as an adjuvant treatment, or NAC with or without chemo sensitisation, and also in patients refusing or unable to undergo LND or multiagent chemotherapy. However this is suggested based on weak evidence.

Platinum-based systemic therapy is recommended as first-line palliative approach in patients with distant metastatic disease, while RT is offered for symptom control in advanced disease.

Follow-up Regime for Penile Cancer

Follow-up depends on the treatment performed for the primary tumour and LN status. As per EAU guidelines (Table 15.6), a patient who has had penile-preserving surgery (low-risk cohort) and LN under surveillance is reviewed for physical examination and groin ultrasound ± FNA for every 3 month in the first 2 years, and 6 monthly thereafter for 5 years.

Table 15.6 Interval of Follow-up⏎

	Years 1–2	Years 3–5	Examinations	Maximum Follow-up
Primary Penile Tumour				
Penile-preserving treatment	3 months	6 months	Physical examination	5 years
Amputation	3 months	12 months	Physical examination	5 years
Follow-up for Inguinal Lymph Nodes				
Surveillance	3 months	6 months	Physical examination + US groins ± FNA	5 years
pN0	3 months	12 months	Physical examination + US groins ± FNA	5 years
pN+	3 months	6 months	Physical examination + US groins ± FNA + CT chest/abdo/pelvis	5 years

Abbreviations: FNA, fine needle aspiration; US, ultrasound scan.

Patients who had amputation and with pN0 are reviewed for physical examination and groin ultrasound ± FNA for every 3 month in the first 2 years, and annually thereafter for 5 years.

Patients with pN+ are reviewed for physical examination, groin US ± FNA and CT chest abdomen and pelvis for every 3 months in the first 2 years, and 6 monthly thereafter for 5 years [8].

References

1. World Health Organization. International Agency for Research on Cancer. 2022. Available at: *Cancer today* https://gco.iarc.fr/today/home. Accessed December 14, 2022.⏎
2. Thomas A, Necchi A, Muneer A, Tobias-Machado M, Tran ATH, Van Rompuy AS, *et al.* Penile cancer. *Nature Reviews Disease Primers*. 2021 Feb 11;7(1):11.⏎
3. Tseng HF, Morgenstern H, Mack T, Peters RK. Risk factors for penile cancer: results of a population-based case-control study in Los Angeles County (United States). *Cancer Causes and Control*. 2001;12(3):267–277.⏎
4. Hayes JD, Dinkova-Kostova AT, Tew KD. Oxidative stress in cancer. *Cancer Cell* 2020 Aug 10;38(2):167–197.⏎
5. Barbagli G, Palminteri E, Mirri F, G.F. Guazzoni, Turini D, Lazzeri M. Penile carcinoma in patients with genital lichen sclerosus: a multicenter survey. *The Journal of Urology*. 2006 Apr 1;175(4):1359–1363.⏎
6. Olesen TB, Sand FL, Rasmussen CL, Albieri V, Toft BG, Norrild B, et al. Prevalence of human papillomavirus DNA and p16INK4a in penile cancer and penile intraepithelial neoplasia: a systematic review and meta-analysis. *The Lancet Oncology*. 2019 Jan;20(1):145–158.⏎
7. Eich ML, Del Carmen Rodriguez Pena M, Schwartz L, Granada CP, Rais-Bahrami S, Giannico G, *et al.* Morphology, p16, HPV, and outcomes in squamous cell carcinoma of the penis: a multi-institutional study. *Human Pathology*. 2020 Feb 1;96:79–86.⏎
8. Peng Q, Wang L, Zuo L, Gao S, Jiang X, Han Y, *et al.* HPV E6/E7: insights into their regulatory role and mechanism in signaling pathways in HPV-associated tumor. *Cancer Gene Therapy*. 2024 Jan 1;31(1):9–17.⏎
9. EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6⏎

10. Lont AP, A.P.E. Besnard, M.P.W. Gallee, H. Van Tinteren, S. Horenblas. *A comparison of physical examination and imaging in determining the extent of primary penile carcinoma*. *BJU International*. 2003 Mar 26;91(6):493–495.⏎
11. Bertolotto M, Serafini G, Dogliotti L, Gandolfo N, Gandolfo NG, Belgrano M, et al. Primary and secondary malignancies of the penis: ultrasound features. *Abdominal Imaging*. 2004 Feb;30(1):108–112.⏎
12. Bozzini G, Provenzano M, Javier Romero Otero, Margreiter M, Eduardo Garcia Cruz, Osmolorskij B, *et al.* Role of penile doppler US in the preoperative assessment of penile squamous cell carcinoma patients: results from a large prospective multicenter European study. *Urology*. 2016 Apr 1;90:131–135.⏎
13. Krishna S, Schieda N, Kulkarni GS, Shanbhogue K, Baroni RH, Woo S. Diagnostic accuracy of MRI in local staging (T Category) of penile cancer and the value of artificial erection: a systematic review and meta-analysis. *American Journal of Roentgenology*. 2022 Jul 1;219(1):28–36.⏎
14. Joost A.P. Leijte, Graafland NM, Valdés RA, Hester, Hoefnagel CA, Horenblas S. *Prospective evaluation of hybrid^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in staging clinically node-negative patients with penile carcinoma*. *BJUI*. 2009 Sep 1;104(5):640–644.⏎
15. Wood HM, Angermeier KW. Anatomic considerations of the penis, lymphatic drainage, and biopsy of the sentinel node. *Urologic Clinics of North America*. 2010 Aug 1;37(3):327–334.⏎
16. Ahuja AT, Ying M. Sonographic evaluation of cervical lymph nodes. *American Journal of Roentgenology*. 2005

May;184(5):1691–1699.⏎
17. Kroon BK, Horenblas S, Deurloo EE, Nieweg OE, Teertstra HJ. Ultrasonography-guided fine-needle aspiration cytology before sentinel node biopsy in patients with penile carcinoma. *BJU International*. 2005 Feb 10;95(4):517–521.⏎
18. Fankhauser CD, de M, Roussel E, Jakob Kristian Jakobsen, Issa A, Esther, *et al*. Lymphovascular and perineural invasion are risk factors for inguinal lymph node metastases in men with T1G2 penile cancer. *Journal of Cancer Research and Clinical Oncology*. 2022 Apr 12;148(9):2231–2234.⏎
19. Alnajjar HM, Lam W, Bolgeri M, Rees RW, Perry MJ,Watkin NA. Treatment of carcinoma in situ of the glans penis with topical chemotherapy agents. *Eur Urol*. 2012 Nov;62(5):923–928.⏎
20. Issa A, Sebro K, Kwok A, Janisch F, Grossmann NC, Lee E, *et al*. Treatment options and outcomes for men with penile intraepithelial neoplasia: a systematic review. *European Urology Focus*. 2021 May;8(3):829–832.⏎
21. Cakir OO, Schifano N, Venturino L, Pozzi E, Castiglione F, Alnajjar HM, Muneer A. Surgical technique and outcomes following coronal-sparing glans resurfacing for benign and malignant penile lesions. *Int J Impot Res* 2022 Aug;34(5):495–500.⏎
22. Lont AP, Maarten P.W. Gallee, Meinhardt W, Harm van Tinteren, Horenblas S. Penis conserving treatment for T1 and T2 penile carcinoma: clinical implications of a local recurrence. *The Journal of Urology*. 2006 Aug 1;176(2):575–580.⏎
23. Tang DH, Yan S, Ottenhof SR, *et al*. Laser ablation as monotherapy for penile squamous cell carcinoma: a multi-center cohort analysis. *Urologic Oncology*. 2018;36(4):147–152.⏎

16 Aetiology, Pathophysiology, Clinical Assessment and Management of Testis Cancer

Muhammad Haider, Pinky Kotecha, Nasreen Abdul Aziz, Prabhakar Rajan, Walter Cazzaniga and David Nicol

DOI: 10.1201/b22940-16

Epidemiology

Testicular cancer (TC) accounts for 1% of newly diagnosed cancer cases in men in the United Kingdom, ranking as the 17th most common cancer within this demographic. It constitutes 5% of urological cancers and exhibits a strong correlation with age, with the highest incidence rates observed in the 30–34 age group. Most TCs are testicular germ cell tumours (TGCT), whereas non-germ cell tumours (NGCTs) are rare, comprising less than 5% of all TC rates have increased by more than 7% in men in the UK. The overall survival of TC in England is 91.3% at 10 years.

Globally, there is a geographical variation in incidence rates, which vary over 100-fold, with Scandinavian and Northern European countries (> 10/100,000) having a higher incidence compared to equatorial Africa (< 0.10/100,000) [1, 2].

Aetiology and Risk Factors

The aetiology of TC is unknown, but there are several known risk factors, epidemiological and genetic. The epidemiological risk factors are

summarised in Table 16.1a.

Table 16.1a Epidemiological Risk Factors for TGCT, with Odds Ratio of the Effect Size, Where Applicable⏎

Risk Factor	Effect Size	Notes
Cryptorchidism	4.30 (Cook, Akre et al. 2010)	Cryptorchidism is linked to a 2.2-fold and 5.4-fold increased risk of TGCT in those who underwent orchidopexy before the age of 13 and after the age of 13, respectively (Pettersson, Richiardi et al. 2007)
Inguinal hernia	1.63 (Cook, Akre et al. 2010)	
Low birth weight	1.34 (Cook, Akre et al. 2010)	
Twin	1.22 (Cook, Akre et al. 2010)	
Hypospadias	4.2 (Prener, Engholm et al. 1996)	
Hydrocele	2.4 (Prener, Engholm et al. 1996)	
Subfertility	1.68 (Peng, Zeng et al. 2009)	
Previous TGCT	12.4 (Fosså, Chen et al. 2005) (McGlynn and Trabert 2012)	
Father with TGCT	1.75–3.78 (Swerdlow, De Stavola et al. 1997, Hemminki and Chen 2006)	Tendency towards concordant age at diagnosis of testicular cancer among relatives (Kharazmi, Hemminki et al. 2015). Co-occurrence in families of ovarian germ cell tumour and TGCT has also been reported (Stettner, Hartenbach et al. 1999)
Smoking	1.18–2.31 (Srivastava and Kreiger 2004, Song, Myung et al. 2020)	
Infections EBV, CMV, Parvovirus B19, and HIV	1.79–4.80 (Yousif, Hammer et al. 2013)	
Brother with TGCT	7.55–12.74 (Swerdlow, De Stavola et al. 1997, Hemminki and Chen 2006)	
Syndromes with abnormal testicular development: Klinefelter's syndrome, XY dysgenesis, Down's syndrome	Not known/reported	Impairment of androgen signalling during early development can increase risk of TGCT. Disorders of sex development, such as Down syndrome (trisomy 21) and Klinefelter syndrome (47, XXY karyotype) are caused by foetal androgen insufficiency and are associated with risk of germ cell malignancy (Pleskacova, Hersmus et al. 2010)

There is a high familial risk, with studies showing an up to 8× increased risk when a brother had TC and an up to 3.8-fold increased risk when a father had TC [3, 4]. The existing evidence strongly suggests that the

genomic architecture underlying TGCT after predisposition is characterised by numerous potential common risk loci, influencing a consistent set of biological pathways.

There are a number of associations between risk factors and TC global disease burden, summarised in Table 16.1b [5]. Testicular microlithiasis (TM), a rare condition detected during ultrasound scan (USS) of the scrotum, where small clusters of calcium form in the testicles, is also an epidemiological risk factor [6].

Table 16.1b Associations Between Risk Factor and Testicular Cancer Burden⏎

Risk Factor	Effect Size	Notes
HDI	1.36	
GDP per capita	0.91	
Higher prevalence of alcohol drinking	0.25	
Physical inactivity	0.12	
Overweight	0.10	
Obesity	0.22	
Hypercholesterolaemia	0.37	
Lower prevalence of diabetes	−0.22	

Beta coefficients (β) regenerated from a linear regression analysis (Huang, Chan et al. 2022)
In a multivariate linear regression model, the beta coefficient represents the estimated change in the incidence of testicular cancer for a one-unit change in an associated factor to testicular cancer.

Pathogenesis

There are two main pathways in the pathogenesis of TGCTs – prepubertal and postpubertal.

The aetiology and pathogenesis of the prepubertal pathway involved in infantile TGCT (prepubertal yolk sac tumour and prepubertal teratoma) remains unknown. These tumours are assumed to originate from primordial germ cells but there is no precursor lesion of Germ Cell Neoplasia In-Situ (GCNIS). These tumours do not display isochromosome 12p.

The postpubertal pathway involves progression from preinvasive GCNIS towards invasive TGCT after puberty when GCNIS cells begin to

proliferate, secondary to a rise in testosterone.

GCNIS is the non-invasive precursor of TGCTs. GCNIS arises from foetal germ cells arrested in their development that fail to differentiate to spermatogonia. All patients with GCNIS will develop an invasive TGCT; the incidence of GCNIS is similar to the lifetime risk of developing a TGCT [7].

Isochromosome of the short arm of chromosome 12 (i12p) is pathognomonic of all histological subtypes of adult germ cell tumours which involves polyploidisation and amplification of chromosome 12. This is likely to be a key triggering event for malignant transformation in early adulthood from a non-invasive precursor lesion, probably of foetal origin, which lies dormant through childhood into adolescence. This is commonly acknowledged as the hallmark of TGCT in nearly all tumours, involving the postpubertal pathway. Various genes have been suggested as potential drivers for the selection of i(12p), including KRAS located at 12p11.2–p12.1 and a group of stem-cell-associated genes like NANOG and STELLA at 12p13.31, which are overexpressed in TGCTs (Figure 16.1).

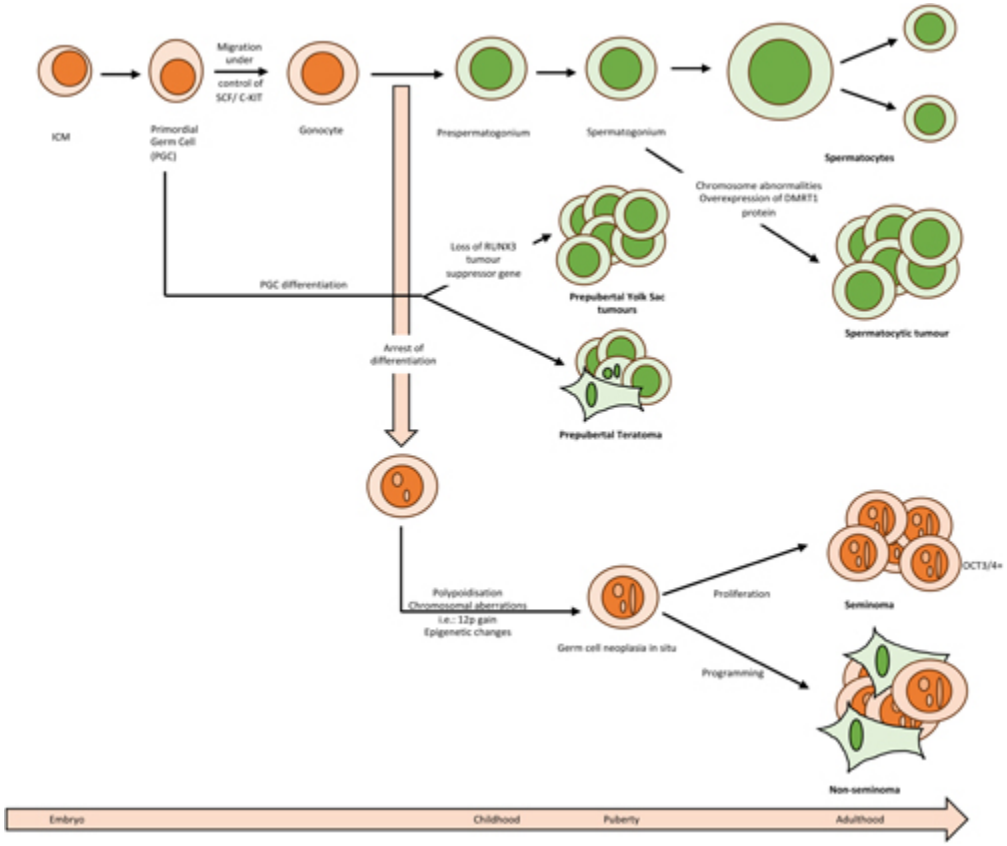


Figure 16.1 Pathogenesis of development of testicular germ cell tumours.⏎

GCNIS, which demonstrates isochromosome 12p (i12p) leads to the development of seminomas and nonseminomas. Tumours that develop from normal germ cells, without GCNIS, are prepubertal yolk sac tumours, prepuberal teratomas and spermatocytic tumours.

Clinical Assessment

History

Testicular cancer commonly presents as a painless unilateral testicular lump in a young man aged between 15 and 45 years. However, pain is not an uncommon symptom, with up to 23.5% of patients reporting pain upon initial presentation [8], which can range from a dull ache or discomfort to acute pain.

There may also be a history of preceding trauma; however, it is not clear if testicular trauma leads to development of cancer or whether this association exists due to incidental detection of testicular masses during examination [9].

A recent review found that 11.39% of patients had distant metastases at diagnosis [10], which can lead to a diverse range of clinical signs and symptoms depending on the site and extent of spread, including those summarised in Table 16.2.

Table 16.2 Clinical Signs and Symptoms of Testicular Cancer Based on Site of Spread⏎

Systemic symptoms	**Fever, anorexia, weight loss, malaise, cachexia**
Lung metastases	Dyspnoea, cough, chest pain, haemoptysis
Lymph node involvement	Enlarged supraclavicular/inguinal lymph nodes
Skeletal metastases	Bone pain
Retro-duodenal metastases	Gastro-intestinal haemorrhage
Retroperitoneal metastases	Lower lumbar back pain due to involvement of psoas muscle or nerve roots

Systemic symptoms	**Fever, anorexia, weight loss, malaise, cachexia**
Central nervous system	Headache or neurological symptoms
Endocrine	Gynecomastia secondary to chorionic gonadotrophin release

Examination

Examination of the testes will typically reveal a unilateral firm, non-tender testicular mass. The contralateral testis should be also carefully examined as ≈0.4% of patients will have a synchronous testicular tumour in the contralateral testicle [11]. Examination may also reveal a secondary hydrocele which can be palpated as a fluctuant swelling which transilluminates. Less commonly, patients may present with signs of inflammation, including a hot, swollen testicle. The exact mechanism behind this is unclear; however, it is thought to be due to intra-tumour haemorrhage [12].

Between 7% and 11% of patients with TC have gynaecomastia on initial presentation [13] (due to an excess in production of oestrogen secondary to increase beta-subunit of chorionic gonadotropin (b-hCG) levels) and 4.5%–15% of patients with primary TC will have neck nodal metastases, particularly with spread to the left supraclavicular lymph node [14]. Therefore, all patients with suspected TC should have abdominal, chest and supraclavicular examination [15].

Imaging

Ultrasound Scan

USS, performed with a high-frequency (>10 MHz) transducer, is the first-line investigation to confirm the presence of testicular tumours due to its cost, ease of scanning and diagnostic accuracy (sensitivity of 92%–98% and specificity of 95%–99.8% [16]). USS can also provide useful information, such as: If the mass is intra or extra-testicular, as the latter tends to be benign in most cases.

European Association Urology (EAU) guidelines also recommend USS for all men with a retroperitoneal or visceral mass with/or without raised beta-subunit of chorionic gonadotropin (b-hCG), or alpha-fetoprotein (AFP) in the absence of a palpable testicular mass [15].

CT Scan

All patients with suspected TC should undergo a contrast enhanced contrast-enhanced computed tomography (CT) scan of the chest, abdomen and pelvis for full staging. Due to the lymphatic drainage of the testes (lumbar and para-aortic nodes), the most common site of spread is to the retroperitoneal lymph nodes – CT can detect approximately 70%–80% of positive retroperitoneal lymph nodes. However, the challenge with CT is that it can be difficult to distinguish between benign and malignant nodes. Lymph node size is typically used to differentiate between the two, with nodes larger than 8–10 mm generally being considered suspicious for cancer [17].

If patients are unable to undergo a CT scan for staging (e.g., if they have a contrast allergy), then magnetic resonance imaging (MRI) may be used as an alternative. MRI has similar diagnostic ability for assessing retroperitoneal lymph nodes.

MRI Scan

Conventional MRI is superior to USS for the detection of intratesticular malignancies and has sensitivity of 100% for intratesticular malignancies [18]. It is also less operator-dependent, but, due to its high cost, it is not recommended for first-line imaging. MRI is particularly useful to help differentiate between benign and malignant lesions for those patients with inconclusive clinical and USS findings. One retrospective review found that MRI was able to correctly diagnose 31/34 (91%) of patients with inconclusive USS findings [18].

EAU guidelines only recommend the use of scrotal MRI in the following scenarios:

- Local staging for testis-sparing surgery (TSS)
- To differentiate between paratesticular and intratesticular lesions
- To characterise intratesticular masses

FDG-PET Scan

There is no role for fludeoxyglucose-18 (FDG) positron emission tomography (PET) scanning in the initial staging of TC. One study

compared the use of CT versus FDG-PET for staging of non-seminoma germ cell tumour (NSGCT) prior to RPLND. They found that FDG-PET was superior compared to CT for the correct staging (83% versus 71%, respectively) and that while the NPV was higher than for CT (78% versus 67%), it is too low to guide patient management [19]. This was further corroborated in a study which found a 38% relapse rate within 1 year for patients with stage I NSGCT with a negative FDG-PET who were managed with surveillance [20].

Bone Scan

Bone scans are not indicated unless there is clinical suspicion, as bone metastases are rare (<1%) [21].

Tumour Markers

Standard of Care Biochemical Biomarkers

The established standard of care biochemical serum biomarkers for TGCT are: AFP, b-hCG and lactate dehydrogenase (LDH), used to guide diagnosis, disease management and treatment response. However, they are neither specific nor sensitive. Approximately 90% of NSGCTs present with elevation of one or more of the markers, but only 30% of seminoma patients display elevated hCG. Overall, at initial diagnosis, only 60% of TGCT patients present increased tumour marker levels. There are also other causes of elevations of AFP and b-hCG as outlined in Table 16.3.

Table 16.3 Standard of Care Biochemical Biomarkers⏎

	AFP	beta-hCG	LDH
Size (daltons)	70,000	38,000	134,000
Half-life	5–7 days	24–36 hours	Varies
Normal range	<40 ug/I	<5 IU/I	1.5–3.2 ukat/I
Tumour type	NSGCT: Yolk sac tumour Embryonal carcinoma Teratoma	Seminoma Choriocarcinoma Embryonal	Any
Other conditions with elevations in tumour markers	• Hepatocellular carcinoma	• Hydatidiform mole • Hypogonadism	• Skeletal muscle disease

	AFP	beta-hCG	LDH
	• Viral hepatitis • Cirrhosis • Gastric, biliary and pancreatic cancer • Bronchial cancer • Antiepileptics • Anaesthetics • hereditary tyrosinemia • ataxia-telangiectasia • Hereditary persistence of AFP	• Breast cancer • Marijuana use • Gonadotroph adenomas • Bladder, liver, pancreas, stomach, lung, kidney cancers • Heterophile antibodies	• Pulmonary embolism • Myocardial infarction • Thalassaemia • Leukaemia • Pernicious anaemia • Haemolysis

Source: Del Real OJ, de la Barra, Carlos Ignacio Calvo, Jiménez JA, Sepulveda F, Domínguez J. Predicting malignancy in small testicular lesions. *Central European Journal of Urology* 2022;75(1):47.

MicroRNA as Serum Biomarkers

MicroRNAs are small, non-coding RNA molecules, which are released by TC cells and found in both serum and plasma. As such, microRNAs are novel serum biomarkers, which can be used as a diagnostic and prognostic marker for TGCT. However, their integration into clinical practice is hampered by uncertainties regarding their utility, diagnostic accuracy, and challenges like cost-effectiveness and standardisation of sample handling and storage [22].

The miR-371-3 cluster (miR-371a-3p, miR-372-3p, and miR-373-3p) located on chromosome 19 is the most clinically useful, among its counterparts. It is associated with both seminoma and non-seminoma but not postpubertal teratoma.

Tissue Biomarkers

Tissue biomarkers are used to histologically identify and classify GCTs. The most commonly used immunohistochemistry markers used in GCTs are: OCT3/4, GPC3 and SALL4.

OCT4 is a POU-domain, octamer-binding transcription factor which is expressed in undifferentiated, pluripotent cells, including human embryonic stem and germ cells. It has been detected in neoplastic germ cells with pluripotent potential, including seminomas. OCT4 has been utilised as a

TGCT biomarker, which has shown very high sensitivity and specificity in IHC analysis of tumour biopsy samples from TGCT patients.

GPC3 is one of the highly over-expressed genes found in yolk sac tumour but not other non-seminoma tumours of the testis. GPC3 may have diagnostic value in identifying non-seminomatous components and distinguishing YSTs from other germ cell tumour subtypes.

SALL4 (Sal-like protein 4) is a zinc-finger transcription factor expressed in embryonic stem cells. SALL4 can be helpful in discerning other rare tumours occurring in the testis such as lymphomas or metastatic carcinomas from TGCTs.

Histological Classification of Tumours

Testicular tumours can broadly be classified into three main categories as per the 2022 World Health Organization (WHO) pathological classification [23].

- Germ cell tumours derived from GCNIS
- Germ cell tumours unrelated to GCNIS
- Sex cord: Stromal tumours of the testis

The vast majority of testicular tumours are GCTs derived from GCNIS, and they can be further subdivided based on histological features into seminoma and NSGCT. The median age of diagnosis differs between the two, with seminoma being more common at 35–39 years compared to 25–30 years for NSGCT (Table 16.4) [24].

Table 16.4 WHO Classification of Testicular Cancer⏎

1. Germ cell tumours derived from germ cell neoplasia in situ
· Non-invasive germ cell neoplasia
– Germ cell neoplasia *in situ*
– Specific forms of intratubular germ cell neoplasia
– Gonadoblastoma
· The germinoma family of tumours
– Seminoma
· Non-seminomatous germ cell tumours

1. Germ cell tumours derived from germ cell neoplasia in situ

– Embryonal carcinoma

– Yolk sac tumour, postpubertal-type

– Choriocarcinoma

– Placental site trophoblastic tumour

– Epithelioid trophoblastic tumour

– Cystic trophoblastic tumour

– Teratoma, postpubertal-type

– Teratoma with somatic-type malignancy

· Mixed germ cell tumours of the testis

– Mixed germ cell tumours

· Germ cell tumours of unknown type

– Regressed germ cell tumours

2. Germ cell tumours unrelated to germ cell neoplasia *in situ*

- Spermatocytic tumour

– Teratoma, prepubertal-type

– Yolk sac tumour, prepubertal-type

– Testicular neuroendocrine tumour, prepubertal-type

– Mixed teratoma and yolk sac tumour, prepubertal-type

3. Sex cord stromal tumours of the testis

· Leydig cell tumour

– Leydig cell tumour

· Sertoli cell tumours

– Sertoli cell tumour

– Large cell calcifying Sertoli cell tumour

· Granulosa cell tumours

– Adult granulosa cell tumour

– Juvenile granulosa cell tumour

· The fibroma thecoma family of tumours

– Tumours in the fibroma thecoma group

· Mixed and other sex cord stromal tumours

– Mixed sex cord stromal tumour

– Signet ring stromal tumour

– Myoid gonadal stromal tumour

· Sex cord stromal tumour NOS

4. Tumours of the testicular adnexa

· Ovarian-type tumours of the collecting ducts and rete testis

– Serous cystadenoma

– Serous tumour of borderline malignancy

1. Germ cell tumours derived from germ cell neoplasia in situ
– Serous cystadenocarcinoma
– Mucinous cystadenoma
– Mucinous borderline tumour
– Mucinous cystadenocarcinoma
– Endometrioid tumours
– Clear cell adenocarcinoma
– Brenner tumour
· Tumours of the collecting ducts and rete testis
– Adenoma of the collecting ducts and rete testis
– Adenocarcinoma of the collecting ducts and rete testis
· Paratesticular mesothelial tumours
– Adenomatoid tumour
– Well-differentiated papillary mesothelial tumour
– Mesothelioma
· Tumours of the epididymis
– Cystadenoma of the epididymis
– Papillary cystadenoma of the epididymis
– Adenocarcinoma of the epididymis
– Squamous cell carcinoma of the epididymis
– Melanotic neuroectodermal tumour of the epididymis

Staging of Testicular Cancer

Germ cell derived TC can be staged according to the 2016 Tumour, Node, Metastasis (TNM) classification of the International Union Against Cancer (UICC). This staging system takes into account the anatomical spread of the tumour and the serum tumour markers (Table 16.5).

Table 16.5 2016 Tumour, Node, Metastasis (TNM) Classification of the International Union Against Cancer (UICC)⏎

5a: TNM Classification for Testicular Cancer	
pT, primary tumour	
pTX	Primary tumour cannot be assessed (see note)
pT0	No evidence of primary tumour (e.g., histological scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma *in situ*)
pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion; tumour may invade tunica albuginea but not tunica vaginalis

5a: TNM Classification for Testicular Cancer

pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis
pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion
pT4	Tumour invades scrotum with or without vascular/lymphatic invasion
N – Regional Lymph Nodes – Clinical	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
Pn – Regional Lymph Nodes – Pathological	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer
	Positive nodes, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
M – Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
	M1a Non-regional lymph node(s) or lung metastasis
	M1b Distant metastasis other than non-regional lymph nodes and lung
S – Serum Tumour Markers (Pre chemotherapy)	
SX	Serum marker studies not available or not performed
S0	Serum marker study levels within normal limits

	LDH (U/l)	hCG (mIU/mL)	AFP (ng/mL)
S1	<1.5 x N and	<5,000 and	<1,000
S2	1.5–10 x N or	5,000–50,000 or	1,000–10,000
S3	>10 x N or	>50,000 or	>10,000

5b: Staging

Stage grouping	T	N	M	S
Stage 0	pTis	N0	M0	S0
Stage I	pT1–T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2–pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1–3

5a: TNM Classification for Testicular Cancer				
Stage II	Any pT/TX	N1-N3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1a	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-N3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-N3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

Surgical Procedures

Radical Inguinal Orchidectomy

Primary management of suspected TC includes surgical excision of tumour via a radical inguinal orchidectomy. This allows for histological confirmation and analysis of the cancer and primary source control of the tumour (is curative in approximately 75% of patients). An inguinal approach is preferred over a scrotal approach due to lower rates of local recurrence, and this approach also avoids seeding into the inguinal lymph nodes.

Patients with synchronous bilateral testicular tumours or a tumour in a solitary testis may be considered for TSS instead of a radical orchidectomy [25].

Pre-operative Considerations

- Germ cell tumours are associated with sperm abnormalities (lower sperm count, abnormal morphology and reduced motility) and subfertility even prior to orchidectomy [26]. Therefore, fertility considerations should be discussed with all patients prior to orchidectomy, including

sperm cryopreservation, semen analysis and fertility assessment (sperm can be extracted during the procedure if necessary, Onco-TESE).

- Patients should be offered testicular prosthesis but must be counselled on risks, including cosmetic dissatisfaction, infection, haematoma, extrusion and pain. If removal of the prosthesis is required, this can potentially delay chemotherapy. However, such risks remain low in clinical practice (Table 16.6).

Table 16.6 International Germ Cell Cancer Collaborative Group (IGCCCG) Classification

Good Risk	
NSGCT	**Seminoma**
Testis/retroperitoneal primary AND No non-pulmonary visceral metastasis AND ALL OF • AFP<1000 ng/ml • b-hCG <5000 ui (1000 ng/ml) • LDH 1.5× upper normal limit	Any primary site AND No non-pulmonary visceral metastasis AND Normal AFP, any b-hCG, and any LDH
Intermediate Risk	
NSGCT	**Seminoma**
Testis/retroperitoneal primary AND No non-pulmonary visceral metastasis AND ANY OF • AFP >/=1000 ng/ml and <10000 ng/ml • b-hCG >/=5000 ui and <50000 ng/ml • LDH >/=1.5× and <10× upper normal limit	Any primary site AND Non-pulmonary visceral metastasis AND Normal AFP, any b-hCG, and any LDH
Poor Risk	
NSGCT	**Seminoma**
Mediastinal primary OR Non-pulmonary visceral metastasis OR ANY OF • AFP>/= 10000 ng/ml • b-hCG>/= 50000 ng/ml • LDH >/= 10× upper normal limit	No patient classified

Common Risks and Side Effects

Operative Steps

- With the patient in a supine position, the lower abdomen, groin and external genitalia are prepped and draped.
- An incision is made 2 cm above and parallel to the inguinal ligament starting above the pubic tubercle.
- The incision is dissected until the Camper's and Scarpa's fascia. These fascial layers are then divided to expose the external oblique aponeurosis and the external inguinal ring.
- The external oblique aponeurosis is then divided starting from the level of the external ring to the level of the internal ring.
- Traditionally, it was thought that the Ilioinguinal nerve should be identified and preserved. However, a recent meta-analysis showed that resection of the nerve did lead to a higher incidence of altered sensation, but it actually reduced the incidence of chronic pain with a mean difference of (−0.29 95% CI −0.48 to −0.11 on 10-point pain scale) at 6 months post-op [27].
- The spermatic cord is then elevated and dissected away from the cremasteric fascia.
- The spermatic cord is then clamped at the proximal end (although some advocate that this is not necessary) and the testis is delivered.
- The Gubernaculum attachments are divided.
- With the addition of another clamp the cord is then divided at the level of the internal ring to achieve maximal oncological control and transfixed. This also enables easier identification of the cord remnant if RPLND is then required.
- Depending on patient preference, a testicular prosthesis may be inserted at this point.
- The incision is closed in layers:
    - External oblique fascia – 2/0 Vicryl continuous
    - Scarpas fascia – 2/0 Vicryl interrupted
    - Skin – 3/0 Monocryl subcuticular

Biopsy of the Contra-lateral Testis

Approximately 5% of patients with unilateral TC will have GCNIS in the contralateral testicle that will develop into an invasive tumour over time [28]. Therefore, while contralateral testis biopsy is not routinely recommended, it may be considered in patients who are <40 years old and are at high risk for GCNIS (history of cryptorchidism and/or testicular volume <12 ml) [25].

Retroperitoneal Lymph Node Dissection

RPLND can be performed for both diagnostic purposes (to enable pathological staging) and therapeutic purposes (to remove affected nodes)

(Figure 16.2). Traditionally, open RPLND was performed with a median laparotomy incision, involving the removal of all lymph nodes from the renal hilar regions down to the common iliac vessels [29].

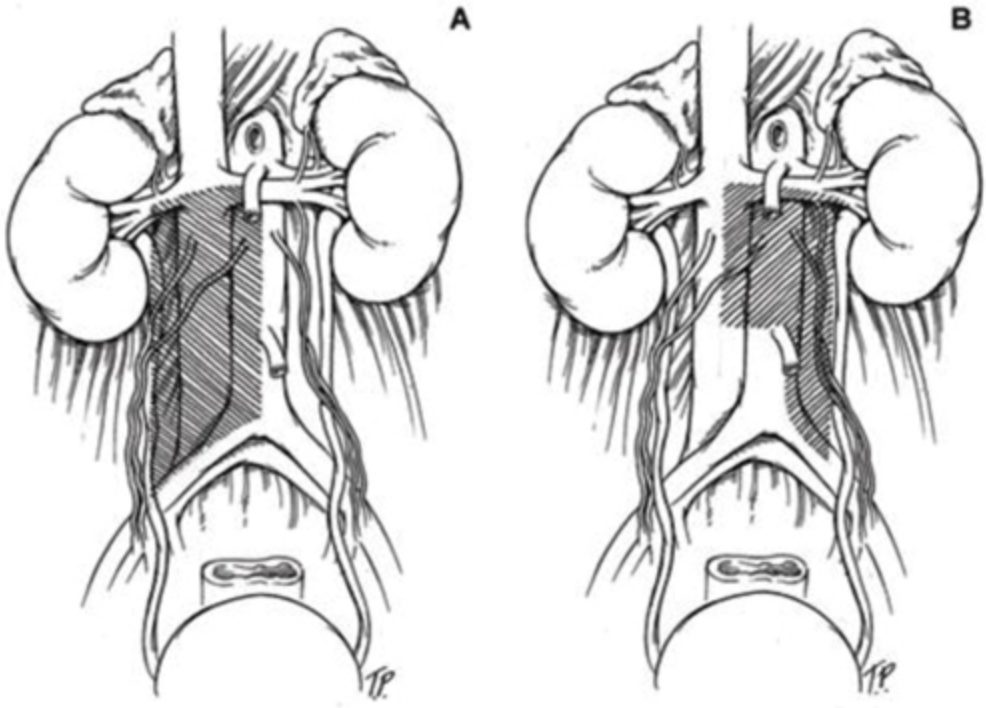


Figure 16.2 Boundaries of retroperitoneal lymph node dissection.⏎

Newer nerve-sparing approaches using template mapping and minimally invasive techniques such as robotic surgery have reduced morbidity. Compared to traditional surgical techniques (open and laparoscopic), robotic surgery leads to reduced intra-operative bleeding, shorter hospital stays, faster recovery times and fewer post-operative complications [30].

Robotic RPLND is seeing increasing use in TC management. However, recent reports of atypical recurrence patterns post-robotic RPLND for primary and post-chemotherapy patients have raised questions about oncologic efficacy [31, 32]. Further research is needed to assess long-term outcomes prior to wider adoption

Boundaries of Dissection

The boundaries for template dissection for RPLND are as follows:

Right-sided tumours	Left-sided tumours
Superior: Renal hilum	*Superior*: Renal hilum
Lateral: Ureter	*Lateral*: Ureter
Medial: Mid-point of Aorta	*medical*: Mid-point of vena cava
Inferior: Bifurcation of iliac vessels	*Distal*: Bifurcation of iliac vessels

Management of Testicular Cancer

Management of Small Testicular Masses

The wider use of scrotal USS has led to a rise in detecting small, non-palpable testicular masses. While there is no universally agreed definition for a small testicular mass, <20 mm is a commonly used cut-off size. Historically, any testicular lesion with malignant potential would be managed with radical orchidectomy. However, given that up to 80% of lesions <20 mm may be benign [33], and to avoid the consequences on fertility and androgen production associated with radical orchidectomy, selected patients may be managed with active surveillance, testicular biopsy or TSS.

There are no universally agreed upon criteria for which patients can be safely managed with active surveillance. One suggested approach involves risk stratification of patients based on the size of the lesion [34]. Patients with lesion <10 mm can managed with active surveillance with a strategy of USS 3, 6 and 12 months and USS-guided biopsy for lesions sized <5 mm and 5–9 mm, respectively (Figure 16.3).

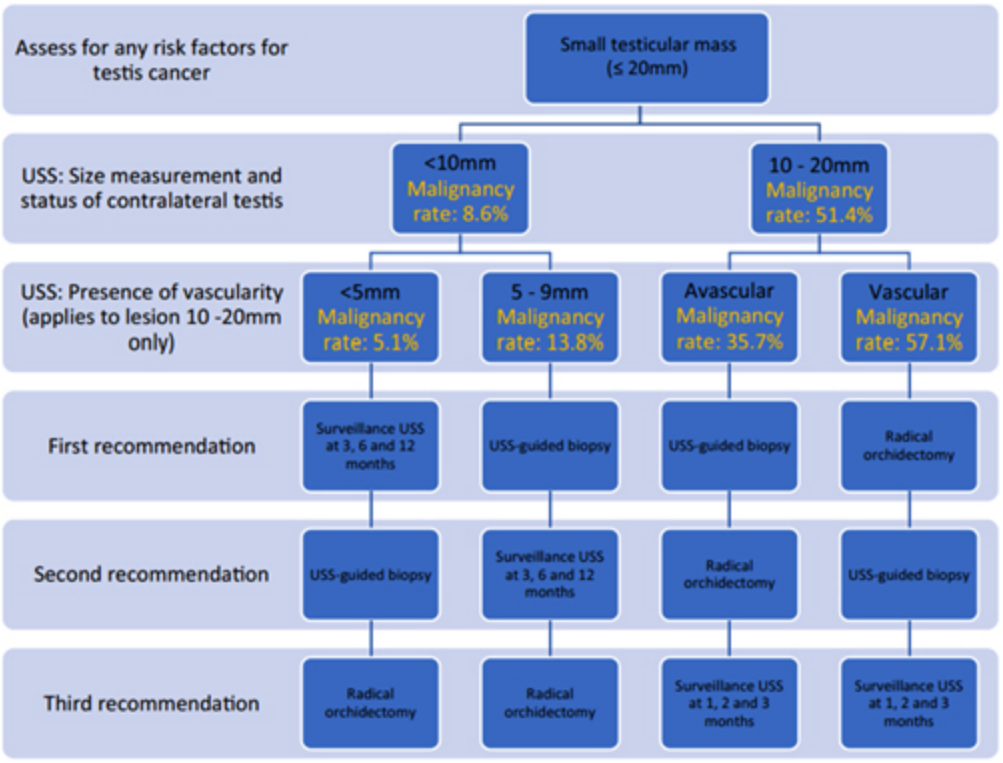


Figure 16.3 Recommended management algorithm for small testicular masses.⏎

For lesions measuring 10–20 mm, the presence of vascularity significantly increases the risk of malignancy from 35.7% to 57.1%, thus warranting radical orchidectomy. In the absence of vascularity, patients can be offered US-guided biopsy as a first-line option.

Current EAU guidelines indicate insufficient evidence for a size-based criterion to safely manage testicular masses with follow-up alone [15]. They suggest that TSS with frozen section examination (FSE) may be offered to patients with small or indeterminate testicular masses, normal tumour markers and a normal contralateral testis. Frozen section performed intra-op has been shown in a recent systematic review to be 93.05% accurate in differentiating between benign and malignant lesions [35]. If there is discrepancy between FSE and final histology, then a delayed orchidectomy may be required.

Management of Stage I Disease

Seminoma

The prognosis for stage I seminoma is excellent, and most patients are cured by orchidectomy alone. Approximately 15%–18% of patients with clinical stage I seminoma relapse after orchidectomy without adjuvant treatment, but nevertheless the cure rate is almost 100% [36]. The treatment strategies postoperatively include surveillance, adjuvant chemotherapy and adjuvant radiotherapy (RT).

The risk of relapse may be reduced with adjuvant treatment, but it is associated with acute and late toxicities. Multiple risk factors, including tumour size (>4 cm) and rete testes infiltration, have been studied for relapse rate estimation. A pooled analysis of four surveillance studies found a 5-year relapse risk of 15% with one risk factor and 31% with two risk factors [37]. Boorman et el. proposed a new risk stratifications model which identified lymphovascular invasion (LVI) as a small subgroup with a high risk of relapse [38].

‘Patients for whom surveillance is unsuitable or have concerns about adhering to the schedule may be offered single agent carboplatin or radiation. In a randomised controlled trial, comparing a single dose of carboplatin AUC 7 (reaching area under curve of 7 mg/mL/min) to radiotherapy (RT), similar 5-year relapse-free rates were observed (94.7% vs 96.0%) [39]. However, studies have reported higher mortality rates from secondary malignancies after RT. Adjuvant RT is generally discouraged, especially for young patients expected to live longer.

Non-seminoma

Similarly, the prognosis for stage I non-seminoma is excellent, with the majority of patients cured by radical orchidectomy alone. However, the presence of LVI increases risk of relapse. In a retrospective study of patients under active surveillance, it was observed that relapseddisease occurred in 44% of patients with LVI, compared to only 14% of those without LVI [40].

In low-risk stage I non-seminoma, characterised by the absence of LVI, active surveillance is the recommended approach. For the high-risk group where LVI is present, adjuvant chemotherapy or primary retroperitoneal lymph node dissection (RPLND) is recommended. Surveillance may be considered for patients with high-risk features (i.e., LVI) but patients must

be fully informed about the risk of relapse, the potential need for more intensive chemotherapy and the significant early and late toxicity with regimens required to treat relapsed disease.

Adjuvant chemotherapy consists of a single cycle of bleomycin, etoposide and cisplatin (BEP), which reduces the risk of relapse by over 90%. RPLND can be an appropriate alternative adjuvant treatment to avoid toxicity from chemotherapy although is generally not recommended. If performed it must be in specialist high-volume centres to minimise complications such as ejaculatory failure and to ensure an adequate dissection.

Approximately 30% of patients will be upstaged to pathological stage 2. Approximately 30% of these will relapse and thus adjuvant treatment with a single cycle of BEP is recommended in this setting. Overall survival demonstrate similarity across all management strategies.

Management of Metastatic Disease

Metastatic disease refers to cancer that has spread outside the primary tumour or if tumour markers increase or fail to normalise following Orchidectomy. The first-line treatment of metastatic germ cell tumours (GCT) depends on the histology of the primary tumour and the International Germ Cell Consensus Classification (IGCCCG) staging system (Table 16.7).

Metastatic Disease Stage II

Seminoma

Stage II disease refers to patients with metastatic spread to the retroperitoneal lymph nodes. Treatment options for stage II seminoma include multi-agent chemotherapy or RT. Chemotherapy typically consists of three cycles of bleomycin, etoposide and cisplatin (BEP) or four cycles of etoposide and cisplatin (EP). A bleomycin-free regimen (i.e., EP) is generally preferred in patients at increased risk of bleomycin-induced pulmonary toxicity. This includes individuals with chronic kidney disease, age over 50 years, chronic obstructive pulmonary disease (COPD) or other underlying pulmonary conditions resulting in impaired lung function [41].

RT is an alternative to chemotherapy but is seldom utilised nowadays. It serves as an option for patients who may experience toxicity from chemotherapy. The target fields for RT for stage IIa/b disease include the paraaortic and ipsilateral iliac lymph nodes with doses of 30 Gy in 2 Gy fraction in stage IIa and 36 Gy in 2 Gy fraction in stage IIb [41].

Table 16.7 Common Risks and Side Effects of Radical Inguinal Orchidectomy, Including Incidence and Subsequent Issues

Risk/Complication	Incidence	Subsequent Issues
Scrotal haematoma	1%–2%	Rarely requires surgical intervention but may take weeks to resolve
Infection	1%	Rarely requires intervention
Postoperative pain	60% initially; 1.8% 1-year post-op	Higher rates of phantom testis syndrome
Phantom testis syndrome	25%	Usually begins >2 month post-op; Triggered by urination, ejaculation or exercise in 40%; Can be chronic in 25%
Ilioinguinal nerve injury	Rare	Can cause chronic pain and paraesthesia of superior medial thigh and anterior scrotum
Inguinal hernia	<1%	May require subsequent hernia repair
Tumour spillage	Rare	Requires post-operative chemotherapy
Reduced fertility	20% oligospermic; 5% azoospermic	Rates of oligospermia and azoospermia higher if pre-existing subfertility
Hypogonadism	0.5% 1-year post-op	Subfertility and metabolic consequences such as weight gain, hypercholesterolaemia, and hypertension; may require adjuvant hormonal therapy

A systematic review found that in stage IIa disease, relapse free survival rates were comparable between radiation therapy and chemotherapy. However, in stage IIb disease, the relapse rate was noted to be higher with radiation (21%) compared to chemotherapy (14%) [42]. Therefore, for bulky disease, chemotherapy is preferred to RT.

Another alternative is RPLND, although it is not recommended in international guidelines. It is currently under evaluation in several trials and large institutional series but awaits longer term follow-up. While not recommended outside of these settings, it appears promising. With RPLND alone, there is a 20%–30% relapse rate, although the disease can be salvaged with BEP/EP.

Carboplatin AUC 10 monotherapy is another alternative that has been used for good-risk stage II metastatic seminoma by some institutions. This de-escalation method has been shown to reduce treatment morbidity while

preserving oncological outcomes. However, the evidence supporting this approach lacks prospective outcomes data, hence this strategy is not recognised as the standard of care.

Non-seminoma (NSGCT)

The primary treatment for patients with stage II non-seminoma post-orchidectomy is largely influenced by serum tumour marker levels and nodal size. For individuals with normal post-orchidectomy levels of AFP and b-hCG who have stage IIa disease, initial surveillance may be considered, with early re-evaluation at 6 weeks [15]. If after 6 weeks the tumour regresses, it can be treated as stage I disease. For stage IIa disease with normal or normalised tumour markers, nerve sparing primary RPLND is recommended and should be conducted in a specialised centre.

Following RPLND, the standard practice depends on the number of positive lymph nodes identified. Surveillance is recommended for patients with pathologic pN0 disease. The risk of relapse in pN2 or pN3 disease after RPLND exceeds 50%. Therefore, for patients with pN2 disease, adjuvant chemotherapy with two cycles of EP is recommended, while for pN3 disease, either three cycles of BEP or four cycles of EP are recommended [43].

For patients with persistently elevated AFP and/or b-hCG levels post-orchidectomy and radiological stage IIA/B at diagnosis or relapse, chemotherapy is recommended, typically three cycles of BEP or four cycles of EP [44]. Patients diagnosed with postpubertal teratoma alone post-RPLND can forego unnecessary chemotherapy since surgery alone is curative.

Given the higher rates of relapse in bulky disease, chemotherapy is generally preferred over RPLND in stage IIc disease.

Metastatic Disease Stage III

Seminoma

For patients classified as good risk seminoma based on the IGCCCG classification, the standard treatment includes either three cycles of BEP or four cycles of EP. A phase III randomised trial demonstrated that four cycles

of EP is non-inferior to three cycles of BEP with respective 4 year overall survival (OS) rates of 92%–96% [45]. Good risk patients generally exhibit a favourable prognosis with approximately 95% OS at 5 years [46].

For those with intermediate risk disease, the standard of care consists of either four cycles of BEP or four cycles of etoposide, ifosfamide and cisplatin (VIP). VIP should be considered for patients with contraindications to bleomycin, such as a chronic kidney failure, age over 50 years, COPD or other lung diseases. Intermediate risk seminomas have a 5-year OS of approximately 88% [46].

Non-seminoma

In the good-risk non-seminoma group, patients are recommended either three cycles of BEP or four cycles of EP, both of which are well-tolerated and result in approximately 95% cure rates [46].

Patients in the intermediate risk and poor risk group are recommended either four cycles of BEP or four cycles of VIP, with VIP being preferred for those at a higher risk of bleomycin-related complications. These standard chemotherapy regimens can achieve a cure rate of approximately 88% and 67%, respectively [46].

Unfortunately, in the poor risk group around 40% experience relapse. Although four cycles of BEP remain the standard approach that is espoused in both the European guidelines and the US guidelines, many expert clinicians feel that this is a suboptimal approach and may not effectively cure the disease. Therefore, dose-intensified regimens such as granulocyte colony-stimulating factor, actinomycin-D, methotrexate, etoposide, and cisplatin (GAMEC); cisplatin, vincristine, methotrexate, bleomycin, dactinomycin, cyclophosphamide, and etoposide (POMB/ACE); and cisplatin, bleomycin, vincristine, carboplatin, and BEP (CBOP/BEP) are being explored to improve treatment durability and survival outcomes in this patient cohort [44].

This dose-intensified chemotherapy comes with significant toxicity and therefore the selection of patients is crucial for this approach. It is crucial that these intensified regimens be administered in high-volume cancer centres. Although none has been proven superior to BEP in randomised

phase III studies, phase II has shown excellent PFS rates compared to four cycles of BEP.

Management of Residual Disease

Seminoma

Seminoma typically responds well to chemotherapy, and residual tumour resection is usually unnecessary; even in cases of large residual tumours, necrosis occurs in 95% of patients. As residual tumour is almost never present, residual disease less than 3 cm should be monitored. However, for masses 3 cm or larger, the use of a fluorodeoxyglucose (FDG) PET scan is recommended. The SEMPET trials suggest that FDG PET scans could be utilised to predict viable seminoma after chemotherapy [47]. However, subsequent studies have revealed false-positive rates of approximately 75% due to post-chemotherapy inflammation [48]. Based on these findings, a repeat FDG-PET is recommended at least 6 weeks after completion of chemotherapy.

PET positive with residual disease >3 cm poses a significant decision-making challenge. Surgical treatment of residual seminoma is complicated due to the desmoplastic reaction surrounding the tissue. Post-chemotherapy RPLND (PC-RPLND) can be offered if the urologist/testis cancer multidisciplinary team considers the risk of morbidity low. Alternatively, if morbidity is deemed unacceptable, observation and salvage chemotherapy upon relapse is suggested.

Non-seminoma

Post-chemotherapy RPLND is indicated in non-seminoma with residual lymph nodes larger than 1 cm in the absence of elevated serum tumour markers [49]. After chemotherapy, approximately 10% of patients still harbour viable cancer, 40% have teratoma and 50% have only necrotic tissue and or fibrosis. However, patients who achieve serological remission following chemotherapy and have radiographic residual tumours of less than 1 cm may be safely observed without residual tumour resection [50]. There is no role for FDG-PET in evaluating residual masses in non-seminoma unlike in seminoma. RPLND is performed for masses in the

retroperitoneum, and masses elsewhere (e.g., lungs, liver, brain) should be resected when feasible [20, 23].

Management of Relapsed Disease

Despite the sensitivity to platinum-based chemotherapy, approximately 40%–50% of patients in the intermediate and poor prognostic groups will encounter relapse following first-line treatment [51]. Typically, relapses manifest within the initial 2 years of treatment. In the salvage setting, two accepted approaches have emerged which are conventional dose chemotherapy (CDCT) or high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT).

Conventional-dose chemotherapy (CDCT) requires the use of previously unused agents such as paclitaxel, ifosfamide, and cisplatin (TIP); ifosfamide, etoposide, and cisplatin (VIP); or vinblastine, ifosfamide, and cisplatin (VeIP). Approximately 20%–40% of patients achieve a cure with CDCT. Although direct comparisons between regimens are lacking, objective response rates and overall survival appear broadly comparable across different combinations. High-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) was pioneered by Indiana University, with carboplatin plus etoposide being the most commonly used high-dose regimen [52].

The choice between CDCT and HDCT as the first salvage treatment in the relapsed setting remains unclear. Petrelli et al. conducted a large systematic review attempting to address this issue. In their pooled analysis, they found no significant differences in efficacy when comparing 1-year OS (64.2% in CDCT vs 63.7% in HDCT), 3-year OS (45.1% vs 46.7%), and 5-year OS (43% vs 45%) [53]. This controversial question may be closer to resolution with TIGER trial, which is an ongoing phase III randomised study (NCT04804007) comparing four cycles of TIP with paclitaxel-ifosfamide followed by three cycles of high-dose carboplatin-etoposide (TICE). Guidelines suggest that both CDCT and HDCT are preferred options for salvage treatment.

Further relapses after salvage chemotherapy are generally deemed incurable. Nonetheless, chemotherapy can still offer some benefits, although its efficacy is limited. In cisplatin-refractory disease, the

combination of gemcitabine, oxaliplatin and paclitaxel has shown efficacy [54].

Treatment Toxicities

Combination chemotherapy for TC poses risks of both early and long-term toxicities. In the short term, patients may experience haematological and non-haematological toxicities, along with an increased likelihood of cardiovascular and thromboembolic diseases. Nephrological, neurological and pulmonary toxicities are also possible, with caution warranted for bleomycin due to its pulmonary toxicity risk, especially in individuals with factors such as advanced age, significant lung disease or a history of active smoking.

In the long term, there is a risk of secondary malignancies and cardiovascular diseases, including metabolic syndrome, characterised by hypertension, obesity and hypercholesterolaemia. Additionally, significant proportions of TC survivors experience obesity, sensory neuropathy, tinnitus, hypogonadism and erectile dysfunction, which can impact daily life activities. RT can also lead to late toxicities, including secondary malignancies. These conditions can significantly affect quality of life and require ongoing management and support.

References

1. Znaor A, Skakkebaek NE, Rajpert-De Meyts E, Kuliš T, Laversanne M, Gurney J, *et al*. Global patterns in testicular cancer incidence and mortality in 2020. *International Journal of Cancer* 2022;151(5):692–698.⏎
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. *Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries*. CA*: A Cancer Journal for Clinicians* 2021;71(3):209–249.⏎

3. Kristensen DM, Sonne SB, Ottesen AM, Perrett RM, Nielsen JE, Almstrup K, *et al*. Origin of pluripotent germ cell tumours: the role of microenvironment during embryonic development. *Mol Cell Endocrinology* 2008;288(1–2):111–118.⏎
4. Skakkebaek NE, Berthelsen JG, Giwercman A, Müller J. Carcinoma-in-situ of the testis: possible origin from gonocytes and precursor of all types of germ cell tumours except spermatocytoma. *International Journal of Andrology* 1987;10(1):19–28.⏎
5. Huang J, Chan SC, Tin MS, Liu X, Lok VT, Ngai CH, *et al*. Worldwide distribution, risk factors, and temporal trends of testicular cancer incidence and mortality: a global analysis. *European Urology Oncology*;5(5):566–576.⏎
6. Balawender K, Orkisz S, Wisz P. Testicular microlithiasis: what urologists should know. A review of the current literature. *Central European Journal of Urology*;71(3):310.⏎
7. Jones TD, Ulbright TM, Eble JN, Cheng L. OCT4: a sensitive and specific biomarker for intratubular germ cell neoplasia of the testis. *Clinical Cancer Research*;10(24):8544–8547.⏎
8. Wilson JP, Cooksey G. Testicular pain as the initial presentation of testicular neoplasms. *Annals of the Royal College of Surgeons of England* 2004;86(4):284.⏎
9. Garner MJ, Turner MC, Ghadirian P, Krewski D. Epidemiology of testicular cancer: an overview. *International Journal of Cancer* 2005;116(3):331–339.⏎
10. Shah YB, Goldberg H, Hu B, Daneshmand S, Chandrasekar T. Metastatic testicular cancer patterns and predictors: A contemporary population-based seer analysis. *Urology* 2023;180:182–189.⏎
11. Bokemeyer C, Schmoll H, Schöffski P, Harstrick A, Bading M, Poliwoda H. Bilateral testicular tumours: prevalence and

clinical implications. *European Journal of Cancer* 1993;29(6):874–876.⏎
12. Aboumarzouk OM. *Blandy's Urology*. John Wiley & Sons; 2019.⏎
13. Hassan HC, Cullen IM, Casey RG, Rogers E. Gynaecomastia: an endocrine manifestation of testicular cancer. *Andrologia* 2008;40(3):152–157.⏎
14. Law C, AlshiekhAli Z, Taylor N, Howlett D. Supraclavicular left neck mass: an unusual presentation of metastatic testicular cancer in two older men. *BMJ Case Reports CP*;13(4):e233368.⏎
15. Patrikidou A, Cazzaniga W, Berney D, Boormans J, de Angst I, Di Nardo D, *et al.* European Association of Urology guidelines on testicular cancer: 2023 update. *European Urology*;83(3):289–301.⏎
16. Coursey Moreno C, Small WC, Camacho JC, Master V, Kokabi N, Lewis M, *et al.* Testicular tumors: what radiologists need to know—differential diagnosis, staging, and management. *Radiographics* 2015;35(2):400–415.⏎
17. Hale GR, Teplitsky S, Truong H, Gold SA, Bloom JB, Agarwal PK. Lymph node imaging in testicular cancer. *Translational Andrology and Urology* 2018;7(5):864.⏎
18. Tsili AC, Argyropoulou MI, Giannakis D, Tsampalas S, Sofikitis N, Tsampoulas K. Diffusion-weighted MR imaging of normal and abnormal scrotum: preliminary results. *Asian Journal of Andrology* 2012;14(4):649.⏎
19. Oechsle K, Hartmann M, Brenner W, Venz S, Weissbach L, Franzius C, *et al.* [18F] Fluorodeoxyglucose positron emission tomography in nonseminomatous germ cell tumors after chemotherapy: the German multicenter positron emission tomography study group. *Journal of Clinical Oncology*;26(36):5930–5935.⏎

20. Huddart RA, O'Doherty MJ, Padhani A, Rustin GJ, Mead GM, Joffe JK, *et al.* 18fluorodeoxyglucose positron emission tomography in the prediction of relapse in patients with high-risk, clinical stage I nonseminomatous germ cell tumors: preliminary report of MRC Trial TE22—the NCRI Testis Tumour Clinical Study Group. *Journal of Clinical Oncology*;25(21):3090–3095.⏎
21. Karpathakis A, Jamal-Hanjani M, Kwan A, Mazhar D, Rudman SM, Powles T, *et al.* Testicular germ cell tumors with bony metastases: Diagnosis, management, and outcomes (a case series). *Journal of Clinical Oncology* 2012;30(5_suppl):343.⏎
22. Leao R, Albersen M, Looijenga LH, Tandstad T, Kollmannsberger C, Murray MJ, *et al.* Circulating MicroRNAs, the next-generation serum biomarkers in testicular germ cell tumours: a systematic review. *European Urology* 2021;80(4):456–466.⏎
23. Moch H, Amin MB, Berney DM, Compérat EM, Gill AJ, Hartmann A, *et al.* The 2022 World Health Organization classification of tumours of the urinary system and male genital organs—part A: renal, penile, and testicular tumours. *European Urology*;82(5):458–468.⏎
24. Drevinskaite M, Patasius A, Kincius M, Jievaltas M, Smailyte G. *A population-based analysis of incidence, mortality, and survival in testicular cancer patients in Lithuania*. *Medicina* 2019;55(9):552.⏎
25. Patrikidou A, Cazzaniga W, Berney D, Boormans J, de Angst I, Di Nardo D, *et al*. European Association of Urology guidelines on testicular cancer: 2023 update. *European Urology*;83(3):289–301⏎
26. Djaladat H, Burner E, Parikh PM, Beroukhim Kay D, Hays K. The association between testis cancer and semen abnormalities

before orchiectomy: a systematic review. *Journal of Adolescent and Young Adult Oncology* 2014;3(4):153–159.⏎
27. Johner A, Faulds J, *Wiseman SM. Planned ilioinguinal nerve excision for prevention of chronic pain after inguinal hernia repair: a meta-analysis*. *Surgery* 2011;150(3):534–541.⏎
28. Heidenreich A. Contralateral testicular biopsy in testis cancer: current concepts and controversies. *BJU International*;104(9b):1346–1350.⏎
29. Afferi L, Baumeister P, Fankhauser C, Mordasini L, Moschini M, Aschwanden F, *et al.* Nerve-sparing robot-assisted retroperitoneal lymph node dissection: the monoblock technique. *European Urology Open Science* 2021;32:1–7.⏎
30. Yuan Y, Zhang D, Ning Y, Luo H, Qiu X, Tan Y, *et al*. Clinical efficacy and safety of robotic retroperitoneal lymph node dissection for testicular cancer: a systematic review and meta-analysis. *Frontiers in Oncology*;13:1257529.⏎
31. Porter J, Eggener S, Castle E, Pierorazio P. Recurrence after robotic retroperitoneal lymph node dissection raises more questions than answers. *European Urology*;76(5):610–611.⏎
32. Calaway AC, Einhorn LH, Masterson TA, Foster RS, Cary C. Adverse surgical outcomes associated with robotic retroperitoneal lymph node dissection among patients with testicular cancer. *European Urology*;76(5):607–609.⏎
33. Del Real OJ, de la Barra, Carlos Ignacio Calvo, Jiménez JA, Sepulveda F, Domínguez J. Predicting malignancy in small testicular lesions. *Central European Journal of Urology*;75(1):47.⏎
34. Wardak S, Pang KH, Castiglione F, Lindsay J, Walkden M, Ho DH, *et al.* Management of small testicular masses: outcomes from a single-centre specialist multidisciplinary team. *BJU International*;131(1):73–81.⏎

35. Henriques D, Mota Pinto A, Donato H, Leão R. Prevalence and management of incidental testicular masses—a systematic review. *Journal of Clinical Medicine* 2022;11(19):5770.⏎
36. Mortensen MS, Lauritsen J, Gundgaard MG, Agerbæk M, Holm NV, Christensen IJ, *et al.* A nationwide cohort study of stage I seminoma patients followed on a surveillance program. *European Urology*;66(6):1172–1178.⏎
37. Warde P, Specht L, Horwich A, Oliver T, Panzarella T, Gospodarowicz M, *et al.* Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. *Journal of Clinical Oncology*;20(22):4448–4452.⏎
38. Boormans JL, Sylvester R, Anson-Cartwright L, Glicksman RM, Hamilton RJ, Hahn E, *et al.* Prognostic factor risk groups for clinical stage I seminoma: An individual patient data analysis by the European association of urology testicular cancer guidelines panel and guidelines office. *European Urology Oncology*;7(3):537–543.⏎
39. Oliver RTD, Mead GM, Rustin GJ, Joffe JK, Aass N, Coleman R, *et al*. Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). *Journal of Clinical Oncology* 2011;29(8):957–962.⏎
40. Kollmannsberger C, Tandstad T, Bedard PL, Cohn-Cedermark G, Chung PW, Jewett MA, *et al.* Patterns of relapse in patients with clinical stage I testicular cancer managed with active surveillance. *Journal of Clinical Oncology*;33(1):51–57.⏎
41. Honecker F, Aparicio J, Berney D, Beyer J, Bokemeyer C, Cathomas R, *et al.* ESMO Consensus Conference on testicular germ cell cancer: diagnosis, treatment and follow-up. *Annals of Oncology*;29(8):1658–1686.⏎

42. Heinzelbecker J, Schmidt S, Lackner J, Busch J, Bokemeyer C, Classen J, *et al.* Therapy of clinical stage IIA and IIB seminoma: a systematic review. *World Journal of Urology* 2022:1–13.⏎
43. National Comprehensive Cancer Network. NCCN Guidelines Version 1.2024 Testicular Cancer. 2024 March 15,⏎
44. Honecker F, Aparicio J, Berney D, Beyer J, Bokemeyer C, Cathomas R, *et al.* ESMO Consensus Conference on testicular germ cell cancer: diagnosis, treatment and follow-up. *Annals of Oncology*;29(8):1658–1686.⏎
45. Culine S, Kerbrat P, Kramar A, Théodore C, Chevreau C, Geoffrois L, *et al.* Refining the optimal chemotherapy regimen for good-risk metastatic nonseminomatous germ-cell tumors: a randomized trial of the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG T93BP). *Annals of Oncology* 2007;18(5):917–924.⏎
46. Gillessen S, Sauvé N, Collette L, Daugaard G, de Wit R, Albany C, *et al.* Predicting outcomes in men with metastatic nonseminomatous germ cell tumors (NSGCT): results from the IGCCCG update consortium. *Journal of Clinical Oncology* 2021;39(14):1563–1574.⏎
47. De Santis M, Becherer A, Bokemeyer C, Stoiber F, Oechsle K, Sellner F, *et al.* 2-18fluoro-deoxy-D-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: an update of the prospective multicentric SEMPET trial. *Journal of Clinical Oncology*;22(6):1034–1039.⏎
48. Decoene J, Winter C, Albers P. False-positive fluorodeoxyglucose positron emission tomography results after chemotherapy in patients with metastatic seminoma. *Urol Oncol*. 2015;33(1):23.e51-23.⏎

49. Heidenreich A, Paffenholz P, Nestler T, Pfister D. Management of residual masses in testicular germ cell tumors. *Expert Review of Anticancer Therapy*;19(4):291–300.⏎
50. Ehrlich Y, Brames MJ, Beck SD, Foster RS, Einhorn LH. Long-term follow-up of cisplatin combination chemotherapy in patients with disseminated nonseminomatous germ cell tumors: is a postchemotherapy retroperitoneal lymph node dissection needed after complete remission? *Journal of Clinical Oncology*;28(4):531–536.⏎
51. Fizazi K, Pagliaro L, Laplanche A, Fléchon A, Mardiak J, Geoffrois L, *et al*. Personalised chemotherapy based on tumour marker decline in poor prognosis germ-cell tumours (GETUG 13): a phase 3, multicentre, randomised trial. *The Lancet Oncology*;15(13):1442–1450.⏎
52. Adra N, Abonour R, Althouse SK, Albany C, Hanna NH, Einhorn LH. High-dose chemotherapy and autologous peripheral-blood stem-cell transplantation for relapsed metastatic germ cell tumors: the Indiana University experience. *Journal of Clinical Oncology*;35(10):1096.⏎
53. Petrelli F, Coinu A, Rosti G, Pedrazzoli P, Barni S. Salvage treatment for testicular cancer with standard-or high-dose chemotherapy: a systematic review of 59 studies. *Medical Oncology*;34:1–12.⏎
54. Bokemeyer C, Oechsle K, Honecker F, Mayer F, Hartmann JT, Waller CF, *et al*. Combination chemotherapy with gemcitabine, oxaliplatin, and paclitaxel in patients with cisplatin-refractory or multiply relapsed germ-cell tumors: a study of the German Testicular Cancer Study Group. *Annals of Oncology*;19(3):448–453.⏎

17 Aetiology, Pathophysiology and Clinical Assessment and Management of Priapism

Jamie Lindsay, Stanley Tang, Karl H. Pang and Asif Muneer

DOI: 10.1201/b22940-17

Introduction

Priapism refers to a persistent and pathological erection of the penis. Historically, the term originates from ‘Priapus’, the name of an ancient Greek God with associations to male reproductive power. Medically, it is defined as an erection prolonged beyond 4 hours in the absence of sexual desire and refractory to ejaculation. Priapism is subcategorised into ischaemic, non-ischaemic and stuttering. Whilst it is an uncommon urological diagnosis, it requires prompt clinical assessment and diagnosis. Ischaemic priapism comprises 95% of clinical presentations. The management of ischaemic priapism is time critical as the delivery of emergency treatment can prevent irreversible corporal smooth muscle damage and associated long-term erectile dysfunction [1].

Pathophysiology

Ischaemic (Previously Low Flow)

The pathophysiological process that occurs with ischaemic priapism is multifactorial. It centres around the dysregulation of the smooth muscle microenvironment within the penile corpora cavernosa. The cascade of

smooth muscle dysregulation is caused by impairment to higher neuronal signalling as well as altered neurotransmitter regulation locally within the corpora. The autonomic control of smooth muscle fibre contraction and relaxation fails and the normal mechanisms that control detumescence are lost. It is hypothesised that this cycle of events is self-perpetuating, and the result is prolonged obstruction to penile venous outflow. Functionally, the events are parallel to that of a ‘compartment syndrome’. The process is characterised by increased intracorporeal pressure beyond that of systemic arterial pressure and subsequent tissue deoxygenation. The physiological high-pressure stasis of blood at a cellular level causes progressive hypoxia, hypercapnia, glucopenia, hyperlactataemia and acidosis. The aberrant haemodynamic and biochemical parameters lead to trabecular interstitial oedema within the corpora. After 24 hours, cellular transformation is seen with fibrosis-like changes occurring to trabecular smooth muscle cells. Approaching 48 hours, thrombus formation as well as sinusoidal endothelial cell destruction occurs, at which point widespread smooth muscle transformation or necrosis is observed [2, 3, 4, 8].

The precise trigger for this pathophysiological process to ensue is wide ranging and no specific cause is identified in a proportion of patients (Table 17.1). Pharmacological agents that interfere with higher centre signalling as well as local neurotransmitter control contribute. These can include vasoactive medications aimed at promoting erection such as PDE5 inhibitors or PDE1 analogues, as well as therapeutic psychiatric medications targeting psychosis and depression (e.g., olanzapine or fluoxetine). Prescribed medications that interfere with the alpha-adrenergic pathway are also recognised, including tamsulosin and doxazosin in addition to drugs used illicitly or for recreation such as cocaine, amphetamines, cannabis and alcohol [2].

Table 17.1 Aetiology of Ischaemic Priapism⏎

Aetiology of Ischaemic Priapism	
Idiopathic	
Medications	*Anti-psychotic*: Risperidone, olanzapine, chlorpromazine *Anti-depressive*: Sertraline, fluoxetine, lithium *Alpha blockers*: Tamsulosin, doxazosin, prazosin *Vasoactive erectile agents*: PE1, PDE5i, papaverine

Aetiology of Ischaemic Priapism	
Haematological	*Haemoglobinopathies*: Sickle cell disease, thalassemia *Malignant*: leukaemia, myeloma
Illicit drugs	cocaine, cannabis, amphetamines
Neoplastic	*Locoregional*: Prostate, bladder, testes, urethral *Metastatic*: Renal cell carcinoma, lung
Neurological	Spinal cord injury, syphilis, cerebrovascular accident, brain tumour
Metabolic	Amyloidosis, gout, Fabry's disease
Toxins	Scorpion sting, spider bite

Source: Modified from Lue 2002 and Broderick 2009.

Priapism can occur secondary to conditions that pathologically increase blood viscosity. Sinusoidal thrombosis occurs with prolonged blood stagnation and mechanical obstruction occurs within the small veins of the subtunical corporal plexus. Priapism is therefore triggered by loss of the normal venous outflow. Sickle cell disease (SCD) is the most common haemoglobinopathy responsible for this. An estimated 50% of males with SCD will experience at least one priapic episode within their lifetime. The process is also evident in Thalassemia disease as well as described in the setting of haematological malignancies such as leukaemia and disseminated intravascular coagulation in sepsis and has been observed in patients who are in receipt of total parenteral nutrition.

Malignant priapism is also reported, which can occur through direct invasion of the tumour into penile corpora (for example, locally advanced prostate, bladder or rectal cancer). Secondary dissemination into the penis via metastasis has been seen in the context of metastatic renal cell carcinoma [2].

Non-ischaemic (Previously High Flow)

Ischaemia was thought to be the only aetiological process responsible for priapism until 1960, when the separate clinical entity of 'high flow' priapism was described. Now known clinically as non-ischaemic priapism, the cause was determined to be due to 'increased arterial influx into the cavernosal bodies'. However, it was not until 1983 when the pathophysiology was interpreted. Trauma to the perineum, most commonly in the form of blunt or a straddle-type, leads to the formation of a fistula between arterial and venous vessels serving the penis. Other described

causes include iatrogenic, either through injection of intracavernosal prostaglandin E1 or rarely penile revascularisation procedures. Around 15% are idiopathic. Angiography has shown that the internal pudendal artery provides the arterial branch of the fistula in almost all cases [5].

It is worth noting that priapism which occurs secondary to spinal cord injury unrelated to pelvic trauma is non-ischaemic; however, it usually transient and considered often to resolve without intervention [6].

Stuttering

Stuttering priapism is a form of recurrent ischaemic priapism and clinical episodes can vary in their frequency and duration. An episode of stuttering priapism can self-resolve or resolve with non-invasive intervention and this typically happens in less than 3 hours. However, between one quarter and a half of patients who suffer with stuttering priapism are at risk of progressing to fulminant ischaemic priapism requiring algorithmic medical and surgical treatment. Patients with a diagnosis of SCD are at significantly heightened risk of stuttering priapism, with the remainder of cases occurring in pre-existing neurological disease or idiopathic scenarios. Of note, it can impact the paediatric SCD population with mean age of presentation at 12 years. The physiological process that occurs in the stuttering subtype is considered the same as ischaemic priapism; however, the relapsing and resolving history is hypothesised to be more complex. Stuttering priapism physiology is considered to involve the interplay of nitric oxide metabolism, endothelial factors and vascular reactivity. A persisting impairment in nitric oxide signalling is proposed to impact several pathways involved in the regulation of corporal smooth muscle tone which lowers its threshold to tumescence. This translates into a pathological over-response in tumescence triggered by both the nocturnal (physiological) and daytime (sexual) pathways. Where the acute priapic episode resolves, the reduced threshold for tumescence is persistent and this is thought to account for the repeated nature of episodes in stuttering priapism [7, 12].

History

A focused history can often allow differentiation between the three types of priapism. Pain is a common presenting symptom and is more severe in cases of ischaemic priapism. The pain tends to increase with increased duration of the erection. Non-ischaemic priapism, conversely, may be uncomfortable or even painless [13]. The duration of the erection is key to guiding management; BAUS has suggested categorising priapism into <48 hours, 48–72 hours and >72 hours. Other specific points to consider include recent perineal or penile trauma, previous episodes of priapism and history of SCD or haemoglobinopathies [14].

It is important to take a thorough drug history to ascertain whether use of PDE5 inhibitors, both oral and injectable, precipitated the priapism. The use of illicit drugs should be established to determine whether they have been erectogenic.

Although malignant priapism is rare, systemic symptoms of malignancy or history of urogenital malignancy will raise suspicions of this cause.

Examination

Initial examination ideally includes a genital and perineal exam. BAUS recommends performing an abdominal and neurological exam to complete the examination. In ischaemic priapism, the corpora tend to be rigid and painful, with a softer glans penis [14]. Non-ischaemic priapism, conversely, typically presents as a less-rigid erection.

A perineal examination is recommended to identify superficial bruising and other stigmata of perineal trauma.

Investigations

After examination, the next step should be corporal aspiration, which is essential in differentiating between ischaemic and non-ischaemic priapism. Table 17.2 demonstrates the typical findings on blood gas analysis between ischaemic and non-ischaemic priapism [1]. Prolonged ischaemic priapism may show glucopenia in corporal blood samples, along with hypoxia, hypercapnia and acidosis. Corporal aspiration may also have a therapeutic effect [15].

Table 17.2 Blood Gas Results from Ischaemic and Non-ischaemic Priapism

	pH	pO_2 (mmHg)	pCO_2 (mmHg)
Ischaemic priapism	<7.25	<30	>60
Normal mixed venous blood (room air)	7.35	40	50
Non-ischaemic priapism	7.4	>90	<40

Source: Adapted from Broderick et al.

Peripheral blood tests should be taken for full blood count, including platelet count, a blood film to screen for sickle cell and other haematological disorders, and an autoimmune screen. Serum prostate specific antigen level may be appropriate if locally advanced prostate cancer is a concern.

Imaging

Imaging modalities may be utilised according to the type of priapism. In general, a penile doppler study should be performed if available. In addition to history and examination, this helps differentiate ischaemic versus non-ischaemic priapism [16]. Doppler studies identify the degree of cavernosal artery inflow and venous sinusoidal outflow velocities.

In ischaemic priapism, there is severely reduced or absent flow within the cavernosal artery, typically <25 cm/s with increased resistive index, indicating high resistance and low peak systolic velocity. Furthermore, comparing the peak flow within the cavernosal artery before and after cavernosal aspiration may assess the degree of improvement [17].

In cases of non-ischaemic priapism, typical findings of penile doppler demonstrate low resistance with normal, high normal or high peak systolic velocity. If there is a fistula present, penile doppler may show turbulent flow.

MRI can reliably provide information on the degree of penile fibrosis and therefore viability of the corporal tissue. MRI has been shown to be extremely sensitive in predicting non-viable smooth muscle when correlated with corporal biopsies. This can influence the decision to proceed to early penile prosthesis in cases of delayed (>48 hours) presentation.

Penile MRI may also demonstrate malignant infiltration of the corporal tissue in cases of malignant priapism [18].

The role of angiography is limited to when there is a high suspicion of an arteriovenous fistula causing priapism, with the intent of embolisation.

The clinical assessment differences between ischaemic and non-ischaemic priapism are shown in Table 17.3.

Table 17.3 Comparison of Clinical Findings in Ischaemic and Non-ischaemic Priapism⏎

	Ischaemic Priapism	**Non-ischaemic Priapism**
History		
Penile pain	Very common	Uncommon
Intracavernosal injection	Common	Uncommon
Haematological condition or abnormality	Sometimes	Uncommon
Perineal trauma or straddle injury	Uncommon	Very common
Examination		
Corpora cavernosa rigidity	Common	Uncommon
Sparing of glans	Common	Common
Investigations		
Colour of aspirated blood	Dark	Bright
Venous blood gas result	Hypoxia, hypercapnia, acidaemia	Oxygenated with normal pH
Penile doppler finding	Decreased or absent	Normal ± turbulence from fistula

Source: Adapted from Broderick et al.

Management

Management of Ischaemic Priapism

Acute ischaemic priapism is a urological emergency, and treatment should be initiated as promptly as possible. In general, treatment should be delivered in a step-wise fashion (Figure 17.1), with regular re-examination to assess response to treatment [16]. The aim is to restore detumescence and prevent corporal fibrosis.

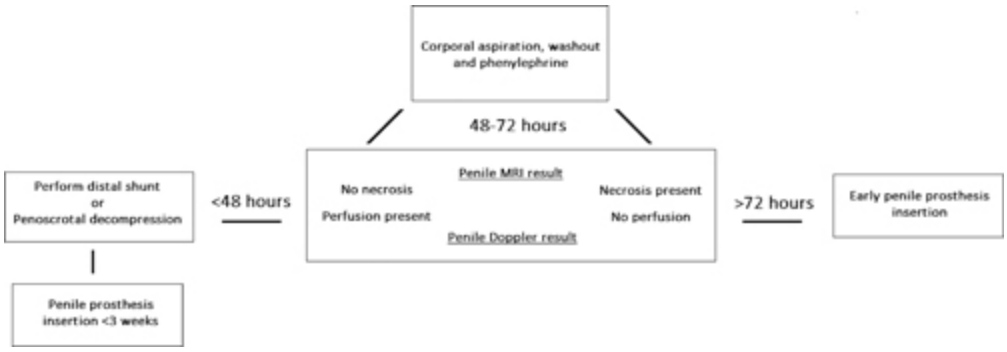


Figure 17.1 Step-wise management of ischaemic priapism.⏎

Corporal Aspiration

This serves the purpose of confirming the diagnosis and can be potentially therapeutic. Penile block with local anaesthetic is recommended before aspiration, especially if multiple attempts are anticipated. Access is gained using a large bore (19 gauge) or butterfly needle. Two common approaches exist: inserting the needle into the lateral aspect of the penile shaft (3 or 9 o'clock position) or through the glans into the tip of the corpus cavernosum. Aspiration alone can resolve from 20% to 30% of acute ischaemic priapism episodes [19].

Intracavernosal Injection

If aspiration fails to achieve detumescence, the next step is intracavernosal injection of a sympathomimetic agent or an alpha-adrenergic agonist [20]. Such drugs can precipitate hypertension and reflex bradycardia if systemically absorbed, therefore continuous monitoring of blood pressure and pulse is recommended during treatment.

Phenylephrine is a selective alpha-1 adrenergic receptor and is most widely used. This can be given in 200 µg aliquots, every 3–5 minutes until detumescence, with the maximum dose of 1 mg per hour.

Surgical Management

Shunting is utilised when priapism is refractory to corporal aspiration and injection. The aim of these procedures is to restore venous outflow. Penile

shunts can be categorised into distal and proximal shunts [1].

Distal Shunts

The winter (or caverno-glanular) shunt utilises a Tru-cut biopsy needle to create a fistula between the corpus spongiosum and the corpus cavernosum. The needle removes cores that consist of tunica albuginea and erectile tissue. Removal of multiple cores is often necessary to achieve detumescence [21] (Figure 17.2).

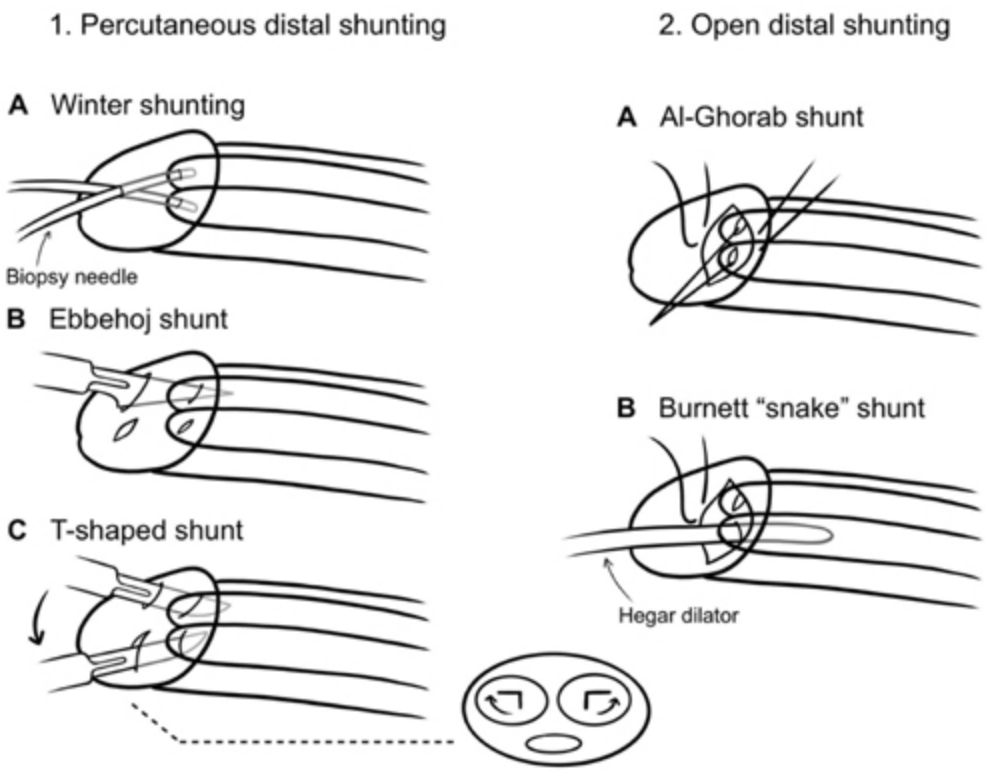


Figure 17.2 Percutaneous and open distal shunts.⏎

An Ebbehoj procedure is similar to the Winter shunt, except an 11 blade is used to create the fistula.

A T-shunt procedure is an example of a percutaneous distal shunt. To decompress the penis, an 11 blade is inserted vertically with the blade running parallel to the external urethral meatus. The blade passes through the glans penis into the distal corporal body. The blade is then rotated laterally at 90^{o}, in a direction away from the urethra. Removing the blade at

this angle opens the tract into the characteristic T shape. Manual compression is applied to the tumescent penis to drain blood and clot through the shunt. The blood should appear dark and viscous. If this is unsuccessful, the contralateral corporal body can be opened. Once a detumescent state is achieved and bright red, oxygenated blood is draining, the glans incision can be closed with dissolvable sutures.

Tunnelling (Snake manoeuvre described by Burnett) can be performed at the same time as the distal shunt. The decision to proceed to tunnelling is dependent on the surgeon's experience and familiarity with the procedure. It involves inserting a straight 8-10Fr Hegar dilator through the glans incision into the corpora cavernosum, stopping at the crura [22].

The Al-Ghorab procedure involves the excision of a circular core of tissue from each corpus to create a cavernous-glandular shunt. The glans is then re-sutured after the penis has been squeezed until oxygenated blood is seen to flow.

Distal shunts have high success rates and are largely uncomplicated. For this reason, patients who present <72 hours after onset of priapism who have failed conservative treatment should be offered a distal shunt. Should this prove unsuccessful, referral to a specialist centre should be sought [14].

Proximal Shunts

The Quackels procedure involves the formation of a shunt between the cavernosal and proximal part of corpus spongiosum where 1 cm windows of tissue are removed.

The Grayhack procedure is a venous shunt created between the saphenous vein and corpus cavernosum. The saphenous vein is isolated and exposed for ~10 cm. The proximal aspect is detached so that it is long enough to reach the penis. An ellipse of tunica is excised and an end-to-side anastomosis.

These shunts are obsolete, are largely abandoned by specialist centres in favour of distal shunts and acute/early penile prosthesis insertion.

When detumescence is achieved by surgical intervention, the patient should be observed for a period in hospital to monitor blood pressure, pain and tumescence.

Patients with priapism lasting >72 hours will inevitably have a degree of fibrosis within the corpus cavernosum. For this reason, after initial management with aspiration and alpha-adrenergic injection, patients should be referred urgently to a specialist centre for consideration of an early penile prosthesis [23].

Sickle Cell Disease

Patients with SCD presenting with priapism should be managed jointly with haematology services. Surgical management of acute ischaemic priapism in this population is the same as for patients without SCD. As part of initial management, patients should be kept hydrated with intravenous fluids and well oxygenated. Etilefrine is the alpha-adrenergic agonist of choice in patients with SCD.

The use of red cell exchange transfusion in the management of the acute ischaemic priapism episode has been debated in scientific literature. EAU consensus recommends that exchange transfusion should not be used as a primary treatment for ischaemic priapism in patients with SCD. In addition, although exchange transfusion was safe to use, it carries the risk of neurological events such as strokes, seizures and focal neurological deficits [24].

Management of Non-ischaemic Priapism

In non-ischaemic priapism, there is no corporal ischaemia or infarction, and if pain is present, tends to be mild. As a result, it is not classified as a urological emergency. Nevertheless, prompt diagnosis using history, examination and penile blood gas is important.

Penile doppler can be both diagnostic and therapeutic in non-ischaemic priapism. If a fistula is present, manual pressure using the ultrasound probe can assist in closing the fistula. This has a higher success rate in paediatric cases. Injection of alpha-adrenergic agonists are contraindicated due to the higher risk of systemic absorption [25].

If conservative treatment fails, selective arterial embolization should be considered at a specialist centre.

Management of Stuttering (Recurrent) Priapism

The goal in managing stuttering or recurrent ischaemic priapism is to treat the acute episode and to prevent or reduce the frequency of future episodes. To this effect, patients presenting to secondary care should be investigated and treated according to the ischaemic priapism pathway described previously. Patients with stuttering priapism may have had multiple previous episodes of priapism and will be proficient in utilising conservative measures such as ejaculation, exercise or an ice pack before seeking admission. The rarity of recurrent ischaemic priapism is reflected in the sparsity of the evidence base for its treatment, which mostly comprises of small case-series or retrospective studies [26].

Hormonal Treatment

Hormonal treatments target testosterone levels by inhibiting or suppressing levels of free testosterone. They can be grouped into anti-androgens and gonadotrophin-releasing hormones. These are a safe and effective first-line prophylaxis. The most common anti-androgen used is cyproterone acetate (CPA). A daily dose of 100 mg of CPA results in a 75% reduction in plasma testosterone [27]. The withdrawal rate is high due to the side effects of low libido and low mood, which may be especially intolerable in young males. Usage of hormonal treatments in prepubertal males should be avoided.

Alpha-adrenergic Agonists

Etilefrine and pseudoephedrine have been shown to be safe and effective as first-line prophylaxis. Their mechanism of action is not well understood although it is suggested they mediate cavernosal smooth muscle contraction to achieve detumescence [28].

Phosphodiesterase-5 Inhibitors

Use of PDE5 inhibitors such as sildenafil and tadalafil in patients with recurrent ischaemic priapism has a paradoxical effect to their usual role as an erectogenic medication. Their usage as a daily prophylaxis was shown to reduce need for admission to the emergency department [29]. Compared to hormonal treatments and alpha adrenergic agonists, the side effect profile of PDE5 inhibitors is the most well-documented and tolerable.

Changes in Management

The sequelae of hypoxia that occurs during ischaemic priapism will lead to scarring and fibrosis of the corporal bodies and when untreated leads to erectile dysfunction, penile induration and shortening. The impact of medical and surgical treatment is generally considered to be more effective at relieving priapism and its consequences when instituted sooner. This was demonstrated in patients with acute priapism of sickle cell aetiology, whereby successful spontaneous erection, measured at 4 weeks post episode, correlated significantly with time to priapism reversal in that results were 100% with time <12 hours and 0% beyond 36 hours [10].

It is considered that when ischaemic priapism is treated successfully within 24 hours then the return of premorbid erectile function is approximately 50%. Beyond 24 hours, the requirement of a urologist to perform a surgical shunt procedure is higher in order to reverse the priapic episode and achieve return of smooth muscle oxygenation. In cases approaching or beyond 48 hours, surgical shunt performance may improve pain and achieve detumescence but may not confer prognostically with a positive erectile function outcome [8, 9].

Early Penile Prosthesis Insertion

The early insertion of a penile prosthesis offers a new standard of care in cases of priapism which are refractory to algorithmic medical and surgical treatment or in which presentation is very delayed. The benefits of prosthesis insertion in the acute setting were demonstrated in the early 2000s whereby eight patients were managed without any significant early complications. These studies later progressed to include a total of 50 patients. The infection rate was 6% and reoperation 12%. Advantages of early implant insertion include treatment of pain by relief of priapic episode and a quicker return of sexual function and activity in addition to avoiding the general complications associated with delayed implant insertion, including penile shortening from prolonged fibrosis. Moreover, it is considered to provide a treatment modality for patients who have been suffering with premorbid erectile dysfunction in addition to providing a solution to patients with recurrent intermittent or stuttering priapism [9].

Insertion of a malleable prosthesis (Figure 17.3a) is favoured in the acute setting <3 weeks, as it is associated with a lower risk of infection compared to inflatable variants. In patients who have recently undergone a distal shunt procedure, a downsized malleable prosthesis is often used to reduce the risk of distal erosion and its associated complications. Upsizing or conversion to a three-piece inflatable penile prosthesis (Figure 17.3b) can be considered after approximately 6 months, if appropriate. Early prosthesis insertion is now supported by clinical guidelines: the BAUS recommends insertion beyond 72 hours, the EAU beyond 48 hours and the AUA states it may be considered in selected patients after 36 hours. Emphasis is placed on careful patient selection and thorough preoperative counselling when pursuing this approach [14, 16, 30].

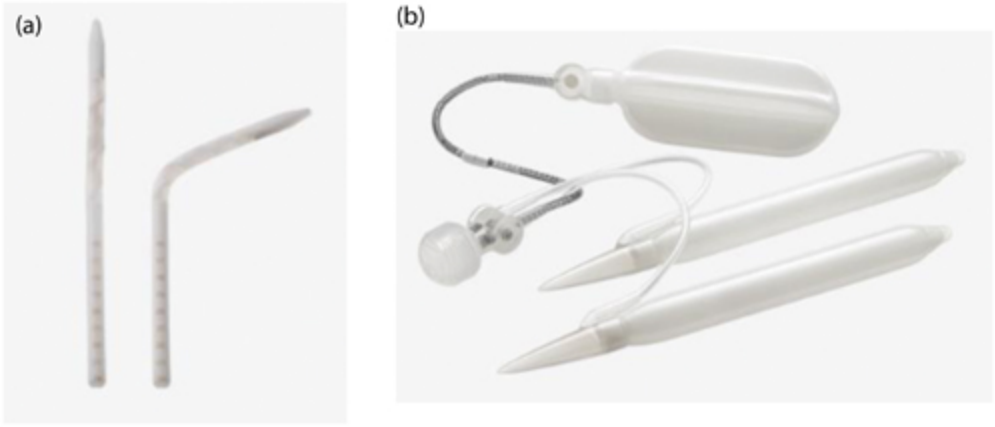


Figure 17.3 Penile prostheses (a) malleable penile prosthesis; (b) inflatable three-piece penile prosthesis (Coloplast^{TM}).⏎

Penoscrotal Decompression

A distal corporoglandular shunt, with or without an intercavernous tunnelling procedure, has been the long-instituted surgical approach to ischaemic priapism refractory to medical management. Between 24 and 48 hours, performing a distal shunt procedure is associated with a 55% chance of priapism resolution and this figure is 30% beyond 48 hours. In recent years, a novel penoscrotal decompression technique has been described with favourable outcomes. The cohort of 25 patients underwent either

unilateral or bilateral (if indicated) penoscrotal decompression at a mean duration of 71 hours, with eventual detumescence being noted in all patients. This technique involves midline incision at the penoscrotal level followed by unilateral longitudinal corporal incision with the aid of a suction device to achieve drainage of ischaemic blood. A bilateral procedure can be performed if response is suboptimal. It is discussed that penoscrotal decompression may offer advantages, not only in successful priapism resolution, but also in preventing the need for early prosthesis insertion. Furthermore, this technique when used as a first-line surgical approach would avoid disruption to the glans and distal corpora should a penile implant insertion be required at any stage. Erectile dysfunction was reported in 40% of those assessed following penoscrotal decompression [9, 10].

Conclusion

Priapism continues to represent one of the many acute urological conditions requiring time-critical evaluation and intervention. While it is an uncommon presentation, andrologists and specialists in urology should be very familiar with its pathogenesis and management. Emphasis is maintained towards the importance of a tailored assessment and quick differentiation as to the presence of ischaemia by corporal blood gas analysis. National urological societal guidelines provide an invaluable resource to refer to for the most up to date and recognised management of this condition. As discussed, the management of all priapism subtypes has progressed over the last several decades, with further ongoing studies awaited to determine how the management of priapism may change in the future. Special attention should be made towards educating patients with SCD, who remain a high risk population for this condition.

References

1. Cherian J, Rao AR, Thwaini A, Kapasi F, Shergill IS, Samman R. Medical and surgical management of priapism. *Postgrad*

Med J Feb;82(964):89–94. doi: 10.1136/pgmj.2005.037291. PMID: 16461470; PMCID: PMC2596691.⏎
2. Broderick GA, Kadioglu A, Bivalacqua TJ, Ghanem H, Nehra A, Shamloul R. Priapism: pathogenesis, epidemiology, and management. *J Sex Med*. 2010 Jan;7(1 Pt 2):476–500. doi: 10.1111/j.1743-6109.2009.01625.x. PMID: 20092449.⏎
3. Muneer A, Cellek S, Dogan A, Kell PD, Ralph DJ, Minhas S. Investigation of cavernosal smooth muscle dysfunction in low flow priapism using an in vitro model. *Int J Impot Res* 2005 Jan–Feb;17(1):10–18. doi: 10.1038/sj.ijir.3901231. PMID: 15071490.⏎
4. Vreugdenhil S, Freire Jorge PJ, van Driel MF, Nijsten MW. Ischemic priapism as a model of exhausted metabolism. *Physiol Rep*. 2019 Mar;7(6):e13999. doi: 10.14814/phy2.13999. PMID: 30916476; PMCID: PMC6436141.⏎
5. Ingram AR, Stillings SA, Jenkins LC. An update on non-ischemic priapism. *Sex Med Rev*. 2020 Jan;8(1):140–149. doi: 10.1016/j.sxmr.2019.03.004. Epub 2019 Apr 12. PMID: 30987934.⏎
6. Gordon SA, Stage KH, Tansey KE, Lotan Y. Conservative management of priapism in acute spinal cord injury. *Urology*. 2005 Jun;65(6):1195–1197. doi: 10.1016/j.urology.2004.12.036. PMID: 15913719.⏎
7. Kousournas G, Muneer A, Ralph D, Zacharakis E. Contemporary best practice in the evaluation and management of stuttering priapism. *Ther Adv Urol*. 2017 Jul 4;9(9–10):227–238. doi: 10.1177/1756287217717913. PMID: 28932276; PMCID: PMC5598804.⏎
8. Muneer A, Alnajjar HM, Ralph D. *Recent advances in the management of priapism*. *F1000Res*. 2018 Jan 10;7:37. doi:

10.12688/f1000research.12828.1. PMID: 29375820; PMCID: PMC5765390.⏎
9. Alnajjar HM, Muneer A. Recent advances in understanding and treating priapism. *Fac Rev*. 2022 Aug 26;11:23. doi: 10.12703/r/11-23. PMID: 36118326; PMCID: PMC9465841.⏎
10. Bennett N, Mulhall J. Sickle cell disease status and outcomes of African-American men presenting with priapism. *J Sex Med*. 2008 May;5(5):1244–1250. doi: 10.1111/j.1743-6109.2008.00770.x. Epub 2008 Feb 25. PMID: 18312286.⏎
11. Baumgarten AS, VanDyke ME, Yi YA, Keith CG, Fuchs JS, Ortiz NM, Cordon BH, Pagliara TJ, Ward EE, Jaderlund JW, Teeple CS, Christine BS, Yafi FA, Hudak SJ, Morey AF. Favourable multi-institutional experience with penoscrotal decompression for prolonged ischaemic priapism. *BJU Int.* 2020 Oct;126(4):441–446. doi: 10.1111/bju.15127. Epub 2020 Jul 31. PMID: 32501654.
12. Champion HC, Bivalacqua TJ, Takimoto E, Kass DA, Burnett AL. Phosphodiesterase-5A dysregulation in penile erectile tissue is a mechanism of priapism. *Proc Natl Acad Sci U S A.* 2005 Feb 1;102(5):1661–1666. doi: 10.1073/pnas.0407183102. Epub 2005 Jan 24. PMID: 15668387; PMCID: PMC547836.⏎
13. Sahdev V, Ralph D, Muneer A. (2017). Priapism. In *Male Sexual Dysfunction* (eds S Minhas, J Mulhall). https://doi.org/10.1002/9781118746509.ch20.⏎
14. BAUS Section of Andrology Genitourethral Surgery, Muneer A, Brown G, Dorkin T, Lucky M, Pearcy R, Shabbir M, Shukla CJ, Rees RW, Summerton DJ. BAUS consensus document for the management of male genital emergencies: priapism. *BJU Int.* 2018 Jun;121(6):835–839.⏎
15. Keoghane SR, Sullivan ME, Miller MA. The aetiology, pathogenesis and management of priapism. *BJU Int.* 2002

Jul;90(2):149–154.⏎
16. EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2022. ISBN 978-94-92671-16-5.⏎
17. von Stempel C, Walkden M. (2017). Duplex ultrasonography and its role in the assessment of male sexual dysfunction. In *Male Sexual Dysfunction* (eds S Minhas, J Mulhall). https://doi.org/10.1002/9781118746509.ch11.⏎
18. Ralph DJ, Borley NC, Allen C, Kirkham A, Freeman A, Minhas S, Muneer A. The use of high-resolution magnetic resonance imaging in the management of patients presenting with priapism. *BJU Int.* 2010 Dec;106(11):1714–1718.⏎
19. Biebel MG, Gross MS, Munarriz R. Review of ischemic and non-ischemic priapism. *Curr Urol Rep*. 2022 Jul;23(7):143–153. doi: 10.1007/s11934-022-01096-8. Epub 2022 May 10.⏎
20. Burnett AL, Sharlip ID. Standard operating procedures for priapism. *J Sex Med*. 2013 Jan;10(1):180–194. doi: 10.1111/j.1743-6109.2012.02707.x. Epub 2012 Mar 29.⏎
21. Johnson MJ, Kristinsson S, Ralph O, Chiriaco G, Ralph D. The surgical management of ischaemic priapism. *Int J Impot Res.* 2020 Jan;32(1):81–88. doi: 10.1038/s41443-019-0197-9. Epub 2019 Sep 30.⏎
22. Kapadia AA, Ostrowski K, Walsh TJ (2021). Priapism. In *A Clinical Guide to Urologic Emergencies* (eds H Wessells, S Horie, RG Gómez).⏎
23. Mishra K, Loeb A, Bukavina L, Baumgarten A, Beilan J, Mendez M, DiGiorgio L, Fu L, Carrion R. Management of priapism: a contemporary review. *Sex Med Rev*. 2020 Jan;8(1):131–139. doi: 10.1016/j.sxmr.2019.01.001. Epub 2019 Mar 19.⏎
24. Ballas SK, Lyon D. Safety and efficacy of blood exchange transfusion for priapism complicating sickle cell disease. *J Clin Apher*. 2016 Feb;31(1):5–10.⏎

25. Bilhim Pisco JM, Kupershmidt M, Thomson KR (2021). 48 - Treatment of high-flow priapism and erectile dysfunction. In *Image-Guided Interventions* (3rd Edition, pp. 379–385.e1). Elsevier Inc. https://doi.org/10.1016/B978-0-323-61204-3.00048-8⏎
26. Muneer A. Comparison of EAU and UK guidelines on priapism. *J Clin Urol* 2018;11(2):127–31.⏎
27. Muneer A, Minhas S, Arya M, Ralph DJ. Stuttering priapism--a review of the therapeutic options. *Int J Clin Pract* 2008;62(8):1265–70.⏎
28. Okpala I, Westerdale N, Jegede T, Cheung B. Etilefrine for the prevention of priapism in adult sickle cell disease. *Br J Haematol* 2002;118(3):918–21.⏎
29. Hou LT, Burnett AL. Regimented phosphodiesterase Type 5 inhibitor use reduces emergency department visits for recurrent ischemic priapism. *J Urol*. 2021 Feb;205(2):545–553.⏎
30. https://www.auanet.org/guidelines-and-quality/guidelines/diagnosis-and-management-of-priapism-aua/smsna-guideline-(2022).⏎

18 Aetiology, Pathophysiology, Clinical Assessment and Management of Fournier's Gangrene

Matthew H.V. Byrne, Paul Hadway and Shafi Wardak

DOI: 10.1201/b22940-18

Definition

Fournier's gangrene (FG) is a progressive necrotising fasciitis involving the perineum and external genitalia [1]. It is a rare urological emergency that is associated with high morbidity and mortality that may occur despite treatment [2].

Epidemiology

The epidemiological evidence base for FG is poor. Due to its rarity, it is mainly described in case reports and case series rather than larger studies. There are two key papers which present epidemiological data: Eke (2002); and Sorensen et al. (2009).

Eke conducted a literature review and identified 1,726 cases of FG [3]. Sorensen et al. reviewed the US State Inpatient Database and identified 1,680 cases of FG [2].

- *Incidence*: 1.6 in 100,000 hospitalised patients [2], most hospitals will encounter less than one patient with FG per year [4].
- *Prevalence*: 10 Males:1 Female [3], most patients are aged 50–79, but FG can affect children and women [2, 3, 5].

Aetiology

FG is most commonly caused by a synergistic polymicrobial infection in patients with underlying comorbidities – notably diabetes mellitus.

Risk Factors

Impaired immunity or microcirculation

- *Diabetes*: 35%–55% of cases [2, 3]
- *Alcoholism*: 30%–40% [5, 6]
- *Obesity*: 50% BMI >25 [5]
- *Immunosuppression* [5]: HIV, leukaemia
- *Renal or liver failure* [5, 8]
- *Immobilisation* [5]
- *Older age* [8]

Colorectal and urological disease [3]

- Peri-anal abscess
- Appendicitis, diverticulitis, colonic carcinoma
- Scrotal abscess
- Urethral catheter, strictures, stones

Trauma

- *Local*: E.g., human bites, anal intercourse [3]
- *Operative*: Case reports have noted FG after general surgical procedures, such as: hernia repair, haemorrhoid, prolapse repair or appendicectomy [5] and urological procedures such as: vasectomy, circumcision, hydrocelectomy and prostate biopsy (although these occurred in a small number of cases [3].

No identifiable cause of disease or risk factor is found in around 30% of cases [2, 3].

Lower socioeconomic status may be a risk factor, although the literature is not clear in distinguishing whether this is an independent risk factor or simply because alcoholism and obesity are higher in these groups [2]. Ethnicity has not been identified as a risk factor [3].

Pathophysiology

FG starts in the subcutaneous tissue, and the epidermis and dermis are spared [9]. Bacteria release endotoxins and exotoxins, which cause necrosis; this facilitates rapid spreading along the fascial planes [10]. Arterial and venous thrombosis occurs and the epidermis and dermis are finally affected [11].

Spread of FG

FG spreads along fascial planes. Infections of anal origin may extend anteriorly via Colles' fascia to the Dartos fascia, involving the penis and scrotum, and superiorly via Scarpa's fascia to the anterior abdominal wall. The spread is limited by the anatomical attachments of Colles' fascia: laterally to the pubic rami and posteriorly to the urogenital diaphragm. If Colles' fascia is breached, the infection can extend into the ischiorectal fossa, buttocks, and thighs [12].

Infection of urogenital origin spreads via Buck's fascia. Infection is limited to the ventral penis initially, but if Buck's fascia is breached there is subsequent spread along Colles' and Dartos fascia as above [12].

Testicular and deeper tissue infection is rare and is associated with intra-abdominal or retroperitoneal disease [1]. If the penis is involved, the corpora is usually spared [3].

Disease Progression

There may be two phases during the disease. Initially, the body's immune system can prevent the spread of the infection, and the disease may progress slowly. Later, however, the disease becomes fulminant FG, progresses rapidly and patients quickly deteriorate [5]. The speed of progression is largely determined by the causative organism [10]. Polymicrobial infections tend to progress slowly over days, whereas monomicrobial infections may initially be insidious and then progress rapidly [10].

Source of Infection

The source of infection may be [3]:

- Local skin (24%)
- Colorectal (21%)
- Urinary tract (19%)
- Unknown

Other small cohort studies have demonstrated higher rates of colorectal origin [7] – up to 50%.

If colorectal and urinary sources have been excluded, it is likely the source has come from the skin [5]. If there is initially a lesion in the skin, the evidence of this may be destroyed as the disease process progresses [5].

Causative Organism

There are four types of necrotising fasciitis generally and these are: polymicrobial, monomicrobial, marine and fungal (Table 18.1).

Table 18.1 Types of Necrotising Fasciitis⏎

Type of Necrotising Fasciitis	Cause	Organism	Course
I	Polymicrobial (~80% of cases)	Aerobic and anaerobic bacteria	Disease is less aggressive Often those who are immunocompromised Lowest mortality
II	Monomicrobial (~20%)	Often group A beta-haemolytic streptococcus	May be associate with toxic shock Mortality is ~30%
III	Marine (rare)	Marine-related e.g., Vibrio spp.	Associated with contaminated water or consumption of raw seafood Mortality is ~40%
IV	Fungal (very rare)	Candida	Associated with trauma or in immunocompromised patients Mortality is ≥50%

Source: Morgan MS. Diagnosis and management of necrotising fasciitis: a multiparametric approach. *J Hosp Infect*. 2010;75(4):249–257. doi:10.1016/J.JHIN.2010.01.028.

Tang et al. completed a literature review and identified 19 articles covering a total of 4,365 patients with FG [8]. In this study, FG was most commonly polymicrobial (54%), with monomicrobial causes being:

- *Escherichia coli* (47%)
- *Streptococcus* (37%)
- *Bacteroides* (36%)
- *Enterobacter* (31%)
- Others (<20%): *Staphylococcus, enterococcus, pseudomonas*

In polymicrobial cases of FG, a synergistic relationship may exist between the bacterial species. Synergism occurs when one bacterium produces a nutrient that supports the growth of another. The second bacterium may, in turn, produce an exotoxin that destroys leukocytes, thereby protecting both organisms from phagocytosis [3]. Synergism also occurs when aerobic and anaerobic bacteria are present. The aerobic bacteria consumes the oxygen in the local environment thus helping the anaerobic bacteria [3].

Clinical Assessment

Clinical assessment starts with an A to E assessment, followed by a full urological history, with particular attention paid to the risk factors described above and symptoms described below. Patients require a thorough examination of the external genitalia and perineum, looking for signs below. An abdominal examination and digital rectal examination should be performed if required.

- Patients may have early and advanced symptoms and signs (Table 18.2 and Figure 18.1) [9, 10, 13]:
    - *Early*: Pain, itching, swelling and erythema
    - *Advanced*: Fever, delirium, dizziness, anxiety, nausea and vomiting, weakness, crepitus, extensive necrosis, bruising, blisters, bullae, dishwater discharge, septic shock and multi-organ failure
- The area affected is primarily the perineum and/or external genitalia. However, the infection can extend to the thigh, buttocks and up the abdominal wall, even to the clavicles [1]. Testicular involvement is rare but can occur if there is an intra-abdominal source [1].
- *Duration*: Progressively worsening over 2–7 days [13].
- There may be a history of trauma, such as insect bites, ulcers, recent surgeries and of preceding infection. If there is a history of foreign travel, consider unusual or drug-resistant micro-organisms as a cause [10].
- *Differential diagnoses*: Cellulitis, epididymo-orchitis, abscess, testicular torsion, incarcerated inguinoscrotal hernia [9, 12].

Table 18.2 Pathophysiological Cause of Clinical Signs⏎

Clinical Sign	Pathophysiological Cause
Underestimated spread	The spread of the disease is more extensive than can be seen on the skin due to the subcutaneous tissue being affected first[a]
Crescendo pain then numbness	Due to worsening hypoxia,[b] but loss of sensation can occur later due to infarction of nerves.[a]

Clinical Sign	Pathophysiological Cause
Crepitus	Due to anaerobic production of hydrogen gas, which unlike CO_2 produced by aerobic organisms, is not water soluble.[c]
'Dishwater' discharge	Possibly caused by leukocyte lysis mixed with serous fluid.[b]

Source: [a] Misiakos EP, Bagias G, Patapis P, Sotiropoulos D, Kanavidis P, Machairas A. Current concepts in the management of necrotizing fasciitis. *Front Surg*. 2014;1:36. doi:10.3389/FSURG.2014.00036; [b] Morgan MS. Diagnosis and management of necrotising fasciitis: a multiparametric approach. *J Hosp Infect*. 2010;75(4):249–257. doi:10.1016/J.JHIN.2010.01.028; [c] Hagedorn JC, Wessells H. A contemporary update on Fournier's gangrene. *Nat Rev Urol*. 2016;14(4):205–214. doi:10.1038/nrurol.2016.243.

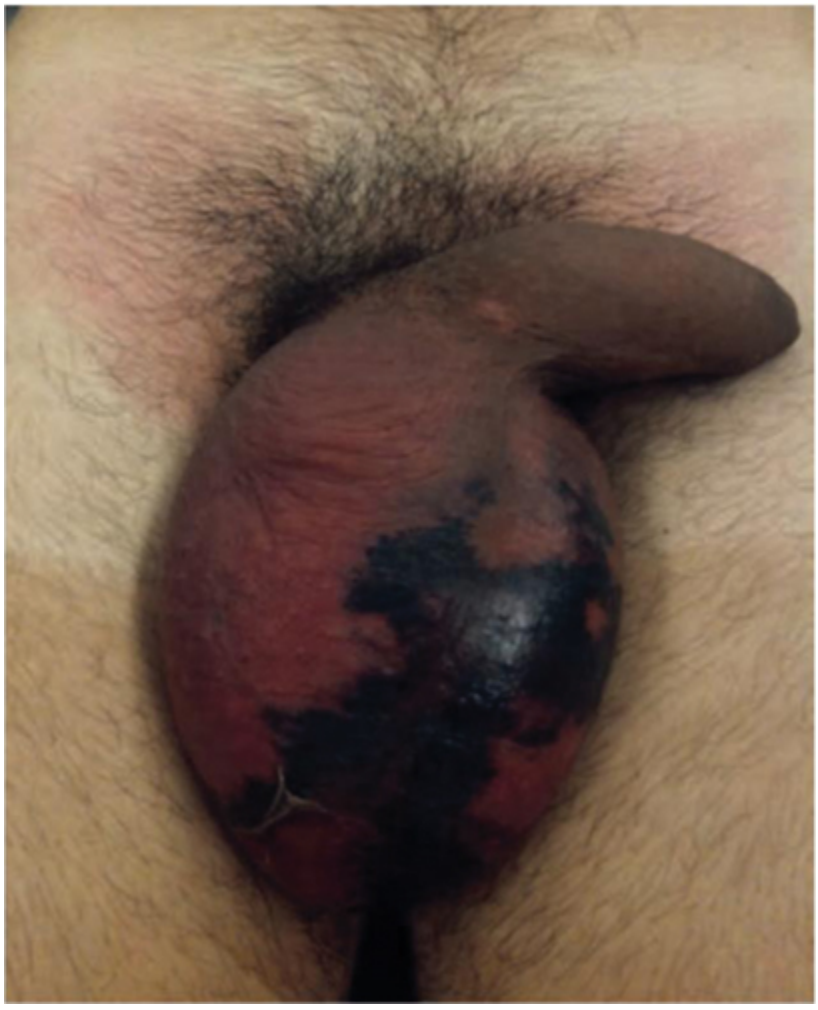


Figure 18.1 Fournier's gangrene of the scrotum. This image demonstrates areas of bilateral necrotic tissue, erythema of the scrotum which extends superiorly to the

inguinal regions and which is suggestive that the disease extends far beyond the areas of necrosis. Image courtesy of Hussain Alnajjar, UCLH.⏎

Investigations

The diagnosis of FG is primarily clinical. Other investigations in FG are useful but should not replace the clinical examination and should not delay intervention [1].

Bedside

- Observations, urine dipstick

Bloods

- FBC, U&E, CRP, glucose, LFTs, clotting, glucose, HbA1c

Imaging

Imaging can be used in cases where the diagnosis is unclear [12]. However, negative imaging should not negate the need for surgery (including laparotomy for an intra-abdominal cause) if clinical suspicion remains high [3].

The primary imaging modality for FG is computed tomography (CT). CT can be used to diagnose, determine extent of disease, and in some cases determine the aetiology of FG [12]. CT has higher specificity than x-ray, ultrasound and clinical examination [12]. CT can be used to identify [12]:

- Gas in the soft tissues. Gas is present in 90% of FG cases and can occur before crepitus is felt clinically (although the absence of gas on CT does not rule out FG).
- Fascial thickening, subcutaneous oedema and free fluid.
- Superficial and deep fascia. This can help better determine the extent of disease than clinical examination alone. Particularly if there is intra-abdominal or retroperitoneal involvement.
- Cause of FG, such as abscess, fistula tracts, intra-abdominal or retroperitoneal infection, colorectal perforation.
- Other soft tissue diseases which may be in the differential diagnosis.
- Response following treatment.

Alternative Imaging Modalities Include

- *X-Ray*: May show radiolucent areas, corresponding to subcutaneous gas, and this may be present before crepitus is felt. However, it cannot identify areas of gas within the deeper fascia [12].
- *Ultrasound*: Can detect gas in the scrotal wall, and reactive hydrocoele may be seen [12]. However, there is poor correlation with changes in the fascia [10]. The epididymis and testes will often be normal due to their separate blood supply to the scrotal wall. If the testicle is involved, this suggests an intra-abdominal or retroperitoneal aetiology [12].
- *MRI*: Can distinguish necrotic tissue from inflamed and oedematous tissue [10], it may be more accurate than CT [9] and can help determine rectal involvement [14]. However, it is unlikely that MRI will be available in a timely manner and surgery should not be delayed; it is also more expensive [9].

Microbiology

- Urine culture, blood culture, wound swab.
- Cultures may return as negative, particularly, if there is dry penile gangrene. In diabetic patients with end-stage renal disease and poor microvascular circulation, ischaemia is probably the primary process, with infection occurring secondarily. While the cultures are negative, this does not mean that infection is not present, only that it has not been detected yet [5].

Histology of FG

- Necrosis, thrombi, vasculitis, micro-organisms, leucocyte infiltrate [10]

Special Tests

Patients may also undergo additional investigations to determine the cause of FG, including cystoscopy, sigmoidoscopy and biopsy for malignancy [3].

Scoring Systems

The Laboratory Risk Indicator for Necrotising Fasciitis (LRINEC) is a scoring system based on haemoglobin, white cell count (WCC), C-reactive protein (CRP), sodium, creatinine and glucose levels. A score of ≥ 6 raises suspicion for necrotising fasciitis, while a score of ≥ 8 is considered strongly predictive [15]. The LRINEC score was developed from a study involving 89 patients with necrotising fasciitis and 225 control patients, and

demonstrated a positive predictive value of 92% at a threshold score of ≥6 [15].

McGillicuddy et al. developed a scoring system based on CT findings of 44 patients with necrotising fasciitis versus 261 control patients. CTs were scored for fascial air, fascial oedema, fluid tracking, lymphadenopathy and subcutaneous oedema. A score of >6 had a sensitivity of 86% and specificity of 92% for necrotising fasciitis [16].

Management Guidelines

There is limited guidance available. The EAU recommendations are shown in Table 18.3.

Table 18.3 EAU Guideline on Fournier's Gangrene⏎

Guideline	Strength of Evidence
• Immediate empirical broad-spectrum intravenous antibiotics, which are tailored to culture results and response to treatment	Strong
• Repeat debridement at 24 hours	Strong
• Avoid wound care adjuncts	Weak

Source: Bonkat G, R. Bartoletti, S.E. Geerlings, B. Köves, R. Veeratterapillay, F. Wagenlehner. *EAU Guidelines on Urological Infections*. 2022. https://uroweb.org/guidelines/urological-infections/chapter/the-guideline.

Pre-operative Management

Prompt Resuscitation Using an A to E Approach

Patients are often critically ill with sepsis, hypovolaemia due to third space fluid losses and electrolyte disturbances [10, 25].

Early Antibiotics

If FG is suspected, treat with antibiotics per hospital guidelines or microbiology advice. This will likely involve an empirical combination of broad-spectrum antibiotics to cover gram negative and positive as well as aerobic and anaerobic bacteria [1, 5]. This regimen usually includes clindamycin, gentamicin, and a third-generation cephalosporin [1], although EAU guidelines differ and recommendations include piperacillin-tazobactam plus vancomycin, or cefotaxime plus metronidazole plus clindamycin [14]. It is important to follow local hospital antibiotic protocols and antimicrobial resistance patterns.

Multidisciplinary Team Approach

Management of patients with FG requires early communication between urologists, plastic surgeons, microbiologists or infections disease specialists, anaesthetics and intensive care physicians [10].

Anaesthesia for necrotising fasciitis can be challenging as patients are likely multi-comorbid and are often haemodynamically unstable, with or without blood loss, may have failure of multiple organs and a coagulopathy [10].

Around 10% of patients with FG require ITU admission after surgical intervention [2]. While this should not delay debridement, plans should be made for ITU bed space or transfer to another centre post-operatively if required [2].

Operative Management

Early surgical debridement is paramount and this is the cornerstone of management. Aim to perform surgery within the first 12 hours as this is associated with better outcomes [17], and any delays are associated with increased mortality [10].

Most patients require wide surgical debridement as the skin necrosis is often less extensive than subcutaneous disease. Relook and re-debridement within 24 hours is recommended by EAU guidelines [14], as the pathological process is ongoing at the time of debridement and so small areas that look healthy can progress [5]. The role of multiple planned

debridement is less clear [17], although patients will have a total of 2–3 planned or unplanned debridements on average [2].

Surgical Technique

The aim of debridement is threefold: (1) excise necrotic tissue; (2) prevent further spread of infection; (3) limit systemic toxicity due to the effects of the necrotic tissue, bacteria and their toxins [3, 5]. The removal of necrotic tissue also helps the penetration of antibiotics [10]. Excision should be aggressive, but radical surgery, including the excision of healthy tissue should be avoided [5].

Hagedorn and Wessells describe their technique for debridement, which consists of [1]:

- Prepare and drape the patient and complete the WHO surgical safety checklist.
- Make an incision through the worst-affected area (necrosis, oedema or erythema).
- Perform blunt dissection with a finger along fascial planes to break down loculations of gas and infection.
- Excise all non-viable skin using sharp dissection.
- Irrigate thoroughly with a large volume of saline.
- Achieve haemostasis using electrocautery, suture ligation and/or vessel clipping, depending on vessel size.
- Reassess the wound for bleeding and any remaining diseased tissue.
- Repeat debridement as needed until only clean and healthy tissue remains [18]. Any retained necrotic tissue is associated with increased mortality [10].
- Apply dressing: cover the wound with saline-soaked gauze.

In male patients, if the penile skin is involved:

- Remove all distal skin up to the corona. If this skin is left there may be disfigurement.

In female patients:

- Due to the difference in anatomy, the infection is more likely to spread into the intra-abdominal or retroperitoneal space.

Hagedorn and Wessells recommend spending one-third of the time debriding and two-thirds of the time on washout, haemostasis and

reassessment. This is because smaller vessels can go into vasospasm and later bleed profusely [1].

Post-operative

Patients should be closely monitored for deterioration or disease progression and taken back to theatre if there is concern that the infected tissue has not been fully resected.

- Cover the wound with betadine-soaked gauze and change this frequently during the day.
- Patients with FG stay for a median of 8 days as an inpatient [2].
- Antibiotics should be adjusted depending on culture results and continue until there is a clinical improvement [1]
- After discharge, approximately 30% require district nurse help with wound care [4].
- Ensure appropriate management is put in place to treat the underlying cause or risk factors for FG [5].

Wound Management Adjuncts

EAU guidelines currently does not recommend the use of adjuncts [14].

- Vacuum-assisted closure (VAC) systems may be applied when no further debridement is anticipated [19] and are beneficial in the perioperative period, both pre- and post-reconstructive surgery [10].
- Benefits
- Aids reconstructive surgery by providing a cleaner wound. Stimulates the formation of granulation tissue before and after grafting [10].
- Reduces the number of dressing changes required, as the VAC only needs to be changed every 3 days [20].
- Improves pain and mobility [21].
- Reduces length of stay [22].
- Reduces local oedema, removes exudates and draws wound edges closer [9].

Disadvantages

- The location can mean it may not be possible to apply a VAC dressing successfully [1]. EAU guidelines state there is no evidence of benefit for the use of VAC dressings in FG.
- Hyperbaric oxygen can shorten the length of healing [22], but few centres have access to this facility [5, 10], and the evidence base is not strong [3]. EAU guidelines do not recommend hyperbaric oxygen [14].

- Medicinal-honey-soaked dressings may reduce length of hospital stay, although the evidence base for this is poor [14].

Additional Procedures

The need for additional procedures depends on the extent of FG. Patients may require:

- Penectomy. Orchidectomy may be required if there is penile or testicular gangrene [3, 5].
- Suprapubic catheterisation may be required if the external genitalia are involved [23].
- Bowel management catheters or defunctioning colostomy if there is peri-anal or colorectal disease (at the digression of the general surgical team). This facilitates a cleaner wound [24].

Reconstructive surgery

The main additional procedure required is reconstruction of the area that has been debrided, once the acute infective episode is resolved.

- Wound closure can be considered using the reconstructive ladder. This starts with healing by secondary intention, followed by primary closure, skin grafts and flaps [25].
- EAU guidelines recommend primary or secondary wound closure in patients with scrotal defects with ≤50% skin loss, and skin grafts or flaps in those with >50% skin loss [14].
- 5–7 days after final debridement.
- Wound bed must be healthy, with granulation tissue present and no necrotic areas [1].

Healing by Secondary Intention

Healing by secondary intention replaces skin loss with granulation tissue [25]. However, this approach is slow and can lead to scarring and contractures [25]. This may be considered for the perineum as grafts here are more likely to fail due to shearing forces while mobilising [1].

Primary Closure

Primary closure is the apposition of tissue edges, and in FG the technique involves a two-layer closure using an absorbable suture [1]. The testes can be placed into anteromedial thigh pouches; this can also be used as a temporising approach if further definitive reconstruction is planned [1].

Split Thickness Skin Graft (STSG)

Split thickness skin graft (STSG) is a piece of tissue consisting of the epidermis and a variable depth of dermis [25]. It is the most common reconstructive approach for FG. The approach that Hagedorn and Wessells recommend for STSG involves [1]:

- Blunt dissection to free testes to the level of the external inguinal ring.
- Granulation tissue removed from testes.
- Testes sutured together in the midline.
- STSG taken from the anterolateral thigh [26]. The graft is harvested using an air dermatome [25], and should be 0.3–0.4 mm (0.016 inches) thick. Approximately 25 cm^2 is required for the scrotum and 15 cm^2 for the shaft of the penis. The scrotal graft may be meshed but an unmeshed graft may be preferred for the penile graft due to cosmesis and contracture (although meshed grafts may be used successfully on the shaft of the penis [26]). For women, the labia majora can be reconstructed with an STSG.
- Graft applied to the wound and fixed with absorbable sutures or staples.
- Multilayer compression dressing for 5 days. The patient should remain bedbound during this period. VAC may be used.

Flaps

A flap is tissue that can be moved while retaining its own blood supply [25]. Rotational and anterolateral thigh flaps may be used in FG; however, care needs to be taken with the placement of the testes: if they lie too deep sperm viability may be affected [1]. The Singapore flap, a pedicled fasciocutaneous flap of the proximal medial thigh, may be used to reconstruct defects in the perineum [27].

Operative complications

Patients may require additional procedures, as described above. In addition to these, major complications include septic shock, multiorgan failure (including respiratory, renal, and hepatic failure), disseminated intravascular coagulation and diabetic ketoacidosis [3, 7].

Prognosis

Mortality

Mortality is around 7.5%–16% [2, 3], although some case series have demonstrated significantly higher rates [2]. Early aggressive treatment is essential to reduce mortality [3]. Mortality is lower in centres where FG is treated regularly. It is not clear whether FG risk factors influence mortality, but broadly poor health appears to worsen outcomes [1]. Additionally, there does not appear to be a relationship between the bacterial cause and the severity or mortality of FG [1], although in necrotising fasciitis more generally, polymicrobial infections have better outcomes than monomicrobial infections [10].

Prognosis Prediction Scores

Prognostic prediction scores can be divided into disease-specific and general. Disease-specific scores include the Fournier's gangrene severity index (FGSI) and the Uludag FGSI. General scores include the age-adjusted Charlson Comorbidity Index and the Surgical Apgar Score.

Fournier's Gangrene Severity Index

Laor et al. produced a FGSI. This can be used to estimate the prognosis of FG. There are nine parameters that are based on observations (temperature, heart rate and respiratory rate) and blood tests (serum sodium, potassium, creatinine, bicarbonate, white cell count and haematocrit). Each parameter receives a score of 0–4. These are combined to give the final FGSI score. The authors set a threshold score of 9, at which a score of ≤9 indicates a 78% chance of survival, whereas a score of >9 indicates a 75% change of mortality [28]. This score was developed in 1995 and was based on 30 patients. As such, the reliability of the index is questionable, with some studies supporting it and others not [29, 30].

The Uludag Fournier's Gangrene Severity Index

The Uludag FGSI combines the FGSI produced by Laor et al. to give a physiological score, and has additional scoring for age and disease extent. A score of ≤9 indicates a chance of survival of 81% and a score of >9 indicates a 94% chance of mortality [31].

Comparison to General Prognosis Scores

In a study of 50 patients, FGSI, UFGSI and age-adjusted Charleson Comorbidity Index were compared and only UFGSI could predict mortality; however, the authors were unable to support the threshold value of 9 [32]. Despite this, a study of 44 patients found that age-adjusted Charleson Comorbidity Index and Surgical Apgar Score were as good at predicting mortality as FGSI and UGSI [33]. Therefore, the quality of the evidence is not strong enough to recommend a particular risk prognosis tool, and physicians should investigate and treat patients based on clinical suspicion [1].

Conclusion

Fournier's gangrene is a serious urological emergency and is associated with a high morbidity and mortality. Early recognition, resuscitation and surgical debridement are critical. The extent of debridement depends on the degree of tissue involvement, and post-debridement often requires reconstructive surgery with a skin graft or flaps.

References

1. Hagedorn JC, Wessells H. A contemporary update on Fournier's gangrene. *Nat Rev Urol*. 2016;14(4):205–214. doi:10.1038/nrurol.2016.243.⏎
2. Sorensen MD, Krieger JN, Rivara FP, et al. Fournier's gangrene: population based epidemiology and outcomes. *J Urol*. 2009;181(5):2120–2126. doi:10.1016/J.JURO.2009.01.034.⏎
3. Eke N. Fournier's gangrene: a review of 1726 cases. *Br J Surg*. 2002;87(6):718–728. doi:10.1046/J.1365-2168.2000.01497.X.⏎
4. Sorensen MD, Krieger JN. Fournier's gangrene: epidemiology and outcomes in the general US population. *Urol Int*

2016;97(3):249–259. doi:10.1159/000445695.⏎
5. Czymek R, Hildebrand P, Kleemann M, *et al. New insights into the epidemiology and etiology of Fournier's gangrene: a review of 33 patients*. *Infection*. 2009;37(4):306–312. doi:10.1007/S15010-008-8169-X.⏎
6. Clayton MD, Fowler JE, Sharifi R, Pearl RK. Causes, presentation and survival of fifty-seven patients with necrotizing fasciitis of the male genitalia. *Surg Gynecol Obstet*. 1990;170(1):49–55. https://europepmc.org/article/med/2294630. Accessed March 21, 2022.⏎
7. Kuo CF, Wang WS, Lee CM, Liu CP, Tseng HK. Fournier's gangrene: ten-year experience in a medical center in northern Taiwan. *J Microbiol Immunol Infect*. 2007;40(6):500–506. https://europepmc.org/article/med/18087630. Accessed March 21, 2022.⏎
8. Tang LM, Su YJ, Lai YC. The evaluation of microbiology and prognosis of fournier's gangrene in past five years. *Springerplus*. 2015;4(1):14. doi:10.1186/S40064-014-0783-8.⏎
9. Misiakos EP, Bagias G, Patapis P, Sotiropoulos D, Kanavidis P, Machairas A. Current concepts in the management of necrotizing fasciitis. *Front Surg*. 2014;1:36. doi:10.3389/FSURG.2014.00036.⏎
10. Morgan MS. Diagnosis and management of necrotising fasciitis: a multiparametric approach. *J Hosp Infect*. 2010;75(4):249–257. doi:0.1016/J.JHIN.2010.01.028.⏎
11. Şahin H, Aflay U, Kılınç N, Bircan MK. Coagulation parameters in the patients with Fournier's Gangrene. *Int Urol Nephrol*. 2005;37(4):733–737. doi:10.1007/S11255-005-8437-Y.⏎

12. Levenson RB, Singh AK, Novelline RA. Fournier gangrene: role of imaging. *Radiographics*. 2008;28(2):519–528. doi:10.1148/RG.282075048.⏎
13. Ferreira PC, Reis JC, Amarante JM, *et al.* Fournier's gangrene: a review of 43 reconstructive cases. *Plast Reconstr Surg*. 2007;119(1):175–184. doi:10.1097/01.PRS.0000244925.80290.57.⏎
14. Bonkat G, R. Bartoletti, S.E. Geerlings, B. Köves, R. Veeratterapillay, F. Wagenlehner. *EAU Guidelines on Urological Infections*. 2022. https://uroweb.org/guidelines/urological-infections/chapter/the-guideline. Accessed March 22, 2022.⏎
15. Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med*. 2004;32(7):1535–1541. doi:10.1097/01.CCM.0000129486.35458.7D.⏎
16. McGillicuddy EA, Lischuk AW, Schuster KM, et al. Development of a computed tomography-based scoring system for necrotizing soft-tissue infections. *J Trauma*. 2011;70(4):894–899. doi:10.1097/TA.0B013E3182134A76.⏎
17. Eckmann C. The importance of source control in the management of severe skin and soft tissue infections. *Curr Opin Infect Dis*. 2016;29(2):139–144. doi:10.1097/QCO.0000000000000240.⏎
18. Scott S, Dawes RFH, Tate JJT, Royle G, Karran SJ. The practical management of Fournier's gangrene. *Ann R Coll Surg Engl*. 1988;70(1):16. /pmc/articles/PMC2498669/?report=abstract. Accessed March 21, 2022.⏎
19. Ye J, Xie T, Wu M, Ni P, Lu S. Negative pressure wound therapy applied before and after split-thickness skin graft helps healing of Fournier gangrene: A case report (CARE-

compliant). *Med (United States)*. 2015;94(5):e426. doi:10.1097/MD.0000000000000426.⏎
20. Assenza M, Cozza V, Sacco E, *et al.* VAC (Vacuum Assisted Closure) treatment in Fournier's gangrene: personal experience and literature review. *Clin Ter* 2011;162(1):e1–5. https://europepmc.org/article/med/21448535. Accessed March 22, 2022.⏎
21. Ozturk E, Ozguc H, Yilmazlar T. The use of vacuum assisted closure therapy in the management of Fournier's gangrene. *Am J Surg*. 2009;197(5):660–665. doi:10.1016/J.AMJSURG.2008.04.018.⏎
22. Milanese G, Quaresima L, Dellabella M, et al. A conservative approach to perineal Fournier's gangrene. *Arch Ital di Urol Androl organo Uff [di] Soc Ital di Ecogr Urol e Nefrol*. 2015;87(1):28–32. doi:10.4081/AIUA.2015.1.28.⏎
23. Corman JM, Moody JA, Aronson WJ. Fournier's gangrene in a modern surgical setting: improved survival with aggressive management. *BJU Int* 1999;84(1):85–88. doi:10.1046/J.1464-410X.1999.00140.X.⏎
24. Alper A, Sozuer E, Akyildiz H, Yilmaz N, Kucuk C, Ok E. Necessity of preventive colostomy for Fournier's gangrene of anorectal region. *Ulus Travma Acil Cerrahi Derg*. 2009;15(4):342–346. https://tjtes.org/jvi.aspx?pdir=travma&plng=eng&un=UTD-43043&look4=. Accessed March 22, 2022.⏎
25. Boyce DE, Shokrollahi K. ABC of wound healing: reconstructive surgery. *BMJ Br Med J* 2006;332(7543):710. doi:10.1136/BMJ.332.7543.710.⏎
26. Black PC, Friedrich JB, Engrav LH, Wessells H. Meshed unexpanded split-thickness skin grafting for reconstruction of penile skin loss. *J Urol*. 2004;172(3):976–979. doi:10.1097/01.JU.0000133972.65501.44.⏎

27. 27.Maharaj D, Naraynsingh V, Perry A, Ramdass M. The scrotal reconstruction using the “Singapore Sling”. *Plast Reconstr Surg*. 2002 Jul;110(1):203-5. doi: 10.1097/00006534-200207000-00034. PMID: 12087254.⏎
28. Laor E, Palmer LS, Tolia BM, Reid RE, Winter HI. Outcome prediction in patients with Fournier’s gangrene. *J Urol*. 1995;154(1):89–92. doi:10.1016/S0022-5347(01)67236-7.⏎
29. Corcoran AT, Smaldone MC, Gibbons EP, Walsh TJ, Davies BJ. Validation of the Fournier’s gangrene severity index in a large contemporary series. *J Urol*. 2008;180(3):944–948. doi:10.1016/J.JURO.2008.05.021.⏎
30. Luján Marco S, Budía A, Di Capua C, Broseta E, Cruz FJ. Evaluation of a severity score to predict the prognosis of Fournier’s gangrene. *BJU Int*. 2010;106(3):373–376. doi:10.1111/J.1464-410X.2009.09075.X.⏎
31. Yilmazlar T, Ozturk E, Ozguc H, Ercan I, Vuruskan H, Oktay B. Fournier’s gangrene: an analysis of 80 patients and a novel scoring system. *Tech Coloproctol*. 2010;14(3):217–223. doi:10.1007/S10151-010-0592-1.⏎
32. Tuncel A, Keten T, Aslan Y, et al. Comparison of different scoring systems for outcome prediction in patients with Fournier’s gangrene: experience with 50 patients. *Scand J Urol*. 2014;48(4):393–399. doi:10.3109/21681805.2014.886289.⏎
33. Roghmann F, Von Bodman C, Löppenberg B, Hinkel A, Palisaar J, Noldus J. Is there a need for the Fournier’s gangrene severity index? Comparison of scoring systems for outcome prediction in patients with Fournier’s gangrene. *BJU Int*. 2012;110(9):1359–1365. doi:10.1111/J.1464-410X.2012.11082.X.⏎

19 Aetiology, Pathophysiology, Clinical Assessment and Management of Genito-Urethral Trauma

Luca Ongaro, Francesco Claps, Carlo Trombetta, Giovanni Liguori and Giulio Garaffa

DOI: 10.1201/b22940-19

Epidemiology, Aetiology and Pathophysiology

Genital trauma accounts for approximately 33%–66% of urological injuries [1] and most frequently affects males between the age of 15–40 years [2].

Genital injuries might result in significant long-term morbidity, encompassing hormonal impairment, sexual and voiding disfunction, infertility and psychological distress. Therefore, appropriate assessment and management are crucial [2].

The leading cause of genital trauma are blunt injuries in up to 80% of cases [2]. More than 50% of blunt injuries are due to road traffic accidents. The trauma could be associated with sexual intercourse (e.g., penile fracture), workplace related accidents and violence related in 22%,18% and 3% of cases, respectively [3]. In addition, scrotal injuries can occur with contact sports, such as rugby or football [4].

Conversely, the majority of penetrating injuries are related to violence and can be both self-inflicted (~37%) or resulting from external aggression (~48%). Penetrating traumas encompass animal and human bites, stabbing and bullet wounds, as well as self-mutilation or amputation in transsexuals or psychotic patients [3].

In addition to penetrating injuries, trauma and avulsion, other scenarios such as penile strangulation and urethral injury caused by the insertion of foreign body in the urethra and bladder during autoeroticism practices are documented [5]. Genital burns (especially in industrial workplaces) and trauma following genital piercing have also been described [2].

Penile Trauma

Among the blunt genital injuries, penile fracture might be the most common presentation, and it is characterized by the rupture of the tunica albuginea of the corpora cavernosa, which during erections becomes 0.25 mm thin and is particularly vulnerable to injuries [6]. The most frequently reported cause of penile fracture is sexual intercourse, which accounts for around 46% of cases [7]. The fracture occurs when the erect penis forcibly bends while hitting the pelvis. Forced flexion (taqaandan) of the shaft to obtain a rapid detumescence, vigorous masturbation and rolling over the erect penis can result in penile fracture in 21%, 18% and 8.2% of cases respectively [7]. Lesions of the corpus spongiosum or urethra can be associated in 10%–22% of cases of penile fracture [8]. Moreover, blunt trauma can also result in injury to the bulbar urethra due to compression against the pubic bone [2].

Testicular Trauma

Testicular trauma more frequently occurs in road traffic accidents and can be bilateral in up to 25% of cases. Blunt direct scrotal trauma can produce a testicular rupture in up to 50% of cases. It is due to an intense compression of the testicle against the pubic ramus or the symphysis. A force of approximately 50 kg is usually necessary to produce a rupture of the tunica albuginea of the testicles [2].

Anterior Urethral Injury

The bulbar urethra is the most affected site. The bulb is compressed against the pubic symphysis in bulbar injuries resulting in urethral rupture at the site of compression. Mechanisms include straddle injuries or direct trauma to the perineum. Penetrating injuries are uncommon and may be caused by gunshot or stab wounds, dog bites, impalement or penile amputations.

Insertion of foreign bodies can also cause anterior urethral injury. The incidence of male urethral injury during transurethral catheterization is around 13.4 per 1,000 catheter insertions. In addition, the risk of urethral perforation during penile prosthesis insertion is 0.1%–4%.

Posterior Urethral Injuries

Blunt posterior urethral injuries are most related to pelvic fractures caused by road traffic accidents – 'pelvic fracture urethral injuries' (PFUI), which may be partial or complete. In complete ruptures, there is a gap between the ruptured ends, which fills with scar tissue. Injuries of the bladder neck and prostate are rare and occur at the anterior midline of both the bladder neck and prostatic urethra. Concomitant polytrauma to the neck, thorax, abdomen and/or spine are frequent in up to ~66%. Pelvic fractures are associated with bladder injury in ~3% of cases and with urethral injury in 5%–20% of cases. Penetrating injuries such as gunshot wounds to the pelvis, perineum or buttocks can also cause posterior urethral injury.

Delayed morbidities of posterior urethral injuries include strictures, urinary incontinence and erectile dysfunction. The pooled estimate of erectile dysfunction following PFUI is ~34%.

Clinical Assessment

In severe trauma, the priority is to rule out the presence of life-threatening injuries and to achieve adequate pain control [9]. Once the patient is haemodynamically stable, the urogenital system must be assessed thoroughly in order to identify any visible injury [2, 9].

Penile Trauma

Patients with suspected penile fracture may report a sudden cracking or popping sound during intercourse, followed by immediate onset of severe pain, detumescence and swelling.

An enlarging haematoma leading to the formation of an 'eggplant deformity' of the shaft can be seen when Buck's fascia has been breached (Figure 19.1). Typically, the haematoma tends to follow Colles' fascia, producing the typical 'butterfly-pattern' ecchymosis at the level of

perineum, scrotum and lower abdominal wall (Figure 19.2). In such cases, the albugineal defect might be palpable, and a localized clot may form over the fracture's site, which can be perceived as an immobile lump by rolling a finger over the area ('rolling sign') [2, 7, 10, 11]. While patients presenting with an audible cracking sound followed by immediate detumescence and penile haematoma, may have a penile fracture in virtually all cases, other scenarios, known as 'false' fractures are also possible. These encompass penile vascular injuries occurring during intercourse, involving the superficial dorsal vein, deep dorsal vessels and non-specific bleeding from the dartos layer, as well as suspensory ligament ruptures. The key features to differentiate these cases from true fractures are the absence of a rapid detumescence, the preserved ability to achieve erections after the trauma and the absence of albugineal defects. Although the tunica albuginea has not been breached, a popping sound may be present in up to 22% of patients with 'false' fractures. In suspensory ligament rupture, penile hypermobility and a palpable gap between the base of penis and the symphysis pubis might be present, along with minimal bruising or pain and the lack of detumescence [10].

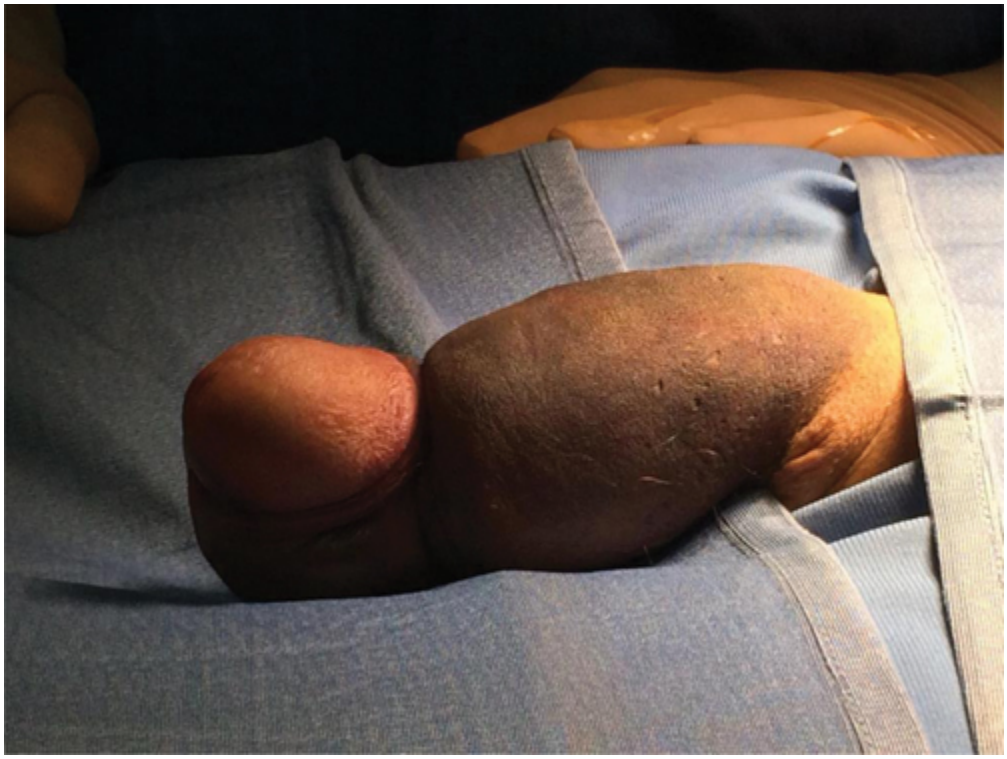


Figure 19.1 Penile trauma with ‘eggplant deformity’. Courtesy of Prof. G. Liguori.⏎

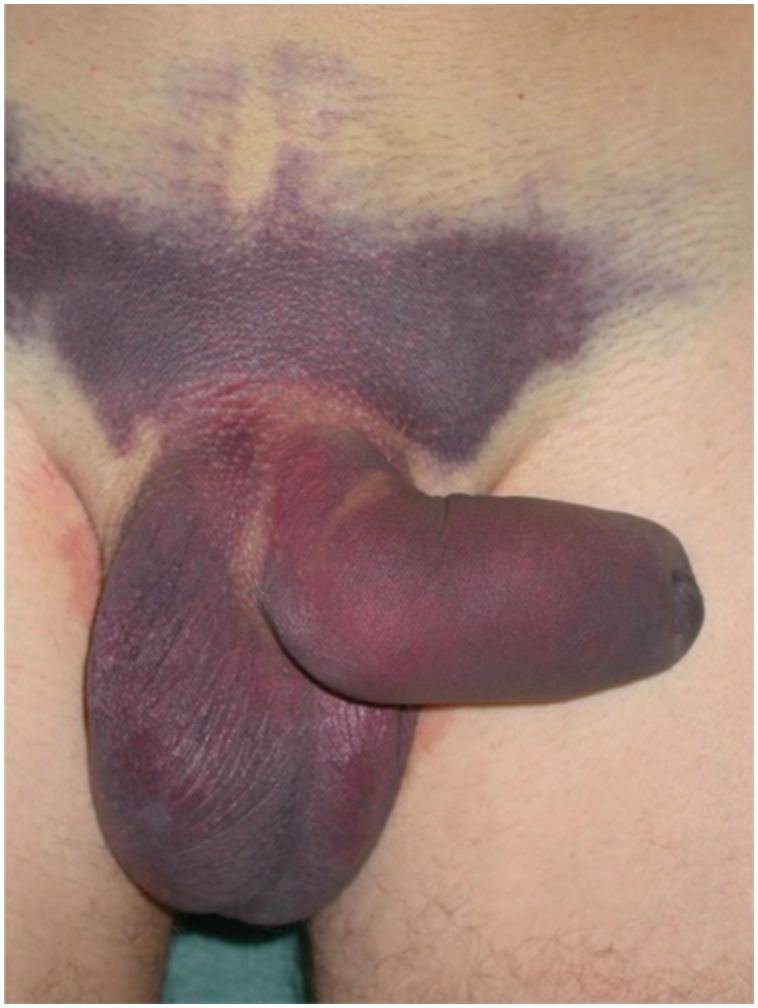


Figure 19.2 ‘Butterfly-pattern’ ecchymosis. Courtesy of Prof. G. Liguori.⏎

A concomitant urethral injury, even if not immediately apparent, should be suspected, if there is presence of blood at the meatus, microscopic or visible haematuria, voiding pain and difficulties in urinating [2, 3].

Testicular Trauma

Testicular blunt trauma is usually associated with a tender, swollen, painful scrotum and a variable degree of scrotal ecchymosis. The injured testis

itself might be difficult to palpate. Patients might complain of neurovegetative symptoms such as pain, nausea and vomiting, as well as fainting [2]. Trauma can result in traumatic torsion, particularly in the presence of predisposing factors, such as the ‘bell clapper’ deformity. Traumatic torsion should be suspected in patients presenting with a disproportionate pain compared to the force of the trauma [13].

Urethral Injuries

Blood at the meatus is the cardinal sign, but its absence does not exclude urethral injuries. Complete urethral ruptures create a gap between the two disrupted stumps, typically resulting in inability to void, acute urinary retention and a distended bladder. The suspicion of a complete rupture should also arise when the placement of a urethral catheter is difficult or not possible. Urinary extravasation and bleeding might cause a variable degree of scrotal, penile and/or perineal swelling and ecchymosis. Importantly, these symptoms might be delayed and present beyond 1 hour [2]. A digital rectal examination may reveal a ‘high riding’ prostate as a result of a haematoma displacing the prostate. A rectal injury (up to 5% of cases) may also be detected on rectal examination.

In significant haematuria, the presence of intra-abdominal trauma needs to be ruled out with a full body trauma CT, especially in patients who have sustained penetrating gunshot wounds [12].

Imaging

Penile Trauma

Penile injuries should be primarily investigated with ultrasound (US), which is immediately available and cost effective. Typical findings include disruption of the tunica (visualized as a hypoechoic line or area), intracavernosal and/or extracavernosal haematomas (Figure 19.3). Sensitivity and specificity rates of US at detecting the presence of albugineal tears reach 88% and 100%, respectively; however, it is relatively lower when it comes to identifying urethral injuries [10]. Magnetic resonance imaging (MRI) is another useful tool in patients with suspected

penile fracture. It can detect even smaller albugineal tears [11] with a sensitivity and a negative predictive value of 100%, as well as a localization accuracy of around 97%. The accuracy in detecting lesions of the corpus spongiosum is lower, with a specificity of 78% and a sensitivity of around 60%. Since MRI is a time-consuming, expensive and not readily available investigation, especially in an emergency setting, its routine use in clinical practice is limited in some centres [10].

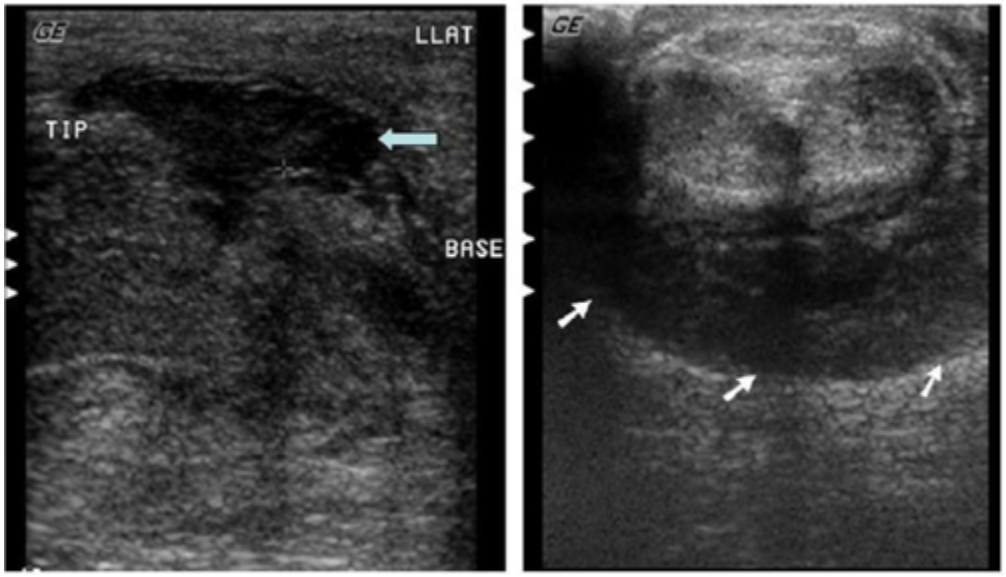


Figure 19.3 Ultrasound imaging showing an albugineal tear (on the left, see arrow) and penile haematoma encircling the shaft (on the right, see arrows). *Source*: Adapted from Shenoy-Bhangle A, Perez-Johnston R, Singh A. Penile imaging. *Radiol Clin North Am.* 2012 Nov;50(6):1167-81. doi: 10.1016/j.rcl.2012.08.009. PMID: 23122044.⏎

Cavernosography is still cited by the latest version (2025) of the European Association of Urology Guidelines [2] as a potential diagnostic tool in the assessment of patients with suspected penile fracture. However, cavernosography is rarely used nowadays because it is an invasive test with potential complications such as infection, corporal fibrosis and priapism. In addition, it has a false-negative rate of ~28%, as in some cases a clot might

block the contrast extravasation through the albugineal defect. This investigation might still have a role only intraoperatively, when a fracture is suspected but has not been detected with conventional imaging [10, 11].

Testicular Trauma

Ultrasonography is the technique of choice in the evaluation of testicular trauma, as it allows accurate assessment of the scrotal contents enabling the detection of testicular contusion and rupture, as well as intra- and extra-testicular haematomas (Figure 19.4). Doppler US study provides information on testicular perfusion and hilum integrity [2, 9]. Key sonographic features of testicular rupture are lack of parenchymal homogeneity with the presence of geographical areas of impaired flow, the loss of testicular contour and tears of the tunica albuginea. MRI can be used in equivocal diagnoses of testicular rupture [14].

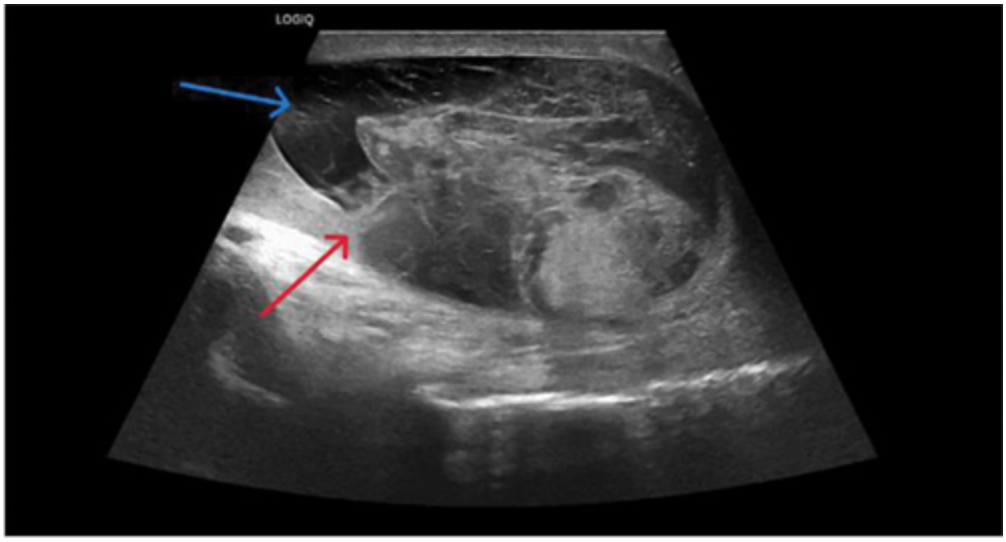


Figure 19.4 Ultrasound imaging showing testicular albuginea disruption (red arrow) and haematoma (blue arrow) consistent with testicular rupture. *Source*: Adapted from Eldore LW, Borries T, Malick H, Mason K, DePrisco G. Testicular Rupture Following Motorcycle Accident. *Cureus*. 2023 Jul 9;15(7):e41609. doi:

10.7759/cureus.41609. PMID: 37565108; PMCID: PMC10409644.⏎

Urethral Injuries

A retrograde urethrogram (RUG) (Figure 19.5) or a flexible cystoscopy are recommended if a urethral lesion is suspected, or in case of bilateral fracture of the corpora cavernosa, as a simultaneous urethral rupture is often present in these cases [10]. A RUG is performed by injecting 30–50 ml of contrast material via an 8 Fr Foley catheter or feeding tube at the navicular fossa. X-rays are taken in a 30 degrees oblique position, and in PFUI, the x-ray arm should rotate to the 30 degrees angle rather than repositioning the patient. Extravasation of contrast is suggestive of a urethral rupture. Prior to deferred treatment, both a RUG and an antegrade cysto-urethrogram should be performed to evaluate the site and extent of the urethral stenosis, and to examine the competence of the bladder neck.

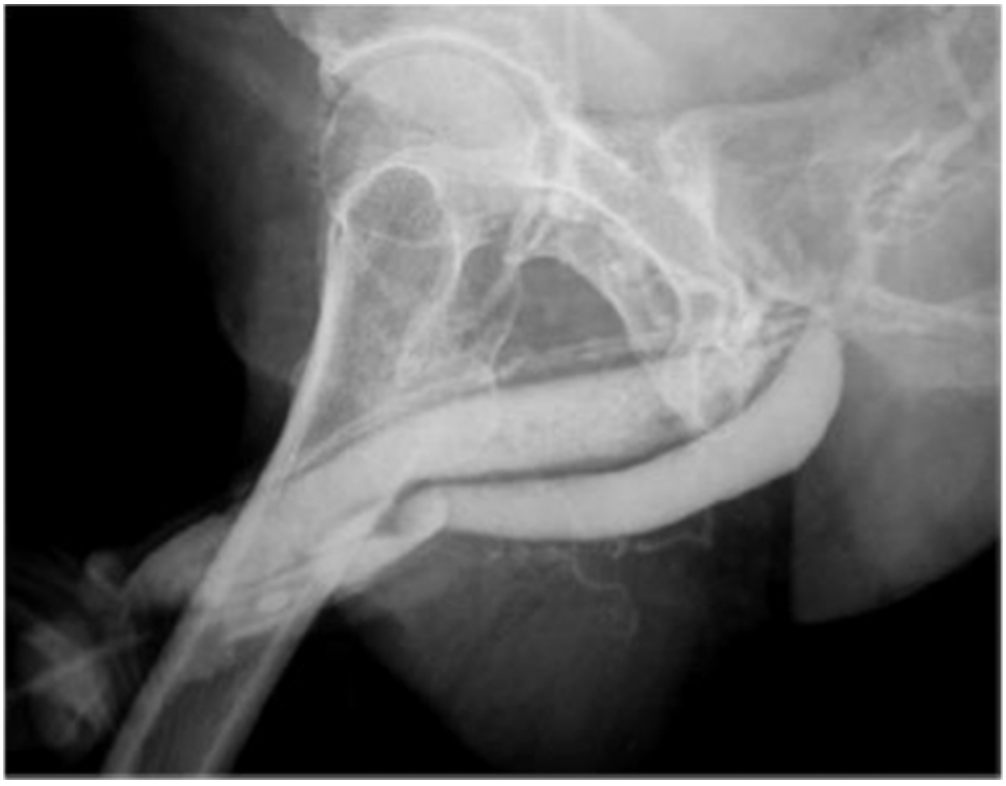


Figure 19.5 Retrograde urethrogram showing a urethral injury with contrast extravasation into the cavernosal body. *Source*: Adapted from Simms A, Baradaran N, Lue TF, Breyer BN. Penile Fractures: Evaluation and Management. *Urol Clin North Am.* 2021 Nov;48(4):557-563. doi: 10.1016/j.ucl.2021.06.011. Epub 2021 Aug 21. PMID: 34602175.⏎

Management

Penile Trauma

Blunt penile traumas without albugineal tears usually do not require surgical intervention. In these cases, a conservative management with non-steroidal analgesics and ice packing might be sufficient to promote a quicker resolution of symptoms [2].

Penile injuries with albugineal tears require surgical exploration, which can be performed immediately or at the latest within 24 hours. It entails precise preoperative identification of the location of the tear, haematoma evacuation and repair of the tunical tear and any associated urethral injury. Fractures could be exposed through a subcoronal approach; however, degloving may be quite challenging in the presence of bruising and oedema of the dartos. Around two-thirds of fractures occur on the ventral aspect of the proximal penile shaft and therefore fractures should preferably be accessed through a longitudinal penoscrotal incision along the raphe (Figure 19.6). Tunical tears are repaired using high-tensile-strength, slowly absorbable sutures (e.g., 2-0 or 0 PDS), in a manner similar to that described for Nesbit's penile plication surgery. Urethral injuries can be repaired using 5-0 polyglactin sutures. Patients are usually discharged with a compressive dressing and antibiotic cover. If a urethral repair is performed, the urethral catheter is usually removed 2 weeks postoperatively, once a pericatheter urethrogram has ruled out the presence of a leak. A clear consensus on inhibition of erections as well as a clear recommendation on the duration of sexual abstinence is lacking [15]. However, patients should be followed up after 2 weeks and refrain from

sexual activities for around 6 weeks. Surgical repair (as compared to conservative management) of penile fracture reduces the incidence of fibrosis and penile curvature from 35% to 5%, and erectile dysfunction from 62% to 5%.

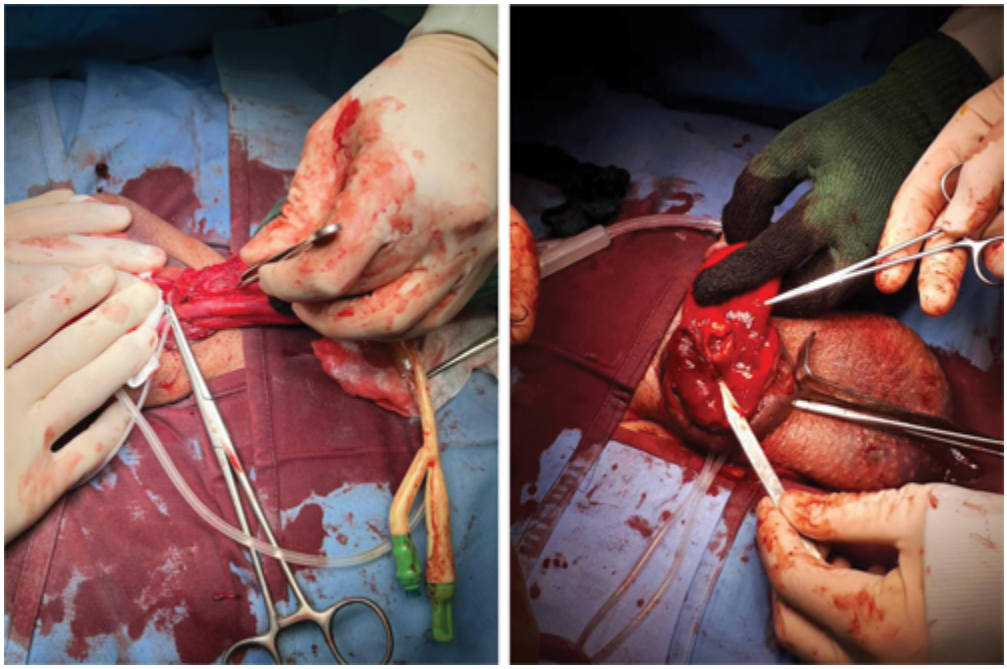


Figure –b 19.6a Surgical exploration with degloving for penile fracture. Courtesy of Prof. G. Liguori and Prof. C. Trombetta.⏎

Penetrating injuries can be managed conservatively if Buck's fascia has not been breached, otherwise surgical exploration is required. It is important to preserve as much viable tissues as possible, ensuring accurate haemostasis, diverting urine whenever necessary and removing all foreign bodies that are present. Extensive albugineal defects repair might require the use of patches from autologous saphenous vein or xenograft (e.g., bovine pericardial patch), while skin grafts may be necessary for large skin defects coverage [2].

Additionally, in case of human and animal bites, the infective complications related to bacteria and blood borne viruses must be

considered and addressed with the relevant post-exposure prophylaxes, antibiotic therapies and vaccinations [2].

In cases of penile avulsion or amputation, acute management entails resuscitation and preparation for surgical reimplantation of the penis, which, whenever possible and technically feasible, should be attempted within 24 hours. The penis should be washed using sterile saline, wrapped in saline-soaked gauze and preserved in iced water in a sterile bag avoiding a direct contact with the ice. A pressure dressing or a tourniquet may be placed around the penile stump to limit blood loss. Surgical reimplantation can be performed either using a microsurgical or a non-microsurgical technique, with the former being the approach of choice as it yields superior functional and cosmetic outcomes [16]. Urinary diversion is performed by placing either a urethral or a suprapubic catheter. If the amputated penis cannot be retrieved or is unsuitable for reimplantation the wound should be either primary closed or a split thickness skin graft reconstruction is performed in a fashion similar to the one used following a partial penectomy, preserving as much tissue as possible in consideration for a possible delayed phallic reconstruction [2].

In cases of penile strangulation, the priority is to remove the constricting object in order to reinstate the blood circulation in the penis. Once circulation has been reinstated, the genitalia need to be assessed to establish the type and extent of injury. Subsequent management is tailored according to the severity of the injury and the extent of the ischemic damage [5].

Testicular Trauma

Blunt testicular trauma is unilateral in most cases and amenable to conservative treatment consisting of elevation, ice packing, compression, bed rest, appropriate antibiotic coverage and analgesics [9, 17].

This approach applies to small intra-testicular haematomas causing mild to moderate pain and showing no progression or worsening on reassessment US at 48 hours. Surgical exploration is mandatory in testicular rupture and large haematoceles, especially if they are large and more than 3 times the size of the contralateral testis [2]. Operative management is also indicated in penetrating injuries, when conservative management fails to show any improvement within the first 72 hours, the haematoma is expanding, there is

no flow on the Doppler US study and/or radiological findings are equivocal or inconclusive [2, 9]. During surgical exploration, haematomas and clots are evacuated, the testis is inspected, debridement of the necrotic tissue is performed and accurate haemostasis is carried out (Figure 19.7). The tunica albuginea is then approximated using 4-0 polyglactin absorbable sutures. A patch of tunica vaginalis might be required in cases of large defects. When testicular viability is uncertain, the testis should be wrapped for 5 minutes in a warm saline-soaked gauze to see if an improvement in blood flow occurs. If the testicle is not viable and/or the patient is unstable, or reconstruction cannot be achieved, an orchidectomy may be required [2, 9]. In large haematoceles, early surgical intervention might reduce hospitalization as well as orchidectomy rates from 90% to 40%–45%, when compared to delayed exploration [2].

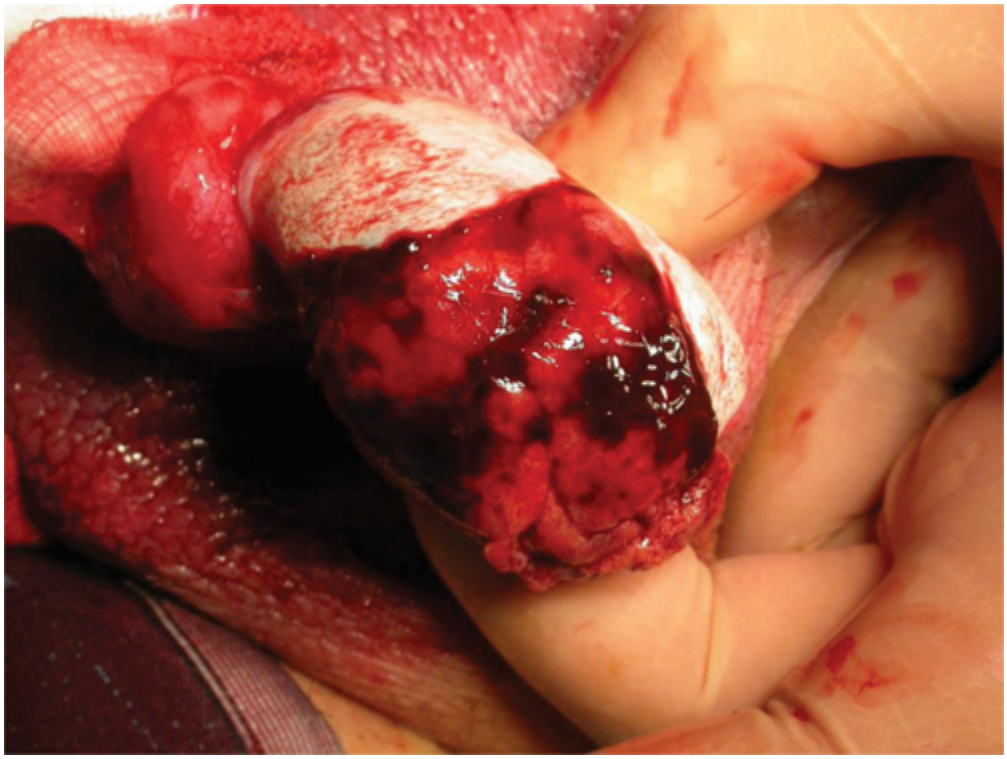


Figure 19.7 Scrotal exploration showing testicular rupture with parenchymal extrusion. Courtesy of Prof. G. Liguori.⏎

In testicular amputation, the reimplantation of the severed testis can be attempted if the patient presents within 12 hours from the time of the trauma and a microsurgical team is available [9].

Testicular dislocation can either be subcutaneous with epifascial displacement, or internal, with the testis being pushed back into the superficial external inguinal ring, in the inguinal canal or in the abdominal cavity. Indirect inguinal hernia and atrophic testicles are known to be predisposing factors for dislocation. In the first instance, manual repositioning followed by secondary orchidopexy should be attempted. When manual repositioning is not successful, immediate orchidopexy is recommended [2, 9].

Postoperative management of patients who have undergone surgical exploration include administration of broad-spectrum antibiotics, analgesia, scrotal compression and bed rest in order to promote recovery [9].

Skin loss should be managed with saline irrigation to clear all the debris, debridement should be performed, and, whenever possible, primary closure of the defect should be carried out. Whenever primary closure is not possible, immediate or delayed repair with the use of skin grafts should be considered [9].

Fertility status should always be assessed, as semen cryopreservation or surgical sperm retrieval may be required in extensive testicular injury, especially in bilateral cases. Testosterone and hormonal profile should be checked at follow-up and testosterone replacement therapy offered accordingly.

Anterior Urethral Injuries

Small urethral tears and complete anterior urethral ruptures without extensive tissue loss should be repaired immediately by simple closure or anastomotic repair respectively (Figure 19.8), using 5-0 absorbable sutures in a watertight fashion, usually over a 16 Fr indwelling urethral catheter [10, 15]. Around 2% of cases develop a urethral stricture following immediate urethral reconstruction for penile fracture.

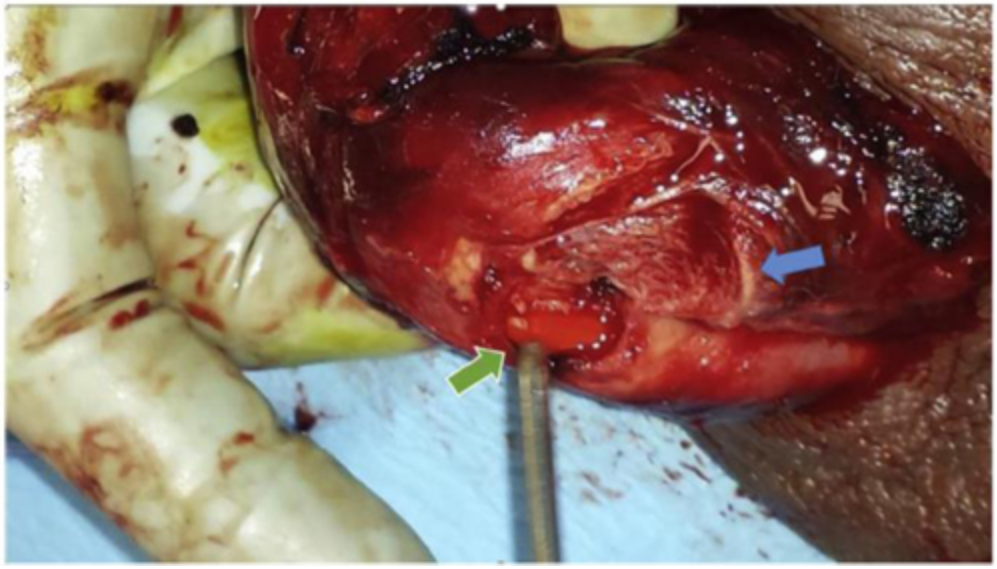


Figure 19.8 Surgical exploration with ventral midline penoscrotal approach (preferred approach) showing penile albuginea's fracture (blue arrow) and concomitant urethral tear (green arrow). *Source*: Adapted from Simms A, Baradaran N, Lue TF, Breyer BN. Penile Fractures: Evaluation and Management. *Urol Clin North Am*. 2021 Nov;48(4):557-563. doi: 10.1016/j.ucl.2021.06.011. Epub 2021 Aug 21. PMID: 34602175.⏎

Immediate urethroplasty might be considered in some selected anterior urethral injuries if a dedicated surgical expertise is available in theatre [2]. The patency and potency rates after immediate urethroplasty are similar to patients initially treated with suprapubic urinary diversion and delayed urethroplasty. Immediate urethroplasty has the advantage of reducing the time to spontaneous voiding from 2–6 months to around 3 weeks.

Where immediate treatment is not feasible due to the presence of extensive defects, concomitant infection, life-threatening lesions or in case of blunt or iatrogenic traumas, a transurethral or suprapubic urinary diversion is performed. In these cases, definitive treatment is deferred, and a staged reconstruction might be needed. Urinary diversion should be maintained for 1–2 weeks in partial ruptures and 3 weeks in complete ones. Thereafter, a RUG is warranted to confirm urethral healing [2].

Posterior Urethral Injuries

Posterior urethral injuries are usually associated with severe intra-abdominal injuries; hence the priority is to stabilize the patient's condition. The preferred initial treatment is suprapubic catheterization, which allows urinary output monitoring, address urinary retention and limit the extent of urinary extravasation and of the consequences it may lead to, such as infection and fibrosis. However, a cautious attempt at urethral catheterization might be considered by a urologist in specific circumstances such as in unstable trauma patients with a displaced bladder due to a pelvic haematoma, or poor bladder filling as a result of hemodynamic shock, or the presence of bladder injury [2].

Urinary diversion might be sufficient for mild partial tears, which tend to heal spontaneously without significant sequelae [18]. However, with complete posterior injuries, active treatment is required which can be carried out early, within the first 6 weeks, or deferred, at least 3 months after the trauma [2].

Early realignment can be attempted in a stable patient either while surgeries for other injuries are being performed, or as a stand-alone intervention. The aim of this procedure is to reduce urinary extravasation in partial injuries and the risk of dense stricture formation in patients who have sustained complete lesions where a gap between the 2 urethral stumps is present (strictures might form but can be treated endoscopically in almost half of the cases following early realignment) [19, 20].

Realignment is preferably performed endoscopically under fluoroscopic guidance and, in some cases, a combined approach (retrograde per urethra and antegrade via suprapubic/bladder neck route) can be attempted. Catheterization, for 3 and 6 weeks, followed by a RUG, is sufficient for partial and complete ruptures, respectively [2]. With contemporary endoscopic realignment procedures, the stricture formation rate is reduced to 44%–49%, compared to 89%–94% with suprapubic diversion.

When early realignment is either not feasible or fails, or in cases of long strictures not amenable with direct vision urethrotomy, the standard treatment after suprapubic catheterization remains deferred urethroplasty. This should be carried out at least 3 months after trauma to allow the patient

to be stabilized, haematoma to be resolved, the prostate to descend back into its normal position and the fibrosis to be stabilized.

In selected patients with a short urethral defect and a soft perineum who can tolerate a lithotomy position, an early urethroplasty might be an option, which can be performed up to 6 weeks after the injury [2]. This avoids a long period of suprapubic diversion and the outcomes (stricture recurrence, incontinence and impotence) are equivalent to delayed urethroplasty.

Complications and Follow-up

There are potential short- and long-term complications in patients who have experienced genito-urethral trauma. The complications depend on what structures have been injured, but include erectile dysfunction, genital disfigurement, voiding issues, urethral strictures, infertility as well as psychological distress [2].

Following penile trauma, postoperative complications have been reported in 20% of cases, with plaques or nodules developing in 13.9% of cases and curvatures or deformities in 2.8%. De novo erectile dysfunction occurs in 1.9% of patients, being more common in men over 50 years of age and in those who have experienced bilateral corporal fractures [2, 7]. Urethral strictures might arise in up to 8.5% of patients [18]. Delayed or conservative management is associated with a higher short- and long-term complication rates [7].

Postoperative complications are recorded in 8% of patients undergoing testicular repair after penetrating injuries [19]. Delayed complications such as chronic pain and testicular atrophy might occur [2]. In patients who have experienced postoperative testicular atrophy, infertility and hypogonadism have to be taken into account [21].

References

1. Brandes SB, Buckman RF, Chelsky MJ, Hanno PM. External genitalia gunshot wounds: a ten-year experience with fifty-six

cases. *J Trauma* 1995 Aug;39(2):266–71; discussion 271–272. doi: 10.1097/00005373-199508000-00013. PMID: 7674395.⏎
2. EAU guidelines on Urological Trauma 2023, https://uroweb.org/guidelines/urological-trauma⏎
3. McCormick CS, Dumais MG, Johnsen NV, Voelzke BB, Hagedorn JC. Male genital trauma at a level 1 trauma center. *World J Urol*. 2020 Dec;38(12):3283–3289. doi: 10.1007/s00345-020-03115-0. Epub 2020 Feb 20. PMID: 32077992.⏎
4. Lawson JS, Rotem T, Wilson SF. Catastrophic injuries to the eyes and testicles in footballers. *Med J Aust*. 1995 Sep 4;163(5):242–244. doi: 10.5694/j.1326-5377.1995.tb124558.x. PMID: 7565208.⏎
5. Gaspar SS, Dias JS, Martins F, Lopes TM. Sexual urological emergencies. *Sex Med Rev*. 2015 Apr;3(2):93–100. doi: 10.1002/smrj.44. Epub 2015 Dec 2. PMID: 27784550.⏎
6. Lee SH, Bak CW, Choi MH, Lee HS, Lee MS, Yoon SJ. Trauma to male genital organs: a 10-year review of 156 patients, including 118 treated by surgery. *BJU Int*.2008 Jan;101(2):211–215. doi: 10.1111/j.1464-410X.2007.07265.x. Epub 2007 Oct 8. PMID: 17922859.⏎
7. Amer T, Wilson R, Chlosta P, AlBuheissi S, Qazi H, Fraser M, Aboumarzouk OM. Penile fracture: a meta-analysis. *Urol Int*. 2016;96(3):315–329. doi: 10.1159/000444884. Epub 2016 Mar 9. PMID: 26953932.⏎
8. Tsang T, Demby AM. Penile fracture with urethral injury. *J Urol*. 1992 Feb;147(2):466–468. doi: 10.1016/s0022-5347(17)37276-2. PMID: 1732623.⏎
9. Lucky M, Brown G, Dorkin T, Pearcy R, Shabbir M, Shukla CJ, Rees RW, Summerton DJ, Muneer A. BAUS Section of Andrology and Genitourethral Surgery (AGUS). British Association of Urological Surgeons (BAUS) consensus

document for the management of male genital emergencies - testicular trauma. *BJU Int.* 2018 Jun;121(6):840–4. doi: 10.1111/bju.14163. Epub 2018 Apr 10. PMID: 29635819.⏎
10. Simms A, Baradaran N, Lue TF, Breyer BN. Penile fractures: evaluation and management. *Urol Clin North Am*. 2021 Nov;48(4):557–563. doi: 10.1016/j.ucl.2021.06.011. Epub 2021 Aug 21. PMID: 34602175.⏎
11. Gontero P, Muir GH, Frea B. Pathological findings of penile fractures and their surgical management. *Urol Int.* 2003;71(1):77–82. doi: 10.1159/000071099. PMID: 12845266.⏎
12. Wessells H, Long L. Penile and genital injuries. *Urol Clin North Am*. 2006 Feb;33(1):117–126, vii. doi: 10.1016/j.ucl.2005.11.003.⏎
13. Ogbetere FE. Traumatic testicular torsion: A call to look beyond the obvious. *Urol Ann.* 2021 Oct–Dec;13(4):431–433. doi: 10.4103/UA.UA_159_20. Epub 2021 Sep 2. PMID: 34759658; PMCID: PMC8525482.⏎
14. Wang Z, Yang JR, Huang YM, Wang L, Liu LF, Wei YB, Huang L, Zhu Q, Zeng MQ, Tang ZY. Diagnosis and management of testicular rupture after blunt scrotal trauma: a literature review. *Int Urol Nephrol*. 2016 Dec;48(12):1967–1976. doi: 10.1007/s11255-016-1402-0. Epub 2016 Aug 27. PMID: 27567912.⏎
15. Kominsky H, Beebe S, Shah N, Jenkins LC. Surgical reconstruction for penile fracture: a systematic review. *Int J Impot Res.* 2020 Jan;32(1):75–80. doi: 10.1038/s41443-019-0212-1. Epub 2019 Nov 4. PMID: 31685943.⏎
16. Virasoro R, Tonkin JB, McCammon KA, Jordan GH. Penile amputation: cosmetic and functional results. *Sex Med Rev*. 2015 Jul;3(3):214–222. doi: 10.1002/smrj.50. Epub 2015 Oct 8. PMID: 27784611.⏎

17. Lee SH, Bak CW, Choi MH, Lee HS, Lee MS, Yoon SJ. Trauma to male genital organs: a 10-year review of 156 patients, including 118 treated by surgery. *BJU Int.* 2008 Jan;101(2):211–215. doi: 10.1111/j.1464-410X.2007.07265.x. Epub 2007 Oct 8. PMID: 17922859.⏎
18. Mundy AR, Andrich DE. Urethral trauma. Part I: introduction, history, anatomy, pathology, assessment and emergency management. *BJU Int.* 2011 Aug;108(3):310–327. doi: 10.1111/j.1464-410X.2011.10339.x. PMID: 21771241.⏎
19. Shebl SE. The presentation and outcomes of penile fracture with associated urethral injury: a systematic literature review. *Arch Ital Urol Androl*. 2023 May 31;95(2):11082. doi: 10.4081/aiua.2023.11082. PMID: 37259814.⏎
20. Elshout PJ, Veskimae E, MacLennan S, Yuan Y, Lumen N, Gonsalves M, Kitrey ND, Sharma DM, Summerton DJ, Kuehhas FE. Outcomes of early endoscopic realignment versus suprapubic cystostomy and delayed urethroplasty for pelvic fracture-related posterior urethral injuries: a systematic review. *Eur Urol Focus*. 2017 Dec;3(6):545–553. doi: 10.1016/j.euf.2017.03.001. Epub 2017 Apr 6. PMID: 28753868.⏎
21. Starmer BZ, Baird A, Lucky MA. Considerations in fertility preservation in cases of testicular trauma. *BJU Int* 2018 Mar;121(3):466–471. doi: 10.1111/bju.14084. Epub 2017 Dec 10. PMID: 29164757.⏎

Index

A

B

C

D

E

F

G

H

I

K

L

M

N

O

P

Q

R

S

T

U

V

W

Y