# Endocrine Infertility

# 14

Giorgio D. Piubello

## 14.1 Definition

This chapter encompasses all spermatogenesis-altering conditions affecting the normal male endocrine balance. Such conditions can be caused by either testicular abnormalities (or other endocrine gland or pituitary-hypothalamus disorders) or the effect of exogenous substances (endocrine disruptors).

## 14.2 Epidemiology

Male infertility is caused by endocrine alterations in 18–30 % of cases [1].

## 14.3 Etiopathogenesis

### 14.3.1 Hypogonadisms

The development, endocrine function, and reproductive function of the gonads are regulated by the hypothalamic-pituitary-gonadal axis. In the hypothalamus, specialized neurons release pulses of gonadotropin-releasing hormone (GnRH), which modulates the secretion of gonadotropins from the pituitary gland. In turn, the anterior pituitary gland produces luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which stimulate steroid secretion and germ cell production in the testes. A complex interaction of endogenous inputs, chronobiological signals, and exogenous stressors regulates the whole process.

G.D. Piubello
Istituto Medicina Interna D, Università degli Studi di Verona,
Piazzale L. A. Scuro 1, Verona 37134, Italy
e-mail: giorgiopiubello@alice.it



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**Table 14.1** Classification of male hypogonadism

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|---|
| Secondary hypogonadism (hypogonadism hypogonadotropic) |
| Panhypopituitarism |
| Failure of the gonadotrophic function of the pituitary |
| Isolated LH deficiency |
| Isolated FSH deficiency |
| Altered LH biological activity |
| Altered FSH biological activity |
| Primary hypogonadism (hypogonadism hypergonadotropic) |
| Congenital or acquired anorchidism |
| Cryptorchidism |
| Mumps orchitis |
| Genetic and developmental conditions: Klinefelter syndrome, androgen receptor, LH receptor and enzyme defects |
| Sertoli cell only syndrome |
| Radiation treatment or chemotherapy |
| Testicular trauma |
| Testicular torsion |

Male hypogonadism is defined as a clinical situation presenting a deficit in the testicular function. This defect can be a consequence of a disorder first originating in the testis (primitive or hypergonadotropic hypogonadism) or can be caused by insufficient stimulation of pituitary gonadotropins in the testis (hypogonadotropic hypogonadism). This condition can in turn be due to a defect in the pituitary (secondary hypogonadotropic hypogonadism) or an alteration in the secretion of hypothalamic GnRH (tertiary hypogonadotropic hypogonadism). The classification of male hypogonadism is reported in Table 14.1.

Late-onset hypogonadism, a condition in which androgens decline with advancing age, is instead imputable to the hypothalamus-pituitary and/or the testes.

Isolated deficiencies of FSH and LH also have been reported. Subjects with the rare isolated LH deficiency show eunuchoid body habitus, large testes, and small-volume ejaculates containing few spermatozoa. Plasma testosterone is low while FSH levels are normal.

Isolated FSH deficiency is also a rare condition that allows normal virilization and testosterone levels, albeit with low levels of FSH and oligospermia or azoospermia. Its cause may be an FSH β-subunit deficiency, an idiopathic genetic defect, or excess inhibin-B (idiopathic or resulting from a granulosa cell tumor).

### 14.3.2 Testicular Steroidogenesis Congenital Disorders

Hormone biosynthesis is carried out in both the adrenal cortex and the gonads. Many steps of this process are common to both, while others are only possible in the adrenal cortex. A congenital deficit of an enzyme of one of the steps of steroidogenesis

produces a deficit in the hormones of the next step, and an increase in the hormones of preceding steps.

A series of complex syndromes are produced by the lack of certain hormones, which should have been synthesized, and by the increase of their precursors in circulation.

The most common condition is reduced virilization in the male embryo (male pseudohermaphroditism). There are eight known enzymatic defects able to affect testosterone synthesis, the most frequent of which is 21-hydroxylase deficit, which accounts for 95 % of such defects.

### 14.3.3 Androgen Resistance Syndromes

Androgen resistance syndromes are caused by alterations of the androgen receptor or the 5α-reductase enzyme, which hinder the androgenic action. Virilization defects shown by affected individuals are highly variable and have been classified according to five phenotypic variants, ranging from complete testicular feminization syndrome to simple, and sometimes slight, virilization defects. Spermatogenesis is absent or reduced, but can be normal in rare cases.

### 14.3.4 Other Endocrine Diseases

#### 14.3.4.1 Hyperprolactinemia

A chronic prolactin excess interferes with gonadic function, reducing testosterone levels and causing oligospermia. The mechanisms by which hyperprolactinemia inhibit testicular function are not yet fully verified, even though experimental data indicate that it is likely the result of a combined action at the pituitary-hypothalamic level (by reducing the GnRH/gonadotropic secretion) and at the testicular level (by interfering with testosterone synthesis and secretion). Spermatogenesis alterations are probably secondary with respect to the testosterone deficit, while it is unknown whether prolactin is able to act negatively at a tubular level.

A routine check of prolactin levels in asymptomatic infertile men is not recommended. In fact, mild increases in prolactin are of doubtful significance, as they may be caused by medications or several other medical conditions. Prolactin-secreting tumors are rare, with prolactin levels beyond 50 ng/mL appearing in adenomas larger than 1 cm [2].

#### 14.3.4.2 Thyroid Disease

Male infertility is more frequent in thyroid diseases, particularly in hyperthyroidism [3, 4]. Nonetheless, most men with thyroid abnormalities are not infertile, either before or after treatment. Thyroid abnormalities, if present, often lead to oligospermia rather than azoospermia. The following mechanisms have been proposed: alterations in sex steroid metabolism, testicular and pituitary developmental abnormalities, changes in sex hormone binding globulin (SHBG), and increased

levels of estradiol. Severe congenital hypothyroidism may cause global developmental abnormalities of the hypothalamic-pituitary-gonadal axis.

#### 14.3.4.3 Growth Hormone Alterations

There are few data confirming a role of growth hormone (GH) in endocrine dysfunction in fertility [5]. In fact it is difficult to identify a reliable method of measuring GH secretion patterns that may relate to fertility. However, acromegaly may inhibit spermatogenesis [6].

#### 14.3.4.4 Hyperestrogenism

High levels of estrogens caused by peripheral aromatization in adipose tissue, mainly in obese subjects, can inhibit pituitary function [7] and, therefore, spermatogenesis.

#### 14.3.4.5 Cushing Syndrome

In Cushing syndrome, the glucocorticoid excess not only can suppress LH function but may also have a direct contributing role in affecting spermatogenesis and maturation arrest [8].

#### 14.3.4.6 Diabetes Mellitus

Infertility rates in individuals with diabetes are higher than average (16 and 19.1 %, respectively, for primary and secondary infertility) [9]. Excessive weight, and obesity in particular, seem to be the leading contributors to infertility.

Three main dysfunctional mechanisms may be postulated to explain the sperm damage observed in diabetic patients: endocrine disorders, diabetic neuropathy, and oxidative stress. In insulin-dependent diabetes:

1. Leydig cell function and testosterone production decrease because of the lack of stimulatory effect of insulin on these cells
2. An insulin-dependent decrease in FSH reduces LH levels
3. The FSH decrease also reduces sperm output and fertility

As a result, in diabetic patients serum testosterone is decreased and gonadotropin levels are increased. Moreover, a steroidogenetic defect in Leydig cells can be observed.

### 14.3.5 Endocrine Disruptors

Endocrine manipulation in male infertility starts with ruling out possible endocrine disruptors [10].

Micropollutants in the environment, in particular steroid mimetics (in water supplies, food sources, etc.), may contribute to an overall decline in male fertility.

The increasing use of phytoestrogen has also been claimed to contribute. In fact, many dietary supplements contain significant levels of plant phytoestrogens that mimic testosterone and estrogen.

## 14.4 Diagnosis

Clinical history and physical examination are the cornerstones of the diagnosis: penis and testis volume, weight, height, and secondary sexual characteristics should be evaluated. The occurrence of headaches, visual disturbances, bitemporal visual field losses, cranial nerve palsies, and cerebrospinal fluid rhinorrhea should also be investigated.

A small set of basal hormones (testosterone, LH, FSH, estradiol, SHBG, prolactin) is usually sufficient for diagnosis (Fig. 14.1) [11]. It should be remembered that FSH and LH are secreted in short pulses, and a single measurement may not be sufficient to clarify the diagnosis.

### 14.4.1 Dynamic Tests

Persistent borderline low hormonal values may be further evaluated with the GnRH stimulation test, the clomiphene stimulation test, and the human chorionic gonadotropin (hCG) stimulation test [12].

#### 14.4.1.1 GnRH Stimulation Test

This test is indicated in adult men with low testosterone levels and normal or low-to-normal gonadotropins. The patient receives GnRH 100 μg intravenously. LH and FSH both are expected to rise, with a peak occurring between 15 and 60 min; LH increases threefold to sixfold while FSH increases about 20–50 % above the baseline.

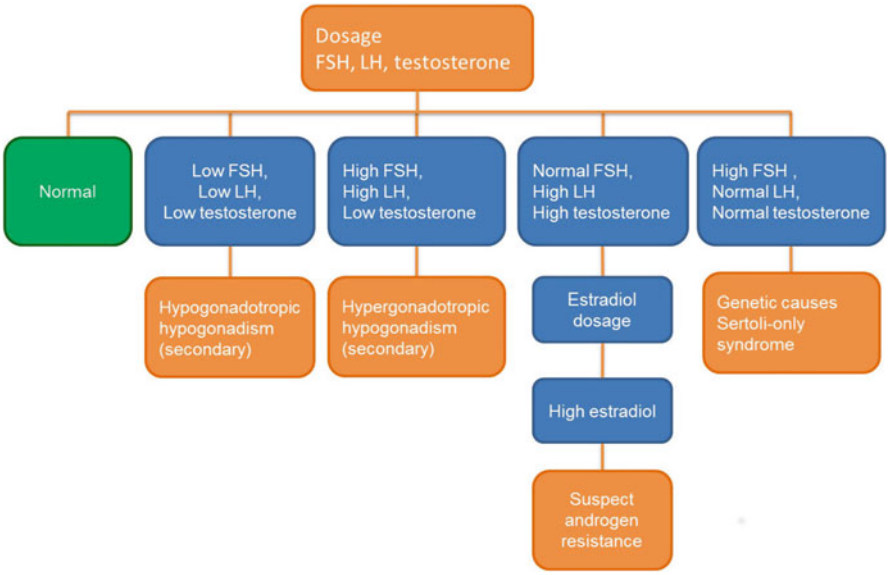


**Fig. 14.1** Diagnostic flow chart of male hypogonadism

#### 14.4.1.2 Clomiphene Stimulation Test

This test is indicated in suspected gonadotropin deficiencies. Clomiphene acts as an antiestrogen centrally and as a weak estrogen peripherally. The central antiestrogen effect, interrupting the negative feedback of estrogen on GnRH release, induces a rise in LH and FSH. The patient is treated for 5–7 days with 100 mg clomiphene citrate. A doubling of LH and a 20–50 % increase in FSH are considered normal.

#### 14.4.1.3 Human Chorionic Gonadotropin Stimulation Test

The hCG stimulation test is indicated in adults, in the differential diagnosis of combined testicular and pituitary failure versus secondary hypogonadism. A single dose of hCG (5,000 IU intramuscularly) is administered, and testosterone values are measured at the baseline and every 24 h up to day 5. In adult hypogonadism the lack of an increase in testosterone after hCG suggests a lack of functioning testicular tissue. Conversely, a rise suggests an intact Leydig cell system. In gonadotropin deficiency with no primary testicular abnormality, the basal testosterone value should triple after hCG.

## 14.5 Therapy

Several sites can be influenced by selective drugs (Fig. 14.2).

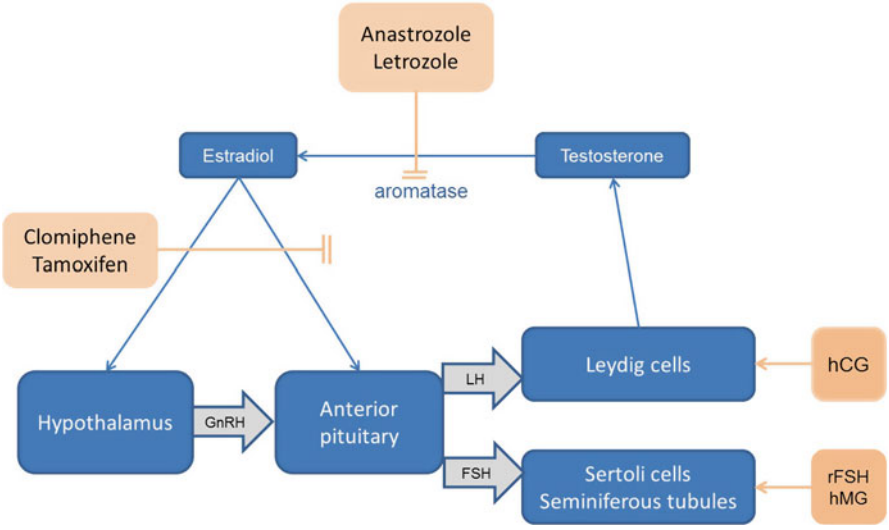


**Fig. 14.2** Sites of action of drugs used for treating male hypogonadic infertility

### 14.5.1 Estrogen Receptor Modifiers

Both clomiphene and tamoxifen are selective estrogen receptor modifiers (SERMs); inhibiting estrogen receptor at the level of the pituitary, both FSH and LH levels increase. As a result testosterone increases, thus favoring sperm growth and maturation [13].

In hypogonadism and oligospermia, clomiphene is used as monotherapy [14]. Starting dose is 25 mg once daily; as clomiphene is normally available in 50-mg tablets, a starting dose might be 50 mg every other day. When testosterone remains low, clomiphene can be titrated up to 100 mg once daily.

Clomiphene has also been used on hypogonadic patients with azoospermia. Increases in testosterone in the testis may favor production of sufficient sperm in the ejaculate. Tamoxifen is used for the same indications [15], at a dosage of 10 mg once daily.

### 14.5.2 Aromatase Inhibitors

Anastrazole and letrozole are aromatase inhibitors, directly limiting estrogen feedback to the pituitary, thus increasing the production of FSH and LH [16]. Some men with severely defective sperm production have excessive aromatase activity, documented by low serum testosterone and relatively high estradiol levels. Aromatase inhibitors can increase endogenous testosterone production and serum testosterone levels. Treatment of infertile males with aromatase inhibitors has been associated with increased sperm production and return of sperm to the ejaculate in men with nonobstructive azoospermia.

Anastrazole (1 mg once daily) and letrozole (2.5 mg once daily) are used for impaired spermatogenesis, although this represents an off-label use.

Enclomiphene citrate [17] (an isomer of clomiphene) is in phase 3 trials for the treatment of hypogonadism infertility.

### 14.5.3 Gonadotropins

SERMs and aromatase inhibitors are effective and relatively inexpensive, and thus are used as first-line agents for the treatment of endocrine dysfunction in the hypogonadal infertile male.

However, in cases of severe hypogonadotropic hypogonadism, the LH homologue hCG is the gold standard for treatment [18]. hCG 2,000 IU subcutaneously, three times per week, is usually sufficient to achieve desired testosterone levels and induce spermatogenesis. Direct testosterone administration has proved to be ineffective [19, 20].

In congenital forms, a 6-month titration is often required to be followed by the use of recombinant FSH or an FSH analogue, human menopausal gonadotropin.

The usual dosage for both is 75 IU or 150 IU three times weekly, as the usual vial contains 75 IU. Even in acquired hypogonadotropic hypogonadism, however, combination hCG/FSH analogues may be more effective than hCG alone in stimulating spermatogenesis.

### 14.5.4 Future Therapy

The new horizon of idiopathic male infertility treatment is personalized pharmacogenetic therapy.

Gene therapy is one of the frontiers of modern medicine. A viral vector can be used as a delivery device to reconstitute a key missing promoter sequence encoding a vital protein for cellular function. Unfortunately, little is known about the genetic loci involved in spermatogenesis. Moreover, it may be difficult to affect testis and/or spermatozoa with gene therapy without affecting the germline. The Sertoli cells, because of their special tolerogenic properties, may represent an ideal candidate for cell-based gene therapy.

Further possibilities are tissue grafting and spermatogonial stem cell transplantation.

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