Male infertility: causes and investigations

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In the first of a two-part series, the authors discuss the causes of male infertility and outline the investigations required. Part 2 will cover medical and surgical treatments for male infertility.

Infertility affects up to 15 per cent of couples. A male factor is solely responsible in about 20 per cent of infertile couples and contributory in 30–40 per cent of cases. Azoospermia is found in 15–20 per cent of the infertile male population, and in 10 per cent the sperm density is below 1 million/ml.

CAUSES OF MALE INFERTILITY

Male infertility can be classified into three major groups:

- non-obstructive infertility (60 per cent): inadequate sperm production by the testes (Box 1)
- obstructive infertility (38 per cent): normal sperm production, but there is a blockage in the genital tract (Box 2)
- coital infertility (2 per cent): normal sperm production and patent genital tract; however, infertility is secondary to sexual dysfunction, which impairs intromission or ejaculation (Box 3).

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The percentages given for non-obstructive and obstructive infertility are based on studies of men with complete absence of sperm in their ejaculate (azoospermia).1–3

CAUSES OF NON-OBSTRUCTIVE INFERTILITY
Hormonal abnormalities
Idiopathic hypogonadotrophic hypogonadism is caused by a deficiency of follicle-stimulating hormone (FSH) and luteinising hormone (LH). The main congenital type is Kallmann’s syndrome, which occurs in one in every 10 000 males at birth, and is caused by a deficiency in gonadotrophin-releasing hormone.

Brain tumours, head injuries and radiotherapy may also cause hormone abnormalities, leading to infertility. Other hormonal abnormalities such as thyroid gland disorders, elevated levels of prolactin and low testosterone levels will also impair sperm production (Figure 1).

Genetic causes
Structural and numerical chromosomal abnormalities are found in approximately 5 per cent of infertile males and the prevalence may increase in men with complete absence of sperm. Genetic abnormalities include Y chromosome microdeletions, aneuploidy and chromosomal translocations. Klinefelter’s syndrome (47 XXY), the most common example of a numerical abnormality, occurs in 1:600 live male births and in up to 10 per cent of men with non-obstructive azoospermia. There are numerous other genes not yet identified that regulate sperm production, hormone production and hormone receptors. Any defect in such genes will impair fertility.

Varicocele
The theory is that impaired venous drainage leads to disruption of the counter-current exchange of heat mechanism from the spermatic cord, which elevates scrotal temperature and impairs spermatogenesis. Other postulated mechanisms include impaired drainage of gonadotoxins from the testes and hypoxia.4

Undescended testes
Exposure of the testes to the higher intra-abdominal temperatures impairs spermatogenesis; for this reason it is better to perform orchidopexy by the age of two years in infants with undescended testes. Genetic factors may affect the occurrence of undescended testes and the association with infertility and increased risk of testicular neoplasia.

Exposure to gonadotoxins
Gonadotoxins include chemicals, recreational drugs, tobacco, alcohol, insecticides, pesticides and heavy metals.

Iatrogenic causes
These include antiandrogens, steroids, radiotherapy and chemotherapy, especially...
alkylating agents for haematological disease.

Orchitis
Mumps orchitis is commonly associated with infertility. Orchitis may also be caused by an ascending urogenital tract infection such as post-gonorrhoeal and chlamydial infections. Inflammation and oedema of the testicular tissue with a surrounding tough tunica albuginea leads to increase of intratesticular pressure with damage and fibrosis of the germinal epithelium.

Testicular torsion
If testicular torsion is not corrected within six hours, it leads to permanent damage and shrinking of the affected testis as a result of ischaemic necrosis. Moreover, this may be followed by production of antisperm antibodies, which affect the other healthy testis.

Testicular trauma
Blunt trauma to the scrotum may lead to intratesticular haematoma or even rupture of the testis; this causes damage of the testicular tissue and breach of the blood–germinal epithelium barrier, causing production of antisperm antibodies.

Testicular tumours
Testicular tumours lead to infertility by destroying and compressing the healthy testicular tissue. Treatment of testicular cancer, whether by orchidectomy, chemotherapy or radiotherapy, also impairs fertility. The incidence rate of testicular cancer in infertile men is 0.5–1 per cent compared to 0.001–0.01 per cent in the general population. This may well be caused by genetic factors that predispose to both conditions.

Autoimmune infertility
Antisperm antibodies are produced in autoimmune infertility. Germ cells are normally sequestrestrated from the immune system by the blood–testis barrier formed by Sertoli cells. Conditions that cause disruption of this barrier, such as trauma, testicular surgery, varicocele and orchitis, lead to exposure of the germ cells to the immune system and production of antisperm antibodies.

CAUSES OF OBSTRUCTIVE INFERTILITY
Congenital absence of the vas deferens
This may be unilateral or bilateral; it is caused by two types of genetic defect and occurs in 1 per cent of the infertile male population.

Cystic fibrosis affects 1:1600 people of Caucasian descent. It occurs as a result of mutations in both alleles of the cystic fibrosis gene. This gene encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which maintains sodium/chloride balance in epithelial secretions. All men with cystic fibrosis disease have vasal aplasia. Men who present only with vasal aplasia have a mild form of cystic fibrosis that lacks the pulmonary and pancreatic symptoms and presents only with azoospermia. Another form of vasal aplasia is caused by other gene mutations (non-CFTR). This type may be associated with unilateral renal aplasia.

Vasal obstruction
The most common cause of isolated vasal obstruction is postoperative after surgeries in the region of the inguinal canal or pelvis, such as hernia repair and orchidopexy.

Epididymal obstruction
Obstruction at this level may be post-inflammatory, as in sexually transmitted infections such as chlamydia and gonorrhoea, or after urinary tract infections, where the microbes travel in a retrograde manner from the urethra, causing inflammation of the epididymis followed by obstruction.

Ejaculatory duct obstruction
Obstruction may be caused by congenital prostatic cysts or stones, or prostatitis (Figure 2). In addition to infertility, patients may have a variety of symptoms such as painful ejaculation, reduced force and volume of ejaculate, haemospermia, dysuria, pelvic pain and scrotal pain.

CAUSES OF COITAL INFERTILITY
Erectile dysfunction
Patients with severe erectile dysfunction will have difficulties in intromission and deposition of semen in the vagina.

Premature ejaculation
In severe cases, ejaculation occurs before penetration, outside of the vagina.

Penile deformities
Patients with penile curvature, as in Peyronie's disease or congenital penile curvature, and patients with abnormal position of the urethral meatus, as in hypospadias or epispadias, will have problems in vaginal penetration and sperm deposition.

Anejaculation
Primary anejaculation (anorgasmia) may occur as a result of psychosexual factors or neurological causes such as decreased sensitivity of the genital organs or high threshold of the ejaculatory reflex. Secondary anejaculation may occur following surgeries in the pelvis or abdomen that cause injury of the sympathetic chain, as in retroperitoneal lymph node dissection and panproctocolectomy. It may also occur in diabetic autonomic neuropathy and in other causes of autonomic neuropathy. Certain drugs such as antidepressants...
and alpha-blockers may also lead to anejaculation.

Retrograde ejaculation
The causes of retrograde ejaculation are similar to those of anejaculation. It is common after surgery for benign prostatic hyperplasia and in men who are taking alpha-blockers.

HISTORY AND EXAMINATION OF THE MALE PARTNER OF AN INFERTILE COUPLE
A detailed medical history is taken from the male partner to detect any predisposing factors for infertility. A general examination is performed to evaluate the secondary sexual characters, such as body hair, fat distribution and the presence of gynaecomastia.

A local examination of the genitalia is then performed to assess testicular size, consistency and the presence or absence of testicular lumps. The epididymis is then examined to detect swellings and nodules that indicate obstruction, the vasa are palpated to confirm their presence, and the cord is palpated to exclude the presence of a varicocele.

INVESTIGATIONS FOR MALE INFERTILITY
Semen analysis
At least two tests are performed, three weeks apart. This is the baseline investigation for male infertility. The results of semen analysis provide a guide to whether or not other investigations are needed (Table 1).

Semen culture
Semen culture is indicated in the presence of chronic infections of the genital tract. This is indicated by genital pain, painful ejaculation or the presence of white blood cells in semen (>5 per high-power field).

Male reproductive genetic profile
This includes karyotype, Y chromosome microdeletions and cystic fibrosis gene mutations. However, there are numerous other genes involved in male fertility that have not yet been identified.

Hormonal profiles
The basic hormones that are tested are FSH, LH, prolactin and testosterone. Other hormones may be tested if there is a clinical indication.

Imaging
Scrotal ultrasound and colour Doppler is done to assess the testes and epididymis to detect their dimensions and exclude the presence of tumours or varicocele. A transrectal ultrasound scan may be performed if there is a suspicion of distal genital tract blockage or abnormality (Figures 2 and 3).

Magnetic resonance imaging of the pelvis may help in diagnosing obstructions and abnormalities in the distal genital tract. It may also help in locating the testes in cases of undescended testes.

TREATMENT
Once the cause of male infertility is known, treatment should be provided, directed at treating the cause of the problem, leading to a cure. The medical and surgical treatments available will be discussed in the second part of this article.

Declaration of interests: none declared.

REFERENCES

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<td>Sperm concentration (10⁶ per ml)</td>
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<td>Peroxidase-positive leukocytes (10⁶ per ml)</td>
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Table 1. Lower reference limits for semen analysis.