Endocrinopathies

5

Sam Haywood, Isaac Lam, Eric L. Laborde, and Robert Brannigan

Key Points

- Hypogonadotropic hypogonadism, characterized by deficient production of gonadotropins (FSH and LH), results in low testosterone levels and can arise due to either congenital or acquired causes.
- Males with Klinefelter syndrome have a 47, XXY karyotype and also commonly have hypergonadotropic hypogonadism with impaired or absent spermatogenesis.
- Androgen excess, which commonly arises through the use of prescription exogenous testosterone therapy or illicit use of anabolic steroids, suppresses intratesticular testosterone production which typically results in partial or complete suppression of spermatogenesis.
- Estrogen excess, which is commonly associated with obesity, results from the conversion of testosterone to estradiol by aromatase in adipose tissue and can lead to low testosterone levels.
- Clomiphene citrate and human chorionic gonadotropin (hCG) are both off-label therapies for testosterone deficiency that can support both intratesticular testosterone production and spermatogenesis.

S. Haywood
Glickman Urological and Kidney Institute, Cleveland Clinic Foundation, Cleveland, OH, USA

I. Lam
Department of Urology, Northwestern Memorial Hospital, Chicago, IL, USA
e-mail: Isaac.lam@northwestern.edu

E. L. Laborde
Department of Urology, Ochsner Health Systems, New Orleans, LA, USA

R. Brannigan (✉)
Department of Urology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: r-brannigan@northwestern.edu

5.1 Introduction

Spermatogenesis depends on an intricate interplay of hormonal factors both centrally and in the testis. Centrally, the hypothalamus releases gonadotropin-releasing hormone (GnRH), which acts on the anterior pituitary to cause secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). At the level of the testis, FSH acts on Sertoli cells to induce the maturation process in spermatogonia. LH exerts its effect on Leydig cells, stimulating the production of testosterone. Effective spermatogenesis requires local testosterone concentrations to be much higher than serum concentrations. This intratesticular testosterone then acts indirectly to stimulate germ cell maturation through actions on Sertoli cells [1].

Although endocrinopathies only account for a small minority of cases of male infertility, about 1%–2% [2], the treatment of these conditions offers patients a strategy of directed therapy. Broad classification of endocrinopathies involves two main categories, that is, hormonal deficiency and hormonal excess, with specific hormonal abnormalities falling under each of the previously mentioned categorizations.

In this chapter, we provide an overview on diseases in which hormonal imbalance can negatively impact fertility. We discuss the etiology and clinical presentation for each disease. The standard diagnostic process and best management approach will be addressed as well, and future directions for research in this area will be explored.

5.2 Hormonal Deficiency

5.2.1 Hypogonadotropic Hypogonadism

As the name suggests, hypogonadotropic hypogonadism is a state of testosterone deficiency associated with subnormal levels of gonadotropins (FSH and LH). Etiologies of hypogonadotropic hypogonadism can be numerous and are divided into congenital and acquired causes.

S. J. Parekattil et al. (eds.), *Male Infertility*, https://doi.org/10.1007/978-3-030-32300-4_5

Kallmann syndrome is one identified congenital etiology of hypogonadotropic hypogonadism. Inherited in an X-linked recessive fashion, Kallmann syndrome can arise due to a variety of mutations, the most prevalent of which involves the KAL1 gene. Features include hypogonadism as well as anosmia, facial defects, renal agenesis, and neurologic abnormalities [3]. The hypogonadism and associated clinical sequelae (delayed puberty, infertility) result from a failure of migration of GnRH-secreting neurons. This failure of migration leads to the absence of GnRH secretion which in turn leads to the absence of LH and FSH secretion [2].

Hypogonadotropic hypogonadism can also be acquired, as in the case of pituitary insufficiency resulting from pituitary tumors, surgery, infarct, or infiltrative disease. Regardless of the myriad etiologies of hypogonadotropic hypogonadism, the underlying disturbance is low gonadotropin levels, and treatment can be affected through pharmacologic replacement.

Treating hypogonadotropic hypogonadism involves replacement of the deficient hormones through gonadotropin therapy. Agents used in this therapy include human chorionic gonadotropin (hCG), human menopausal gonadotropin (hMG), and recombinant follicle-stimulating hormone (rFSH). Human chorionic gonadotropin use stems from its properties as an LH analogue, acting at the Leydig cell to stimulate androgen secretion. Human menopausal gonadotropin is a product purified from the urine of postmenopausal women that contains both LH and FSH. Regimens of gonadotropin therapy for men with hypogonadotropic hypogonadism typically begin with hCG administration alone for 3–6 months. Dosages range from 1000 to 1500 USP units either IM or SC three times per week. Adequacy of therapy can be assessed by measuring serum testosterone levels, with the goal of achieving sustained normal levels. Although the pertinent goal for spermatogenesis is adequate intratesticular testosterone concentrations, this value is not normally assessed in gonadotropin replacement therapy. However, intratesticular testosterone levels show linear correlation with administered hCG dosage [4]. After titration to sustained normal testosterone levels, usually after 3–6 months of hCG monotherapy, therapy is initiated to replace FSH levels. One method of FSH replacement involves hMG given at doses of 75–150 IU IM/SC three times a week at a separate injection site. Alternatively, rFSH can be used at dosages of 150 IU SC three times a week [5]. Relative efficacy of hMG versus rFSH has been studied to some extent in women undergoing IVF, but comparisons in male patients are lacking. Replacing gonadotropins in this manner has shown promising results as more than 90% of treated males experience spermatogenesis [2]. The time to spermatogenesis can be quite variable, with the average response occurring in about 6–9 months. However, therapy may be required for up to 1–2 years before a response may occur, and some individuals unfortunately never respond to this modality [6]. An Australian study of 38 men with hypogonadotropic hypogonadism found that median time to first sperm in the ejaculate was 7.1 months, while median time to conception was 28.2 months [7].

While spermatogenesis occurs in a strong majority of patients, sperm concentrations achieved through gonadotropin therapy still sometimes fall below goal ranges (<20 million sperm/mL). Despite this, fertility outcomes with gonadotropin therapy are very good. In a study of 24 men with hypogonadotropic hypogonadism treated with gonadotropin therapy, 22 men achieved pregnancy, even though mean sperm concentration was 16.7 million sperm/mL [8]. A retrospective study of Japanese men found sperm production in 71% of men treated with hCG (3000 IU) and hMG (75IU), provided testicular size was greater than prepubertal sizes (>4 mL) [9]. A recently published Saudi Arabian paper studied 87 infertile men with hypogonadotropic hypogonadism treated with IM gonadotropins for a median of 26 months, with the primary outcome of fertility. Overall, 35 of the 87 patients (40%) were able to achieve pregnancy [10].

An important area of newer research focuses on determining predictors of response to gonadotropin therapy. The aforementioned long-term study in Japanese men found a correlation between testicular size pretreatment and response to gonadotropin therapy. Men with testicular size >4 mL had a 71% chance of responding to treatment, whereas men with testicular size <4 mL had only a 36% chance of responding to treatment [9]. In addition, the above Saudi Arabian study found that only pretreatment testicular size was predictive of conception. In particular, responders to treatment had a mean testicular pretreatment volume of 9.0 ± 3.6 mL, while the pretreatment testicular volume of nonresponders was only 5.7 ± 2.0 mL. Interestingly, there was no significant difference in conception rates between men with hypogonadotropic hypogonadism due to congenital or acquired etiologies [10]. Larger baseline testicular size has also been shown as an independent predictor of response time to gonadotropin therapy, and achieving summed testis volume >20 mL after treatment increased the odds of achieving both goal sperm parameters and pregnancy by at least twofold [7]. It is worth noting that the lower sperm concentrations found in these studies, while below traditional goals of infertility management, may allow for pregnancy with adjunctive use of assisted reproductive therapies such as intrauterine insemination or in vitro fertilization. Additionally, such medical treatment may allow increased efficacy of surgical sperm extraction.

Another method of treatment for men with hypogonadotropic hypogonadism involves the use of antiestrogen agents. These agents competitively bind to estrogen receptor sites in the hypothalamus. Normally, estradiol acts via negative feedback at this endocrine center to inhibit gonadotropin secretion.

By binding at these sites, antiestrogen agents block estradiol's feedback inhibition of the hypothalamus and thus increase the hypothalamic secretion of GnRH. The increased secretion of GnRH leads to increased pituitary secretion of gonadotropins, which thereby stimulates an increase in intratesticular testosterone production. The most commonly used agent in this class is clomiphene citrate, but similar agents include tamoxifen, raloxifene, and toremifene. These drugs have been previously studied in the setting of empiric therapy for idiopathic infertility with mixed results [6]. However, the directed use of clomiphene in patients with proven hypogonadotropic hypogonadism has shown to be useful in limited settings. An American study treated four men with hypogonadotropic hypogonadism with clomiphene citrate 50 mg three times a week and found improved testosterone levels and semen parameters in three of these patients. Subsequently, two of these three men achieved documented pregnancy [11]. Similar success at the biochemical level has also been described in case reports, although fertility was not a goal of these treatments [12, 13]. A recent retrospective study of 31 men compared clomiphene citrate with testosterone therapy. Serum testosterone levels were highest in the group injected with testosterone and lower for the groups that received topical testosterone and clomiphene treatment. Despite these findings, the ADAM questionnaire determined that level of satisfaction was similar in all groups [14]. Clomiphene treatment of male infertility can be associated with such side effects as visual disturbances, GI upset, weight gain, hypertension, and insomnia [6].

Although using testosterone therapy to improve spermatogenesis is not recommended, a significant number of providers still utilize this approach. A recent study found that around one fourth of urologists surveyed have prescribed testosterone in an attempt to enhance spermatogenesis [15]. However, exogenous testosterone actually has detrimental effects on spermatogenesis. Increased levels of exogenous testosterone result in negative feedback to the hypothalamus, leading to lower levels of GnRH, gonadotropin, and ultimately intratesticular testosterone. Previous research indicates that suppression of intratesticular testosterone to levels less than 20 ng/mL can substantially impair normal spermatogenesis [16].

It is worth noting that exogenous GnRH treatment represents another avenue of medical therapy for hypogonadotropic hypogonadism. Synthetic analogues of GnRH can be administered to stimulate secretion of gonadotropins. However, the short half-life of these agents combined with the necessary pulsatile release to recreate normal physiology requires a method of frequent administration, such as frequent injections, nasal sprays, or an implantable pump. These methods are obviously less convenient, and further, studies have not shown this treatment to have a strong benefit for hypogonadotropic hypogonadism [1].

5.2.2 Hypergonadotropic Hypogonadism

In hypergonadotropic hypogonadism, the main perturbation is an inadequate or absent function of the testes. Gonadotropins are appropriately elevated secondary to lack of negative feedback from estradiol, testosterone, and inhibin B from the testis. Without appropriate androgen secretion, spermatogenesis is impaired. These men also typically have significant testicular atrophy with fibrosis and markedly reduced germ cell number, also leading to abnormally low levels of spermatogenesis. Hypergonadotropic hypogonadism can occur as a result of genetic etiologies (e.g., Klinefelter syndrome) or from acquired conditions. Acquired etiologies of hypergonadotropic hypogonadism include destruction of normal gonadal tissue from chemotherapy or radiation, trauma, mumps orchitis, or androgen decline in the aging male. Men with hypergonadotropic hypogonadism not desiring fertility can be treated with exogenous testosterone therapy, but men trying to conceive should generally not be given exogenous testosterone. The treatment for men trying to conceive is less well characterized. Aromatase inhibitors have been suggested as treatment for men with Klinefelter syndrome [4]. A small cohort of patients with Klinefelter syndrome treated with aromatase inhibitors showed hormonal improvements with treatment, although the study did not comment on semen parameters in the Klinefelter subset. In particular, for this subset of patients, testolactone therapy was more efficacious with respect to hormonal levels than anastrozole [17].

It is important to mention the additional potential advantage in the setting of surgical sperm extraction after adjuvant medical therapy in men with Klinefelter syndrome. Surgical sperm extraction alone has resulted in successful retrieval in up to 50% of attempts [18]. Ramasamy et al. retrospectively studied 68 azoospermic men with Klinefelter syndrome. Of these 68 men, 56 were treated for low testosterone levels (<300 ng/dL) with a combination of medical therapies (aromatase inhibitors, hCG, clomiphene) before microdissection TESE. Of the 56 men receiving medical therapy before TESE, 28 received testolactone alone, 12 received testolactone and weekly hCG, 9 received anastrozole alone, 1 received anastrozole and hCG, and 4 received hCG alone. Three patients received clomiphene citrate. While there was no difference among specific agents in terms of successful sperm extraction, these medical regimens collectively resulted in improved sperm retrieval when patients responded to medical therapies with posttreatment testosterone >250 ng/dL. More specifically, successful sperm extraction was seen in 77% of men with posttreatment testosterone >250 ng/dL versus 55% of men with posttreatment testosterone <250 ng/dL [18].

Most commonly, androgen supplementation is initiated when luteinizing hormone levels rise above normal during puberty. Despite the paucity of data, studies in progress may

help provide the foundation for producing evidence-based guidelines on the timeline of androgen supplementation. A recent retrospective study found that infants with Klinefelter syndrome who received testosterone treatment had superior cognitive development at 3 and 6 years old, but the generalizability of these findings is questionable due to the lack of randomization and blinding [19]. To date, no randomized controlled trials of testosterone supplementation in Klinefelter syndrome children have been published, but a study is currently in progress at Children's Hospital Colorado. Another randomized controlled trial on Klinefelter syndrome in early adolescence is in the process of enrolling as well, with the purpose of evaluating the psychosocial impact of topical testosterone [20]. Despite the deficit in data, studies in progress may help provide the foundation for producing evidence-based guidelines on the timeline of androgen supplementation.

The rate of diagnosis of Klinefelter syndrome may increase substantially in the coming years as prenatal testing for the disease may be integrated into routine prenatal care in the near future. This change would lead to an estimated increase in rate of diagnosis by up to five times the current rate [21]. As a result, the higher rate of diagnosis may potentially drive the research community to allocate more energy and resources to studying patient-centered Klinefelter syndrome health and treatment outcomes.

5.2.3 Hypothyroidism

Thyroid hormones are essential in organ development and routine metabolism. However, there have been few studies evaluating hypothyroidism and male reproduction in humans. Substantial research has been performed on rats studying the relationship between hypothyroidism and male fertility. Rats with drug-induced hypothyroidism have been shown to have fewer and smaller seminiferous tubules, lighter testes, less testicular germ cells, and impaired sperm parameters in contrast to their control rat counterparts [22–24].

In humans, hypothyroidism has long been associated with diminished libido and erectile dysfunction [25]. Additionally, a recent study by Meeker et al. revealed a correlation between thyroxine (T4) level and sperm concentration, with higher T4 being correlated with better sperm concentrations [26]. Sperm concentration may not be the only parameter affected, as a study by Krassas et al. showed that men with hypothyroidism have a lower than normal percentage of sperm with normal morphology as well as impaired sperm motility and decreased ejaculate volume. Correcting the hypothyroidism resulted in 76% of the patients having a normal morphology [27]. Overall, there is a relative scarcity of data regarding hypothyroidism and semen parameters. Nonetheless, these studies do suggest a link between thyroid function and spermatogenesis.

5.3 Hormonal Excess

5.3.1 Androgen Excess

Within the hypothalamic–pituitary–testis axis, testosterone exerts negative feedback inhibition on the hypothalamic secretion of GnRH. This effect is indirect and thought to occur via aromatization of testosterone to estradiol. Acting in this manner, excess circulating testosterone can suppress this axis and cause inhibition of spermatogenesis.

Testosterone excess can result from exogenous testosterone administration or from endogenous production.

Therapeutic administration can inadvertently result in testosterone excess, but testosterone excess can also result from the illicit use of anabolic steroids. Regardless of the cause, exogenous androgens typically suppress gonadotropin secretion with resultant decreased levels of intratesticular testosterone and decreased spermatogenesis. Diagnosis is suggested by normal to high serum testosterone levels with suppressed gonadotropins. The first step in treating a male with suspected androgen excess is to remove the exogenous source. Return of spermatogenesis usually occurs within 4 months but in some instances can take up to 3 years [28, 29]. If sperm parameters do not improve adequately or are slow to improve, then some evidence suggests beneficial effects of gonadotropin therapy in improving intratesticular testosterone levels [29, 30]. If response to treatment remains suboptimal after a trial of gonadotropin therapy, then limited evidence suggests a possible use of clomiphene in reestablishing the hypothalamic–pituitary–testis axis [31].

Although abuse of anabolic androgenic steroids has not been a focus in mainstream medicine, a recent review has brought to light the toll this issue has had on the health of young men in America. Retrospective analysis of over 6000 patients revealed that steroid abuse was the etiology in over a third of the patients with profound hypogonadism, and perhaps even more worrisomely, about one fifth of men treated for symptomatic hypogonadism reported previous use of anabolic androgenic steroids [32]. Given the rise in incidence of steroid abuse, growing numbers of psychiatrists accept anabolic androgenic steroid dependence as a diagnostic entity [33]. Counseling patients with anabolic steroid-associated hypogonadism and understanding the patients' motivation for use is crucial for both preventing future use and recognizing other diseases the patient may have such as primary hypogonadism that the provider can safely medically manage.

Androgen excess can also result from endogenous androgen production. The most common endogenous source is congenital adrenal hyperplasia, although functional tumors (adrenal or testicular) and androgen insensitivity syndromes could also be responsible [2]. Although congenital adrenal hyperplasia is more commonly discussed in the context of female fertility, there have been multiple studies linking the

disease to decreased fertility in men [34, 35]. In one of these studies, only two thirds of men with congenital adrenal hyperplasia who attempted pregnancy achieved success [36]. In terms of treatment, numerous strategies have been studied and proven efficacious, including hCG with FSH, clomiphene citrate, and intracytoplasmic sperm injection [37–39].

5.3.2 Estrogen Excess

As mentioned earlier, testosterone's ability to inhibit GnRH secretion at the hypothalamus is mediated through conversion to estrogens. A primary excess of estrogens can act similarly to inhibit the hypothalamic–pituitary–testis axis and thus contribute to decreased fertility. While estrogens are produced in the testis along with testosterone, the main source of estrogens in males is peripheral aromatization of testosterone by the enzyme aromatase, found in adipose tissue. The rising prevalence of obesity in our society puts more men at risk for estrogen excess. In particular, the ratio of testosterone to estradiol (T:E2) appears to be an important measure of estrogen excess, with a goal ratio > 10:1 sought by many clinicians. Pavlovich et al. examined a cohort of infertile men and found significantly reduced T:E2 ratios in the infertile men compared with a fertile control group (6.9 vs. 14.5) [40].

Treatment of relative estrogen excess involves inhibitors of the aromatase enzyme. There are two main classes of aromatase inhibitors: steroidal agents (e.g., testolactone) and nonsteroidal agents (e.g., anastrozole). Both have shown utility in treatment of infertile men with low T:E2 ratios. The above Pavlovich study treated 63 men with male factor infertility and low T:E2 ratios with testolactone, 50–100 mg twice daily. Treatment was effective in improving both T:E2 ratio and sperm quality, as defined by concentrations and motility [40]. A more recent study by Raman and Schlegel treated 140 infertile men with abnormal T:E2 ratios with either testolactone (100–200 mg daily) or anastrozole (1 mg daily). Both treatment arms showed improvement in T:E2 ratio and improved sperm concentration and motility. Further, the study did not show any significant difference between the two classes of aromatase inhibitors in terms of hormonal profile or semen analysis, except in the setting of Klinefelter syndrome, where testolactone was superior in treating the abnormal T:E2 ratios [17]. These studies combined show a clear role for aromatase inhibitors in infertile men with abnormal T:E2 ratios. This treatment strategy may be of particular importance in obese patients [41].

5.3.3 Thyroid Excess

As was touched upon earlier, the role of thyroid hormones in spermatogenesis is not entirely clear. However, hyperthyroidism appears to adversely affect semen parameters. Abalovich et al. found that patients with hyperthyroidism have lower bioavailable testosterone, higher sex-hormone-binding globulin, and higher LH levels compared with controls [42]. Hyperthyroid patients were reported to have markedly impaired semen parameters, including low motility, low ejaculate volume, low sperm concentration, and abnormal morphology. The authors noted that 85% of the seminal abnormalities normalized on semen testing conducted 7–19 months after achievement of euthyroid status. A more recent study also found that hyperthyroidism can impair semen parameters [43]. The authors of this study reported that hyperthyroid patients had significantly lower sperm motility than controls. Motility was improved after euthyroid status was achieved with medical thyroid ablation. Just as with hypothyroidism, there is a scarcity of data regarding hyperthyroidism and spermatogenesis. However, the available studies seem to suggest that hyperthyroidism can adversely affect semen parameters.

5.3.4 Prolactin Excess

Hyperprolactinemia, an excess of the hormone prolactin, is another hormonal etiology of male infertility. The diagnosis is relatively straightforward, as hyperprolactinemia can be detected on routine serum testing, but determination of a particular etiology can be more challenging. Hyperprolactinemia can occur in the case of hypothyroidism, liver disease, stress, use of certain medications (i.e., phenothiazines, tricyclic antidepressants), and with functional pituitary adenomas (prolactinomas). Clinical suspicion must be high for excess prolactin, as the manifestations can range from asymptomatic in many patients to galactorrhea or hypoandrogenic states (i.e., low libido, erectile dysfunction) in affected patients. Patients with pituitary adenomas may also present with bilateral temporal visual field defects. This state, known as bitemporal hemianopsia, is the result of the close anatomic proximity of the pituitary gland to the optic chiasm. Growth of the pituitary tumor compresses the optic nerve, leading to visual field deficits.

Hyperprolactinemia can cause male infertility through its inhibitory effects on the hypothalamus. The high levels of prolactin suppress the secretion of GnRH from the hypothalamus, which subsequently impairs the release of gonadotropins, the production of testosterone, and spermatogenesis. The multiple effects on the hypothalamic–pituitary–testicular axis can result in a patient presenting with multiple problems such as decreased libido, inability to achieve erection, and abnormal semen parameters.

Once the diagnosis of hyperprolactinemia is made, the practitioner should obtain an MRI study focusing on the pituitary gland. If a prolactinoma is found, then it can be

characterized based on its size and appearance. The main differentiation is between microadenomas, lesions <10 mm, and macroadenomas, which are lesions >10 mm. If a prolactinoma is discovered, then medical therapy focuses on blocking the secretion of prolactin through the use of dopamine agonists. Examples of these agents include bromocriptine, cabergoline, pergolide, and quinagolide, with the most well-characterized agents being bromocriptine and cabergoline. These agonists make use of the natural inhibition of prolactin secretion by dopamine. This can actually cause regression of the tumor, although the process generally occurs over months. Possible side effects of dopamine agonists include nausea, vomiting, and postural hypotension. While inhibition of excess prolactin secretion prevents the disruption of the hypothalamic–pituitary axis, there have been few studies specifically elucidating the effects of these dopamine agonists on spermatogenesis and fertility. A 1974 study treated men with functional prolactinomas and hypogonadism with bromocriptine and found no increase in sperm motility [44]. However, more recently, DeRosa and colleagues compared bromocriptine and cabergoline in such patients. Both treatments showed overall improvements in sperm number, motility, rapid progression, and morphology within 6 months of therapy [45]. A subsequent study from the same institution compared seminal fluid parameters between men with prolactinomas and control men. After 24 months of treatment with cabergoline (initial dose 0.5 mg weekly, subsequently titrated to PRL levels), two-thirds of men showed restored gonadal function as compared against healthy control men [46].

Comparing cabergoline and bromocriptine, it appears that cabergoline is more efficacious at normalization of prolactin levels and regressing tumor burden [47]. Further, a higher percentage of patients show a clinical response to cabergoline when compared with bromocriptine. Finally, there is a higher overall rate of permanent remission and fewer side effects with cabergoline compared to bromocriptine [47]. Considering all of these findings, cabergoline is often the first therapy utilized in treating men with prolactinomas.

While treatment of prolactinomas with dopamine agonists can be effective in many cases, a significant percentage of men may still remain persistently hypogonadotropic. Recent research suggests that clomiphene citrate may be an effective treatment for these men. Ribiero and Abucham treated 14 persistently hypogonadal men with clomiphene (50 mg/day for 12 weeks) and noted both improved testosterone levels and sperm motility [48].

Ablative therapy for prolactinomas—in the form of radiation therapy or transsphenoidal resection—is also available. Ablative therapy is typically reserved for those who fail medical management. Ablative treatments remove the source of prolactin and thus the inhibition of GnRH secretion. Measurement of the patient's gonadotropin levels posttreatment remains important, as further intervention with exogenous gonadotropins may be necessary to optimize therapeutic benefit.

Medical treatments for male infertility have traditionally centered on empiric approaches to enhance spermatogenesis. Over the past two decades, improved insight has been gained into the pathophysiology of male infertility and the outcomes associated with empiric therapy. With this insight, more targeted and directed use of medical agents has been described. As such, "empiric therapy" is used with less frequency now than was the case 20 years ago. Many available medical therapies for infertile men are used to optimize the hormonal milieu and thus optimize spermatogenesis. This has indeed been the focus of this chapter. However, numerous other medical agents are used routinely to address other specific pathophysiologic conditions leading to male factor infertility. These agents include antimicrobial drugs, anti-inflammatory medications, and sympathetic agonists. Each of these classes of drugs has clear indications for use in specifically targeted subgroups of infertile men, and they are each described in other specific chapters of this text.

One important point clearly delineated in the literature over recent years is this: empiric medical therapy generally has limited utility and benefit in the treatment of infertile men. While randomized, double-blinded, placebo-controlled studies are costly in terms of time and money, they remain the proving ground for effective medical therapies. More than one agent has failed to pass this test in recent years, but this is a good thing. While the armamentarium of available medical agents for the treatment of male infertility is somewhat limited, this fact should push us to strive harder to gain enhanced insight into the pathophysiological mechanisms leading to decreased male reproductive potential. It is with this enhanced insight into the fundamental problems leading to male infertility that we will develop additional, effective medical therapies.

5.4 Conclusion

Male fertility relies on an intricate hormonal balance and thus a deficiency or excess in a number of hormones can result in impaired fertility. This imbalance can impact fertility by affecting the more central hypothalamic–pituitary axis or by causing dysregulation in the testis where LH and FSH act on Sertoli cells and Leydig cells, respectively, to stimulate maturation of spermatogonia. Despite the low percentage of infertility cases involving endocrinopathies, further research on better understanding the etiology of the mechanism behind infertility is essential as it may lead to the development of more tailored therapies for endocrinopathy-induced infertility. As the rates of metabolic diseases continue to rise

in this country, addressing the impact of hormonal imbalance on male fertility will play an increasingly important role in improving patient quality of life.

5.5 Review Criteria

A meticulous search of studies addressing the topic of endocrinopathies related to male infertility was performed using the search engines PubMed and MEDLINE. The start and end dates for these searches were November 2018 and December 2018, respectively. Manuscripts published in academic meeting proceedings were not included. The overall strategy for study identification and data extraction was based on the following key words: male infertility, spermatogenesis, endocrinopathy, hypogonadotropic hypogonadism, hypergonadotropic hypogonadism, hyperprolactinemia, hyperthyroidism, androgen excess, and estrogen excess.

References

1. Lipshultz LI, Howards SS, Niederberger CS. Infertility in the male. 4th ed. Cambridge, UK/New York: Cambridge University Press; 2009. xi, 677 p., 8 p. of plates p.
2. Kim HH, Schlegel PN. Endocrine manipulation in male infertility. Urol Clin North Am. 2008;35(2):303–18, x.
3. Sussman EM, Chudnovsky A, Niederberger CS. Hormonal evaluation of the infertile male: has it evolved? Urol Clin North Am. 2008;35(2):147–55, vii.
4. Coviello AD, Matsumoto AM, Bremner WJ, Herbst KL, Amory JK, Anawalt BD, et al. Low-dose human chorionic gonadotropin maintains intratesticular testosterone in normal men with testosterone-induced gonadotropin suppression. J Clin Endocrinol Metab. 2005;90(5):2595–602.
5. Bouloux PM, Nieschlag E, Burger HG, Skakkebaek NE, Wu FC, Handelsman DJ, et al. Induction of spermatogenesis by recombinant follicle-stimulating hormone (puregon) in hypogonadotropic azoospermic men who failed to respond to human chorionic gonadotropin alone. J Androl. 2003;24(4):604–11.
6. Schiff JD, Ramirez ML, Bar-Chama N. Medical and surgical management male infertility. Endocrinol Metab Clin N Am. 2007;36(2):313–31.
7. Liu PY, Baker HW, Jayadev V, Zacharin M, Conway AJ, Handelsman DJ. Induction of spermatogenesis and fertility during gonadotropin treatment of gonadotropin-deficient infertile men: predictors of fertility outcome. J Clin Endocrinol Metab. 2009;94(3):801–8.
8. Burris AS, Clark RV, Vantman DJ, Sherins RJ. A low sperm concentration does not preclude fertility in men with isolated hypogonadotropic hypogonadism after gonadotropin therapy. Fertil Steril. 1988;50(2):343–7.
9. Miyagawa Y, Tsujimura A, Matsumiya K, Takao T, Tohda A, Koga M, et al. Outcome of gonadotropin therapy for male hypogonadotropic hypogonadism at university affiliated male infertility centers: a 30-year retrospective study. J Urol. 2005;173(6):2072–5.
10. Farhat R, Al-zidjali F, Alzahrani AS. Outcome of gonadotropin therapy for male infertility due to hypogonadotrophic hypogonadism. Pituitary. 2010;13(2):105–10.
11. Whitten SJ, Nangia AK, Kolettis PN. Select patients with hypogonadotropic hypogonadism may respond to treatment with clomiphene citrate. Fertil Steril. 2006;86(6):1664–8.
12. Ioannidou-Kadis S, Wright PJ, Neely RD, Quinton R. Complete reversal of adult-onset isolated hypogonadotropic hypogonadism with clomiphene citrate. Fertil Steril. 2006;86(5):1513.e5–9.
13. Burge MR, Lanzi RA, Skarda ST, Eaton RP. Idiopathic hypogonadotropic hypogonadism in a male runner is reversed by clomiphene citrate. Fertil Steril. 1997;67(4):783–5.
14. Ramasamy R, Scovell JM, Kovac JR, Lipshultz LI. Testosterone supplementation versus clomiphene citrate for hypogonadism: an age matched comparison of satisfaction and efficacy. J Urol. 2014;192(3):875–9.
15. Layton JB, Li D, Meier CR, Sharpless JL, Sturmer T, Jick SS, et al. Testosterone lab testing and initiation in the United Kingdom and the United States, 2000 to 2011. J Clin Endocrinol Metab. 2014;99(3):835–42.
16. Zirkin BR, Santulli R, Awoniyi CA, Ewing LL. Maintenance of advanced spermatogenic cells in the adult rat testis: quantitative relationship to testosterone concentration within the testis. Endocrinology. 1989;124(6):3043–9.
17. Raman JD, Schlegel PN. Aromatase inhibitors for male infertility. J Urol. 2002;167(2 Pt 1):624–9.
18. Ramasamy R, Ricci JA, Palermo GD, Gosden LV, Rosenwaks Z, Schlegel PN. Successful fertility treatment for Klinefelter's syndrome. J Urol. 2009;182(3):1108–13.
19. Samango-Sprouse CA, Sadeghin T, Mitchell FL, Dixon T, Stapleton E, Kingery M, et al. Positive effects of short course androgen therapy on the neurodevelopmental outcome in boys with 47,XXY syndrome at 36 and 72 months of age. Am J Med Genet A. 2013;161A(3):501–8.
20. Davis SM, Rogol AD, Ross JL. Testis development and fertility potential in boys with Klinefelter syndrome. Endocrinol Metab Clin N Am. 2015;44(4):843–65.
21. Lo JO, Cori DF, Norton ME, Caughey AB. Noninvasive prenatal testing. Obstet Gynecol Surv. 2014;69(2):89–99.
22. Sahoo DK, Roy A, Bhanja S, Chainy GB. Hypothyroidism impairs antioxidant defence system and testicular physiology during development and maturation. Gen Comp Endocrinol. 2008;156(1):63–70.
23. Romano RM, Gomes SN, Cardoso NC, Schiessl L, Romano MA, Oliveira CA. New insights for male infertility revealed by alterations in spermatic function and differential testicular expression of thyroid-related genes. Endocrine. 2017;55(2):607–17.
24. Choudhury S, Chainy GB, Mishro MM. Experimentally induced hypo- and hyper-thyroidism influence on the antioxidant defence system in adult rat testis. Andrologia. 2003;35(3):131–40.
25. Griboff SI. Semen analysis in myxedema. Fertil Steril. 1962;13:436–43.
26. Meeker JD, Godfrey-Bailey L, Hauser R. Relationships between serum hormone levels and semen quality among men from an infertility clinic. J Androl. 2007;28(3):397–406.
27. Krassas GE, Papadopoulou F, Tziomalos K, Zeginiadou T, Pontikides N. Hypothyroidism has an adverse effect on human spermatogenesis: a prospective, controlled study. Thyroid. 2008;18(12):1255–9.
28. Dohle GR, Smit M, Weber RF. Androgens and male fertility. World J Urol. 2003;21(5):341–5.
29. Turek PJ, Williams RH, Gilbaugh JH 3rd, Lipshultz LI. The reversibility of anabolic steroid-induced azoospermia. J Urol. 1995;153(5):1628–30.
30. Menon DK. Successful treatment of anabolic steroid-induced azoospermia with human chorionic gonadotropin and human menopausal gonadotropin. Fertil Steril. 2003;79(Suppl 3):1659–61.
31. Tan RS, Vasudevan D. Use of clomiphene citrate to reverse premature andropause secondary to steroid abuse. Fertil Steril. 2003;79(1):203–5.
32. Coward RM, Rajanahally S, Kovac JR, Smith RP, Pastuszak AW, Lipshultz LI. Anabolic steroid induced hypogonadism in young men. J Urol. 2013;190(6):2200–5.

33. Kanayama G, Brower KJ, Wood RI, Hudson JI, Pope HG Jr. Anabolic-androgenic steroid dependence: an emerging disorder. Addiction. 2009;104(12):1966–78.
34. Falhammar H, Nystrom HF, Ekstrom U, Granberg S, Wedell A, Thoren M. Fertility, sexuality and testicular adrenal rest tumors in adult males with congenital adrenal hyperplasia. Eur J Endocrinol. 2012;166(3):441–9.
35. Jaaskelainen J, Kiekara O, Hippelainen M, Voutilainen R. Pituitary gonadal axis and child rate in males with classical 21-hydroxylase deficiency. J Endocrinol Investig. 2000;23(1):23–7.
36. Arlt W, Willis DS, Wild SH, Krone N, Doherty EJ, Hahner S, et al. Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients. J Clin Endocrinol Metab. 2010;95(11):5110–21.
37. Murphy H, George C, de Kretser D, Judd S. Successful treatment with ICSI of infertility caused by azoospermia associated with adrenal rests in the testes: case report. Hum Reprod. 2001;16(2):263–7.
38. Yang RM, Fefferman RA, Shapiro CE. Reversible infertility in a man with 21-hydroxylase deficiency congenital adrenal hyperplasia. Fertil Steril. 2005;83(1):223–5.
39. Rohayem J, Tuttelmann F, Mallidis C, Nieschlag E, Kliesch S, Zitzmann M. Restoration of fertility by gonadotropin replacement in a man with hypogonadotropic azoospermia and testicular adrenal rest tumors due to untreated simple virilizing congenital adrenal hyperplasia. Eur J Endocrinol. 2014;170(4):K11–7.
40. Pavlovich CP, King P, Goldstein M, Schlegel PN. Evidence of a treatable endocrinopathy in infertile men. J Urol. 2001;165(3):837–41.
41. Roth MY, Amory JK, Page ST. Treatment of male infertility secondary to morbid obesity. Nat Clin Pract Endocrinol Metab. 2008;4(7):415–9.
42. Abalovich M, Levalle O, Hermes R, Scaglia H, Aranda C, Zylbersztein C, et al. Hypothalamic-pituitary-testicular axis and seminal parameters in hyperthyroid males. Thyroid. 1999;9(9):857–63.
43. Krassas GE, Pontikides N, Deligianni V, Miras K. A prospective controlled study of the impact of hyperthyroidism on reproductive function in males. J Clin Endocrinol Metab. 2002;87(8):3667–71.
44. Thorner MO, McNeilly AS, Hagan C, Besser GM. Long-term treatment of galactorrhoea and hypogonadism with bromocriptine. Br Med J. 1974;2(5916):419–22.
45. De Rosa M, Colao A, Di Sarno A, Ferone D, Landi ML, Zarrilli S, et al. Cabergoline treatment rapidly improves gonadal function in hyperprolactinemic males: a comparison with bromocriptine. Eur J Endocrinol. 1998;138(3):286–93.
46. De Rosa M, Ciccarelli A, Zarrilli S, Guerra E, Gaccione M, Di Sarno A, et al. The treatment with cabergoline for 24 month normalizes the quality of seminal fluid in hyperprolactinaemic males. Clin Endocrinol. 2006;64(3):307–13.
47. Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. Endocr Rev. 2006;27(5):485–534.
48. Ribeiro RS, Abucham J. Recovery of persistent hypogonadism by clomiphene in males with prolactinomas under dopamine agonist treatment. Eur J Endocrinol. 2009;161(1):163–9.