Chapter 9
Fertility Preservation in Hypogonadal Men

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Introduction

Testicular failure is defined as the impairment or loss of both endocrine function of the testis (production of testosterone, or T) and exocrine function (production of spermatozoa). Testicular failure can result from pathology of the testis itself, or disorder at any point in the hypothalamo-pituitary-gonadal axis. Primary testicular failure is characterized by normal/low T in the presence of elevated follicle-stimulating hormone (FSH) indicating intact feedback loops to promote spermatogenesis and testosterone production in the central nervous system. Etiologies may be acquired or congenital, with congenital causes being most common.

Conversely, low serum FSH, luteinizing hormone (LH), and T correspond to a state of hypogonadotropic hypogonadism (HH). This state may arise as a result of congenital gonadotropin-releasing hormone (GnRH) deficiency, and neurologic and systemic diseases affecting the normal hypothalamo-pituitary axis, or it may be idiopathic (IHH). Treatment of the underlying disorder, when identifiable, may allow for restoration of the normal hormonal axis with subsequent improvements in endogenous testosterone production and spermatogenesis. When necessary, medical treatment for fertility preservation can be successful in these cases of ondary testicular failure, whereas in idiopathic primary failure, our lack of knowledge regarding the pathogenesis leaves us with no targets for medical therapy [1].

Recent evidence suggests that the prevalence of hypogonadal men in the United States is substantial, approaching 39% in men aged 45 years or older in a multicenter study of men presenting to primary care centers [2]. Additionally, the use of exogenous testosterone in this same age group has increased exponentially in the last decade, as much as threefold, as revealed by a large-scale population study [3]. The

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widespread use of testosterone supplementation therapy (TST) on the part of urologists and primary care providers in men with hypogonadism for the treatment of symptoms including decreased libido, fatigue and exercise capacity, depression, and erectile dysfunction has significant implications on potential fertility. This is due to the known negative feedback inhibition of exogenous testosterone on the normal intratesticular testosterone production necessary for spermatogenesis. The same phenomenon is observed in active individuals and athletes using anabolic steroids. The prevalence of anabolic steroid use is significant, ranging from 1 to 3 million people in the United States, which creates a unique population of men with anabolic steroid-induced hypogonadism who may also present with fertility concerns [4].

This chapter reviews currently available medical treatment to restore spermatogenesis in hypogonadal men naïve to TST as well as patients currently on TST. Recommendations and treatment algorithms will also be provided for the maintenance of spermatogenesis in men considering initiation of TST.

Fertility Preservation in the Hypogonadal Man Naïve to Androgen Supplementation

Selective Estrogen Receptor Modulators (SERMs)

SERMs are a class of agents with estrogen receptor agonist or antagonist activity, such as clomiphene citrate and tamoxifen. While their use has been well established in the stimulation of ovulatory cycles, treatment of osteoporosis, and breast cancer in women, the utility of these agents for the treatment of male infertility in the setting of ondary hypogonadism remains off-label. They are an attractive method of treatment given their low cost, east of administration, and favorable side effect profile. Clomiphene citrate has antiestrogenic effects on the hypothalamus and pituitary, blocking the negative feedback inhibition of estrogen in the central nervous system and promoting increased LH and FSH retion which drives endogenous testosterone production and spermatogenesis in the testis [5]. Its safety and efficacy have previously been established. In 2012, Katz et al. published their prospective study on the efficacy of clomiphene citrate in men with confirmed hypogonadism and baseline serum testosterone <300 ng/dL. Eighty-six men with an average age of 29 years were treated with 25 mg of clomiphene citrate administered every other day over an average period of 19 months to a goal serum testosterone range of 500–600 ng/dL. As needed to meet this goal, the dose was uptitrated to 50 mg. Their results confirmed an increase in serum testosterone and gonadotropins with symptomatic improvement based on a validated questionnaire for the assessment of male hypogonadism. No major side effects were reported, but may include rare vision disturbances or breast tenderness [6].

With regard to infertility, the efficacy of clomiphene and tamoxifen has been assessed in multiple clinical trials in conjunction with other agents, yet the efficacy of

these drugs alone remains undetermined. A 2010 randomized controlled trial of daily clomiphene citrate with the antioxidant vitamin E (25 mg and 400 mg, respectively) in men with idiopathic oligoasthenozoospermia showed superiority of this regimen over placebo in improving semen analysis parameters including total count, progressive motility, and rates of unassisted pregnancy (36.7% vs. 13.3%, $P = 0.04$) [7]. Hussein et al. published a multicenter case series of 42 men with non-obstructive azoospermia (NOA) treated with dose-titrated clomiphene citrate to achieve serum testosterone between 600 and 800 ng/dL, with periodic semen analyses during the treatment period. With treatment, 64% of patients produced sperm in numbers sufficient for intracytoplasmic sperm injection (ICSI), ranging from 1 to 16 million/mL (mean density 3.8 million/mL) [8]. Notably, the lack of a control group in this study limits our ability to attribute a treatment-related effect on fertility. A 2013 meta-analysis of recent randomized controlled trials investigating the use of either clomiphene citrate or tamoxifen for treatment of idiopathic male infertility with oligo- and/or asthenoteratozoospermia demonstrated a statistically significant increase in pregnancy rates compared to controls (pooled OR 2.42, 95% CI 1.47–3.94, $P = 0.00004$) as well as sperm concentration by a mean difference of 5.24 million ($P = 0.001$) and motility by a mean difference of 4.55 ($P = 0.03$) [9].

Enclomiphene citrate is a more potent trans-isomer of clomiphene citrate with similar antiestrogenic effects in the central nervous system. A recent parallel randomized placebo-controlled multicenter study comparing the use of enclomiphene citrate and topical testosterone (Androgel® 1.62%) in overweight men aged 18–60 years with ondary hypogonadism demonstrated an increase in serum T and serum gonadotropins, as well as normalization of sperm concentration in the enclomiphene citrate group. An expected increase in serum T and decrease in gonadotropins and sperm concentrations were seen in the topical testosterone group [10]. Thus enclomiphene citrate may represent an alternative oral option once approved by the FDA, though as of yet no head-to-head studies comparing clomiphene with its trans-isomer demonstrate superiority and enclomiphene remains investigational.

Aromatase Inhibitors

The aromatase inhibitors (AI), such as anastrozole, testolactone, or letrozole, increase endogenous T levels by inhibiting the peripheral conversion of androgens to estrogens. By doing so, there is less feedback inhibition by estrogens on the hypothalamic-pituitary axis and thus increased gonadotropins [11]. The negative consequences of elevated serum estrogen in combination with low serum testosterone on spermatogenesis have been demonstrated in vivo [12]. The administration of AI can restore a normal T/E_2 ratio and has been shown to improve sperm concentration and motility in oligozoospermic men, though these studies were not placebo controlled and randomized by design [11, 13, 14]. The mean serum T/E_2 ratio in fertile men is 14.5 ± 1.2; conversely in men with NOA and Klinefelter's syndrome, the ratio is 6.9 ± 0.6 and 4.4 ± 0.5, respectively [11, 13]. The patients who benefit

most from such therapy carry a diagnosis of NOA or idiopathic oligoasthenospermia and low T, and have a T/E_2 ratio of <10 [11, 13, 15, 16]. While the use of AI in this indication remains off-label and testolactone is commercially unavailable in the United States, a subset of infertile men with elevated serum estradiol appear to benefit from the use of AI (anastrozole 1 mg daily or letrozole 2.5 mg daily). These medications are generally well tolerated with rare side effects including nausea, decreased libido, and decreased bone mineral density [17, 18]. As suppression of estradiol production to near-undetectable levels with daily dosing may have consequences for bone health and sex drive, we recommend dosing of anastrozole at 1 mg twice weekly for a pretreatment estradiol level between 60 and 80 pg/mL, and 1 mg thrice weekly for a pretreatment estradiol level >80 pg/mL.

Gonadotropins

To review, hypogonadotropic hypogonadism may be idiopathic or due to congenital deficiency of GnRH (Kallman syndrome), central nervous system neoplasm, or systemic disease such as sarcoidosis or hemochromatosis. While treatment of the underlying problem may improve fertility, most men will benefit from gonadotropin replacement to restore normal spermatogenesis [19]. It is understood that the pulsatile release of GnRH from the hypothalamus will in turn stimulate the release of gonadotropins (LH and FSH) from the anterior pituitary promoting testosterone production in the testis and spermatogenesis. This pulsatile retion can be recapitulated by the use of GnRH subcutaneous infusion pump at a dose of 5–20 mcg every 1–2 h, but given the inherent inconvenience, it is largely only available at specialty centers for clinical trials [20]. Pulsatile GnRH replacement therapy is initiated with a starting dose of 25 ng/kg/pulse every 2 h subcutaneously via portable infusion pump with dose adjustment to obtain mid-normal testosterone. Doses up to 200 ng/kg may be needed to induce virilization, at which point it may be reduced [21]. As pulsatile GnRH replacement and recombinant gonadotropins appear equivalent in improving semen analysis parameters and pregnancy rates [22, 23], the mainstay of therapy is gonadotropin replacement.

While gonadotropins were previously extracted from urine, high-quality recombinant human chorionic gonadotropin (hCG), FSH, and LH as well as purified urinary gonadotropins are available for use with no differences in safety or clinical efficacy observed among them [24]. Conventional therapy for gonadotropin deficiency involves the subcutaneous administration of hCG to replace physiologic LH at 1500–3000 IU two or three times weekly, with or without menopausal FSH (75 IU two or three times weekly) or recombinant human FSH (100–150 IU two or three times weekly) (rhFSH). hCG is first administered to correct LH deficiency and the dose is adjusted to achieve nadir T at 48 h post-injection in the normal range. Following administration of hCG for 4–6 months, if no sperm are detected on semen analysis, recombinant or purified FSH can be co-administered, with improvement in semen parameters taking up to 1–2 years [25].

The efficacy of combined hCG and rhFSH has been established and a prospective observational study by Saleh and Agarwal demonstrated an increase in average testicular volume from 4.1 to 12.4 mL and total motile sperm count from zero to 4.8 million [26]. Another study of men with HH treated initially with hCG identified 81 men who had responded in regard to testosterone level but remained azoospermic. Of these, 84% achieved spermatogenesis and 69% achieved a sperm concentration >15 million/mL after the addition of rhFSH [25]. A multi-institutional phase III randomized efficacy and safety study confirmed that weekly rhFSH of 450 IU dosing, in combination with hCG, was adequate to induce spermatogenesis in many men with HH and azoospermia who had failed on hCG alone [27]. Predictors of a good response to gonadotropin therapy include postpubertal onset of gonadotropin deficiency and testicular volume >8 mL indicating less severed gonadotropin deficiency [28, 29]. The addition of FSH to hCG is shown to be most efficacious in restoration of spermatogenesis in patients with prepubertal onset HH, whereas in men with postpubertal onset, hCG alone appears to be sufficient [30].

There is little evidence for the use of gonadotropins in men with idiopathic infertility in the absence of HH; however, there is preliminary evidence suggesting that rhFSH may be of clinical benefit in limited circumstances. One clinical trial randomized 112 men with idiopathic oligozoospermia to treatment with 100 IU of rhFSH every other day for 3 months versus no treatment. The treatment cohort overall showed no benefit, but on subgroup analysis, 30 men (48.4%) with cytologic evidence for hypospermatogenesis without maturation defect on fine-needle aspiration demonstrated improvement in semen parameters and a significantly higher spontaneous pregnancy rate compared to nonresponders and non-treated patients (5/30 [16.7%] vs. 1/32 [3.1%] and 2/50 [4.0%], respectively) [31]. Early evidence also suggests a specific role for rhFSH therapy in men with primary spermatogenic failure who also harbor certain FSH receptor polymorphisms. In one study, patients were randomized to 3 months of rhFSH at 150 IU three times weekly ($n = 70$) and no treatment ($n = 30$). When the 70 treated subjects were divided by genotype, only those men with a serine at position 680 demonstrated a statistical improvement in seminal parameters [32]. Further studies are certainly needed to validate the clinical use of rhFSH in these circumstances.

Antioxidants

The presence of reactive oxygen species (ROS) in seminal fluid has been associated with sperm dysfunction, sperm DNA damage, and impaired fertility, prompting clinicians to offer men antioxidant supplementation [33, 34]. Few clinical trials have suggested that antioxidant therapy may confer improvements in sperm function and DNA integrity. A recent Cochrane Database systematic review analyzed data from 48 randomized controlled trials (RCT) comparing single and combined antioxidants with placebo, no treatment, or other antioxidant in a total population of 4179 men with infertility [35]. Duration of trials ranged from 3 to 26 weeks with follow-up

ranging from 3 weeks to 2 years and the age of men enrolled ranged from 20 to 52 years. Most men had low motility and sperm concentration. The authors indicated that the review was limited by the fact that 25 of the 48 trials reported on sperm parameters as their primary outcome with only 3 of those trials also reporting on live birth or clinical pregnancy. Additional limitations were poor reporting of and inconsistency of study design, imprecision, small sample size in many of the trials included, and lack of adverse event reporting resulting in a designation of the evidence in favor of antioxidant therapy as "very low" to "low." The authors concluded that antioxidants may increase live birth rates (OR 4.21, 95% CI 2.08–8.51, $P < 0.0001$, from 4 RCTs with 277 men) but this was based on only 44 live births from 277 couples in four small studies. As for clinical pregnancy, they suggested that antioxidants may increase pregnancy rates (OR 3.43, 95% CI 1.92–6.11, $P < 0.0001$, from 7 RCTs with 522 men) but again the quality of the evidence was low. There remain no specific recommendations on the use of antioxidants for the treatment of male infertility.

Dopamine Agonists

Men who present with infertility and hyperprolactinemia should be considered to harbor a prolactin-reting micro- or macroadenoma until proven otherwise and diagnostic evaluation for pituitary adenoma should ensue. Elevated serum prolactin inhibits the pulsatile retion of GnRH-inducing hypogonadotropic hypogonadism and infertility, and space-occupying tumors may also lead to symptomatology such as headache or visual field defects due to compression at the optic chiasm. In this context, dopamine agonists such as bromocriptine or cabergoline are indicated for the treatment of both the adenoma and infertility with some evidence suggesting that cabergoline is superior in suppressing prolactin production with normalization of prolactin in 70% of patients who are bromocriptine resistant [36, 37]. Cabergoline is thus the preferred choice and administered at a dose of 0.25–1.0 mg twice weekly. Reversal of infertility is seen in 53% of cases, with those that fail therapy potentially dopamine agonist resistant and thus candidates for surgical retion of the adenoma [38].

Medical Therapy to Optimize Surgical Sperm Retrieval

It is understood that spermatogenesis depends on a local hormonal milieu of high intratesticular T and FSH for Sertoli cell stimulation, and as up to 70% of men with NOA will harbor focal spermatogenesis, optimization of the hormonal profile can be beneficial for maximal surgical sperm retrieval [39]. As previously described in this tion, the use of SERMs, AI, and gonadotropins can increase intratesticular T levels and normalize serum estrogen. A retrospective study of Klinefelter's patients with NOA who received clomiphene, AI, or hCG prior to microTESE with a rebound

of serum testosterone to 250 ng/dL or greater had a 22% higher sperm retrieval rate compared to patients who did not meet that threshold testosterone level [40]. Another study in men without Klinefelter's syndrome but with NOA and hypogonadism demonstrated that these men do respond to medical therapy (SERM, AI, or gonadotropin) with an increase in T levels, but in this context neither pre- nor post-treatment T levels appear to correlate with overall sperm retrieval, clinical pregnancy, or live birth rates [41]. Despite these findings and the lack of well-designed RCTs to assess the use of medical therapy to optimize sperm retrieval, limited data suggest a benefit. One prospective study on the use of clomiphene citrate showed a statistically significant increase in the likelihood of sperm retrieval and favorable testis biopsy patterns in men with maturation arrest or hypospermatogenesis on pre-treatment biopsy [8]. Additionally, the use of hCG and rhFSH is documented to improve posttreatment sperm retrieval in men with NOA and who failed initial microTESE [42, 43], as well as in men who failed initial therapy with clomiphene to normalize serum T levels before microTESE [44]. Future RCTs will be needed to further clarify the benefit these drugs may provide in surgical sperm retrieval.

Conclusions

In this chapter we have summarized available medical therapies for the treatment of hypogonadal men with infertility (see Table 9.1). The goals of therapy are based on our knowledge of the hypothalamic-pituitary-gonadal axis and the importance of optimizing serum LH for endogenous testosterone production, serum FSH for spermatogenesis, and reduction of serum estrogens. Medical therapies should not be used indiscriminately or empirically in men with idiopathic NOA, and certainly not in men with known genetic factors (abnormal karyotype or Y chromosomal microdeletion), as it can delay definitive therapy with assisted reproduction. Further high-quality studies including RCTs are needed to clarify the efficacy of these agents for improving seminal parameters, clinical pregnancy, live birth rates, and surgical sperm retrieval.

Fertility Preservation in the Hypogonadal Man on Androgen Supplementation

Increasing numbers of men in the United States are initiating TST for the treatment of hypogonadism [3]. The majority of prescriptions for testosterone supplements come from endocrinologists (23.73%), followed by general practitioners (16.95%), and thirdly urologists (15.25%) [45]. Perhaps more alarming is the finding that up to 25% of urologists surveyed by the American Urological Association reported using testosterone therapy as a treatment for the indication of infertility despite the known

Table 9.1 Summary of the reviewed available medical treatments for fertility preservation

Medication	Administration	Dosage/frequency	Special considerations
Selective estrogen receptor modulators (SERM)	Oral	Clomiphene citrate 25–50 mg daily, tamoxifen 20 mg daily	Generally well tolerated. Off-label use for male infertility. More potent isomer enclomiphene citrate currently in phase III trials
Aromatase inhibitors (AI)	Oral	Anastrozole 1 mg daily, letrozole 2.5 mg daily	Indicated for men with T/E_2 ratio of <10. Consider twice or thrice weekly dosing for bone health and libido. Side effects include nausea, decreased libido, bone demineralization. Off-label use for male infertility
GnRH	Subcutaneous infusion pump	25–200 ng/kg per pulse every 2 h	Not commonly used outside of clinical trials due to inconvenience of administration
Human chorionic gonadotropin (hCG)	Subcutaneous/intramuscular	1500–3000 IU two to three times per week	FDA approved for fertility preservation in ondary hypogonadism
Recombinant human follicle-stimulating hormone (rhFSH)	Subcutaneous/intramuscular	75 IU two to three times per week	FDA approved for fertility preservation in ondary hypogonadism
Dopamine agonists	Oral	Cabergoline 0.25–1 mg two times per week, bromocriptine 2.5–5.0 mg two times per week	Cabergoline is preferred. Surgical retion of pituitary adenoma indicated for dopamine agonist resistance. Off-label use for male infertility

contraceptive effect of testosterone supplementation [46]. Exogenous testosterone induces negative feedback inhibition on the hypothalamic-pituitary-gonadal axis, thus leading to atrophy of the germinal epithelium in otherwise normal men and suppressing spermatogenesis, with azoospermia inducible by 10 weeks of testosterone use [47]. Testicular atrophy is common with loss in volume due to both suppressed spermatogenesis and decreased Leydig cell function. While otherwise

healthy men may demonstrate rebound of spermatogenesis after 6–18 months of abstinence from exogenous testosterone [47], up to 4–10% of patients with impaired spermatogenesis prior to TST may remain azoospermic after cessation of therapy, with significant implications for their future fertility [48]. Thus, in any patient who desires to maintain fertility and is considering TST, a semen analysis should be obtained prior to initiation of treatment to rule out idiopathic infertility or an undiagnosed hypogonadal state (e.g., Klinefelter's syndrome). Also previously discussed is the increasing population of men on anabolic-androgenic steroids (AAS) [4], many of whom are in their reproductive years, who may present with subfertility as a result of steroid-induced hypogonadism.

In the previous tion, hCG therapy was discussed as a means of replacing LH in hypogonadal men to promote restoration of intratesticular testosterone production. Intramuscular hCG has also been shown to reduce the impact of exogenous testosterone on intratesticular T levels, though data is scarce on its use in men previously on TST/AAS. A RCT was conducted with 29 healthy men receiving 200 mg per week of testosterone enanthate, who were also randomized to receive intramuscular saline placebo, 125, 250, or 500 IU hCG every other day for 3 weeks. Intratesticular testosterone levels and gonadotropins were assessed at days 0 and 21. Intratesticular T levels were suppressed by 94% in the T enanthate/placebo group, 25% in the T enanthate/125 IU hCG treatment group, and 7% in the T enanthate/250 IU hCG treatment group, and were actually increased 26% from baseline levels in the T enanthate/500 IU hCG treatment group [49]. Endogenous LH and FSH levels were not surprisingly suppressed to 5% and 3% of baseline, respectively, in the T enanthate/placebo group. This demonstrated that even supraphysiologic doses of TST can be countered by low-dose hCG to maintain normal levels of intratesticular testosterone. The effect on spermatogenesis was later shown in a retrospective study conducted on 26 hypogonadal men treated with TST via transdermal patches or intramuscular injections, as well as low-dose hCG. Serum total and free T, serum estradiol, semen parameters, and pregnancy rates were assessed. Pretreatment semen parameters included an average volume of 2.9 mL, concentration of 35.2 million/mL, motility of 49.0%, and forward progression of 2.3. There were no observed changes in semen parameters regardless of T formulation over more than 1 year of follow-up, none of the men became azoospermic during the treatment course, and 9 of 26 contributed to a pregnancy with their partners [50]. A recent multi-institutional series of men previously on TST with subsequent azoospermia or severe oligospermia were treated with hCG 3000 IU every other day and supplemented with either FSH, clomiphene citrate, tamoxifen, or anastrozole. Patients on these hCG-based combination therapies demonstrated a recovery of spermatogenesis to a mean density of 22 million/mL in 4 months [51]. These studies suggest a beneficial role for hCG therapy in hypogonadal men who desire both symptomatic relief via TST and preservation of fertility potential during their reproductive years. Data is even more limited on the use of hCG therapy for men with hypogonadism ondary to AAS use. Case reports have documented that hCG alone at doses of

2000 IU three times weekly to 10,000 IU once weekly can restore spermatogenesis and lead to clinical pregnancy [52–54]. hCG and FSH combination therapy (10,000 IU weekly and 75 IU daily, respectively) has also been reported with clinical success in restoring spermatogenesis [55].

The role of SERMs was previously discussed in the treatment of symptomatic hypogonadism via suppression of estrogenic negative feedback inhibition on the hypothalamic-pituitary-gonadal axis, thus promoting increased gonadotropins and downstream intratesticular testosterone production. Data on the use of clomiphene citrate for restoration of spermatogenesis is scarce. Case reports on the use of high-dose clomiphene (100 mg daily) in men with AAS-induced hypogonadism documented restoration of the normal hormonal axis within 2–3 months, but spermatogenesis was not assessed [56, 57]. Also, as mentioned in the previous paragraph, clomiphene in combination with hCG has demonstrated efficacy in recovery of spermatogenesis in men previously on TST [51]. Enclomiphene citrate is a more potent and shorter acting trans-isomer of clomiphene citrate that was evaluated in a randomized, open-label, controlled, phase IIB study designed to assess fertility in 12 men with ondary hypogonadism previously treated with 1% testosterone gel for a minimum of 6 months. After cessation of TST, morning total T values averaged 165 ± 66 pg/dL. The treatment group was then given 25 mg enclomiphene citrate and the control group received 1% testosterone gel with results compared at 3 and 6 months including serum total T, FSH, LH, and semen parameters. In follow-up, only enclomiphene citrate therapy was observed to restore both serum T levels and sperm counts while also elevating LH and FSH in the treatment group [58]. A later randomized, phase IIB, placebo-controlled, parallel, multicenter study of 73 men with ondary hypogonadism was conducted using two oral doses of enclomiphene citrate or 1% topical T gel. All men had either discontinued prior TST for at least 6 months or never been treated. This particular study population was notable for more severe hypogonadism and lower baseline serum T levels than prior studies. Again, enclomiphene was demonstrated to reverse low serum T and gonadotropins compared to placebo while preserving sperm production compared to the TST treatment group [59]. These findings have since been further validated in a phase III RCT [10]. As of this time, enclomiphene is not yet FDA approved for the treatment of male hypogonadism and further phase III studies are pending.

There are no prospective trials in the literature evaluating the use of aromatase inhibitors in men with hypogonadism ondary to TST or AAS use. The previously mentioned retrospective series by Wenker et al. evaluating hCG-based combination therapies (including AI) in men with azoo- or oligospermia following TST demonstrated a 98% success rate at restoring spermatogenesis with no differences noted between supplemental therapy administered with hCG and the type of TST used [51]. Patients who stand to benefit most from therapy with these agents will have low serum T and have a T/E_2 ratio of <10 [11, 13, 15, 16]; thus their role in restoration and maintenance of spermatogenesis in men previously on TST/AAS or who wish to continue TST/AAS will be limited and likely adjunctive.

Recovery of Spermatogenesis with Recent or Current TST or AAS Use

Several options may be presented to the patient who presents with NOA or oligospermia and reported recent or current use of exogenous androgen. Firstly, primary hypogonadism should be ruled out. If the patient and his partner are able to comply, he may cease TST/AAS and await spontaneous recovery of spermatogenesis with probability of recovery approaching 90% at 12 months and 100% at 24 months [48, 60, 61]. Alternatively, for more rapid recovery, following discontinuation of androgen we recommend 2000 IU hCG intramuscularly every other day for 3 or more months with dose titration as needed, with clomiphene citrate 50 mg every other day for 3 months. Co-administration of clomiphene may counter the suppression of endogenous FSH that is observed with higher doses of hCG therapy. At follow-up, hormonal evaluation and semen analysis are repeated. If estradiol is elevated or the T/E_2 ratio is <10, anastrozole may be implemented at 1 mg twice weekly. If FSH remains low, clomiphene may be discontinued in favor of rhFSH at 75 IU every other day for 3 months (see Fig. 9.1). As many men may not tolerate cessation due to recurrent symptoms, may not wish to discontinue treatment, may not be willing to wait for spontaneous recovery, or may not

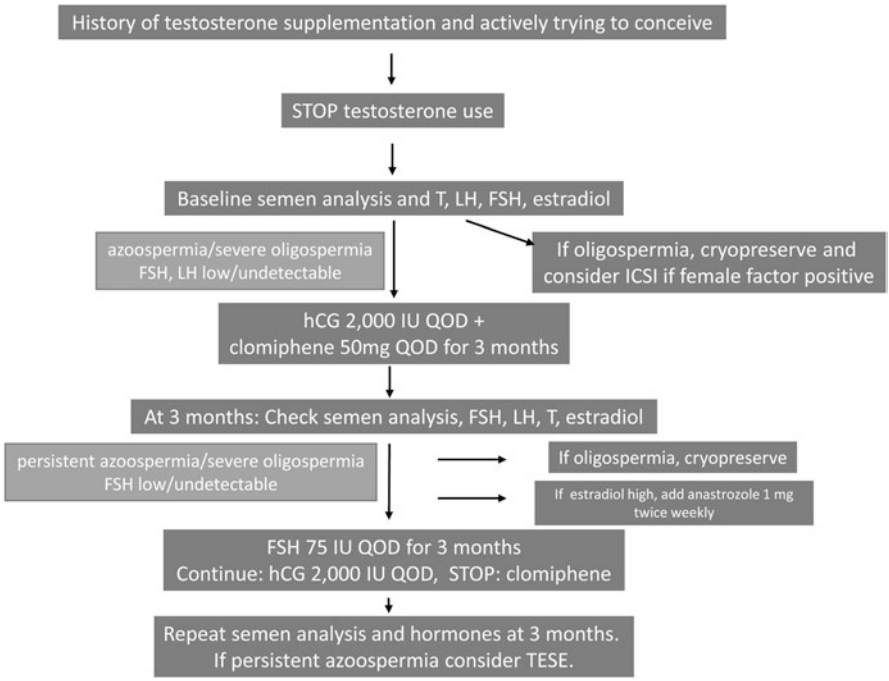

Fig. 9.1 Algorithm for fertility restoration in the hypogonadal man previously on testosterone supplementation therapy. *T* testosterone, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *hCG* human chorionic gonadotropin

be willing to accept the uncertainty of successful spontaneous recovery, restorative treatment may be offered in conjunction with androgen.

Maintenance of Spermatogenesis Prior to Initiation of TST or AAS Use

The maintenance of adequate intratesticular T levels is essential to sustain spermatogenesis. For those men who desire to maintain fertility and also treat symptomatic hypogonadism or engage in the use of AAS, we propose the following algorithm based on historical evidence (see Table 9.2) [62]. In men seeking treatment for hypogonadism, the first question to answer is whether they desire fertility or not. If not, the patient may begin treatment with 1500 IU hCG weekly to maintain testicular size, or alternatively cycle on/off TST with a 4-week treatment cycle of 3000 IU hCG administered every other day at 6-month intervals to enhance the response to TST. If the patient desires to maintain fertility at the outset, then a baseline semen analysis should be obtained and a decision made as to the timing of desired pregnancy. For patients who desire a pregnancy within 6 months, TST should be discontinued immediately and therapy initiated with 3000 IU hCG every other day, with or without 25 mg daily clomiphene citrate, and a semen analysis obtained every 2 months. If semen parameters do not improve sufficiently and FSH remains suppressed, rhFSH at 75 IU every other day may be added with discontinuation of clomiphene citrate. If the patient and his partner anticipate desired pregnancy in 6–12 months, TST may be started or continued with 500 IU hCG given every other day with or without clomiphene citrate at the aforementioned dose. For those patients desiring pregnancy in greater than 1 year, we recommend the patient cycles off TST every 6 months with a 4-week treatment cycle of 3000 IU hCG every other day. Other potential options include enclomiphene citrate which has been shown to recover spermatogenesis in men previously on TST, but not yet studied in men

Table 9.2 Summary of recommendations for maintenance of spermatogenesis with TST or AAS use

Timing of desired pregnancy	Treatment recommendation
<6 months	• *Stop* TST/AAS • *Start* 3000 IU hCG every other day ± clomiphene citrate 25 mg oral daily • Semen analysis every 2 months • No FSH response: discontinue clomiphene and add rhFSH 75 IU every other day
6–12 months	• *Continue* TST/AAS • *Start* 500 IU hCG every other day ± clomiphene citrate 25 mg oral daily
>12 months	• *Continue* TST/AAS • *Cycle off* TST/AAS every 6 months with a 4-week cycle of 3000 IU hCG every other day

desiring fertility while actively on TST; and as described in this tion, further phase III studies are pending. Additionally, AI such as anastrozole or letrozole may be considered in men with T/E_2 ratio of <10 as previously stated.

Conclusions

In this tion we have reviewed the potential role of medical therapy in the restoration and maintenance of spermatogenesis and fertility in men before, during, and after the use of TST or androgenic steroids. Knowledge of male reproductive endocrinology, the available treatment options, and their limitations is essential in counseling patients who wish to pursue treatment of hypogonadism or the use of androgenic steroids while also desiring fertility preservation. As epidemiologic data suggest, the use of TST and AAS is on the rise and role of the provider in warning patients of the potential fertility consequences and educating patients on the current state of the art for fertility preservation will grow ever more critical.

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