# Male infertility: the role of hormonal evaluation in guiding therapy

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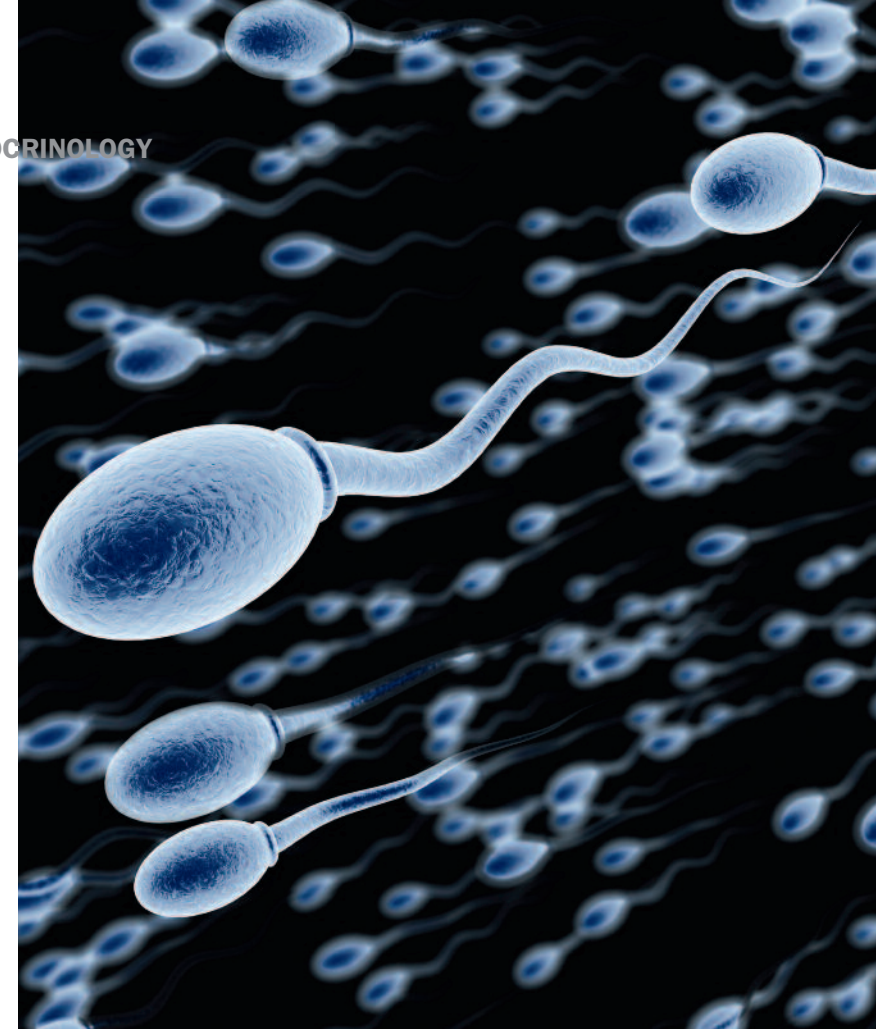
*Although endocrine causes of male infertility are uncommon, reproductive hormonal evaluation is an integral component of the evaluation of male factor infertility. This article discusses the role of hormonal evaluation and demonstrates its capacity to influence therapeutic choices.*



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Male reproductive dysfunction is a significant cause of infertility and a sole or contributory cause in about half of infertile couples.[1] Significant advances in assisted reproductive technologies, most notably intracytoplasmic sperm injection (ICSI), allow fatherhood in men who were previously considered sterile. Yet the evaluation of the infertile man remains essential and requires a comprehensive medical history and examination complemented by laboratory investigations. In addition to semen analysis, reproductive hormone testing assists in identifying remediable causes of infertility and co-existent testosterone deficiency in this at-risk population.

## Physiology of the hypothalamic–pituitary–testicular axis

An intact hypothalamic–pituitary–testicular (HPT) axis is necessary for normal sperm production and testosterone secretion (Figure 1). Hypothalamic gonadotrophin releasing hormone (GnRH) stimulates pituitary gonadotrophin secretion. Follicle-stimulating hormone (FSH) acts on the Sertoli cells to promote spermatogenesis, and luteinising hormone (LH) acts on the Leydig cells to secrete testosterone. The dual roles of testosterone are:

- it enters the circulation to induce and/or maintain virilisation and exerts effects on many tissues
- it is essential for spermatogenesis; to fulfil this function it must be present in a substantially higher concentration in the testis than in other androgen-responsive tissues.

The sex steroids and inhibin B provide negative feedback regulation of LH and FSH. Primary testicular disorders

## Key points

- **As part of the evaluation of the infertile couple, male factor infertility needs to be considered.**
- **In addition to testicular examination and semen analysis, reproductive hormone testing is an important component of the diagnostic workup of infertile men.**
- **Although endocrine causes account for a small proportion of male infertility, they are often remediable by specific therapy.**
- **Testosterone therapy should not be commenced in men with fertility aspirations due to its contraceptive effects.**

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commonly interfere with this feedback loop with reduced inhibin B and testosterone feedback resulting in elevated FSH and LH levels, respectively.

## Causes of male infertility

Male infertility is most often the result of primary testicular disease, including genetic (e.g. Klinefelter's syndrome), congenital (e.g. undescended testes) or acquired disorders (e.g. cytotoxic cancer treatment, infection, torsion) (Figure 2). Obstruction to sperm outflow through the reproductive tract (congenital) or acquired (e.g. vasectomy) account for approximately 30% of cases of male infertility, whereas disorders of intercourse (e.g. frequency and timing) or sexual difficulties (both functional and organic) are sometimes also significant causes. Hormonal causes, such as deficiency of hypothalamic GnRH (e.g. Kallmann's syndrome) or gonadotrophins (e.g. pituitary tumours, prolactinoma and haemochromatosis), represent an uncommon, but potentially treatable, subset of aetiologies. Nevertheless, reproductive hormone levels provide valuable diagnostic information in the workup of infertile men.

## Approach to the diagnosis

Semen analysis is a crucial initial investigation for infertile men (performed using World Health Organization methods) that may reveal azoospermia (no sperm seen) or impaired sperm output and/or quality. Reproductive hormone measurements (morning serum FSH, testosterone and LH) are performed to inform further diagnosis and treatment; repeat measurements may be needed to clarify initial abnormalities. The GP can undertake these basic tests because they will expedite the couple's evaluation and referral to the appropriate specialist (urologist, endocrinologist or a clinician specialising in assisted reproductive technology).

### Azoospermia

Spermatogenic failure and obstruction are both causes of azoospermia and it is important to distinguish between the two. Although clinical pointers may be evident, hormonal evaluation is often required.

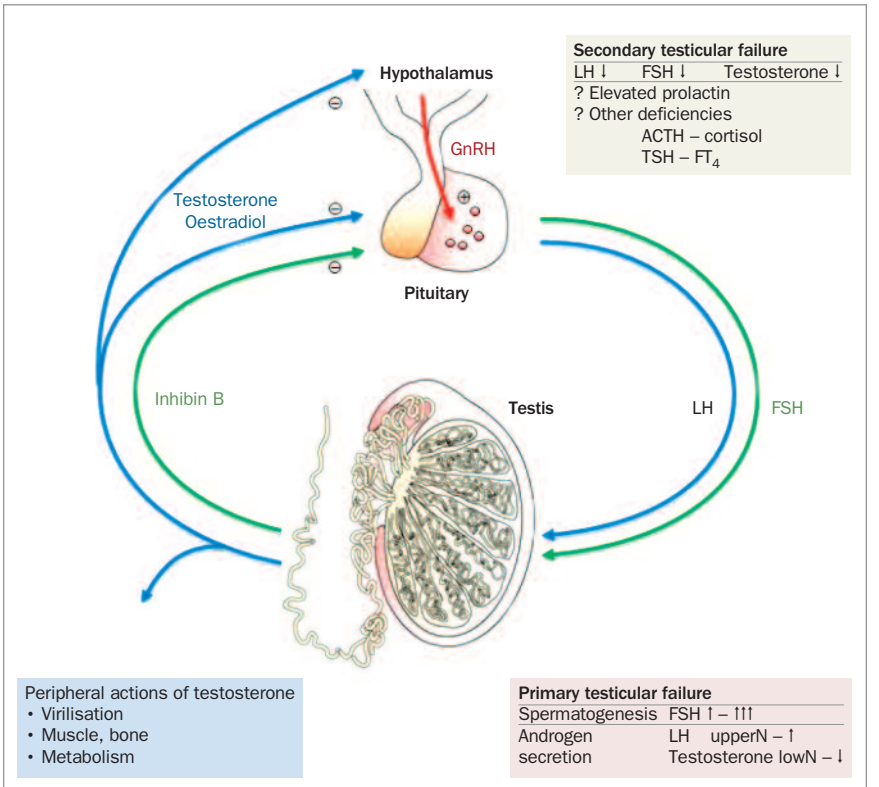


**Figure 1. Inter-relationships of the hypothalamic–pituitary–testicular axis in health and disease.** Under the influence of pulsatile GnRH secretion from hypothalamic neurons, the pituitary gonadotrophs secrete (i) FSH that stimulates the Sertoli cells of the seminiferous tubule to nurture spermatogenesis, and (ii) LH that stimulates the Leydig cells that lie between the tubules to secrete testosterone. In addition to supporting spermatogenesis, it also passes into the bloodstream to deliver testosterone, and its metabolite oestradiol, to the body. These hormones provide negative feedback to maintain gonadotropic homeostasis. In secondary testicular failure, the loss of gonadotrophin secretion is associated with low testosterone levels and perhaps other pituitary hormone abnormalities; in primary testicular disease, reduced spermatogenesis leads to lower inhibin B release and the characteristic rise in serum FSH levels, whereas a falling serum testosterone level and rising LH level suggest impaired androgen secretion.

ABBREVIATIONS: ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; FT4 = free thyroxine; GnRH = gonadotrophin-releasing hormone; LH = luteinising hormone; TSH = thyroid-stimulating hormone.

### *Primary testicular (spermatogenic) failure*

Primary testicular failure is a broad term covering a range of genetic, congenital and acquired disorders and is the leading cause of azoospermia. Elevated serum FSH levels, reduced testicular volumes and azoospermia are the classic triad.

The most common cause of primary testicular failure is Klinefelter's syndrome (47, XXY), a condition affecting one in 600 men in the general population and one in 12 men with azoospermia.[2] Clinical features of undervirilisation are variable, with many men not meeting the classic 'textbook' stereotype. The only reliable clinical sign is small (1 to 4 mL) testes; therefore, testicular examination using an orchidometer or ultrasound is important for the evaluation of all infertile men. FSH levels are very high (>20 IU/L), testosterone deficiency is common (low testosterone and high LH levels) and a karyotype is diagnostic of Klinefelter's syndrome.

Further causes of spermatogenic failure include other genetic (chromosomal) disorders,[3] viral (mumps) orchitis, chemotherapy

or radiotherapy, bilateral cryptorchidism and testicular trauma or torsion. Significantly, most cases remain 'idiopathic' and may arise through unrecognised genetic and/or environmental factors. Although there is no therapy to improve spermatogenesis, testicular biopsy (either by percutaneous aspiration or microdissection) may identify a few sperm in about 50% of such men, allowing fertility to be achieved using ICSI.

### *Secondary testicular failure or hypogonadotropic hypogonadism*

Secondary testicular failure is rare and characterised by low serum testosterone levels and sperm production in the setting of low or 'inappropriately' normal serum gonadotrophin levels. This diagnosis is important because it is the main treatable form of male infertility, and deficiencies in other pituitary hormones (thyroid-stimulating hormone, adrenocorticotropic hormone) may co-exist, resulting in significant nonreproductive sequelae. Clinical features may include pubertal failure in congenital cases (e.g. Kallmann's syndrome, other forms of idiopathic hypogonadotropic hypogonadism) or severe androgen deficiency in adult-onset disease (e.g. pituitary surgery, radiotherapy, trauma, haemochromatosis).

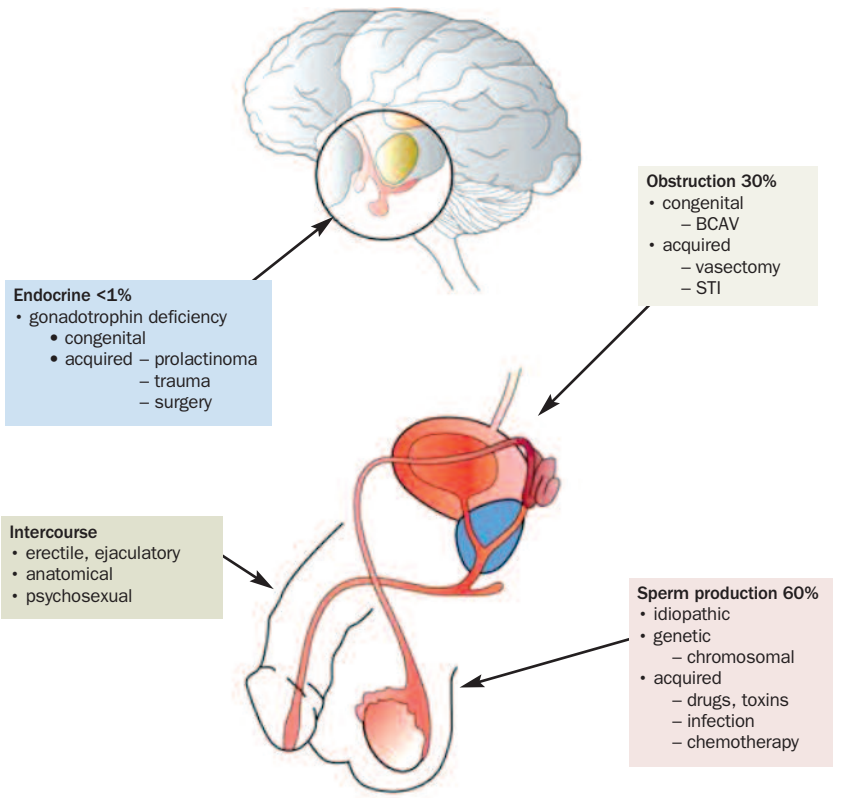


**Figure 2. The common diagnostic categories of male infertility.**
Impaired sperm production due to testicular damage, genetic or unknown causes account for most cases of male infertility and is reflected in variably reduced semen quality. Obstruction to sperm outflow is the next most common cause with congenital or acquired blockages at variable points in the tract. Disorders of intercourse that limit the frequency of ejaculatory vaginal intercourse may be associated with organic or psychosocial problems. Finally a hypothalamo-pituitary disorder is a relatively rare but critical diagnosis demanding specific therapy.

ABBREVIATIONS: BCAV = bilateral congenital absence of the vas; STI = sexually transmitted infection.

If testosterone, LH and FSH levels are all low, both serum prolactin levels (e.g. for prolactinoma) and iron studies (for haemochromatosis) should be assessed and specialist referral of the patient undertaken, following which additional pituitary function testing and imaging may be required. Such disorders demand specific treatment, with therapy often restoring natural fertility (e.g. cabergoline in men with hyperprolactinaemia).

Men with hypogonadotropic hypogonadism can have their fertility restored by use of human chorionic gonadotrophin injections (as a long-acting natural LH substitute) to restore testicular testosterone production, and FSH injections to stimulate further spermatogenesis.[4] Although taking up to two years to assess its full effects, therapy induces testicular growth and spermatogenesis in most men. If the sperm output remains inadequate for natural fertility, ICSI may be used. Following the establishment of a secure pregnancy (i.e. entry into the second trimester) life-long testosterone therapy is resumed.

Testosterone therapy as a cause of infertility requires special mention. Through negative feedback on gonadotrophin secretion, physiological testosterone replacement therapy suppresses sperm output; indeed this is a basis of proposed male hormonal contraception. This is an important point as, although about one in seven infertile men has evidence of testosterone deficiency,[5] testosterone therapy may not be required[6] and in any event should not be considered until their fertility aspirations have been resolved.

By extension, secondary hypogonadotropic hypogonadism and reversible infertility is common in men who abuse anabolic steroids. Although testosterone administration would result in a high serum testosterone level, synthetic androgens, such as nandrolone, remain undetectable by testosterone immunoassay and thus mimic hypogonadotropic hypogonadism secondary to pituitary failure (low FSH, LH and testosterone levels). Following withdrawal of exogenous androgens, recovery of the HPT axis can be very slow (up to one year), with an extended period of androgen deficiency while awaiting recovery of the HPT axis. Specialist referral should be sought.

### *Obstruction*

Obstruction to sperm outflow due to epididymal (e.g. post infective), vas deferens (e.g. vasectomy or congenital absence) and bladder base problems (e.g. infective, surgical) is associated with normal testicular volumes and normal FSH levels as the feedback axis is unaffected. Surgical repair in selected cases, or ICSI in any setting using surgically recovered sperm, provides excellent outcomes. Congenital bilateral absence of the vas deferens accounts for about 3% of obstructive azoospermia; this genetic condition lies within the cystic fibrosis disease spectrum. Genetic counselling and screening of the couple for *CFTR* gene mutations are therefore required before performing ICSI.

An important practice point is that serum FSH levels of about 8 IU/L provides the best discriminator between spermatogenic failure and obstruction irrespective of the stated laboratory upper reference interval for FSH.[7] In the setting where the diagnosis remains unclear, diagnostic testicular biopsy will readily distinguish the two by showing normal spermatogenesis (obstruction) or evidence of spermatogenic failure.

### Severe oligozoospermia

Oligozoospermia almost always reflects poor spermatogenesis rather than obstruction, and is characterised by sperm of diminished number, motility and/or function. Clinical assessment should seek underlying or reversible factors. Again, morning serum FSH, morning testosterone and LH levels should be measured, usually more than once, with an elevated FSH level being suggestive of impaired spermatogenesis. Concomitant androgen deficiency (low testosterone and elevated LH levels) is seen in more severe cases of primary testicular disease and long-term follow up should be considered to monitor for a deterioration in Leydig cell function.

Although usually apparent when taking a patient's history, it must be recognised that severe medical illness, such as chronic renal or hepatic failure, can be associated with poor semen quality and infertility. Severe thyroid dysfunction in young men is rare but of interest. Untreated hypothyroidism may result in lower libido and poor semen quality by alterations in sex steroid metabolism and hyperprolactinaemia. Hyperthyroidism can decrease fertility through its effect on androgen metabolism, marked elevation of sex hormone-binding globulin and altered hypothalamic feedback mechanisms. In particular, the peripheral conversion of testosterone to oestradiol is increased, resulting in poorer sperm quality and gynaecomastia.[8]

## Conclusion

The evaluation of reproductive hormones is a key element in the evaluation of the infertile man because it identifies cases for attempts at restoring natural fertility, aids the management using assisted reproductive technology and reveals co-existent disease especially androgen deficiency. Although primary hormonal problems account for a small proportion of cases of male infertility, identification of these conditions is essential. They are often treatable and/or reversible and their diagnosis allows appropriate specific therapy that addresses systemic sequelae and restores fertility in many men. **ET**

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