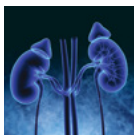
Male infertility – The other side of the equation



Darren J Katz, Patrick Teloken, Ohad Shoshany

CPD

Background

A male factor contributes to infertility in approximately 50% of couples who fail to conceive, causing significant psychosocial and marital stress.

Objective

This article reviews the general practitioner's (GP's) evaluation of male infertility and indications for referral to a male infertility specialist, and gives an overview of the specialist management of male infertility.

Discussion

Male infertility can result from anatomical or genetic abnormalities, systemic or neurological diseases, infections, trauma, iatrogenic injury, gonadotoxins and development of sperm antibodies. When a couple fails to achieve pregnancy after 12 months of regular, unprotected sexual intercourse, a screening evaluation of both partners is essential. For the male partner this includes history, physical examination, endocrine assessment and semen analysis. Several lifestyle and environmental factors can have a negative impact on male fertility, and the GP has a pivotal role in educating patients about modifiable factors.

Infertility is typically defined as the inability to conceive after at least one year of regular, unprotected sex. This affects 15–20% of couples.[1] A male factor is estimated to be present in about 50% of cases, with sole responsibility in 30% of cases and a co-contributing female factor in 20% of factors.[2] Male infertility is associated with significant psychosocial and marital stress.[3]

'Normal' male fertility hinges on the production and transport of sperm, a highly complex process that involves the endocrine, immune and neural systems. Evaluating the fertility potential of the male partner represents an important part in the assessment of a couple who have failed to achieve pregnancy. This evaluation should be performed simultaneously with the evaluation of the female partner, but it is not performed in at least 18% of cases.[4,5] By not performing a complete evaluation of the male patient, one not only compromises the fertility prognosis of the couple, but also misses an opportunity to improve health outcomes in male patients. Male infertility is associated with poorer overall health, increased cancer risk and decreased life expectancy.[6] Therefore, general practitioners (GPs) have an important role in maximising the fertility potential and improving the overall health of the male patient.

Causes

Male infertility can be caused by a wide range of conditions, encompassing anatomical or genetic abnormalities, systemic or neurological diseases, infections, trauma, iatrogenic injury, gonadotoxins and development of sperm antibodies (Table 1). In 30–40% of male infertility cases, no cause is identified (idiopathic male infertility).[5]

Indications for basic evaluation of the male partner

A screening evaluation of the male partner is indicated when the couple fails to achieve pregnancy after 12 months of regular, unprotected sexual intercourse. This period is reduced to six months if the female partner is aged >35 years.[1] Evaluation can also

be triggered sooner if there is suspicion about the fertility of the male partner because of prior history or comorbidities. Men who are not trying to conceive but have concerns about their fertility can be offered a screening evaluation after appropriate counselling.

History

Evaluation begins with a thorough history, encompassing possible medical, surgical, genetic, congenital, behavioural and environmental causes. This includes a detailed reproductive and sexual history, followed by a thorough past general medical and surgical history, exposures and lifestyle, family history, and review of systems. Box 1 highlights important aspects to be covered. An assessment tool that can be used in clinical practice is available from Andrology Australia (www.andrologyaustralia.org/wp-content/uploads/Male-Fertility-Assessment-Form_FINAL2012.pdf).

Physical examination

The main goals of the physical examination are to determine:

- penile anatomy
- degree of virilisation
- testicular and epididymal characteristics (ie presence, size, consistency)
- presence of vasa deferentia
- presence of varicoceles
- abnormalities on digital rectal examination
- evidence of previous inguinal, scrotal, pelvic or abdominal surgery.

Important aspects of the physical examination are shown in Box 2.

Endocrine evaluation

The minimal assessment includes measurement of serum follicle stimulating hormone (FSH) and morning testosterone levels. In patients with low testosterone, further investigations, including a repeat morning testosterone, free testosterone (measured or calculated from total testosterone, sex hormone-binding globulin and albumin, depending on local availability), luteinising hormone (LH) and prolactin, are recommended. The relationship between these hormones allows the source of the abnormality to be determined in most cases. Typical hormonal profiles of different clinical scenarios are presented in Table 2. Many patients with abnormal spermatogenesis have normal FSH levels, but a result close to the upper limit of normal is suggestive of abnormal spermatogenesis, and a marked elevation is a clear indication of such an abnormality.

Hypogonadotropic hypogonadism, also known as secondary hypogonadism, results from failure of the hypothalamic–pituitary axis to stimulate normal gonadal function. Causes include congenital syndromes, brain tumours, infiltrative diseases, trauma, drugs, infection or systemic illness. Management is contingent on the primary aetiology.

Even if hypogonadism is identified, exogenous testosterone use is contraindicated in patients seeking fertility treatment.

Table 1. Causes of male infertility stratified by mechanism

Pre-testicular	
• Hypogonadotrophic hypogonadism – Kallmann syndrome	
• Hyperprolactinaemia	
• Pharmacological	
Testicular	
• Varicocele	• Y-chromosome microdeletions
• Cryptorchidism	• Klinefelter syndrome
• Testicular cancer	• Environmental
• Radiation	• Infection
• Chemotherapy or pharmacological	• Injury or trauma
• Genetic azoospermia or oligospermia	• Primary ciliary dyskinesia
	• Sertoli cell-only syndrome
	• Anti-sperm antibodies
Post-testicular	
• Coital	• Young's syndrome
• Pharmacological	• Nerve injury
• Retrograde ejaculation	• Spinal cord injury
• Congenital bilateral absence of the vas deferens	• Retroperitoneal lymph node dissection
• Ejaculatory duct obstruction or seminal vesicle dysfunction	• Systemic disease
• Vasectomy or latrogenic injury to the vas deferens	

Box 1. Important aspects in the history

History

- Age of patient and partner
- Reproductive history of male and partner: time trying to conceive, previous pregnancy and offspring in current or past relationship, previous investigations and treatment
- Sexual practices: frequency, penetration, use of lubricant, timing of intercourse with ovulation
- Sexual function: libido, erection, ejaculation
- Paediatric history: cryptorchidism, hypospadias, testicular torsion, mumps orchitis
- Development: age of puberty
- Previous surgery: scrotum, inguinal region, abdomen/retroperitoneum, prostate, bladder
- Genital: sexually transmissible infection, epididymo-orchitis, scrotal pain
- Urinary: lower urinary tract symptoms, prostatitis
- Exposures: alcohol, smoking, occupational, environmental, lifestyle (heat exposure)
- Medications and drug use: medications, testosterone and supplement use, illicit drugs
- Cancer history: radiotherapy, chemotherapy
- Medical history: recent febrile illness, diabetes, neurological conditions, spinal injury, respiratory infections
- Review of systems: anosmia, visual field defects
- Family history: infertility, genetic diseases

Spermatogenesis requires a certain level of intratesticular testosterone, and exogenous testosterone use, by inhibiting the production of LH, supresses endogenous testicular testosterone production. This results in lower intratesticular testosterone levels

and impairs spermatogenesis. Management of patients who are infertile and have hormonal abnormalities is complex and requires specialist input.

Semen analysis

While semen analysis is the most important test in the evaluation of a male patient, it is not definitive in determining a man's fertility. Individuals with abnormal test results may still be able to conceive and, conversely, individuals with results within the reference range may be unable to conceive. Adequate collection of semen specimen is paramount to obtain a representative result. Different abstinence periods have been suggested, but two to three days of abstinence may be optimal.[7] Shorter periods can have a negative impact on sperm count, while longer intervals can affect motility. Collection should be made directly into a sterile container. If samples are collected at home, they should be kept at body temperature during transport to the laboratory, and need to be analysed within one hour. The normal values established by the World Health Organization (WHO) are presented in Table 3.[8]

In patients with normal results, a single test is sufficient. However, as significant variability exists, a repeat semen analysis is recommended in patients with abnormal results, preferably at a specialised andrology laboratory. The repeat semen analysis is recommended after one to three months for those with mild or moderate derangements, and within two to four weeks for those with severe oligospermia or azoospermia.[1]

Patients with a leukocyte count of >1 x 10^6/mL in the ejaculate need further investigation with urine culture, urine polymerase chain reaction (PCR) for chlamydia and gonorrhoea, and semen culture. Infections of the male accessory glands (eg urethritis, prostatitis, orchitis, epididymitis) are potentially treatable causes of infertility. Patients should be treated as per sensitivities, and in case of sexually transmissible infection, the partner also needs assessment and treatment.

Scrotal ultrasonography

Scrotal ultrasonography is indicated in patients with infertility and risk factors for testicular cancer (eg cryptorchidism, atrophic testis, first-degree relative with testicular neoplasm), and can be useful in clarifying physical examination findings. While it should not be a substitute for a physical examination, a low threshold for requesting is appropriate.[5]

Box 2. Key aspects of the physical examination

Physical examination

- General, height, weight
- Secondary sexual characteristics:
  - Hair distribution: face, trunk, axilla, pubic
  - Muscle mass
  - Adiposity
- Gynaecomastia
- Abdomen or inguinal: scars from previous surgery
- Penis: position of meatus
- Scrotum:
  - Testicular size, consistency, presence of masses, location
  - Epididymis: induration, engorgement, cyst
  - Vasa deferentia: agenesis, atresia, granuloma
  - Spermatic cord: varicocele

General practice management

Male fertility can be affected by several lifestyle and environmental factors.[9] Patients evaluated for prolonged time to conception, or men who desire to evaluate their fertility potential, should be given general advice about modifiable factors that may affect fertility at the initial consultation (Table 4). Andrology Australia has produced a booklet for patients (available at www.andrologyaustralia.org/wp-content/uploads/BL-Spermbooklet_final.pdf).

At least 10 antioxidants have been shown to reduce oxidative stress and improve semen quality in several small studies without pregnancy and live birth outcomes. Currently, there is low-quality evidence suggesting that these may increase pregnancy and live birth rates.[10] If patients choose to take over-the-counter supplements, we recommend taking a single product that has been specifically constituted rather than multiple different supplements.

Table 2. Hormonal profiles of different clinical scenarios

	Follicle-stimulating hormone	Luteinising hormone	Testosterone	Prolactin
Hypogonadotropic hypogonadism	Low	Low	Low	Normal or high
Abnormal spermatogenesis	High or normal	Normal	Normal	Normal
Testicular failure or hypergonadotropic hypogonadism	High	High	Low	Normal
Prolactinoma	Normal or low	Normal or low	Low	High

Indications for referral to male infertility specialist

Indications for referral to a specialist in male infertility include:

- abnormality identified in basic evaluation (ie hormonal, anatomical, pathological [eg semen analysis])
  - certain hormonal abnormalities such as hypogonadotropic hypogonadism may also need a subspecialist endocrinologist
- couples with unexplained infertility (male and female investigations normal)
- couples failing to conceive despite successful treatment of female factor
- patients about to undergo gonadotoxic treatment who might desire future fertility.

The above sections in this article deal specifically with general practice management of a male patient who presents with infertility. The remainder of the article will deal with how a specialist may choose to further investigate and treat a patient who has been referred. We believe that it is important for GPs to have an understanding about other steps that may be taken once a patient is referred to a male fertility specialist.

Specialist investigation of the male partner

Once a patient is referred to a specialist, a more detailed investigation of the male partner is done according to findings from the basic evaluation.

Post-ejaculatory urine analysis

An examination of post-ejaculatory urine allows for exclusion of retrograde ejaculation, and is indicated in patients with an ejaculate volume <1.0 mL without an alternative explanation. A low-volume or absent ejaculation can result from incomplete collection, short abstinence interval, retrograde ejaculation, lack of emission, ejaculatory duct obstruction, hypogonadism, or congenital bilateral absence of the vas deferens (CBAVD).

In patients with azoospermia, detection of any sperm suggests retrograde ejaculation. In patients with low-ejaculate volume and oligospermia, there is no consensus on the number of sperm that should be considered 'significant', as even in individuals who are considered 'normal', there are sperm present in the post-ejaculatory urine analysis.

Transrectal ultrasound and magnetic resonance imaging

Transrectal ultrasound (TRUS) and magnetic resonance imaging (MRI) are useful to investigate ejaculatory duct obstruction. It is generally recommended for patients with oligospermia and low-volume acidic ejaculate. Seminal vesicles >1.5 cm in anteroposterior diameter, dilated ejaculatory ducts and/or midline cystic structures in the prostate are suggestive of complete or partial ejaculatory duct obstruction.

Table 3. Semen analysis – World Health Organization reference values[8]

Volume	≥1.5 mL
pH	≥7.2
Sperm concentration	≥15 million/mL
Total sperm count	≥39 million
Total motility	≥40%
Progressive motility	≥32%
Vitality	≥58%
Normal morphology	≥4%
Leukocytes	<1.0 x 10^6/mL

Table 4. Patient counselling recommendations[1]

Alcohol	Consumption of up to three to four units per day is unlikely to affect sperm quality, but excessive consumption is detrimental
Smoking	Associated with decreased semen quality
Obesity	Obesity (body mass index >30 kg/m^2) is likely to reduce fertility
Scrotal temperature	Scrotal exposure to elevated temperatures is associated with reduced semen quality
Prescription, over-the-counter and recreational drugs	Certain drugs can interfere with fertility (eg testosterone, opioids, psychotropic agents, cannabis)
Occupation	Certain occupations that involve exposures to heat, ionising radiation, vibrations, pesticides and/or solvents may reduce fertility
Frequency of intercourse	Vaginal intercourse timed around ovulation or every two to three days

Testicular biopsy and/or fine needle aspiration

Diagnostic fine needle aspiration and/or testicular biopsy were historically used to differentiate patients with obstructive and non-obstructive azoospermia. However, it has been demonstrated that in many men with azoospermia and diagnostic biopsies showing spermatogenic arrest or Sertoli cell-only syndrome, it is possible to find localised foci of spermatogenesis with the aid of microscopic testicular sperm extraction. Diagnostic biopsy, therefore, is no longer routinely recommended as it is an invasive procedure and does not confer a definitive diagnosis or predict if sperm will be found by more sophisticated microsurgical techniques.

Anti-sperm antibodies

Antibodies against sperm can form when there is disruption in the blood–testis barrier and sperm antigens prime the immune

system. This can occur after vasectomy, trauma, biopsy, orchitis, torsion or testicular cancer. Anti-sperm antibodies can be quantified in serum, seminal fluid or directly bound to sperm. Sperm-bound antibodies can decrease motility, block penetration of the cervical mucus and prevent fertilisation.[11] It has been suggested that anti-sperm antibodies can be measured in couples with unexplained infertility and in men with isolated low motility.

Sperm DNA fragmentation tests

Greater sperm DNA fragmentation is seen in patients who are infertile, and is associated with worse pregnancy outcomes.[12] Varicocele repair and use of antioxidants have been shown to decrease DNA fragmentation. While sperm DNA fragmentation tests may provide some prognostic information, its role in management of an infertile male is yet to be established.

Genetic testing

Genetic testing is indicated for patients with severe oligospermia (<5 million/mL).[5]

Cystic fibrosis gene mutation

CFTR gene testing is indicated in patients with unilateral or bilateral absence of the vas deferens. Testing of the partner is also indicated to determine the risk to potential offspring should a *CFTR* mutation be present in the one partner. However, it is important to note that currently available methods do not detect all possible *CFTR* mutations. As some patients with unilateral or bilateral absence of the vas have other genitourinary anomalies, an abdominal ultrasound is also indicated.

Karyotype

Karyotype testing is indicated in patients with severe oligospermia (<5 million/mL), because the prevalence of karyotype abnormalities is inversely proportional to sperm count: <1% with normal sperm count, 5% with severe oligospermia (<5 million/mL) and 10–15% with azoospermia.[13] The most common abnormality is Klinefelter syndrome (47, XXY), which accounts for approximately two-thirds of abnormalities in men who are infertile.[14] Offspring of patients with Klinefelter syndrome rarely pass on the mutation to their offspring; however, genetic counselling is advised for the couple. A gross karyotypic abnormality is associated with increased risk of miscarriage and offspring with chromosomal and congenital abnormality.

Y-chromosome microdeletions

A specific region, named *AZF* (azoospermia factor), in the long arm of the Y chromosome is critical to normal spermatogenesis.[15] Genetic testing for microdeletions in this region is indicated in patients with severe oligospermia (<5 million/mL) and azoospermia, which are found in approximately 16% of these individuals. Microdeletions can be further classified according to the specific region where they occur, *AZFa* (proximal), *AZFb* (central) and *AZFc* (distal). This location provides important prognostic information that helps direct further management.

Overview of specialist management of male infertility

Hypogonadotropic hypogonadism

In patients with hypogonadotropic hypogonadism that is secondary to hyperprolactinaemia, the first step is normalisation of prolactin. This may involve surgery, use of a dopamine receptor agonist, or ceasing a causative drug. If normalisation of testosterone does not occur after six months, treatment with gonadotropin is indicated. Hypogonadotropic hypogonadism of hypothalamic origin can be managed with gonadotropin-releasing hormone (GnRH; pulsatile subcutaneous or intravenous) or gonadotropin. Patients with a pituitary origin require gonadotropin treatment in the form of human chorionic gonadotropin (hCG). Patients who remain azoospermic or severely oligospermic after six to nine months should also be treated with menopausal gonadotropin or recombinant FSH.

Varicocele

Correction of varicocele is indicated in patients with a clinically detectable varicocele and abnormal semen analysis as it improves pregnancy rates.[16] Patients with subclinical varicocele (only detectable on Doppler ultrasound) do not seem to benefit from intervention. Varicoceles can be corrected by surgical ligation (eg open, microscopic, laparoscopic) or embolisation. Microsurgical ligation is associated with the lowest recurrence and complication rates.[5]

Retrograde ejaculation

Sympathomimetic agents, such as pseudoephedrine, can be used in an attempt to close the bladder neck and lead to antegrade ejaculation. In patients who are still unable to ejaculate in an antegrade manner, the urine is alkalinised and post-ejaculatory urine is obtained (and sperm retrieved) for assisted reproductive techniques (ART).

Anejaculation

In patients with anejaculation who retain sufficient peripheral neural function, neurostimulation with penile vibratory devices can be useful. In other patients (such as those with spinal cord injury), electroejaculation via a rectal electrode can be used to retrieve sperm for ART.

Ejaculatory duct obstruction

In patients with azoospermia due to ejaculatory duct obstruction, transurethral resection of the ejaculatory ducts (TURED) has a 50% success rate.[17] Potential complications include reflux of urine into the ejaculatory ducts causing epididymitis and retrograde ejaculation.

Obstructive azoospermia

Many patients with obstructive azoospermia can undergo reconstructive surgery to restore sperm transport continuity. Those with previous vasectomy, or evidence of epididymal or vas deferens obstruction secondary to infection, trauma or iatrogenic injury, are potential candidates for microsurgical vasovasostomy (vasectomy reversal) or vasoepididymostomy.[18] In general, vasectomy reversal is preferable (and cheaper) to ART when more than one child is desired, and there are no overt female fertility factors that would need ART regardless of the male.

When reconstructive surgery is not possible or desired, or when there is urgency due to a female factor, sperm retrieval techniques, such as percutaneous epididymal or testicular aspiration or microscopic epididymal sperm aspiration, represent an option for patients with obstructive azoospermia.[19]

Non-obstructive azoospermia

Microsurgical testicular sperm extraction (microTESE) allows for identification and selective excision of larger seminiferous tubules, which are more likely to yield sperm. This increases the chances of success while minimising testicular damage. In approximately 40–50% of patients with non-obstructive azoospermia, sperm can be found with the use of microTESE, including patients with Klinefelter syndrome, *AZFc* microdeletion, previous diagnosis of Sertoli cell-only syndrome or maturation arrest on diagnostic biopsy, post-chemotherapy, and post-orchidopexy for cryptorchidism.[20]

Cryopreservation of sperm

Cryopreservation of semen is recommended for patients who desire future biological offspring and are about to undergo chemotherapy, radiotherapy or surgery that can potentially affect fertility.[5] It can also be offered to men with severe oligozoospermia, as insurance in case they become azoospermic by the time ART begins. The maximum storage time for human sperm in unknown, but sperm cryopreserved for 28 years have been successfully used to conceive a healthy child.[21]

Key points

- Selected male partners should be referred to a male infertility specialist.
- Evaluation of the male partner is indicated if pregnancy is not achieved after 12 months of regular, unprotected sexual intercourse.
- The GP's evaluation of male infertility should include a thorough history, physical examination, hormonal assessment and semen analysis.
- Exogenous testosterone is contraindicated in men seeking fertility as it suppresses spermatogenesis.
- Advice about modifiable factors that have an impact on fertility is an important component in the management of patients desiring offspring.

Authors

Darren J Katz MBBS, FRACS (Urology), Urologist and Prosthetic Surgeon, Male Fertility Microsurgeon, Men's Health Melbourne; and Urology Consultant, Western Health, Vic. dkatz@menshealthmelbourne.com.au

Patrick Teloken MBBS, Urology Registrar, Princess Alexandra Hospital, Wooloongaba, Qld

Ohad Shoshany MD, Andrology and Sexual Health Fellow, Men's Health Melbourne and Western Health, Vic

Competing interests: None.

Provenance and peer review: Commissioned, externally peer reviewed.

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