# Male infertility

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## Abstract

It is estimated that one in seven couples in the United Kingdom (UK) experience some difficulty conceiving at some point in their reproductive life. The true incidence of male infertility is unknown due to variability in the prevalence of infertility reported from different countries. A sub-optimal semen result has been reported in 30–50% of subfertile couples: which could be either low sperm count, poor sperm motility or sperm with abnormal size and shape (morphology). In more than 50% of cases of male infertility, the aetiology remains unknown and the infertility is classified as idiopathic. It is vital to establish the cause in order to streamline the investigation and management.

**Keywords** intracytoplasmic sperm injection; male infertility; semen analysis

## Introduction

The true prevalence of male sub-fertility is difficult to estimate due to lack of population based epidemiological studies in the prevalence of male infertility. The NICE guidelines (NICE CG no 156) has quoted that 30–50% cases of infertility are due to male factors. In the UK, low sperm count or quality is considered to be the cause of infertility in about 20% of couples, and is also a contributory factor in another 25% of couples. Although several treatable conditions affect spermatogenesis and lead to male subfertility, many aspects of male infertility are still unclear. Diagnostic work-up of male sub-fertility had come a long way from semen analysis to a comprehensive approach which includes: a detailed clinical history, physical examination, endocrines assessment, genetic testing and sperm function studies in addition to routine semen analysis.

## Spermatogenesis

At about sixth week of human embryonic development, undifferentiated primordial gonads are formed from somatic mesenchymal tissue. These cells in the gonads differentiate into support cells and hormone producing cells whereas germ cells migrate to the gonads from yolk sac. The sex determining region of Y chromosome gets activated during the development and kick start the synthesis of a protein named testicular determining factor (TDF). This in turn causes testicular development and testosterone synthesis by Leydig cells. Mullerian inhibiting factor from testis prevent the development of Mullerian ducts and allows the Wolffian duct to develop into epididymis, vas deferens and seminal vesicles. The germ cells or spermatogonia in the seminiferous tubules undergo mitosis and meiosis to produce mature but non-motile spermatozoa, which takes around 74 days. Spermatozoa acquire motility in epididymis and this process of spermatogenesis including the transport in ductal system takes 3 months.

## Aetiology

Conditions leading to male infertility can be broadly classified as below (Figure 1)

- Hypothalamic-hypophyseal tract
- Testicular disorders
- Disorders of the seminal tract
- Immunological
- Psychosomatic
- Previous treatments for cancers (chemotherapy) and other medicines like testosterone supplements, anabolic steroids, antifungals like ketoconazole and some antihypertensives.

### Diagnostic work-up

The diagnostic workflow for male subfertility should follow a systematic approach to ascertain the impact of past factors influencing present fertility status. A thorough medical history and physical examination should be followed by semen analysis and hormonal profile. Further investigations such as chromosomal analysis and sperm function tests may be necessary depending upon the results of the initial investigations.

### Clinical history

The medical history should pay particular attention to history of undescended testes, pubertal development delay, genital surgery or infection, fertility in the current or previous relationships and coital frequency, erection or ejaculation problems (Table 1)

### Physical examination

Examination should look for evidence of sexually transmitted diseases, conditions of testis, epididymis and presence of hernias.

General physical examination should look for the presence of male pattern escutcheon, distribution and density of axillary hair, pubic hair and beard. Presence of small testes, phallus, and prostate, scant pubic and axillary hair, and disproportionately long arms and legs because of delayed epiphyseal closure (arm span $\geq$5 cm greater than height) are suggestive of Klinefelter's syndrome. A reduced male musculature, gynaecomastia and persistently high-pitched voice are suggestive of hypogonadism before puberty.

### Testicular examination

Testicular volume should be measured using Prader orchidometer which consist of a string of twelve numbered wooden or plastic beads of increasing size from about 1 to 25 ml. As germinal tissue approximately forms 85% of testicular mass, reduced germinal tissue is associated with reduced testicular volume and soft consistency. Although ethnic and racial origin influences testicular size, testicular growth is an indicator of pubertal progression. A testicular volume of <4 ml is prepubertal, 4–15 ml are considered peri-pubertal and 12–25 ml are taken as adult size testis.

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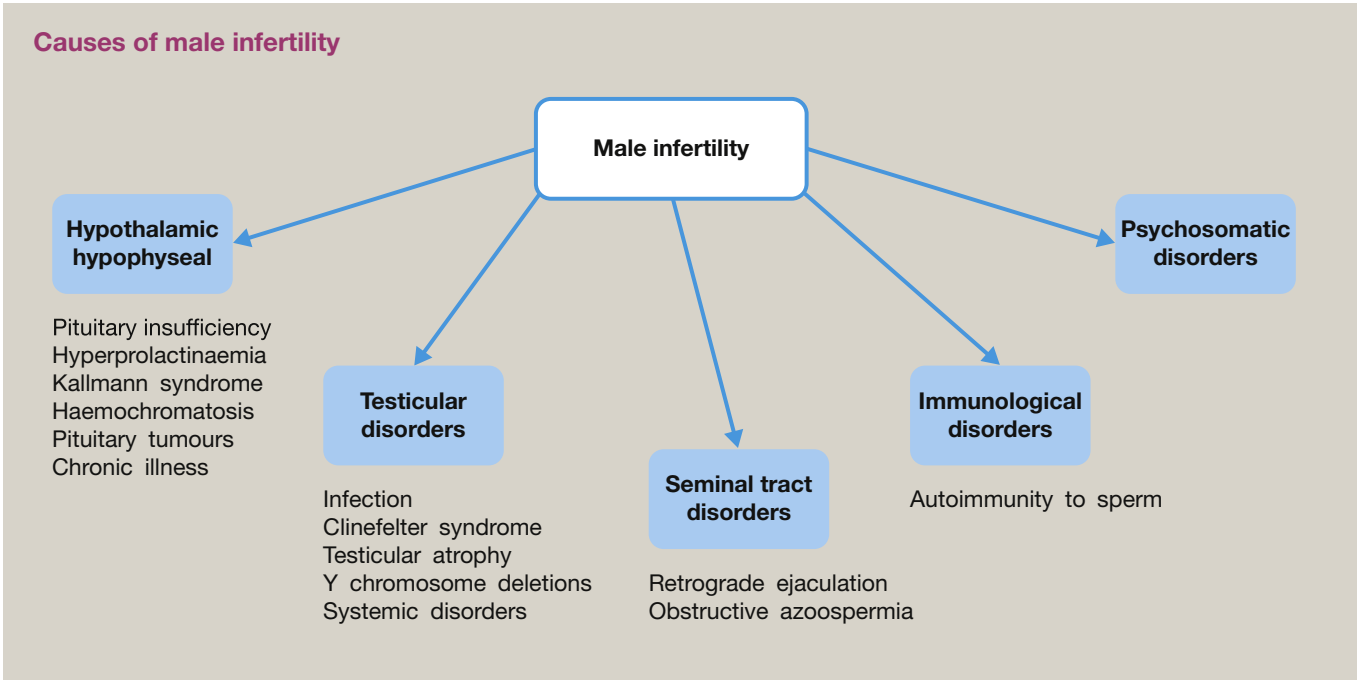


**Figure 1**

### Scrotal examination

Scrotal examination should look for any masses, scars of previous surgeries, varicocele and presence of palpable epididymis. The presence of a varicocele should be confirmed with the man standing and performing a Valsalva manoeuvre. Length of stretched penis ranges from 10 to 17 cm in adults and 4–8 cm in prepuberty. Examination should also look for the presence of hernias and if there is any evidence of sexually transmitted diseases, then further investigations should be considered.

### Testicular ultrasound

Testicular ultrasound should ideally be performed with high resolution 7.5–12 MHz linear transducer. It provides objective evidence of testicular volume which can be 15% more precise than palpation. Ultrasound improves the detection of testicular (hydrocele, haematocele, spermatocele, testicular tumours) and epididymal pathologies. The evidence of blood reflux on duplex ultrasonography along with increased venous diameter on Valsalva manoeuvre provides objective evidence of a possible clinically significant varicocele. Epididymal caput size greater than 7.5 mm in diameter provides objective evidence for possible obstruction. Further, trans-rectal ultrasound for prostrate and seminal pathologies may be considered in cases of obstruction. There is an argument in favour of carrying out routine testicular ultrasound in sub-fertile men, because an increased risk of testicular tumours (1 in 200–300 men) has been reported in this group of men. Most often these tumours may not be palpable. Ultrasonography improves the detection rate of scrotal pathologies; the detection rate is described in Table 2.

### Semen analysis

Semen analysis is a primary tool to assess male fertility potential. WHO 2010 standards for assessing semen quality are referred to as 'reference' values as opposed to 'normal' values because these standards are derived from a population of fertile men. These have been elaborated in detail in Tables 3 and 4. Semen assessment using WHO reference values is only valid if WHO described methodology is used for testing. It has been suggested that although WHO criteria has a sensitivity of 89.6% but, it has low specificity to detect true semen abnormalities. Performing a second semen analysis will falsely identify 2% of men as abnormal as opposed to a figure of 10% with a single semen analysis. Ideally the second analysis should be scheduled at an interval of three months from the first abnormal one as that is the length of the sperm formation cycle. If this delay seems to cause anxiety to male partner, then the test may be repeated in 6–8-week time. In case of azoospermia second sperm test should be performed in 2–4 weeks time.

### Endocrinology profile

Hormone testing is the backbone of andrology work-up and should be done when two semen analysis show severe oligozoospermia or azoospermia. Testing for serum Follicle stimulating hormone (FSH), Luteinising hormone (LH) and testosterone can provide important input in differentiating hyper gonadotrophic hypogonadism (primary testicular failure) from Hypogonadotrophic hypogonadism (hypothalamic-pituitary failure).

**FSH** level testing is more likely to be accurate on single blood sample testing as FSH has a longer half life. Measurements of **LH** on single sample may be erroneous on the other hand because of its pulsatile release and shorter half life. As circulatory **testosterone** levels are highest in morning hours, it should be ideally tested in the morning. Total circulatory testosterone level should always be interpreted in light of clinical symptoms and along with FSH and LH levels as these levels are influenced by variations in sex hormone binding globulin (SHBG). Increased SHBG