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Primer

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Male infertility

Michael L. Eisenberg[1,2] ✉, Sandro C. Esteves[3,4], Dolores J. Lamb[5,6,7], James M. Hotaling[8], Aleksander Giwercman[9], Kathleen Hwang[10] & Yu-Sheng Cheng[11]

Abstract

Clinical infertility is the inability of a couple to conceive after 12 months of trying. Male factors are estimated to contribute to 30–50% of cases of infertility. Infertility or reduced fertility can result from testicular dysfunction, endocrinopathies, lifestyle factors (such as tobacco and obesity), congenital anatomical factors, gonadotoxic exposures and ageing, among others. The evaluation of male infertility includes detailed history taking, focused physical examination and selective laboratory testing, including semen analysis. Treatments include lifestyle optimization, empirical or targeted medical therapy as well as surgical therapies that lead to measurable improvement in fertility. Although male infertility is recognized as a disease with effects on quality of life for both members of the infertile couple, fewer data exist on specific quantification and impact compared with other health-related conditions.

Sections

[1]Department of Urology, Stanford University School of Medicine, Stanford, CA, USA. [2]Department of Obstetrics & Gynecology, Stanford University School of Medicine, Stanford, CA, USA. [3]ANDROFERT Andrology and Human Reproduction Clinic, Campinas, Brazil. [4]Division of Urology, Department of Surgery, Faculty of Medical Sciences, State University of Campinas (UNICAMP), Campinas, Brazil. [5]Center for Reproductive Genomics, Weill Cornell Medical College, New York, NY, USA. [6]Englander Institute for Precision Medicine, Weill Cornell Medical College, New York, NY, USA. [7]Department of Urology, Weill Cornell Medical College, New York, NY, USA. [8]Division of Urology, Department of Surgery, University of Utah School of Medicine, Salt Lake City, UT, USA. [9]Department of Translational Medicine, Lund University, Malmö, Sweden. [10]University of Pittsburgh Medical Center, Pittsburgh, PA, USA. [11]Department of Urology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan. ✉e-mail: eisenberg@stanford.edu

Introduction

Clinical infertility is defined as the inability of a couple to conceive after 12 months of trying. It is estimated that approximately 10–20% of couples in the world are infertile[1]. Importantly, the concept of reproductive success is defined at the couple level. Consequently, the aetiology of infertility of a couple could be attributed to either or both members of the couple[2,3]. Most studies estimate that a male factor contributes to 30–50% of infertility cases[4,5]. Clinical guidelines recommend the evaluation of both members of an infertile couple at the inception of testing; however, evaluation of the male partner is not undertaken in up to 25% of cases[3,6,7].

Definitions regarding reproduction are important, as it is crucial to understand what is being discussed, measured or treated (Box 1). Fecundity is generally defined as the biological ability to reproduce, whereas fertility relates to successful reproduction as measured by a live birth. Furthermore, the fertility rates of a population are defined by the number of births per reproductive-age woman. Thus, as fertility rates decline in many developed parts of the world (Fig. 1), identifying the aetiology for such decline centres on whether there is a change in fecundity or in reproductive intent (Box 2).

Male fertility is most commonly defined on the basis of semen quality. Although studies have questioned the clinical effectiveness of defining a man's reproductive potential based on semen quality, several studies do support an association between semen quality and pregnancy[8–12]. Clinical guidelines state the need to include a semen analysis in the initial work-up of an infertile couple[3,13]. The semen parameters assessed include semen volume and sperm concentration, motility and morphology. Interpretation of semen quality centres on levels that are average for a population or adequate for pregnancy, recognizing that the test does not assess sperm function beyond motility (that is, events needed for fertilization–capacitation, oocyte activation, sperm head decondensation and so forth). Since 1980, the WHO has published the *WHO Laboratory Manual for the Examination and Processing of Human Semen*, which is currently in its 6th edition[14,15]. Standardized techniques are crucial to the accurate evaluation of semen quality given the imprecision that can arise owing to inadequate protocols as well as normal biological variability that can exist between samples from the same man[14,16–20].

In addition to providing guidance on the correct procedure for semen analysis, the WHO manual also offers reference ranges to enable patient counselling. Data from several thousand men around the world were used to obtain distributions of semen parameters and provide definitions, labelling levels at the 5th percentile (that is, a level lower than 95% of values in the reference population) as thresholds below which semen quality is considered abnormal, although a subset of men with values in this lower range may be fertile without the use of assisted reproductive technology (ART)[10,14,21–31].

However, the results of a semen analysis, and the sperm count in particular, cannot be used to predict whether a man is fertile or infertile, unless no sperm are detected in the ejaculate or the sperm display a severe morphological or functional defect. The inability to meaningfully and accurately assess fertility based on semen analysis data is due, in part, to the fact that it is the fertility potential of the couple that determines the likelihood of achieving a pregnancy. One subfertile partner could be fertile with one partner but infertile with another. Although a higher motile sperm count increases the chances of pregnancy, it does not ensure that a pregnancy will occur. This is because a man with completely normal semen parameters can have sperm that fail to function correctly. Conversely, the scientific literature has documented how men with seemingly low-quality semen samples were able to achieve a pregnancy. For example, in the 1970s, researchers analysed the semen parameters of men who achieved pregnancies without ART and were seeking a vasectomy[23]. This study showed that nearly a quarter of these fertile men were considered to have oligozoospermia (a low sperm count, defined as <20 million/ml) and that 11% of them had sperm counts <10 million/ml (Box 1).

In this Primer, we describe the epidemiology of male infertility, the aetiology, evaluation and treatment, and opportunities for future advancement of these aspects. Our primary focus in this Primer is on impairments in spermatogenesis and not on other disorders that can lead to infertility (such as ejaculatory or sexual dysfunction).

Epidemiology

Prevalence

The prevalence of infertility among couples globally is estimated to range between 10% and 20%, with about 50 million reproductive-age couples failing to achieve a pregnancy after 12 months or more of timed intercourse (having sexual intercourse when a woman is predicted to be most fertile)[1,32]. The prevalence seems to be highest in South Asia, sub-Saharan Africa, North Africa and the Middle East, central and eastern Europe, and Central Asia, with no apparent changes in the levels of infertility over recent years in most regions[32]. However, gaps in survey data have been identified for many countries, particularly in central and eastern Europe and Central Asia.

As infertility might be linked to problems that affect the male reproductive system[33–41], accurate estimates about how often a male factor contributes to a couple's ability to reproduce are imperative. Data from a large 1992 WHO study involving 8,500 infertile couples in 25 countries showed that infertility was due to female factors in 37% of cases, both male and female factors in 35%, male factors alone in 8% and undetermined in the remaining 20% of cases[42]. However, a 2015 systematic review reported considerable variation in male infertility prevalence, ranging from 2% to 12% globally and accounting for 20–70% of all infertility cases[5]. Some variability may also arise from inconsistent evaluation of the male partner[6,7]. In addition, definitions of infertility may vary between an inability to conceive after a year of timed intercourse and the finding of low semen parameters. The review authors aggregated direct and extrapolated data from 16 studies to compute estimates and showed that male infertility prevalence was highest in central and eastern Europe (8–12%), followed by Australia (8–9%) and North America (4.5–6%). However, male infertility prevalence is poorly documented and remains largely unknown for Asia, Latin America and the Middle East[5]. This uncertainty relates to the lack of accurate national-level data and variations in definition, data collection methods and outcomes reported in existing studies.

The limited available data suggest that the prevalence of male infertility varies by several sociodemographic factors such as country and/or region, age, ethnicity, coital frequency and fertility intentions[5,43]. Also, the prevalence of secondary infertility (that is, a couple with at least one prior pregnancy and difficulty attempting to achieve an additional pregnancy) is fivefold higher (10.5% versus 1.9%) than that of primary infertility (difficulty achieving a pregnancy with no previous pregnancy)[32], a finding that is particularly applicable to low- and middle-income countries, possibly attributable to the increased incidence of post-infection infertility in these countries[32,43].

Paternal and maternal age at first birth is increasing in many parts of the world[44], which might result in a greater need for infertility treatment given the well-established age-related fertility decline for both

Box 1

Definition of selected reproductive terms

Fertility. Successful reproduction as measured by a live birth.

Total fertility rate. The number of births per woman of reproductive age (that is, 15–45 years of age) in a population.

Fecundity. The biological ability to reproduce, which can be defined for a population or for each individual. It may be measured indirectly by several means, including hormonal profiles (men and women), gamete number (men and women), menstruation and ovulation (women), follicle count (women) and testis size (men).

Fecundability. The probability of conception in a month or a menstrual cycle.

Azoospermia. No spermatozoa in the fresh ejaculate even after centrifugation and microscopic examination of centrifuged pellet.

Oligozoospermia. Concentration of spermatozoa below the 5th percentile reference limit established by the *WHO Laboratory Manual for the Examination and Processing of Human Semen*.

Asthenozoospermia. Percentage of motile spermatozoa below the 5th percentile reference limit established by the WHO manual for examination of human semen (absolute asthenozoospermia refers to absence of motile spermatozoa in the ejaculate).

Teratozoospermia. Percentage of morphologically normal spermatozoa below the 5th percentile reference limit established by the WHO manual for examination of human semen.

Oligoasthenozoospermia. Concentration of spermatozoa and percentage of motile spermatozoa below the reference limits established by the WHO manual for examination of human semen.

Asthenoteratozoospermia. Percentage of motile and of morphologically normal spermatozoa both below the lower reference limits established by the WHO manual for examination of human semen.

Oligoteratozoospermia. Concentration of spermatozoa and percentage of morphologically normal spermatozoa both below the lower reference limits established by the WHO manual for examination of human semen.

Oligoasthenoteratozoospermia. Concentration of spermatozoa and percentage of motile and of morphologically normal spermatozoa all below the reference limits established by the WHO manual for examination of human semen.

Necrozoospermia. Percentage of live spermatozoa in the ejaculate below the reference limits established by the WHO manual for examination of human semen with a high percentage of immotile sperm (complete necrozoospermia refers to absence of any live spermatozoa in the ejaculate).

Normozoospermia. Concentration of spermatozoa, and percentages of motile and morphologically normal spermatozoa all within the reference limits established by the WHO manual for examination of human semen.

Globozoospermia. Presence of spermatozoa in the ejaculate with small acrosome vesicles or total absence of the acrosomal vesicle.

Leukocytospermia. Presence of leukocytes in the ejaculate above the threshold value of 1 million/ml.

Cryptozoospermia. No spermatozoa in the fresh ejaculate but observed after microscopic examination of centrifuged pellet.

Assisted reproductive technology. Any technique involving manipulation of eggs or embryos (for example, in vitro fertilization); intrauterine insemination or medications to stimulate egg production are not included.

Intracytoplasmic sperm injection. Direct injection of a single sperm into an egg.

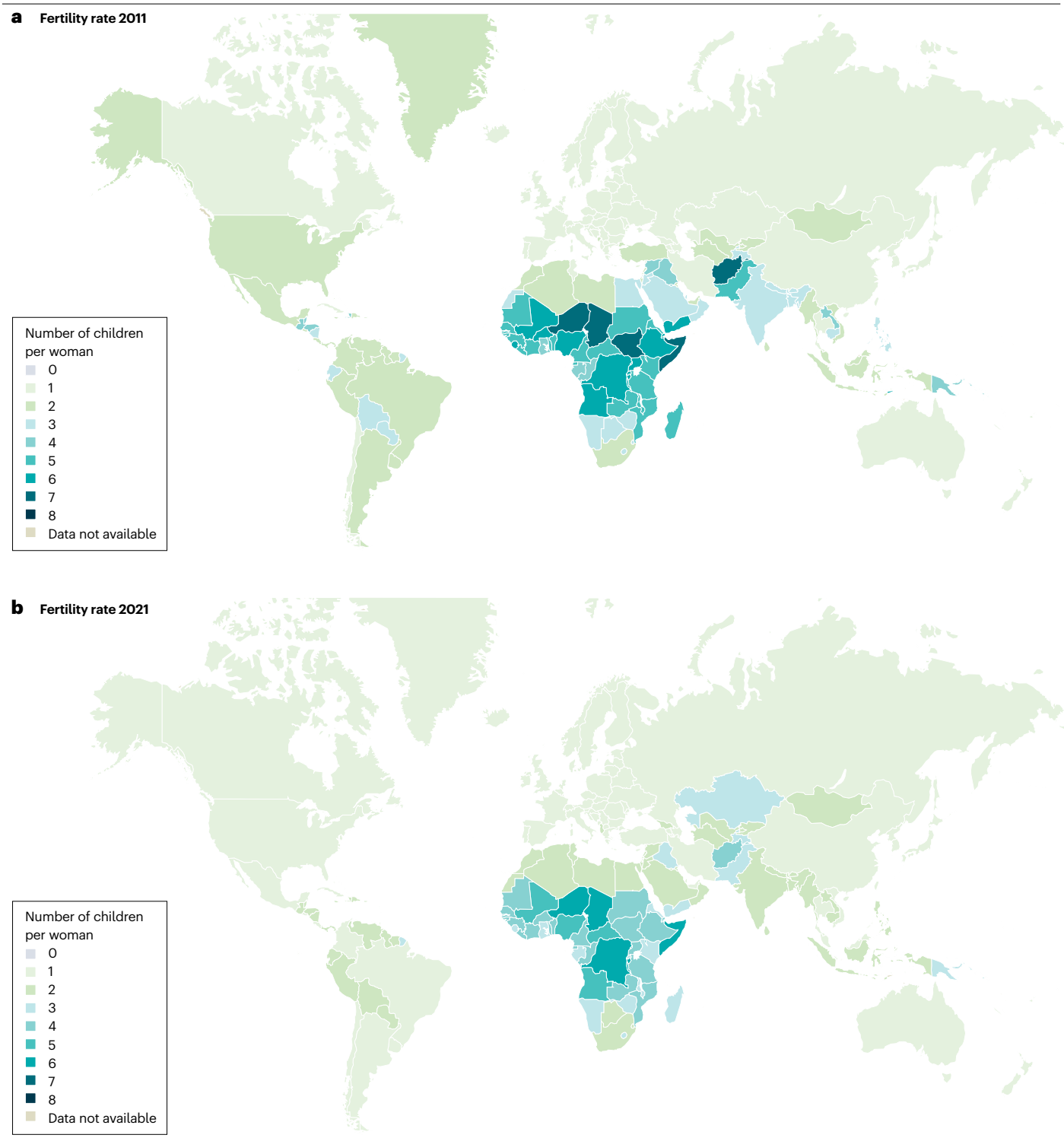
Intrauterine insemination. Direct placement of sperm into the uterus.

In vitro fertilization. Removal of an egg from the ovary and fertilization with sperm in a laboratory setting.

Ejaculatory duct obstruction. A blockage in the ejaculatory duct that prevents passage of ejaculate into the urethra.

Retrograde ejaculation. A condition in which semen progresses in a retrograde direction into the bladder instead of an antegrade direction towards the urethral meatus.

men and women[45–47]. Of note, ART use has increased steadily across the globe, particularly for first-time parents with increasingly later marriages and family building. ART use is employed as a proxy for the prevalence of infertility (of which about 50% is due to male factors alone or combined with female factors). More than 2.5 million in vitro fertilization (IVF) cycles are carried out annually worldwide, resulting in more than a half-million deliveries[48]. The latest data generated by the International Committee for Monitoring Assisted Reproductive Technologies (ICMART), involving 2,746 fertility centres in 76 countries, reveal that an estimated 1.93 million ART cycles were carried out, representing ~66% of global ART activity, resulting in the birth of 439,039 babies[49]. An analysis of ART data reported to the United States National Assisted Reproductive Technology Surveillance System in 2018 revealed that 203,119 ART procedures were performed in



456 fertility clinics (~3,000 procedures per million women), resulting in 73,831 live births, corresponding to 2% of all infants born in the USA[50].

Of note, other studies estimate that more than 1,000 ART procedures per million women are performed in developed countries annually, and 2–10% of newborns are conceived using ART[48,51–53]. By contrast, the overall impact of ART on global fertility levels is <0.5%, with some regions, such as sub-Saharan Africa[48,51,52], reporting five ART cycles per million inhabitants performed per year, indicating marked disparities in availability, quality and access to fertility care.

ART is widely used to treat severe male infertility, mainly by intracytoplasmic sperm injection (ICSI; Box 1) as the fertilization method[54]. Globally, the use of ICSI (as a percentage of ART procedures) rose from

Fig. 1 | Global fertility rates. The fertility rate refers to the number of children per reproductive-age woman. A rate of 2.1 is considered necessary for a steady state of a population excluding immigration. Thus, fertility rates of <2.1 suggest that population numbers would be expected to decline over time if no immigration occurs. Reprinted from ref. 303, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/), based on data from the United Nations, World Population Prospects (2022)[304].

36.4% in 1996 to 76.2% in 2012, with substantial variation by region (~100% of ART procedures in the Middle East, 85% in Latin America, 76% in the USA, 71% in Europe and 55% in Asia)[51–53]. Furthermore, a study using data from the years 2017–2018 of the United States National ART Surveillance System reported that 30.4% of all ART cycles performed were because of a male infertility diagnosis[55]. Importantly, the cost of infertility is likely measured in more than IVF cycles given the physical, social, emotional, spiritual, intellectual and financial impact that infertility has on individuals and couples. To date, no cost estimate exists for male infertility as it does for several other chronic conditions[56].

Health-related issues

Male infertility has been linked to serious adverse health, psychological, social and economic outcomes[57]. Infertile men have a higher risk of cancer (for example, testis, prostate, lymphoma, breast) and other adverse health outcomes, such as heart disease, diabetes and autoimmune diseases, than fertile controls[57–64]. A study analysing US insurance claims data for the period 2001–2009 found a higher incidence of malignancies in infertile men than in fertile controls (hazard ratio (HR) 1.49; 95% confidence interval (CI) 1.37–1.63)[58]. A study involving 24,000 Danish men found that individuals diagnosed with male infertility had an increased risk for multiple sclerosis (HR 1.28; 95% CI 0.76–2.17)[64]. A study analysing US insurance claims data for more than 450,000 men for the period 2001–2008 found that infertile men were at increased risk of presenting with autoimmune diseases, such as psoriasis (HR 1.20; 95% CI 1.04–1.37), systemic lupus erythematosus (HR 2.12; 95% CI 1.52–2.96), Graves' disease (HR 1.46; 95% CI 1.10–1.92), thyroiditis (HR 1.60; 95% CI 1.02–2.52) and multiple sclerosis (HR 1.91; 95% CI 1.10–3.31) compared with age-matched controls, in the ~3–3.5 years after an infertility diagnosis[60].

In another large US insurance claims-based analysis, a male infertility diagnosis was associated with an increased risk of all-cause mortality (HR 1.42; 95% CI 1.27–1.60)[62]. Another study showed a positive relationship between the likelihood of death and spermatogenesis impairment, particularly in individuals with azoospermia (HR 2.01; 95% CI 1.60–2.53)[61].

Male infertility is also a concern for cancer survivors owing to gonadotoxic cancer treatments[63]. A Norwegian national registry study of 2,687 male survivors of cancer and controls born during the period 1965–1985 showed reduced paternity (HR 0.72; 95% CI 0.68–0.76) and increased ART use (relative risk (RR) 3.32; 95% CI 2.68–4.11) among the male cancer survivors[65]. These effects were more pronounced in men diagnosed with cancer before age 15 than after this age and among survivors of testicular cancer, brain tumours, lymphoma, leukaemia and bone tumours than among survivors of other cancers.

Genetic and congenital conditions

As up to 10% of the male genome is involved with reproduction, it is not surprising that male infertility has a strong genetic basis, with the prevalence of genetic abnormalities increasing as sperm concentration decreases[38,39,66,67]. Chromosomal anomalies, such as Robertsonian translocations, sex chromosome and numerical autosomal abnormalities, single-gene mutations and Y-chromosome microdeletions, are found in about 15% of men with non-obstructive azoospermia (NOA) and ~5% of men with oligozoospermia; by contrast, these conditions are found in <1% of men with a sperm concentration >19 million/ml (refs. 68,69).

Klinefelter syndrome (KS; 47,XXY) is the most common sex chromosome anomaly, affecting about 1 in every 600 male pregnancies. Classically, these patients exhibit small testes, gynaecomastia (enlargement of the breast tissue; in ~40% of cases), hypogonadism and azoospermia[33,39]. Among men with NOA, KS is found in ~10% of cases[39]. Y-chromosome microdeletions are also a common cause of male infertility. The prevalence of Y-chromosome microdeletions among infertile men ranges between 4% and 17%, with most cases being associated with azoospermia[39,70,71]. Genetic hypothalamic disorders are also associated with male infertility[37,39]. The incidence of congenital hypogonadotropic hypogonadism is 1–10 cases in 100,000 live births; approximately two-thirds of cases are due to Kallmann syndrome and one-third to normosmic hypogonadotropic hypogonadism[72]. In addition, oligozoospermia and azoospermia were seen in 31% and 42% of men with a history of bilateral cryptorchidism (both tests undescended), respectively[73,74].

Most men with cystic fibrosis transmembrane conductance regulator (CFTR)-damaging gene mutations are infertile, owing to obstructive azoospermia caused by abnormalities of the vas deferens (for example, congenital bilateral absence of the vas deferens (CBAVD) or epididymal obstruction)[39,75]. CBAVD accounts for approximately 2% of infertility cases and 6–25% of obstructive azoospermia cases[76]. Approximately 78% of men with CBAVD carry *CFTR* mutations, and the frequency and type of mutation vary between men of European descent and those of non-European descent[77]. Importantly, *CFTR* mutations may be present in males with oligozoospermia or NOA[78].

Mechanisms/pathophysiology

The positioning of the testes external to the body in the scrotum is required for normal spermatogenesis, as it is important to maintain a testis temperature that is about 2–3 °C lower than core body temperature. The testis is suspended by the spermatic cord, which consists of the vas deferens, spermatic artery and venous and lymphatic plexus (Fig. 2). Within the testis, each seminiferous tubule forms long looping structures that open at both ends into the rete testis, and these are surrounded by interstitial tissues that include the Leydig cells, blood and lymphatic vessels and macrophages[79]. The testicular architecture is crucial to the functioning of the testis. Subtle disruptions of the vascular structures by various conditions, such as a varicocele (that is, dilated veins in the scrotum), can have substantial negative impacts on testicular function[3,80].

The testis has three main functions. The exocrine function is involved in the production of mature sperm and requires the Sertoli cells to support the developing germ cells and maintain the blood–testis barrier. The endocrine function relates to the production of androgens by the Leydig cells and inhibin and Müllerian-inhibiting substance by the Sertoli cells. The paracrine function involves complex local controls of spermatogenesis and intercompartmental signalling between the seminiferous tubules, the interstitial cells and the peritubular myoid cells[81].

Box 2

Global fertility rates and male reproductive health

Global fertility rates, measured by the average number of children per woman of reproductive age, have declined in nearly all regions of the world over the past 20 years, with most high-income countries failing below the replacement level of 2.1 children per couple[305,306] (Fig. 1). Although social and economic factors can explain the trend[307], a possible decline in overall male reproductive health and semen quality has been postulated to be a contributory factor[308], given its plausible association with industrialization and increased exposure to harmful environmental pollutants[309]. A 2017 meta-analysis reported a marked decline in sperm concentration globally over the past 40 years (1973–2011; slope meta-regression −0.64 million/ml per year; 95% confidence interval (CI) −1.06 to −0.22; P=0.003), mainly driven by a reduction observed in industrialized nations[308]. The meta-analysis was updated in 2022, with additional data from around the globe. In all, the authors examined 288 studies reporting data collected from 1973 to 2018 and demonstrated a continued decline in sperm concentration (slope meta-regression −0.71 million/ml per year; 95% CI −0.90 to −0.27), which became steeper in the later years of analysis[310].

Whether male fertility is declining remains the subject of debate[311], and studies investigating temporal trends in unselected populations recruited and analysed with the same protocol over a long period and adjusted for lifestyle factors have failed to confirm this hypothesis[312]. Nevertheless, studies have reported that currently up to 35% of unselected men have low sperm quality[312,313].

Geographical location, environmental factors, diet, lifestyle and ethnicity might affect the male reproductive system in various ways[301]. For example, it has been suggested that some countries have an increased incidence of post-infection (for example, including sexually transmitted diseases) male infertility[43]. A large observational study in the USA revealed marked differences in semen parameters in relation to sociodemographic factors[314]. Indeed, pooled multicentre data that were used to generate semen parameter thresholds have been criticized for not adequately reflecting population differences[259,315–317]. Owing to limited data, it is challenging to accurately determine the distribution of pathogen species, genetic variants or any other subtype, including differences between countries and ethnicities. Also, whether regional reference values for semen analysis would be more clinically meaningful than values obtained by pooling data from diverse populations remains to be determined.

The hypothalamic–pituitary–gonadal axis

There are well-defined feedback loops that regulate steroidogenesis by Leydig cells and the function of Sertoli cells[81] (Fig. 3). This is a key integrated pathway that is absolutely required for male reproductive health. Dysfunction underlies a wide range of conditions, including ambiguous genitalia and sex reversal, pubertal issues, various degrees of spermatogenic failure and other problems throughout the body.

Sertoli cells. Sertoli cells mediate the endocrine effects of testosterone, follicle-stimulating hormone (FSH) and other endocrine hormones on the developing spermatogenic cells[81] (Table 1). Sertoli cells also have an endocrine function, secreting the peptide hormone inhibin B that feeds back to the pituitary gland to regulate secretion of gonadotropins, specifically FSH. Other functions of Sertoli cells include phagocytosis of residual bodies generated during the process of spermatid differentiation (spermiogenesis), the release of the mature sperm into the lumen of the seminiferous tubule (spermiation), secretion of ions and proteins, and the creation of the blood–testis barrier, which separates the testes from the circulation and other body fluids and separates the seminiferous tubule into adluminal and basal compartments[82]. Proliferation of Sertoli cells occurs before puberty and is influenced by FSH, activin and thyroxin. Disruption of any of these functions affects spermatogenesis.

Peritubular myoid cells. Peritubular myoid cells are smooth-muscle type cells located adjacent to the seminiferous tubule basement membrane[83,84]. Androgens act to induce the differentiation of these cells to produce smooth-muscle actin, whereas FSH seems to have an additive role via paracrine factors secreted by Sertoli cells. These components may influence paracrine signalling in the testis, as well as contribute to the spermatogonial stem cell niche[83,84].

Leydig cells. These cells are present in the interstitial space between the seminiferous tubules and are responsible for the biosynthesis of testosterone[81]. Testosterone biosynthesis is upregulated by luteinizing hormone (LH) released by the anterior pituitary gland, and testosterone feeds back to downregulate LH release by the pituitary gland (Fig. 3).

The germ cells in the testis

Testicular germ cells collectively encompass all the cells in the testis that are at various developmental stages and have the potential to eventually differentiate into mature sperm. The following sections summarize the key germ cell-related events during spermatogenesis (Fig. 3).

Mitosis in the seminiferous tubule. The spermatogonial stem cell is the pluripotent progenitor of the type A spermatogonia. These cells have the ability to rejuvenate spermatogenesis after a toxic insult[85]. Spermatogonial stem cells are largely quiescent but can undergo self-renewal and thus have the capacity to repopulate the testis with spermatogenic cells and re-establish spermatogenesis after a toxic insult, such as exposure to gonadotoxins such as chemotherapeutic agents, radiation, occupational exposures to some chemicals. Spermatogonial stem cells have the potential to regenerate tissues and organs and can even show germline transmission when injected into blastocysts in mouse models[86].

In mice these progenitor cells are referred to as the A_{single} spermatogonia (also called $A_{isolated}$ spermatogonia), which then divide to form the A_{paired} spermatogonia that again proliferate to form the

$A_{aligned}$ spermatogonia. These early spermatogonia do not undergo normal cytokinesis during development and yield germ cells connected to each other by cytoplasmic bridges, and this characteristic defines the early spermatozoan precursors that allow cohorts of cells to develop together in time[87]. Type A spermatogonia proliferate to ensure the relatively constant production of sperm by the testis. Type A1 spermatogonia give rise to a series of differentiation spermatogonial cell types (A1→ A2→ A3→ A4→ Int→B). Type B spermatogonia are those committed to enter meiosis and then differentiate to produce mature sperm. In humans, the nomenclature is a bit less defined as type A dark, type A pale, and type B spermatogonia, which enter meiosis[82].

Meiosis. During meiosis, the germ cells undergo a series of DNA replications resulting in a tetraploid gamete, followed by meiotic recombination with double-strand breaks, crossing over and DNA repair. Two successive reductive divisions then occur to yield the haploid spermatid[88].

Spermiogenesis. The process of differentiation of the round spermatid into a mature spermatozoon (plural spermatozoa) is termed spermiogenesis. This process involves morphological changes to develop an acrosome (a membranous organelle that contains proteolytic enzymes, which aids penetration of the egg) and flagellum (the sperm tail), nuclear condensation (which effectively protects the genetic material) and cytoplasmic extrusion. Release of a mature spermatozoon by the Sertoli cell is an active process termed spermiation.

The cycle and stages of spermatogenesis. In humans, the entire sequence of spermatogenesis from spermatogonia to spermatozoa takes about 64 days[89]. A new sequence can initiate in the individual spermatogonia before the previous wave or cycle of spermatogenesis is complete. These groupings of cells are known as stages in the cycle of the seminiferous epithelium[90]. In humans, spermatogenesis is divided into six stages of defined cell associations (I–VI) and six spermatid developmental steps that occur in the seminiferous tubule in a random mosaic pattern (Fig. 4). The development of a new generation of germ cells from spermatogonial stem cells is connected in a specified manner with the development of the preceding generation of germ cells. Figure 4 shows the heterogeneous architecture of the seminiferous tubules and cell associations, as well as the different cellular complements at various stages of spermatogenesis.

Leydig cells and androgens in men. In men, androgen production (that is, production of the steroid hormone testosterone, primarily by the Leydig cells of the testis) is pivotal to spermatogenesis and male reproduction and sexual function[91,92]. The concentration of testosterone in the testis is considerably higher than in the serum, with one study detecting concentrations >80-fold higher in the testis[93,94]. Testosterone production is mediated by the hypothalamic–pituitary–gonadal (HPG) axis under the control of gonadotropin-releasing hormone (GnRH), LH and FSH. GnRH is released by the hypothalamus in pulses into the portal blood, where it stimulates production of LH and FSH in the anterior pituitary gland. The testosterone produced then provides negative feedback to the hypothalamus and the pituitary gland, reducing their release of LH and FSH.

Testicular function is largely dependent on the tightly regulated communication and stimulation from the pituitary gland. For example, patients who use exogenous androgens such as anabolic steroids have an anabolic steroid-induced hypogonadism that results in suppression of LH and FSH release[95]. The decreased FSH and LH levels adversely affect testicular function (that is, Sertoli and Leydig cell function) and ultimately testosterone production and spermatogenesis[96–98]. Despite this suppression, patients taking exogenous androgens will typically see a return of spermatogenesis after cessation of anabolic steroid use and reactivation of the HPG axis[95]. The use of exogenous androgens can have a profound effect on fertility. Multiple trials using various testosterone preparations for testosterone therapy demonstrate a

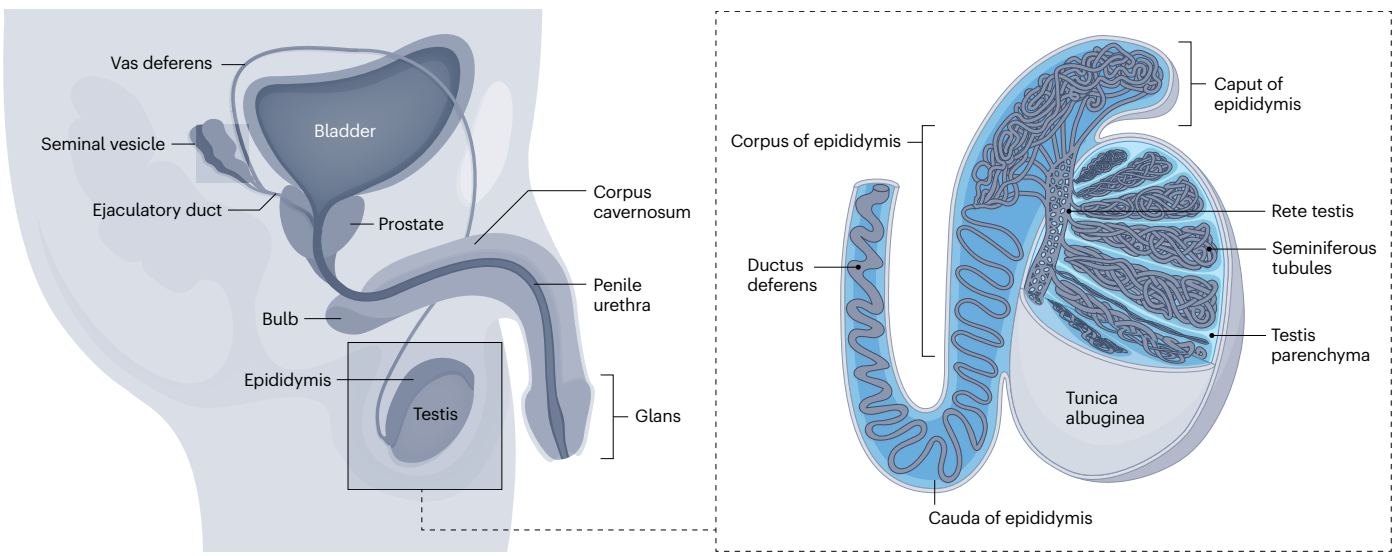


Fig. 2 | Anatomy of the male reproductive tract. Spermatogenesis occurs in the testis. Sperm then moves through the rete testis to the epididymis where sperm maturation is completed. Sperm then traverses the vas deferens against gravity into the pelvis. Sperm is stored in the ampulla of the vas deferens until ejaculation. On ejaculation, fluid from the vasa deferentia and prostate are expelled into the posterior urethra followed by fluid from the seminal vesicles. The ejaculate is then expelled from the urethra.

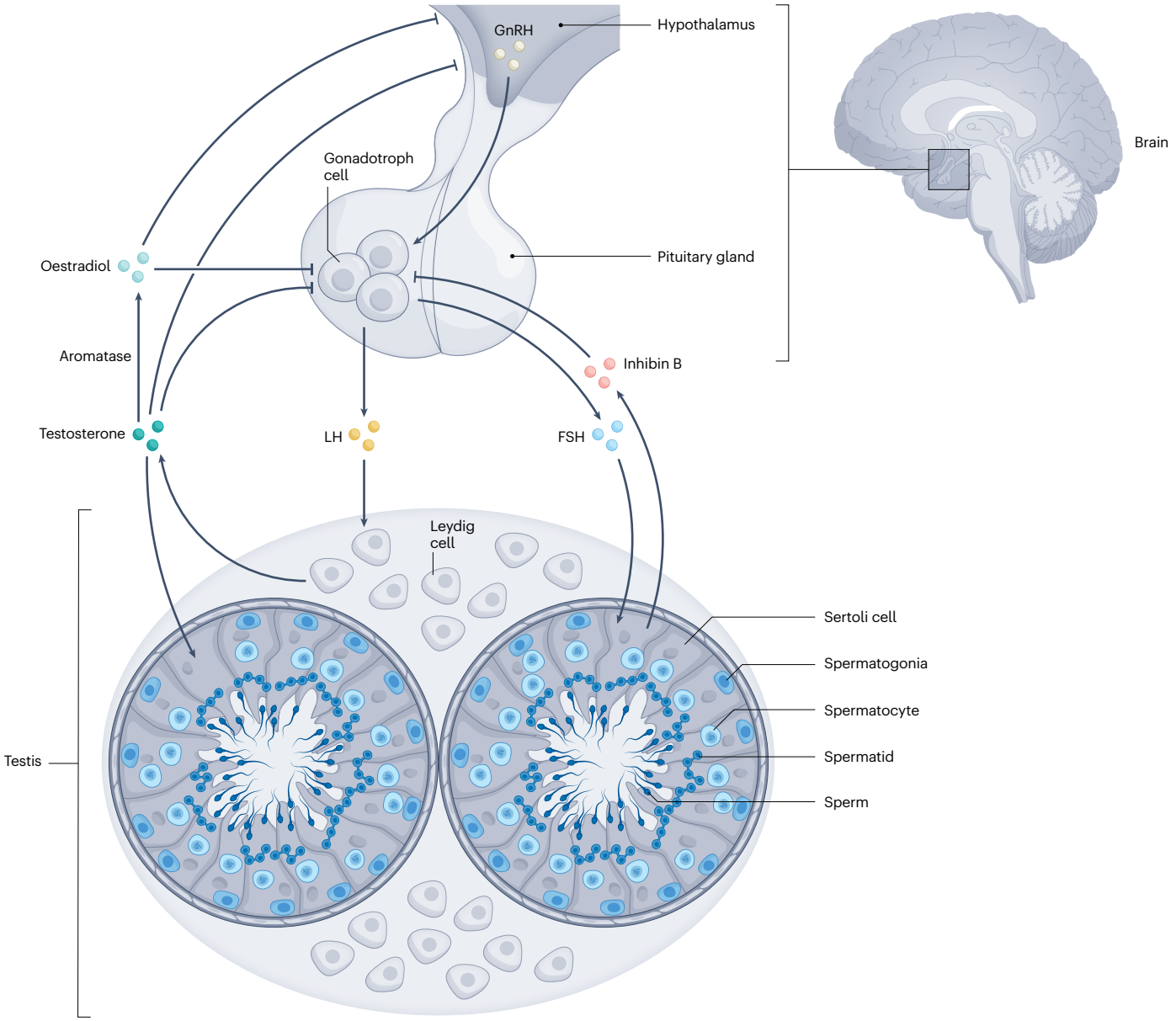


Fig. 3 | The role of the hypothalamic–pituitary–gonadal axis in male fertility. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary gland to secrete the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH stimulates the Leydig cells in the testis to produce testosterone. FSH stimulates Sertoli cells to induce spermatogenesis. Negative feedback from the testes to the hypothalamus and pituitary occurs through the production of inhibin by Sertoli cells and testosterone (via peripheral conversion into oestradiol).

median time to spermatogenesis suppression to <1 million sperm per millilitre of 3.5 months[99]. The same data demonstrate a median time to recovery (~3–6 months) before achieving 20 million sperm per millilitre after discontinuation of the testosterone therapy. Data also suggest that older age, longer duration of testosterone therapy and Asian ethnicity might result in a reduced likelihood of recovery of sperm in the ejaculate after cessation of testosterone therapy[99–102]. Spontaneous recovery of spermatogenesis after cessation of testosterone therapy is certainly possible but is unpredictable and may not always occur.

Exposures leading to dysfunction. There are several exposures that influence spermatogenesis and the ultrasensitive germ cells. Rapidly dividing cells such as spermatogenic cells in the testis are highly sensitive to the gonadotoxic effects of radiation and some chemotherapy treatments. Consequently, many of the treatments that target cancer result in impaired fertility[103]. Chemotherapeutic agents may cross the blood–testis barrier, putting testicular tissue at risk of harmful effects. These treatments and individual agents, particularly the alkylators, act in an aggregate manner and their effects are dependent on treatment dosage and duration[104]. Men are generally counselled to wait at least

12 months after gonadotoxic exposure before attempting to conceive with ejaculated sperm, to allow adequate spermatogenic cycles to 'wash out' residual damage[80]. Radiation doses start to negatively impact spermatogenesis at 0.1–1.2 Gy, with irreversible damage at a dose of 4 Gy[105].

Importance of paternal ageing. For centuries, it has been appreciated that there is a natural end to a woman's fertility when menopause occurs. Although the biological potential for paternity persists as men continue to produce sperm throughout their adult lifespan, a man's reproductive health also declines with age. Indeed, it is now recognized that there is a major contribution of the ageing male gamete to reproductive outcomes. A common effect of ageing in men is male hypogonadism resulting from a progressive decline in testosterone level beginning in the third or fourth decade of life and continuing throughout the entire lifespan[106]. Associated with this decline is a decline in all semen parameters (volume, sperm count, morphology, concentration and motility, as well as an increase in DNA fragmentation and sperm aneuploidies)[107,108]. Pregnancy complications occur at a higher rate in female partners of older men than in those of younger men, as do poor obstetric outcomes (low birthweight, increased risk of pre-term birth and late still-birth)[109]. After controlling for maternal age, partners of older men (in one study defined as >35 years of age) are also at higher risk of miscarriage than those of younger men, for both natural conceptions and those achieved with ART[109].

An adverse effect of advanced paternal age was first noted more than 100 years ago by Wilhelm Weinberg in 1912, who noted that the last-born children in the German city where he worked were more likely to have achondroplasia (a form of dwarfism) — a concept more clearly defined by Penrose in 1955 (ref. 110) and Krooth in 1953 (ref. 111,112). In 2012, paternal age effect (PAE) disorders were officially described as genetic conditions caused by a bias in paternal origin of mutations, with a strong PAE and high germline mutation rate (reviewed eslewhere[109]). In addition to achondroplasia, other adverse health risks in offspring that are associated with advanced paternal age and for which there are strong levels of evidence include osteogenesis imperfecta, neurofibromatosis type 1, Marfan syndrome, cleft palate, acute lymphocytic leukaemia, schizophrenia and/or psychosis and autism spectrum disorder[109]; many other conditions have been reported in the literature.

The mechanisms of the adverse health outcomes of paternal ageing have been investigated. An analysis of genome-wide patterns and properties of de novo mutations in 250 families by whole-genome sequencing identified slightly more than 11,000 de novo mutations, which were far more numerous in children of older fathers than in those of younger fathers[113]. Offspring of 40-year-old fathers had twice as many mutations in coding regions of genes than offspring of 20-year-old fathers. Most new mutations in offspring are of paternal origin, and the number of de novo mutations increases by about 2 for each year of increased paternal age, given the constant cell replication that occurs during spermatogenesis[114] (Fig. 5). Indeed, paternal age explains 95% of the variation in global mutation rate in the human population. By contrast, the maternal germline mutation rate is about 25% of that in men[115].

Accordingly, recent male reproductive guidelines advocate counselling couples in which the man is 40 years of age or older about the risks to the pregnancy and child from advanced male age[3].

Diagnosis, screening and prevention

Complete clinical evaluation of infertile men includes detailed history taking, focused physical examination and selective laboratory testing, including semen analysis[116,117]. Importantly, the complete enquiry for infertile men should include sexual and reproductive history, history of genitourinary infections, childhood development and illness[118], surgical history, systemic medical illness and notification of relevant family history (for example, cystic fibrosis), lifestyle and current medical conditions including potential gonadotoxic treatments or medications[119,120].

Surgical history

Some surgical procedures might disrupt the physiological regulation of male reproductive function or the anatomical integrity of the genital tract. For example, brain or pituitary surgery or trauma might interfere with regulation of the HPG axis (Fig. 3), decreasing testicular gonadotropic stimulation of spermatogenesis and testosterone production[121]. In addition, spinal cord injury and pelvic or retroperitoneal surgery could

Table 1 | The major organs, cell types, hormones, paracrine factors and receptors that regulate human spermatogenesis

Organ	Cell type	Receptor	Major hormones produced
Hypothalamus	GnRH-producing neurons	GnRH receptor	GnRH
Hypothalamus, pre-optic nucleus, amygdala	GnRH-producing neurons	Androgen receptor Oestrogen receptor	GnRH
Pituitary gland	Gonadotrophs	GnRH	Follicle-stimulating hormone Luteinizing hormone
Testis	Sertoli cells	Follicle-stimulating hormone receptor Androgen receptor Oestrogen receptor, thyroid hormone receptor, relaxin receptor	Inhibin B Mullerian inhibiting substance
	Leydig cells	Luteinizing hormone receptor Prolactin receptor Growth factor receptor Insulin and insulin-like growth factor receptors Fibroblast growth factor receptors Platelet-derived growth factor receptor-α (fetal)	Testosterone Insulin-like growth factor 3

GnRH, gonadotropin-releasing hormone.

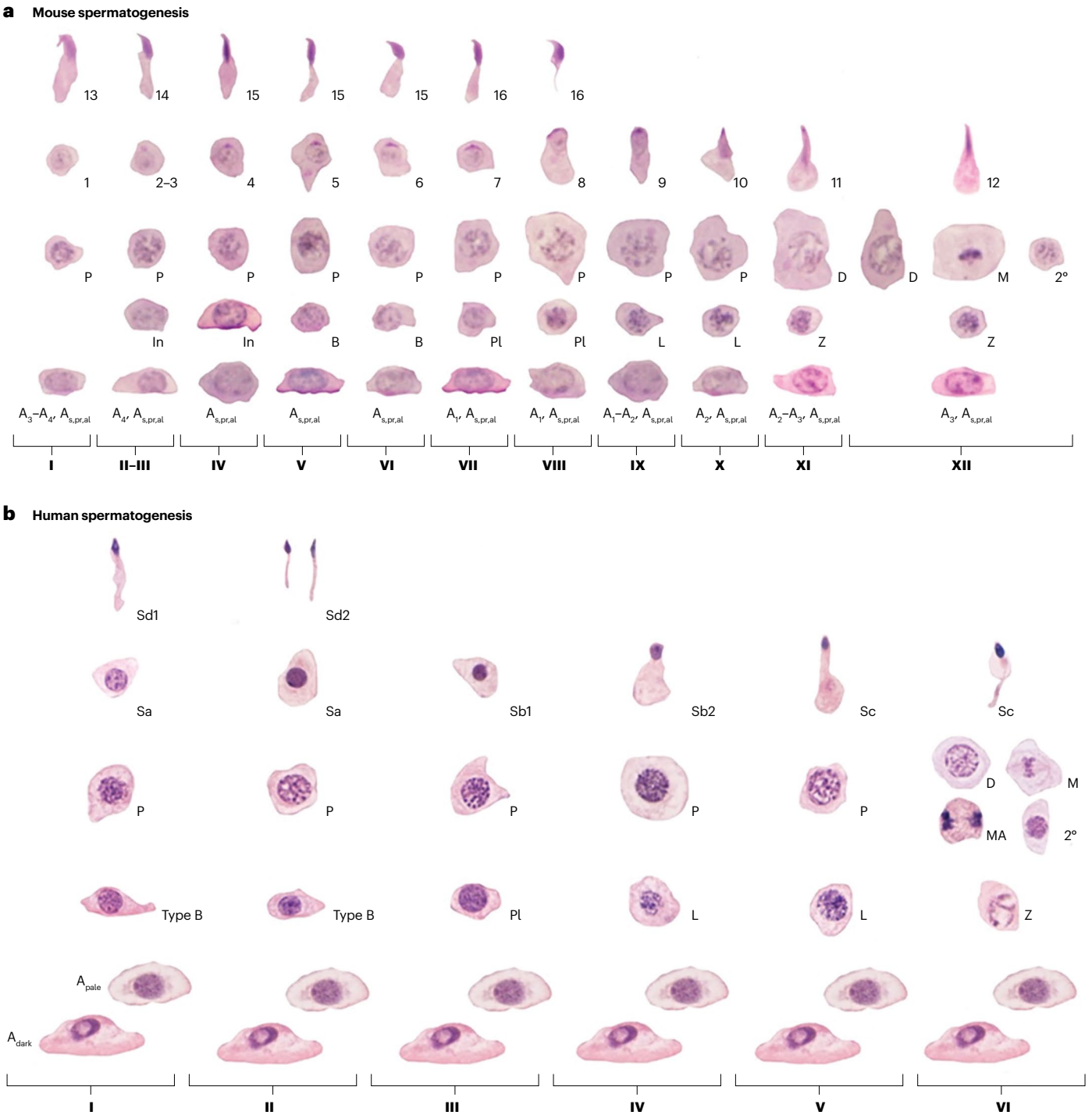


Fig. 4 | Stages of spermatogenesis in mice and humans. a,**b**, Stages of spermatogenesis in mouse and human based on germ cell associations and morphology. Sections of mouse and human testes are stained with periodic acid–Schiff reagent (PAS)–haematoxylin. Spermatogenesis is the process of sperm development and involves phases of mitosis, meiosis and spermiogenesis (morphological cell changes). Spermatogenesis is divided into 12 stages (I–XII) and 16 spermatid developmental steps (1–16) in mice (part **a**) and six stages (I–VI) and six spermatid developmental steps (Sa, Sb1, Sb2, Sc, Sd1 and Sd2) in humans (part **b**). 2°, secondary spermatocytes; MA, meiotic anaphase; A, type A spermatogonia; A_{al}, A-aligned spermatogonia; A_{dark}, type A dark spermatogonia; A_{pale}, type A pale spermatogonia; A_{pr}, A-paired spermatogonia; A_{s}, A-single spermatogonia; B, type B spermatogonia; D, diplotene; In, intermediate spermatogonia; L, leptotene; M, meiotic metaphase; P, pachytene; Pl, preleptotene; Z, zygotene. Adapted with permission from ref. 82, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

impair penile erection and ejaculatory function by disrupting normal physiological reflex pathways[122,123]. Prostatic surgery might result in retrograde ejaculation through impairment of bladder neck coaptation or emission. Of note, inguinal hernia repair could inadvertently injure the vas deferens or compromise its blood supply or its luminal patency as a result of local adhesive fibrosis associated with the mesh, subsequently leading to vasal obstruction. In addition, scrotal procedures (such as hydrocelectomy, orchidopexy and spermatocelectomy) might cause injury and genital tract obstruction at the level of the vas deferens or epididymis. Moreover, prior testicular trauma or torsion might also cause genital tract obstruction or lead to testicular scarring and atrophy.

Systemic medical illness

Systemic medical conditions should also be identified as they or their treatment might impact male fertility. For example, men with diabetes mellitus or multiple sclerosis might have erectile or ejaculatory dysfunction[124,125]. In addition, treatment for some conditions might also impair male fertility. α-Blockers for the treatment of lower urinary tract symptoms and 5α-reductase inhibitors for the treatment of benign prostatic hyperplasia and male pattern hair loss can impede ejaculation or spermatogenesis[126–128]. Testosterone therapy can also lower sperm production[99,127]. Given the sensitivity of sperm production to temperature, a febrile illness can impair spermatogenesis for up to 3 months even if it does not directly involve the genitourinary tract[129,130]. Men with renal failure can have infertility due to several factors, such as hypogonadism, erectile dysfunction and lower sperm concentrations[131,132]. Some cancers and their treatments might also affect male fertility. Testicular cancer, lymphoma and leukaemia are associated with lower semen quality even before treatment[133,134]. Furthermore, prescribed chemotherapy or radiotherapy for these conditions or other malignancies might disrupt spermatogenesis and result in azoospermia. Although sperm production can return, it might take years after the completion of treatment and will depend on the specific treatment protocol[80,135,136]. When possible, these men are counselled about the importance of pretreatment sperm cryopreservation[80].

Lifestyle

Clinicians should be aware that some lifestyles can have a negative impact on male reproduction. For example, smoking increases oxidative stress and DNA adduct formation (and DNA fragmentation and damage), which can result in semen impairment and miscarriage[137]. Although moderate alcohol intake has not been shown to affect sperm production in most men, heavy use or use by men with genetic susceptibility might pose a risk to male fertility[138–140]. In addition, marijuana use has been inconsistently associated with semen quality[141,142].

Obesity can interfere with the HPG axis and lead to detrimental effects on spermatogenesis, subsequently resulting in infertility[143,144]. Although physical training or weight loss seem to have a positive or neutral effect on semen parameters in some studies[145–149], others do not consistently support improvement[150–152]. Moreover, it is important to notice any occupational or environmental exposure to gonadotoxins such as pesticides, heavy metals or other chemicals because these substances may harm spermatogenesis[153,154]. Scrotal heat exposure (for example, in saunas and hot tubs) impairs spermatogenesis[155]. Interestingly, the modern lifestyle characterized by long-term working on laptop computers in a laptop position might elevate scrotal temperature and impair spermatogenesis[156].

Medications

In addition to cytotoxic drugs, other pharmacological treatments that negatively affect male fertility through various mechanisms must be addressed. These drugs can directly or indirectly lead to sexual dysfunction and alterations in epididymal maturation by interfering with the HPG axis or by nonhormonal mechanisms. Testosterone, anabolic steroids and cyproterone acetate could substantially suppress spermatogenesis and result in oligozoospermia or even azoospermia, which are usually but not always reversible after the discontinuation of these agents[91,157,158] (Fig. 3). Chronic use of opioids can also impair the HPG axis, resulting in reproductive dysfunction[159]. The use of 5α-reductase inhibitors (treatment for voiding symptoms or alopecia) decreases dihydrotestosterone (DHT) and might impair sperm count and motility as well as impair ejaculation[160]. α-Blockers (used for voiding dysfunction or hypertension) may also induce ejaculatory disorders, such as retrograde ejaculation or anejaculation[161]. Selective serotonin reuptake inhibitors (used for treatment of depression) can lead to sexual dysfunction, ejaculatory dysfunction and increased sperm DNA fragmentation[162,163]. Chronic use of sulfasalazine for treating inflammatory bowel disease has been associated with oligoasthenozoospermia[164].

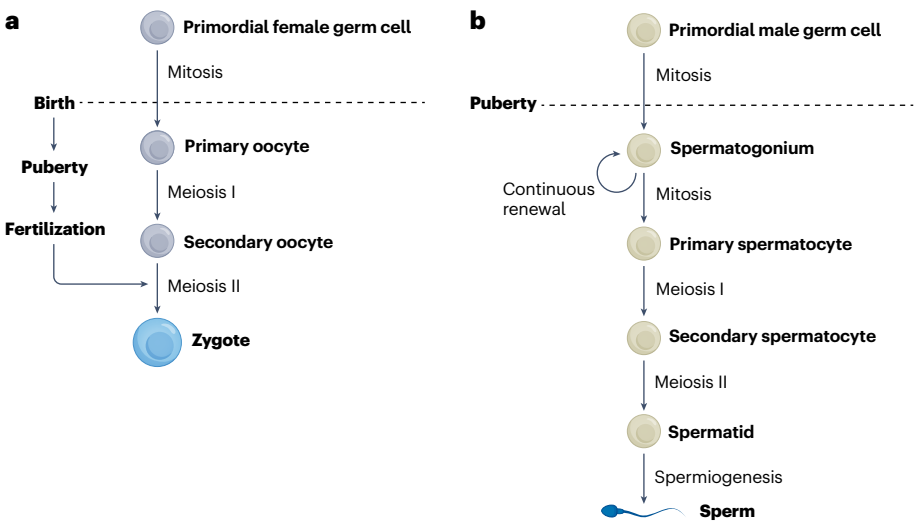


Fig. 5 | Gametogenesis in humans. a, Oogenesis. All possible oocytes are produced by the time of birth, so that only meiotic divisions occur thereafter. **b**, Spermatogenesis is continuous, so that with ageing the number of total chromosome replication events (and opportunities for errors) increases.

Table 2 | WHO semen analysis lower reference limits

Parameter	Reference limits (95% CI)	
	5th edition	6th edition
Semen volume (ml)	1.5 (1.4–1.7)	1.4 (1.3–1.5)
Sperm concentration (10^6 per ml)	15 (12–16)	16 (15–18)
Total sperm number (10^6 per ejaculate)	39 (33–46)	39 (35–40)
Total motility (PR+NP, %)	40 (38–42)	42 (40–43)
Progressive motility (PR, %)	32 (31–34)	30 (29–31)
Morphology (normal forms by strict criteria, %)	4 (3.0–4.0)	4 (3.9–4.0)
Vitality (%)	58 (55–63)	54 (50–56)
Other consensus threshold values		
pH	>7.2	>7.2
Peroxidase-positive leukocytes (10^6 per ml)	<1.0	<1.0

Semen parameters for the lowest 5% of fathers evaluated, for the 5th (published in 2010) and 6th (published in 2021) editions of the *WHO Laboratory Manual for the Examination and Processing of Human Semen*[14,302]. The lower 5th percentile represents the level below which only results from 5% of the men in the reference population were determined. CI, confidence interval; NP, non-progressive motility; PR, progressive motility.

However, most other medications for inflammatory bowel disease are not associated with impaired male fertility[165]. Sirolimus (used to prevent organ transplant rejection) could lower intratesticular testosterone levels and block spermatogenesis[166,167]. Sperm cryopreservation should be considered before the initiation of gonadotoxic therapies (such as testosterone, sulfasalazine, GnRH analogues and sirolimus), especially if long-term exposure is anticipated, as the adverse effects on sperm quality might be irreversible[168].

Physical examination

A complete physical examination of an infertile man should not be limited to a genital examination but should also include a detailed general examination[119]. A body habitus with a eunuchoid appearance, abnormalities of the secondary sex characteristics and changes in the pattern of virilization might indicate a congenital endocrine disorder such as KS. Gynaecomastia suggests an imbalance between oestrogen and androgen levels or increased prolactin levels[169].

Nevertheless, a detailed genital examination is a key part of evaluating male infertility and can help to identify potential causes. The entire genital area should be inspected for any findings suggestive of sexually transmitted diseases. The penis should be examined for any curvature or palpable plaques. The urethral opening should be located because hypospadias with severe penile curvature could interfere with the normal delivery of semen into the vagina. A scrotal examination should be performed. The testis should be carefully palpated to assess its consistency and rule out any intratesticular mass[170]. Testicular volume could be assessed by orchidometer[119]. Testicular volumes of 20 ml are adequate for white and African-American men[171], whereas Asian men normally have smaller testicles but higher sperm production per cubic centimetre, which may help to explain known variations in semen parameters by race or ethnicity[172]. Decreased testicular size, either unilateral or bilateral, might be associated with impaired spermatogenesis[173]. The epididymis is located on the posterior-lateral side of the testicle. It is essential to determine the presence of the epididymal head, body and tail. Palpable induration (thickening and hardening) or fullness of the epididymis suggests epididymal obstruction. In addition, the vasa deferentia must be carefully palpated to ensure that each vas deferens is present and to exclude areas of atresia. The presence of any masses should be noted. Moreover, transillumination helps to confirm cystic versus solid lesions. Finally, special attention should be paid to examining the spermatic cord, as it might reveal the presence of a varicocele, the most common correctable cause of male factor infertility (MFI)[174,175].

Laboratory assessment

Semen analysis. A semen analysis (or semen examination) remains the cornerstone of the laboratory evaluation of infertile men. However, it is important to remember that the quality (accuracy and precision, reliability) of semen analysis test results varies widely between clinical diagnostic laboratories. It is well recognized in the literature that some clinical diagnostic laboratories performing semen analysis that claim to follow the WHO manual procedures do not perform the laboratory procedures detailed in the WHO manual correctly, and this failure is even found in some publications claiming to do so[17]. Major deficiencies in the laboratory operational procedures (methodologies), personnel training, internal quality control and external proficiency assessments are present. Accordingly, despite the detailed information and methodologies described in the WHO manual for semen examination and the recent International Organization for Standardization 23162:2021 standard[14], the semen analysis remains among the most variable tests performed. Although not a perfect measure of fertility potential, the chances of pregnancy through intercourse are lower when the primary semen parameters (that is, sperm concentration, motility and morphology) are poor and higher when the semen parameters are adequate[8–11,176]. Sperm count or total motile sperm count (TMSC) may be a better marker to predict fertility than any parameter individually[177]. Semen volume can provide information about ejaculation and regarding the possibility of pathology such as ejaculatory duct obstruction or retrograde ejaculation. The interpretation of the semen analysis is based on reference ranges suggested by the WHO, which define reference ranges using the principles of clinical chemistry used for quantitative laboratory results to enable normal values to be distinguished from abnormal values of the semen parameters, not fertilizing potential (Table 2). Importantly, the values do not distinguish fertile from infertile men unless the ejaculate is azoospermic or there is a severe morphology defect (such as globozoospermia or macrozoospermia) or total immotility.

Endocrine evaluation. An endocrine assessment of serum FSH and testosterone is not recommended as the routine laboratory test for all infertile men but is required if oligozoospermia (<10 million sperm per millilitre) or azoospermia is present[3]. Hypergonadotropic hypogonadism is usually present in men with testicular deficiency. Generally, FSH levels negatively correlate with the number of spermatogonia[178]. Further LH evaluation is indicated in infertile men with low serum testosterone to determine whether the source is testicular (primary hypogonadism) or pituitary (secondary hypogonadism). Prolactin evaluation is indicated in infertile men with hypogonadotropic hypogonadism or low libido[3]. The finding of high prolactin levels should be further evaluated with an endocrine evaluation and cranial imaging to determine whether a pituitary lesion is present.

Genetics studies. Clinicians should be aware of the common genetic abnormalities associated with male infertility to provide accurate advice to couples seeking fertility treatment. Compared with the general population, patients with severe oligozoospermia (sperm

count <5 million/ml) have a 10-fold higher risk of having an autosomal structural abnormality[179,180]. In a survey of pooled data from 9,766 infertile men, the incidence of chromosomal abnormalities was 5.8%. Of these, sex chromosome abnormalities (KS and variants (47,XXY; 46,XY/47,XX mosaicism)) accounted for 4.2% and autosomal abnormalities for 1.5%[181].

In addition, Y-chromosome microdeletions are present in 8–12% of men with azoospermia and 3–7% of men with oligozoospermia[182]. Three regions of the Y chromosome seem to be particularly sensitive to deletions: AZFa, AZFb and AZFc. AZFc region deletions are most common (65–70%), followed by AZFb and AZFb + c or AZFa + b + c regions (25–30%). Isolated AZFa region deletions are rare (5%)[183]. Therefore, karyotype and Y-chromosome microdeletion analysis are recommended for men with a sperm concentration <5 million/ml (ref. 3).

Cystic fibrosis, the most common genetic disease of people of European descent (~1/25 carrier prevalence), is an autosomal-recessive disorder[184]. *CFTR* gene alteration might lead to CBAVD[75]. Unilateral absence of the vas deferens is also possible. Clinicians should recommend *CFTR* mutation testing (including assessment of the 5T allele) in men without palpable vasa deferentia or with idiopathic obstructive azoospermia[3]. *CFTR* evaluation of female partners and genetic counselling should be recommended for men with *CFTR* mutations, given the risk of an affected child through conception via ART[3].

Selective imaging. Imaging is indicated in selected cases of male infertility (see below). Scrotal ultrasonography can help with a difficult exam due to patient body habitus that impairs visualization or examination of the scrotum or to gather additional anatomical information[185]. Scrotal ultrasonography can also provide valuable information on testicular size, vascularity, parenchymal oedema, microlithiasis, testicular cysts, tumours, infarcts or scars, epididymal lesions and epididymitis, hydroceles and varicoceles (Fig. 6). Transrectal ultrasonography is an excellent procedure for imaging of the seminal vesicles, vasa deferentia, ejaculatory ducts and prostate in men with findings suggestive of ejaculatory duct obstruction (that is, low ejaculate azoospermia, acidic ejaculate and ejaculatory pain). Because MRI has excellent contrast resolution and reliability to assess vascularity, it becomes a valuable supplement to ultrasonography for imaging of indeterminate testicular lesions, suspected ejaculatory duct obstruction (Fig. 7) and prostatic nodules[119]. Retroperitoneal ultrasonography is indicated in men with vasal agenesis given the increased prevalence of associated renal abnormalities[3,186,187].

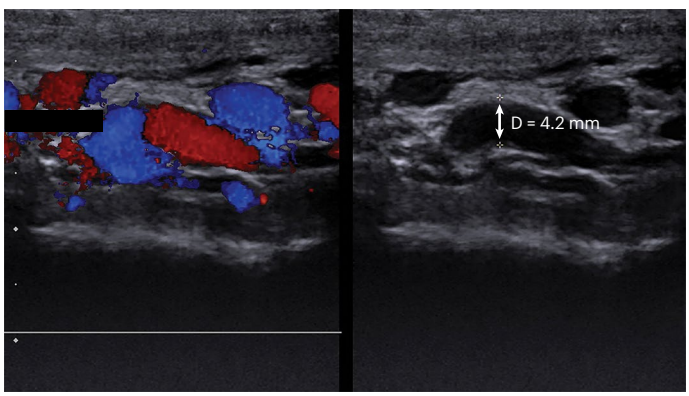


Fig. 6 | Scrotal ultrasonography for measurement of spermatic veins. The ultrasonography images demonstrate dilated spermatic veins. A diameter (D) of >3 mm (here 4.2 mm; double-headed arrow) is diagnostic of a varicocele based on imaging criteria. The panel on the right is the grey-scale image, and the left panel shows colour images representing blood flow direction (red indicates flow towards the probe and blue away from the probe, not venous versus arterial blood).

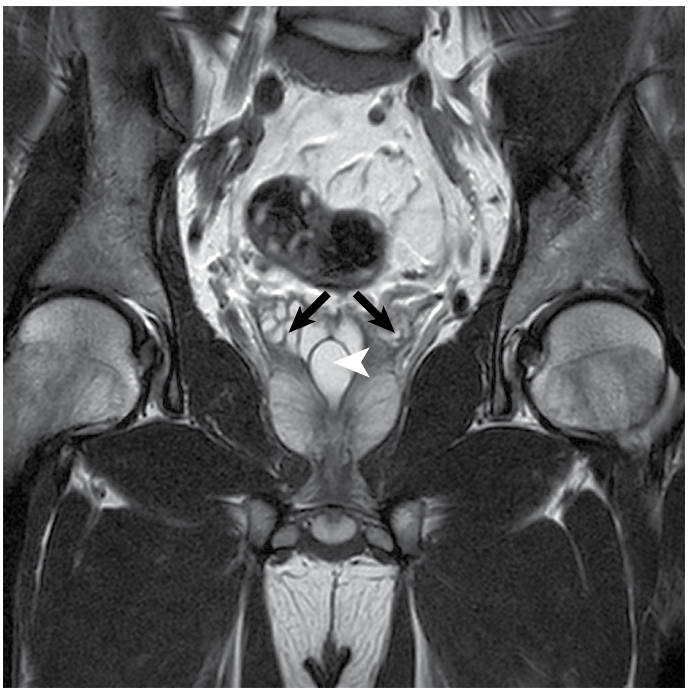


Fig. 7 | MRI assessment of male pelvic anatomy. The MRI T2 image indicates a hyperintensity prostatic utricle cyst (arrowhead) causing ejaculatory duct obstruction and subsequent bilateral seminal vesicle dilatation (arrows).

Management

Personalized MFI treatment lags 15 or more years behind interventions designed to optimize female fertility despite a male factor being implicated in 50% of all infertility cases and being solely responsible in 20%[14,188]. Despite this gap, there are still multiple proven modalities that can optimize a man's reproductive potential, yet 27% of male partners of couples struggling with infertility are not offered treatment[7]. Although ART can circumvent MFI, it can also minimize the importance of treatment to optimize men's reproductive health for ART and other therapies and is a lost opportunity to identify serious underlying medical conditions that cause infertility[189–192].

In the ensuing discussion we first cover treatments that can be implemented for all types of male infertility and then treatments for specific types in more detail. Treatments for MFI all begin with lifestyle optimization and proceed with medical and then surgical therapies. The goal of all these treatments is to optimize male reproductive potential through improvement of TMSC, which can improve all aspects of male reproduction, including IVF and ICSI[193–195].

General treatments

Lifestyle interventions. Lifestyle and environmental exposures have an important role in MFI and often can be easily addressed through low-cost interventions, although guidelines make mixed

recommendations based on differences in the efficacy of these interventions[3]. An initial evaluation often identifies factors such as poor diet, elevated BMI, sexual dysfunction or environmental exposures that can be easily addressed. Diet has a considerable effect in spermatogenesis, given the high-throughput nature of human spermatogenesis, which generates approximately 1,000 sperm per second. The Western diet commonly found in countries such as the USA has resulted in 42% of the population being obese (that is, BMI >30)[196]. Both obesity and its associated metabolic derangements can markedly affect spermatogenesis, with decreased testosterone, elevated oestradiol and disruption of the leptin–ghrellin axis (that is, hormones involved in satiety and appetite) all negatively affecting spermatogenesis[197,198].

Diet and exercise can substantially improve sperm parameters. Although men seek health care at lower rates than women, they are actually more likely to have success with weight loss efforts[199,200]. Weight loss can be achieved by many modalities but regular lifestyle coaching (that is, diet and exercise), referral to a bariatric centre for medical or surgical interventions or enrolment in a structured programme of diet and/or exercise can be effective[149]. Weight loss can improve endocrine parameters, treat erectile dysfunction and improve TMSC, metabolic derangements in offspring, mitochondrial function, DNA fragmentation and epigenetic profile as well as increase sperm retrieval rates on micro-testicular sperm extraction (microTESE)[201–204].

Macronutrients are also important and there are ample data that eating a diet high in fruits, vegetables and healthy protein and low in sugar and both processed and ultra-processsed food can improve semen profiles[205]. A large systematic review in 2018 of 1,944 articles selected 35 for qualitative analysis[206] and found that diets rich in foods high in macronutrients such as omega-3 fatty acids and in antioxidants and low in saturated and trans fatty acids were associated with improved sperm parameters. Conversely, high sugar, processed meat, soy foods, full-fat dairy products, alcohol and sugar-sweetened beverages were all associated with worsened sperm parameters. The role of supplements for male infertilty remains controversial and it is not clear that there is a substantial benefit from supplements[207–209]. The largest trial of supplements, the prospective, blinded, randomized, controlled Folic Acid and Zinc Supplementation Trial (FAZST) of more than 2,370 men found that use of these supplements did not improve sperm parameters[210].

Limiting environmental exposures. Reduction in environmental toxins and in exposure to scrotal heat have been shown to improve sperm parameters[142,211]. Environmental exposures, such as pesticides, pthalates, plasticizers, bisphenol A, industrial solvents, air pollution, scrotal heat and ionizing radiation, reduce sperm counts and worsen genetic and epigenetic sperm parameters, and reducing these exposures represents a simple intervention[3,80,212–215]. Smoking cessation and reduction of recreational use of drugs such as marijuana and cocaine might also improve sperm parameters[142,211]. The data on exposure to non-ionizing radiofrequency radiation from WiFi and cellular networks remain mixed, but these exposures are generally considered to be safe[216].

Sexual dysfunction is very common in men with infertility and occurs in about 20% of men seeking infertility care[217]. Erectile dysfunction and premature ejaculation are commonly found and can be readily treated through phosphodiesterase type 5 inhibitors (PDE5i, such as sildenafil), injection therapy or a penile prosthesis for erectile dysfunction. Premature ejaculation can be addressed through sex therapy, topical lidocaine-based therapies or SSRIs. Anejaculation can sometimes be addressed through sex therapy or medical therapy, although often treatment is surgical sperm extraction[218].

Focused therapy

If possible, withdrawal of common spermatotoxic medications (such as testosterone, sirolimus and sulfasalazine) should be standard of care in optimizing male reproductive potential. An exhaustive review of these medications is beyond the scope of this Primer but an excellent summary can be found elsewhere[168,219].

Pharmacological treatments. Currently, there are no FDA-approved medications to treat male infertility. However, there are several medications with proven efficacy. For men with some diagnosed hormonal abnormalities, targeted treatment might be appropriate. Hypogonadism is common in infertile men and is correctable through medications to optimize the endocrine axis and improve spermatogenesis. For example, men with hypogonadotropic hypogonadism might be treated successfully with gonadotropin therapy (for example, human chorionic gonadotropin (HCG) alone or in combination with FSH)[80]. In addition, men with hyperprolactinaemia due to a prolactinoma can respond to dopamine antagonist therapy (for example, cabergoline) to lower prolactin secretion and restore normal pituitary signalling and testicular function[220].

In addition to targeted therapies, several medications are also used empirically[221,222]. Multiple society guidelines recommend evaluating a targeted hormone panel and treating accordingly[3,80]. Selective oestrogen receptor modulators (SERMS; such as clomiphene citrate) or aromatase inhibitors (such as anastrozole) have been described. By inhibiting feedback inhition of the HPG axis, increased production of gonadotropins might stimulate testicular function (Fig. 3). Alternatively, treatment with gonadotropins (such as HCG or FSH) can be used to directly stimulate the testes[223,224]. For men with a specific pathology leading to endocrinopathy, tailored treatments can be recommended. For example, if a prolactinoma is discovered based on laboratory abnormalities and brain MRI findings, dopamine agonist (for example, cabergoline) and referral to an endocrinologist are indicated[220].

A potential medical therapy for ejaculatory dysfunction (for example, retrograde ejaculation or anejaculation) is pseudoephedrine (a sympathomimetic that can enhance ejaculate deposition into the urethra)[80], which can be combined with alkalinization of the urine before catheterization with medium to obtain viable sperm for intrauterine insemination (IUI)[80].

Surgical therapy. Surgical therapy for male infertility can be categorized as surgeries to optimize spermatogenesis, to obtain sperm for natural conception, IUI or IVF and ICSI, or to improve sperm transport[3,13,80,225]. Varicocele is the most common cause of male inferitlity (~40% of cases)[226]. Surgical varicocelectomy is favoured in most countries or regions given its low morbidity and favourable efficacy[3,80,227] (Fig. 8).

Procedures to obtain sperm can be catgorized as those for treatment of obstructive azoospermia and those for NOA treatment. Obstructive azoospermia is typically treated with surgical sperm extraction using one of several techniques: percutaneous sperm extraction from the testis using testicular sperm aspiration (TESA), percutaneous epididymal sperm aspiration (PESA) or TESE, or microsurgical epididymal sperm aspiration (MESA). These procedures approach 100% efficacy in men without signs of spermatogenic failure and clear

causes of obstruction (for example, prior vasectomy, CBAVD) and can often provide ample sperm for IVF and cryopreservation to facilitate multiple IVF attempts if desired[3,80,228]. Surgical sperm extraction may also be indicated in the setting of high DNA fragmentation in ejaculated sperm and prior failed IVF[229]. Electroejaculation is also a viable option for patients with spinal cord injury or psychogenic ejaculatory dysfunction whereby electrical stimulation can allow collection of ejaculated sperm. Depending on the anatomical level of spinal cord injury, this procedure can be performed in the clinic, but patients must be monitored for autonomic dysreflexia (abnormal overreaction of the autonomic nervous system to stimulation, which can result in nausea, headache or haemodynamic changes). Vibratory stimulation also remains another option for men with spinal cord injury[230,231].

Genital tract reconstruction and vasectomy reversal (vasovasostomy or vasoepididymostomy) are also excellent options for men who have had either surgery or trauma that causes obstruction (for example, inguinal hernia repair), a vasectomy or for some forms of congenital obstruction. In cases where the vasal obstruction can be identified and sperm is confirmed in vasal fluid proximal to the blockage, a microsurgical vasovasostomy can be performed with success rates higher than 90%[232]. If no sperm are present in the vasal fluid proximal to the blockage, a epididymovasostomy is indicated, in which an intussesception technique is used to connect the abdominal end of the vas deferens to the epididymis after verifying that the epididymal fluid has sperm; success rates are around 60–70%[232]. Simultaneous surgical sperm extraction can also be performed with these procedures to cryopreserve sperm for future use in IVF with ICSI[228,232,233].

Other procedures, such as transurethral resection of the ejaculatory ducts (TURED), can be performed to treat ejaculatory duct obstruction and allow natural pregnancy through an endoscopic resection of the ejaculatory ducts performed under direct vision[234–236]. Balloon dilation of the ejaculatory ducts may also provide additional treatment for genital tract obstruction[237].

For men with NOA, a microTESE is indicated to maximize the efficiency of sperm identification (up to 50% in most series)[80,238,239]. This procedure involves opening the testis under surgical microscope magnification (~×10–20 magnification) and then examining each seminiferous tubule to identify those that may have viable sperm that can be used for IVF with ICSI. Magnification allows identification of larger, more opaque, tubules, which is characteristic of tubules containing intact spermatogenesis. The sperm can either be used fresh or cryopreserved[240]. This procedure has revolutionized care for men with NOA and is used all over the world.

Quality of life

Increasingly, male infertility is recognized as a disease and a public health concern that adversely affects the quality of life (QoL) of affected individuals and their partners[241] (Box 3). Although prevention and management of male infertility are advocated as an integral part of an inclusive sexual and reproductive health agenda, with the final goal of having a positive effect on men's health, pregnancy prospects and offspring well-being[34], the impact of specific male infertility interventions on QoL is largely unknown. Indeed, the Priority Setting Partnership for Infertility, which involves health-care professionals, patients and other stakeholders, elaborated a research priority agenda for male infertility that included crucial elements related to QoL, such as the impact of male infertility on emotional and psychological health and whether addressing these factors improves outcomes, and the role of comorbidities and how their treatment might affect fertility outcomes and general health[242].

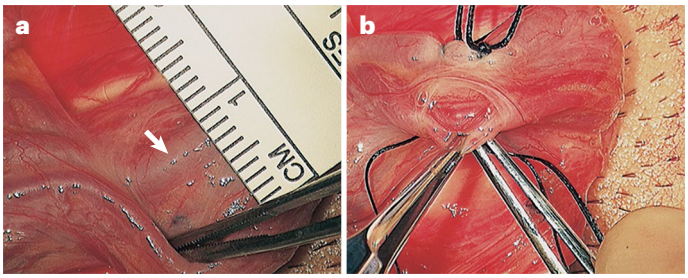


Fig. 8 | Internal spermatic vein ligation. a,**b**, Surgical microscopic image depicting the spermatic vein before (part **a**) and after (part **b**) ligation with silk suture.

Although QoL has become an essential end point in medical and health research, uniform definitions and interpretations across disciplines are lacking. Health-related QoL (HRQoL) is probably the best pragmatic approach to QoL in the context of male infertility, as it considers the impact of disease and treatment on physical, mental, emotional and social aspects and daily functioning, reflecting an individual's ability to live a fulfilling life[243].

Measuring QoL objectively is essential to evaluate the impact of care provision on disease alleviation. For example, patients' perception of QoL might show that some therapies offer little benefit in this health quality dimension, and as a result, modifications and improvements in care provision could be undertaken. Generic and fertility-specific questionaries have been developed for this purpose. The most widely used instruments include WHO Quality of Life (WHOQOL), 36-item Short Form Health Survey (SF-36), Fertility quality of life tool (FertiQOL), Fertility Problem Inventory and Copenhagen Multi-Center Psychosocial Infertility (COMPI) Fertility Problem Stress Scales[241,244–252] (Table 3).

Nevertheless, specific data on the physical and psychosocial dimensions of QoL of infertile men are limited, as most studies have focused primarily on the female partner in couples. However, a few studies indicate that the QoL of men who experience infertility deteriorates slowly as they experience unfavourable circumstances when trying to have children or, more suddenly, when receiving a diagnosis of infertility or finishing unsuccessful fertility treatment[253]. Male infertility might trigger a grief period and a challenging adjustment process of variable duration[254–256]. Educational level, unemployment, willingness to have children, poor marital relationship, previous IVF attempts and infertility duration are predictors of lower mental and sexual health scores in infertile men[257]. Importantly, when the QoL of infertile males is compared with that of infertile women, women consistently exhibit poorer FertiQOL scores than their male counterparts[253].

Growing evidence indicates that male infertility is a marker of health and adversely affects lifespan owing to its association with an increased risk of cancer and metabolic disease[57]. However, the extent to which specific interventions positively affect the QoL of affected individuals is largely unknown. Presently, the minimal data that exist indicate that psychological interventions might improve QoL scores of couples experiencing fertility problems[244]. In addition, treating male hypogonadotropic hypogonadism with gonadotropins improved scores of all SF-36 QoL domains[258].

Notwithstanding the limited data about the impact of male infertility treatment on QoL, it is recognized that andrological education and evaluation by specialists provide a unique opportunity to identify correctable aetiologies of infertility and health-threatening issues or coexistent diseases that require medical attention (for example, obesity, metabolic syndrome, erectile dysfunction, hypogonadism, kidney diseases and cancer)[13,34,259]. Nevertheless, in real-world settings, most men are poorly educated about infertility risk factors and do not follow basic recommendations for a healthy lifestyle[260]. This lack of education is aggravated by the fact that the clinical evaluation of infertile men is suboptimal, particularly in IVF clinics, where about 40% of specialists report taking only a brief medical history from men, and 24% report that they never perform a physical examination of the male partner[261]. Indeed, a male fertility evaluation is bypassed 17–27% of the time when couples are seen for fertility concerns[6,7]. Efforts should be undertaken to fill the many existing knowledge gaps in this area, particularly concerning the impact of information provision, lifestyle interventions and specific treatment on the QoL of men with infertility.

Box 3

Patient experience

In 2018, at the age of 36, I was diagnosed with azoospermia after a consultation with a urologist. A fact that took me by surprise and brought me sadness, profoundly affecting my quality of life, because with it came several questions. After a long conversation with my wife, we decided to look for more information and alternatives, improve some habits to have a chance to become parents and try to find possible treatments.

In a first attempt, my wife visited a fertility centre in our home town, which promptly recommended that we use a sperm bank without further evaluation. But that was not at all what we wanted; our dream was not only to have a child of our own but also to understand and take care of our health. So we declined and started looking for other options. In our search, my wife found a specialized doctor in male infertility who presented us with a treatment we accepted. We started the procedure with collection of my wife's eggs, and I underwent a microsurgical testicular sperm retrieval in January 2019. Unfortunately, no sperm were found; only immature germ cells were present. After that, the doctor proposed a medical treatment I found a bit aggressive to the body and we decided to seek a second opinion.

Once again, we returned to our search and arrived at a referral centre for male reproductive health. After further examination and understanding of my condition, we started a medical treatment, which I considered acceptable as it would not affect my body too much. At that time, I had already performed tests of various types, including genetic tests. Along with the treatment, the doctor told me to eat healthily, avoid excessive consumption of alcoholic beverages and do physical exercises regularly. Besides that, my wife's support and resilience were decisive for getting through the almost 8 months of treatment.

In May 2022, after a new microTESE (micro-testicular sperm extraction), the good news is that spermatozoa were found with the necessary conditions to fertilize the eggs. We currently have three embryos cryopreserved and spare sperm frozen for future use if needed. My wife is now preparing to get the embryos back into the uterus.

Outlook

Future diagnostics and treatments

Many new research advances will impact the overall field of andrology and more specifically the diagnosis and treatment of the disease of male infertility, and we mention some of the promising advances. These include technical advancements in artificial intelligence or machine learning to improve the treatment of infertility[262], in the diagnosis of male infertility[262,263] and in the identification of possible links between male infertility and increased risk of poor health outcomes[17,57,58,60,61,64,264–281].

Omics technologies include, but are not limited to, next-generation sequencing (whole-exome and whole-genome sequencing). Such technologies improve the ability to identify underlying defects that contribute to and cause infertility in men. Defects of reproductive system development are frequently ignored in the evaluation of male infertility. For example, cryptorchidism is a major well-known cause of infertility[282], and damaging mutations and copy number variants (microdeletions and microduplications) can affect reproductive system development[283–285] and adult sexual function[286–288]. Several of the major known causes of genitourinary birth defects can affect fetal, childhood, adolescent and/or adult development and/or function of other organ systems in the body and are syndromic[282,289–293]. In fact, today there are many known genetic and genomic variants associated with human male infertility. GeneCards lists >4,400 such gene defects and another >3,200 genes associated with genitourinary birth defects causing abnormal male reproductive development and function. Although many of these defects are rare, ultimately this knowledge will improve clinical diagnosis and treatment when applied to routine testing.

Transcriptomics involves techniques such as RNA sequencing (RNA-seq) and more recently single-cell RNA-seq, mapping cells to locations with landmark genes expressed or linking to specific cell types or cell lineages that have been used to develop a transcriptional cell 'atlas' of the adult human testis; these techniques are expected to provide new insights into germ cell developmental transitions and plasticity[294,295].

Novel computational methods for the analysis of large sets of data are showing great potential for andrology. A report of the application of machine learning and artificial intelligence to perform automated histological classification of testis biopsy samples has the potential to substantially improve the pathological diagnosis of these samples and identify both common and subtle disruptions to spermatogenesis that underlie some forms of spermatogenic failure and other types of male infertility[296].

Despite recent innovations in surgical approaches for azoospermia, therapeutic advances for male infertility remain relatively stagnant. There is still considerable interest in the development of methods to achieve spermatogenesis in vitro[297] and to regenerate or rejuvenate spermatogenesis in vivo for the treatment of secondary infertility due to exposure to gonadotoxins, such as occurs in cancer treatments (radiation and chemotherapy). In the laboratory, novel methods are in development to effectively use spermatogonial stem cells to rejuvenate spermatogenesis after gonadotoxin exposures such as chemotherapy[298–300].

The rapid pace of technology development and application to research into the causes of male infertility will allow important advancements in defining the aetiology of most cases of male infertility. This in turn will vastly improve our diagnostic abilities, both in the pathology

Table 3 | Tools to assess the quality of life of infertile couples

Name	Characteristics	Website	Refs.
Generic			
36-Item Short Form Health Survey (SF-36)	A 36-item questionnaire that includes physical functioning, role — physical, bodily pain, general health, vitality, social functioning, role — emotional and mental health	https://www.clintools.com/victims/resources/assessment/health/sf36.html	248
WHO Quality of Life brief version (WHOQOL-BREF)	An abbreviated version of WHOQOL-100 that includes 26 items distributed into four domains (physical, psychological, social relationship and environmental)	https://www.who.int/tools/whoqol	249
Condition specific			
Fertility quality of life tool (FertiQoL)	A 36-item questionnaire that measures fertility quality of life in four personal domains (emotional, social, relational, mind/body) and two treatment domains (tolerability, environment)	http://www.fertiqol.com/	250,252
Fertility Problem Inventory	A 46-item self-rating scale including five domains: social concern, sexual concern, relationship concern, need for parenthood and rejection of a childless lifestyle. Participants respond on a 6-point Likert scale ranging from 1 to 6. A high item score indicates considerable fertility-related stress	NA	251
Copenhagen Multi-center Psychosocial Infertility (COMPI) Fertility Problem Stress Scales	Fourteen items to assess the impact of infertility on personal, social and marital domains. Items are scored using a 4- or 5-point Likert scale, with higher scores indicating higher stress	NA	247

NA, not applicable.

laboratory for assessment of biopsy samples for human spermatogenesis and to improve the ability to define precise aetiologies, identify comorbidities and eventually (perhaps) develop medically based treatments for male infertility.

Required public health measures

There is no doubt that on the global map of public health measures, the issues of male fertility represent one of the areas lacking sufficient information, for which meaningful measures are urgently needed.

In the past three decades, several reports indicate the negative impacts of environmental and lifestyle-related exposures on male fertility[301]. Thus, the decreasing fertility rates being witnessed in many countries might not be related only to the postponement of child-bearing but also to potentially preventable, yet currently unrecognized, biological effects (Box 2). Low fertility rates lead to population decline and an age structure that is demographically less sustainable. Fertility is also an important aspect of family planning, which is considered one of the key prerequisites for achieving the 17 Sustainable Development Goals defined by the United Nations.

Moreover, emerging data that male subfertility is linked to increased risks of non-communicable diseases later in life, such as diabetes, metabolic syndrome, cardiovascular events and certain cancers, also demand more focus on male reproductive health as part of a strategy to prevent the major causes of morbidity and mortality in men. Unlike women, young men do not undergo routine health screenings. Thus, contact with health services as part of an infertility work-up might represent a window of opportunity for early disease discovery in men.

Current infertility diagnostics and treatment are largely focused on the female member of a couple. Indeed, the general perception of society and even of physicians, is that reproduction is a female concern and responsibility. Today, most cases of infertility are treated by means of ART, which necessarily places a large burden on the female member of the couple regardless of the aetiology of infertility. Nevertheless, reproduction involves both a man and a woman. There is a substantial need for training more urologists specialized in the care of the infertile man. Importantly, an increased focus on male fertility also has implications for the health of women and offspring. Developing strategies for treating male subfertility and increasing the number of specialists in male reproduction might make infertility treatment cheaper and more accessible for individuals for whom ART is unfeasibly costly and might save women the burden of ovulation induction and the other procedures involved in ART.

Currently, less education, awareness and research are devoted to the reproductive health of men than to that of women, both before and after conception. However, male reproductive health is equally important, as the problems of increasing age discussed earlier apply not only to the fertility concerns of older and less fertile women but also to paternal ageing. Growing evidence indicates that the age of the father, as well as his lifestyle and presence of comorbidities, might be associated with pregnancy outcome for the female partner and with the health of the child. Improved understanding of the complex molecular mechanisms that underlie the association between paternal factors and pregnancy trajectory and birth outcomes could contribute to a better understanding of the biological events involved in development and gestation. Thus, from a public health point of view, an increased focus on male fertility is needed, not only for men's health but also for the health of women and of future generations.

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