Infertility in men

Causes, risk factors, prevention and treatment

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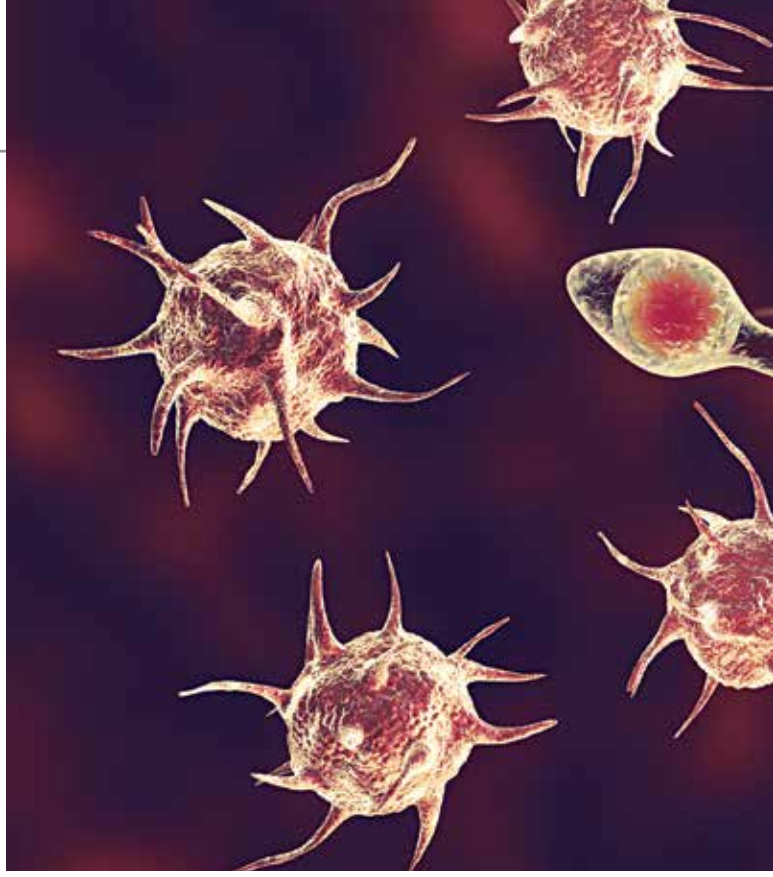

Infertility affects one in 20 men and is a contributory factor in one in two couples undergoing assisted reproduction treatment (ART). Significantly, although most men can have biological children with ART, comprehensive evaluation of male infertility and general health assessment are important to allow accurate diagnosis, genetic counselling where appropriate and modification of reversible factors.

KEY POINTS

- Infertility affects one in 20 men and is a contributory factor in half of all couples undergoing assisted reproduction treatments.
- Lifestyle factors such as smoking, obesity and alcohol play an important contributory role.
- Environmental factors such as endocrine disrupting chemical exposure and exogenous androgen use are increasingly recognised as contributing factors.
- A detailed history and thorough clinical examination should be followed by semen analysis and assessment of the reproductive axis.
- Assisted reproductive treatment (ART), particularly intracytoplasmic sperm injection (ICSI), allows many men to father children using their own sperm.
- Microdissection testicular sperm extraction (microTESE) can provide sperm for ICSI in half of men with nonobstructive azoospermia (NOA).

GPs are usually the first healthcare professionals to see couples seeking information and advice regarding fertility. It is therefore important that GPs are able to answer questions and provide initial assessment to these couples. Furthermore, it is important to appreciate that infertility should be assessed as a couple and that male factor infertility is common and affects approximately one in 20 men. This article provides an overview of the causes and risk factors for male infertility and how these can be treated and prevented. Common questions regarding male infertility are presented in Box 1.

Causes of infertility in men

Azoospermia is the absence of sperm in the semen and can occur as a result of either an obstruction in the reproductive tract (obstructive azoospermia) or inadequate production of sperm (nonobstructive azoospermia; NOA). Impairment or failure of spermatogenesis accounts for around 75% of cases of male factor infertility. Currently, in men with azoospermia, the likelihood of detecting a genetic problem is about 25%.[1] The most common genetic causes are Klinefelter's syndrome and Y chromosome microdeletions. Klinefelter's syndrome, a condition characterised by one or more additional X chromosomes (47,XXY karyotype),

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affects one in 600 men in the general population, while remaining undiagnosed in 70% of cases. Notably, it accounts for one in seven cases of NOA.

Genes that regulate spermatogenesis are located in the azoospermia factor (AZF) region of the long arm of the Y chromosome. Structural chromosomal anomalies within the AZF region account for 5% of severe infertility. Different deletion sites determine the likelihood of sperm retrieval, and if intracytoplasmic sperm injection (ICSI) is possible, vertical transmission to sons is inevitable.[1] Men with oligospermia (a deficiency of sperm cells in the semen) have a 4 to 8% risk (10 times the general population) of sex chromosomal and autosomal structural anomalies such as Robertsonian translocations, inversions and reciprocal translocations. Genetic testing in severely infertile men is routine before assisted reproduction treatment (ART), as the finding of chromosomal anomalies is significant to the success of treatment and the health of offspring. If anomalies are identified, genetic counselling is necessary and preimplantation genetic diagnosis can be considered.

Other causes of impaired spermatogenesis include testicular injury from infection, mumps orchitis, testicular torsion or surgery, or testicular toxicity from chemotherapy. There is also an association with cryptorchidism, infertility and testicular malignancies.

Obstructive causes of azoospermia include congenital absence of the vas deferens, which is most commonly seen in men with cystic fibrosis. Acquired obstruction can be the result of vasectomy, or scarring following infection or surgery.

Endocrine causes of male infertility include prolactinoma and hypogonadotrophic hypogonadism. Although uncommon, they are potentially treatable, with hypogonadotrophic hypogonadism being amenable to gonadotrophin therapy.

1. FREQUENTLY ASKED QUESTIONS REGARDING MALE FERTILITY

Does male fertility decline with age?
Men can father children well into older age; however, there is some decline in fertility seen particularly after the age of 45 years. Older biological fathers may also have a higher risk of offspring having some neuropsychological and genetic problems.

How long before planned conception should changes to optimise fertility be considered?
The process of making sperm takes about 65 days. However, it is best to start taking steps to optimise general health and fertility months, or ideally years, before planning to conceive.

Do other health conditions or medications negatively impact male fertility?
An illness with a fever can commonly affect sperm count, sometimes for several months. The effect of obesity, smoking, excess alcohol and recreational drug use cannot be underestimated. Medications such as chemotherapy, radiotherapy, some antidepressants and antiepilepsy medications can affect male fertility. Testosterone therapy can have a contraceptive effect through suppression of gonadotrophins. Proton pump inhibitors have not been shown to affect male fertility, nor have most commonly used antibiotics.

Are there any natural or complementary therapies that improve male fertility?
Although there are many supplements and complementary products marketed as effective, there have been no studies that show their use improves fertility outcomes. The most effective therapy is a healthy diet and lifestyle, which also has significant general health benefits. Measures to keep testicles from overheating (e.g. avoiding saunas) may help.

Will taking extra testosterone improve male fertility?
Although endogenous testosterone plays a role in sexual function and fertility, it is important to recognise that testosterone therapy will 'switch off' the body's ability to make testosterone and sperm, and will likely act as a contraceptive. After cessation of testosterone, recovery of spermatogenesis may take months to years.

What is the optimal timing of sexual intercourse for conception?
Two to three days before and on the day of ovulation is when a female partner is most fertile. Ovulation kits and other methods may help with determining this timing. If uncertain, couples should have intercourse every two to three days throughout the cycle (especially around the fertile period) for optimal chances of achieving a pregnancy.

What assisted reproductive technologies (ARTs) are available for men with impaired fertility?
There are several treatment options now available, including in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI). Surgical retrieval of sperm from the testes (testicular sperm extraction, TESE) followed by ICSI can allow many men previously considered infertile to have biological children.

Are there any reliable online sources of information regarding fertility?
Two reliable Australian web resources are listed below:
www.yourfertility.org.au
www.healthymale.org.au

2. CAUSES AND RISK FACTORS FOR INFERTILITY IN MEN

Failure of spermatogenesis (oligozoospermia or azoospermia)
Idiopathic
Genetic:
- Klinefelter's syndrome
- Y-chromosome microdeletion
- Acquired:
- testicular infection
- testicular torsion
- surgery
- drugs and toxins (e.g. chemotherapy)

Hypogonadotrophic hypogonadism
Congenital:
- Kallmann's syndrome

Acquired:
- prolactinoma
- pituitary adenoma
- trauma, infiltrative disease
- iron overload (e.g. haemochromatosis, repeated blood transfusions)
- drug mediated (e.g. drug-induced hyperprolactinaemia, opiate use, anabolic steroid use)

Obstructive azoospermia
Congenital:
- congenital absence of the vas deferens (including cystic fibrosis)

Acquired:
- vasectomy
- epididymal scarring following sexually transmitted infections
- scarring or damage following genital surgery
- ejaculatory duct obstruction (e.g. prostatic cysts, urinary catheterisation)

Disorders of intercourse or ejaculation
Disorders of intercourse:
- too frequent
- wrong timing
- Sexual dysfunction:
- erectile dysfunction
- ejaculatory dysfunction, including retrograde ejaculation
- psychological disorders

Sperm antibodies

Risk factors for infertility in men

There are a number of common genetic and acquired risk factors that contribute to male infertility. A personal or family history of infertility is a recognised risk factor for infertility. Testicular trauma or genital infection can cause infertility by direct toxicity or scarring. Inguinal or pelvic surgery can cause scarring and obstructive azoospermia. Previous chemotherapy or radiotherapy is a well-recognised risk factor and, when possible, the option of sperm cryopreservation should be offered before commencing treatment. Androgenic steroid abuse and testosterone replacement therapy often result in impaired gonadotrophic drive and thus azoospermia.[2]

With a decline in semen quality recognised over the past 40 years in some cohorts, environmental and lifestyle factors are of significant interest as risk factors for male factor/contributory infertility.[3] The prevalence of obesity continues to increase worldwide and correlates with the decline in male fertility. Many reasons for this have been postulated, including the effects on mood, sexual function, reproductive hormones, the testicular microenvironment and epigenetics.[4] Although weight loss would therefore be expected to improve fertility, this has not been conclusively demonstrated in clinical trials. Regardless, the myriad health benefits support addressing obesity as a potentially modifiable risk factor.

The role of endocrine disrupting chemicals (EDCs) such as bisphenol A, phthalates and perfluoryoalkyl substances are increasingly recognised as potential risk factors for male reproductive health. Signs of exposure are evident from in utero and throughout the lifespan.[5,6] Health consequences in adolescent men associated with EDCs include reduction in semen quality, including lower sperm counts and poorer morphology.[5]

The detrimental effect of substance use is well recognised. Although the effects of tobacco and marijuana on serum testosterone, luteinising hormone (LH) and follicle stimulating hormone (FSH) levels differ between studies, there is a consistent finding of impaired spermatogenesis and increased abnormalities in sperm DNA.[6] Heavy alcohol consumption has been shown to lower serum testosterone, increase gonadotrophins, impair spermatogenesis and increase sperm DNA damage.[7]

Assessment of infertility in men

A comprehensive evaluation of a couple's infertility should involve assessment and consideration of both male and female factor infertility. Male factor infertility is a significant contributory cause of infertility in over half of infertile couples. Potential causes of male factor infertility are listed in Box 2.

In addition to obtaining a history of general health, environmental exposures, medications and substance use, clinical evaluation should also include a detailed history of previous cryptorchidism or genitourinary tract surgery, infection or trauma. Pubertal timing and progression, previous fertility and fertility attempts, and symptoms of androgen deficiency should all be enquired after. Clinical examination should assess for degree of virilisation, signs of androgen deficiency, and scrotal examination. The testes should be palpated for size (normal size ranges between 15 and 35 mL) and consistency, the vasa and epididymides palpated to ensure they are present and normal, and varicocoeles noted. A summary of assessing infertility in men is outlined in the Box 3.

Semen analysis is an essential test that gives valuable information on semen parameters including volume, pH, sperm concentration, vitality, morphology and motility. 'Normal' values as defined by the WHO are outlined in the Table. However, other than azoospermia, there is no set point that defines whether a man is fertile or not. It is also important to recognise that semen analysis represents a surrogate marker that estimates the likelihood of natural conception, but does not provide information regarding the ability of sperm to seek, bind and fertilise eggs. Collection of a semen sample should be done onsite and analysed in accordance with WHO guidelines.[8] A subnormal semen analysis result should be confirmed with a repeat sample at least six weeks later. A mixed agglutination reaction (MAR) test evaluates for the presence of antisperm antibodies. Although there are a number of home-testing semen analysis kits now being marketed, they are associated with

significant limitations and do not provide complete and validated evaluation of semen parameters.[9] Genetic testing should be considered for men with infertility: karyotype testing for men with oligozoospermia; and Y chromosome microdeletion testing for men with sperm concentrations of less than 5 million/mL.[1]

Endocrine testing should include a morning fasting blood test for serum total testosterone, LH, FSH and prolactin levels. Primary testicular failure is suggested by a low total testosterone level and elevated LH and FSH levels. Secondary testicular failure is suggested by a low serum testosterone level, low or inappropriately normal LH and FSH levels, small testes and decreased sperm count. In this setting, pituitary function should be assessed, as a prolactinoma or nonfunctioning pituitary tumour may be present.

In the setting of azoospermia, an elevated FSH level (greater than 8.4 U/L) is suggestive of NOA, whereas in patients with a normal FSH level an obstructive cause is more likely. In men with suspected obstructive azoospermia, cystic fibrosis transmembrane conductance regulator (*CFTR*) gene mutation should be considered because of its association with congenital absence of the vas deferens. Furthermore, the presence of the gene mutation may also have implications for possible inheritance by offspring.

Testicular biopsy will distinguish whether azoospermia is caused by obstruction or failure of spermatogenesis, but is rarely required because FSH levels are usually adequate. In patients with obstructive causes of azoospermia, there is normal sperm production, but a blockage along the reproductive tract prevents sperm from reaching the ejaculate; in these cases testicular biopsy should be sufficient to extract sperm to proceed with ICSI. Microdissection testicular sperm extraction (microTESE) is both a diagnostic and therapeutic procedure in patients with NOA, allowing for detailed surgical dissection and examination of the testes in an attempt to recover sperm for ICSI.[10]

Treatment of infertility in men

Lifestyle and supplements

The importance of addressing lifestyle factors in infertility cannot be underestimated, particularly with regard to smoking cessation and minimising alcohol intake.[7] The use of androgenic steroids has contraceptive and other adverse health effects and is an increasingly prevalent issue.[11]

Many supplements have been marketed as improving men's fertility; however, there is no clear evidence to support their use.[12,13] A *Cochrane* review of 61 trials of 18 antioxidants concluded that there was a significant paucity of data, with many small low-quality studies and a frequent failure to report on clinical pregnancy and live birth outcomes.[14]

Hormonal therapies

HCG and FSH

Human chorionic gonadotrophin (HCG) is an effective and widely used therapy for hypogonadotrophic hypogonadism, acting as an LH analogue and increasing testosterone levels. In patients with congenital hypogonadotrophic hypogonadism, the addition of FSH is required to maximise spermatogenesis and fertility potential.[15]

Prolactinomas and thyroid dysfunction

Fertility can often be effectively restored in patients with prolactinomas through normalisation of serum prolactin with dopamine agonists (cabergoline, bromocriptine). Similarly, restoration of euthyroidism would be expected to improve fertility.

Clomifene and aromatase inhibitors

Clomifene citrate is a selective oestrogen receptor modulator that blocks oestrogen feedback at the hypothalamus and pituitary, increasing LH secretion and therefore increasing testicular testosterone production. There are some data to suggest its use before sperm retrieval may improve yield; however, its use is off label and there remains a paucity of evidence on its efficacy and risk.[16] Aromatase inhibitors decrease serum oestrogen and thus elevate gonadotrophin levels, but data supporting their efficacy is of poor quality, with benefits being modest, at best.[16]

3. SUMMARY OF WORK-UP AND REFERRAL REGARDING MALE INFERTILITY IN PRIMARY CARE

Clinical assessment
- History, including testicular surgery, trauma or infection; fertility attempts; symptoms of androgen deficiency
- Examination, including virilisation and scrotal examination

Establish points for discussion
- Reproductive goals
- Pertinent aspects of partner's reproductive health

Tests to order
- Semen analysis (ideally collected on site at specialist laboratory)
- Fasting, morning sample for luteinising hormone, follicle stimulating hormone, testosterone and prolactin
- Others as clinically indicated

When to refer
- Abnormal semen analysis that remains abnormal on repeat
- Abnormal hormonal profile
- Patients with cystic fibrosis, karyotype other than 46XY, Klinefelter's syndrome, previous vasectomy or other recognised cause/contributor to infertility
- Primary or secondary infertility for more than 12 months, or more than 6 months if female partner is older than 35 years

Evidence-based advice for all men
- Healthy weight and lifestyle
- Smoking cessation
- Alcohol cessation/minimisation
- Treatment and prevention of sexually transmitted infections

Surgery

The role of surgical treatment of varicocoeles in infertility treatment remains controversial and data are not conclusive regarding its effect on fertility for subclinical varicocoeles.[17] There is increasing evidence that surgery for clinical varicocoeles can be effective in some cases.[18,19] Surgical intervention to reverse vasectomy may also be considered; however, many men would

TABLE. ELEMENTS OF A SEMEN ANALYSIS REPORT WITH REFERENCE RANGES

Element	Definition	Reference range*
Semen volume	The total amount of fluid ejaculated	≥ 1.5 mL
Sperm concentration (sperm count)	The number of sperm in a measured volume of the ejaculate. Reported as the number of sperm per mL of semen	≥ 15 million/mL
Total sperm number (total sperm count)	The total number of sperm in the ejaculate, calculated by multiplying the semen volume by sperm concentration	≥ 40 million
Sperm motility (the ability of sperm to swim or move forward)	The number of motile sperm is compared with the number of non-motile sperm and reported as a percentage of the total number of sperm	≥ 40% motile within 60 minutes of ejaculation
Sperm vitality ('live' sperm)	The number of sperm in the sample that are 'alive' as a percentage of the total number of sperm	≥ 58%
Sperm morphology (the shape of the sperm)	The number of ideally shaped sperm ('normal') is compared with the number of imperfectly shaped sperm ('abnormal'), reported as a percentage of the total number of sperm	≥ 4%
White blood (inflammatory) cells	White blood cells are often found in semen. When present in large numbers this can be a sign of infection in the reproductive tract. However, in some healthy men it happens for no reason.	< 1 million/mL
Semen pH	Semen should be slightly alkaline. More acidic semen, together with a low volume of semen, may indicate a blockage in the flow of semen.	≥ 7.2
Sperm antibodies	Sperm antibodies are directed against sperm antigens and may interfere with sperm motility and fertilisation. Reported as the percentage of motile sperm showing antibody activity	< 50%

Adapted from Andrology Australia Fact Sheet (www.healthymale.org.au)
* Reference ranges are based on 'normal' values as defined by the WHO.

prefer testicular sperm retrieval and ICSI due to timeliness and a higher likelihood of success. Similarly, although surgical intervention for ejaculatory duct obstruction may be beneficial, testicular sperm can be directly retrieved and used.[20]

Assisted reproductive treatments

Assisted reproductive treatments such as in vitro fertilisation (IVF) have improved fertility outcomes for many couples. Significantly, although IVF typically requires many thousands of motile, functional sperm able to seek, bind and fertilise an egg in vitro, the advent of ICSI has revolutionised the prospects for men with severe oligozoospermia, azoospermia, poor quality sperm or sperm antibodies. ICSI allows direct injection of sperm into an egg, overcoming quantitative and qualitative sperm defects, and can also be an alternative for patients who have undergone vasectomy who opt for testicular sperm extraction rather than vasectomy reversal. Furthermore, microTESE allows retrieval in many azoospermic men who would otherwise be considered sterile. Combined ICSI and microTESE treatment has allowed many men, who were previously considered infertile, to father biological children.

Conclusion

Infertility in men is common and must always be considered when treating men or couples with fertility concerns. Clinical assessment, semen analysis and basic hormone profile form the initial assessment. Environmental and lifestyle factors are important to address, and microTESE and advanced ARTs are playing an increasing role in infertility management. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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