Title

Male Fertility and Testosterone Therapy

ISBN

9781009197557

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Publication Date

2023-11-16

DOI

10.1017/9781009197533.035

Chapter 34

Male Fertility and Testosterone Therapy

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34.1 Hypogonadism, Male Fertility, and Testosterone Therapy

There has been a rise in the use of testosterone therapy for men in their reproductive years. Unfortunately, many of these men are not counseled on the potential for infertility as a side effect of exogenous testosterone. In this chapter, we will first define hypogonadism and prevalence in populations of interest; second, we will describe the epidemiology of hypogonadism; third, we will review testosterone physiology and pathophysiology; fourth, we will provide historical context into the prescribing patterns of testosterone therapy; and finally, we will highlight relevant clinical data and synthesize these into clinical pathways used for patient counseling and management based on patients' timeline for desired fertility.

34.2 Defining Hypogonadism

The diagnosis of clinical hypogonadism requires patients to have signs and/or symptoms of hypogonadism in combination with low testosterone serum levels. The diagnosis of low testosterone requires two separate lab tests performed in the early morning. A total testosterone level $<$300 ng/dL (10.4 nmol/L) is a well-established cut-off [1]. Signs and symptoms associated with testosterone deficiency include physical manifestations, cognitive effects, and sexual dysfunction. Some men may experience loss of body hair, reduced beard growth, or decreased muscle mass while others report reduced energy, endurance, or decreased physical performance. Others notice poor memory, concentration, or motivation as well as depressive symptoms, cognitive dysfunction, and irritability. Furthermore, patients may present with reduced sex drive and erectile dysfunction. Men can present with a combination of these different concerns. A challenge in the diagnosis of hypogonadism is that many of the symptoms reported are nonspecific and can be impacted by other medical health conditions.

34.2.1 Workup of Hypogonadism

It is helpful to differentiate between hypergonadotropic (or primary/testicular) hypogonadism and hypogonadotropic (or secondary/pituitary-hypothalamic) hypogonadism. The American Urological Association (AUA) guidelines recommend measuring luteinizing hormone (LH) in patients with low testosterone levels and performing a reproductive health evaluation for men interested in fertility prior to initiation of exogenous testosterone. This includes evaluating testicular size, measuring follicle-stimulating hormone (FSH), and obtaining a baseline semen analysis (SA) to evaluate fertility potential [1]. In hypergonadotropic hypogonadism, LH and FSH are high and possible causes should be evaluated including cryptorchidism, history of testicular trauma or torsion, orchitis, chemotherapy, or testicular radiation. For hypogonadotropic hypogonadism, LH and FSH are low or inappropriately normal and causes can include genetic disorders such as Kallmann's syndrome, metabolic conditions including diabetes and liver failure, or reversible conditions such as chronic opioid use or prolactinoma.

34.3 Epidemiology of Hypogonadism

The proportion of men with hypogonadism who are interested in fathering children may continue to rise due to two different phenomena: rising rates of hypogonadism in younger men and higher rates of hypogonadism in older men who are growing their families.

34.3.1 Hypogonadism in Reproductive-Age Men

While hypogonadism is more common in older men, the prevalence of clinical hypogonadism in men 20–49 years of age ranges from 3% to 8% [2]. In 2010, men in this reproductive age group made up 42% of the male population in the United States [3]. In 2019, the entire male population of the United States was estimated to be 137,204,120 [4]. Assuming the prevalence of hypogonadism and proportion of men in their reproductive years remain stable, approximately 1,730,000–4,600,000 men age 20–49 may seek treatment for hypogonadal symptoms. The prevalence of hypogonadism will continue to rise due to increasing rates of diabetes, obesity, and chronic opioid use among younger men still interested in fertility [5].

34.3.2 Aging Fathers

The United States also has an aging population of fathers. In 2015, fertility rates for men 30–49 years old were the highest seen in 40 years. Meanwhile, fertility rates for men age 15–29 were at record lows [6]. Given that testosterone levels have been found to decrease by approximately 100 ng/dL (3.5 nmol/L) every 10 years, or an average rate of 1–2% per year beyond age

https://doi.org/10.1017/9781009197533.035

30, the aging population of men who still desire paternity is at increased risk of hypogonadism [5].

34.4 Testosterone Physiology and Pathophysiology

34.4.1 Testosterone Physiology

In healthy adult men, the hypothalamic-pituitary-gonadal (HPG) axis regulates testosterone levels. The hypothalamus secretes gonadotropin-releasing hormone (GnRH) in a pulsatile fashion stimulating the release of LH and FSH from the anterior pituitary. LH acts on Leydig cells to produce testosterone. FSH acts on Sertoli cells and seminiferous tubules to stimulate and support spermatogenesis. Aromatase in peripheral tissues, especially adipose tissues, converts testosterone into estradiol. Both testosterone and estradiol result in negative feedback suppression in the hypothalamic neurons and pituitary gland, thereby inhibiting additional release of GnRH, LH, and FSH [7].

34.4.2 The Role of Intratesticular Testosterone

Intratesticular testosterone (ITT) plays an important role in spermatogenesis. In the normal physiologic state, ITT levels are approximately 100 times higher than serum testosterone levels [8]. ITT works synergistically with FSH to stimulate Sertoli cell function [9]. This was discovered when FSH alone could not induce spermatogenesis in men with hypogonadotropic hypogonadism. Additional work has demonstrated that low ITT results in decreased proliferation of spermatogonia, defects in releasing mature spermatids from Sertoli cells, and accelerated apoptosis of spermatagonia [10].

34.4.3 Testosterone as a Contraceptive

Understanding the negative impact of exogenous testosterone on sperm production requires understanding how supplemental testosterone affects the HPG axis. Exogenous testosterone results in direct suppression of GnRH, FSH, and LH release at the level of the hypothalamus and anterior pituitary. The decrease in LH reduces endogenous testosterone production by Leydig cells, reducing ITT while serum testosterone remains elevated through replacement therapies. With low FSH and ITT levels, there is decreased spermatogenesis as well as decreased germ cell maturation and survival [9].

In fact, exogenous testosterone has been studied as a male contraceptive. In 1990, *The Lancet* published the results of a multicenter study coordinated by the World Health Organization (WHO) Task Force on methods for the regulation of male fertility [11]. A total of 271 healthy, fertile men were started on 200 mg testosterone enanthate weekly by intramuscular injection for one year. Suppression of spermatogenesis occurred in 98% of men and 40% of these men developed azoospermia. The mean time to azoospermia was 120 days and there was only one pregnancy without using other contraception during this 12-month study.

34.5 Trends in Prescribing Patterns

34.5.1 Testosterone Therapy Prescribing Patterns

Exogenous testosterone should be used with caution in men of reproductive age due to its impact on fertility. In a study of more than 600,000 men 40–49 years of age with commercial insurance, exogenous testosterone use rose from 3,370 (0.54%) to 15,900 (2.29%) between 2001 and 2012 [12]. During the same time period, exogenous testosterone use in 30–39 year-old men rose from less than 0.25–0.8% [13]. Over the time course of these studies, approximately 25% of men did not have a testosterone level measured in the year prior to initiating testosterone replacement [13]. Between 2013 and 2016, there was a decrease in proportion of men receiving testosterone prescriptions coinciding with the release of two published reports of adverse cardiovascular events associated with testosterone therapy and an FDA communication [12]. By 2016, rates in men 30–39 and 40–49 years of age dropped to 0.4% and 0.7%, respectively. However, these studies do not account for testosterone that is paid for with cash and not reimbursed through the patients' insurance plans. A 2020 study of 310 "men's health clinics" found that 91.1% of these clinics were not supervised by a urologist or endocrinologist and few were offering evidence-based, standard-of-care treatment options [14]. Therefore, it is challenging to understand the true number of men being offered exogenous testosterone and whether fertility concerns are appropriately discussed.

34.5.2 Anabolic Steroid Prescribing Patterns

In the 1950s, structural modifications to the testosterone model resulted in the creation of androgenic anabolic steroids (AASs) [15]. The mechanism of action of AASs is almost identical to testosterone and therefore also suppresses testicular function and spermatogenesis [16]. AASs were initially used primarily by body builders and athletes. More recently, men seeking the benefits of increased muscle development, enhanced athletic performance, and "rejuvenation" have resulted in estimates of up to 3 million AAS users in the United States [17,18]. In 2013, a retrospective review of 97 patients with profound hypogonadism (with total testosterone 50 ng/dL or less) revealed that 43% had a history of AAS use [19]. Some of these young men who use AAS may never recover normal endogenous testosterone levels.

34.6 Management of Hypogonadal Men Who Are Already on Testosterone and Now Want to Restore Fertility

We now provide an overview of management strategies that can be used to help men using exogenous testosterone who desire restoration of fertility. Understanding these different management strategies will allow providers to engage in shared decision-making and advise men based on how soon they are hoping to conceive children.

https://doi.org/10.1017/9781009197533.035

34.6.1 Testosterone Withdrawal

The most conservative approach for a man on testosterone therapy who is interested in restoring fertility is to stop testosterone and monitor for improvements in spermatogenesis. In the WHO study, healthy men who developed azoospermia on testosterone enanthate had a median time to recovery of 3.7 months to reach sperm concentration of at least 20 million/mL after stopping testosterone therapy. In a pooled analysis of 30 studies examining testosterone therapy as a short-term contraceptive, the probability of sperm concentration recovering to 20 million/mL was 67% within 6 months, 90% within 12 months, and 100% within 24 months [20]. Additional work has demonstrated that both advanced age and increased duration of exogenous testosterone prolong the time to recovery of spermatogenesis [21]. Similar studies in men who have used AAS have shown spontaneous return of sperm concentration to normal levels between 5 and 18 months after AAS cessation [22]. It is important to highlight that most of these time estimates are based off of studies in healthy, fertile men who were taking testosterone for contraception. It is possible that men with hypogonadism may not recover spermatogenesis as quickly or to the same degree without additional interventions. In some cases, recovery could take up to two years or more and sperm production may not return to pretreatment levels [20,23].

The major limitations to testosterone withdrawal include recurrence of bothersome hypogonadal symptoms and prolonged time before recovery of spermatogenesis. Furthermore, men who were started on testosterone therapy without a urologic or endocrinologic evaluation may have underlying endocrinologic disorders, such as hypogonadal hypogonadism, that impact both hypogonadal symptoms and spermatogenesis.

34.6.2 Testosterone Withdrawal and Lifestyle Modification

All hypogonadal men should be counseled on the importance of healthy weight loss, physical activity, and improving sleep hygiene to reduce signs and symptoms of testosterone deficiency [1]. An inverse relationship between testosterone and excess body weight has been reported in men of all ages, with lower testosterone levels found in subjects with higher body mass index (BMI) [24]. It is thought that at least 10% of weight loss is required to achieve increases in testosterone levels [25]. In an study of middle-aged, obese men with median testosterone levels of 199 ng/dL (6.9 nmol/L) randomized to testosterone or placebo in combination with intensive diet program, the placebo group lost 11% of their body weight and this was associated with modest increase in total testosterone by 84 ng/dL (2.9 nmol/L) [26]. However, at follow-up more than one year after completion of the study, many of these men had regained 66% of their weight. Testosterone levels fell back to their prestudy baseline. For morbidly obese patients who are considering bariatric surgery, there are small, nonrandomized studies that also support improvements in testosterone correlating with decreases in BMI [27]. Finally, while studies show conflicting results regarding the relationship between sleep and testosterone levels, most studies suggest a correlation between decreased sleep quality and worse symptoms of testosterone deficiency [28].

While the improvements in testosterone levels with weight loss appear modest, this approach helps optimize the overall health of men and could improve hypogonadal symptoms beyond the measured changes in testosterone levels. The limitations of this approach include prolonged time before recovery of spermatogenesis, likely similar to testosterone withdrawal alone, as well as the challenges associated with achieving and maintaining weight loss.

34.6.3 Testosterone Withdrawal and Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) such as clomiphene citrate and tamoxifen have been used off-label since the 1970s for the treatment of male infertility [29]. These medications inhibit the negative feedback of estrogen at the level of the hypothalamus and pituitary thereby increasing LH and FSH secretion.

While there are no studies evaluating outcomes in men previously on testosterone therapy, the mechanism of action as well as limited data in hypogonadotropic hypogonadal patients [30] supports improvements in spermatogenesis with SERMs. This use of SERMs also reflects current practice patterns in the management of male infertility. Given its effect on the HPG axis, one can hypothesize that using clomiphene citrate would lead to quicker recovery in fertility potential over testosterone withdrawal alone in men without primary testicular failure. Using clomiphene citrate would also reduce hypogonadal symptoms compared to testosterone withdrawal. However, reassessing a hormonal profile at time of repeat SA is important as there have been rare reported cases of azoospermia with initiation of clomiphene citrate [31].

34.6.4 Testosterone Withdrawal and Anastrozole

Anastrozole is a nonsteroidal aromatase inhibitor. It causes reversible inhibition of the aromatase enzyme reducing peripheral conversion of testosterone to estradiol (E_2). The reduced negative feedback inhibition from estrogen on the pituitary and hypothalamus results in increased LH and FSH secretion. Anastrozole has the ability to increase testosterone levels without associated increase in estrogen levels that can sometimes be seen with clomiphene citrate [32]. There have been no studies evaluating the use of anastrozole for hypogonadal symptoms and spermatogenesis in men who have stopped testosterone therapy. However, treatment of infertile men with low serum testosterone levels with anastrozole has been associated with increased serum testosterone from 404 to 808 ng/dL (14–28 nmol/L), decreased E_2 levels, and improved sperm concentration from 5.5 to 15.6 million sperm/mL after three months of therapy [33].

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Anastrozole provides another oral option for promoting gonadotropin secretion. Aromatase is present primarily in adipose tissues and thus may be particularly useful in obese men who convert a greater proportion of testosterone to estradiol. While not specifically studied in men previously on testosterone replacement, anastrozole may be helpful in men with increased estradiol levels or as an alternative agent for the rare case of azoospermia on clomiphine citrate [31,32]. Similar to SERMs, improvements in semen parameters have been seen within three months of initiating anastrozole in general infertility populations.

34.6.5 Testosterone Withdrawal and hCG

Human chorionic gonadotropin (hCG) has the biologic effects of LH and is used to stimulate Leydig cells to secrete testosterone, raising both serum and ITT [34]. By restoring ITT, hCG therapy should restore spermatogenesis for men with an intact HPG axis after cessation of testosterone. Studies in hypogonadal men demonstrate encouraging results for the off-label use of hCG in this setting. hCG has been used to treat hypogonadism associated with anabolic steroid use resulting in the recovery of ITT production with three times per week dosing ranging from 2,000 to 3,000 units [16,22]. In a case report of anabolic steroid–induced hypogonadism and azoospermia, hCG therapy improved testosterone levels and semen parameters with a pregnancy achieved after three months [35].

hCG therapy after testosterone withdrawal should be considered for three to six months. If semen parameters have not improved and pregnancy has not been achieved, combination therapy of hCG with other agents that increase FSH activity should be considered. The major limitations of using hCG include patient comfort with injection therapy and out-of-pocket costs as insurance coverage for hCG can vary.

34.6.6 Testosterone Withdrawal and hCG-Based Combination Therapy

While hCG addresses serum and ITT levels, it has no impact on FSH activity and Sertoli cell function. Therefore, there will be a subset of patients who will require concomitant therapies to increase FSH activity in order to optimize semen parameters. Options include SERMS, aromatase inhibitors, or FSH analogues.

In 2015, a retrospective review of 49 men highlighted the role of hCG-based combination therapy for managing infertility caused by exogenous testosterone use. All men were started on 3,000 units of hCG every other day after discontinuing exogenous testosterone. Supplemental medications were used to raise FSH levels and were based on clinician preference and clinical context. Thirty-five (71%) were prescribed clomiphene citrate, 28 (57%) were prescribed tamoxifen, 10 (20%) were prescribed anastrozole, and one (2%) was prescribed recombinant FSH. After starting hCG-combination therapy, return of spermatogenesis or improvement in sperm concentration to >1 million/mL was documented in 48 (98.0%) of men. Average testosterone levels were within the normal range when sperm first returned to the ejaculate. The average time to first sperm recovery in the ejaculate for men with azoospermia or improvement in sperm concentration above 1 million/mL for men with severe oligozoospermia was 4.6 months; the mean first sperm concentration was 22.6 million/mL. There did not appear to be a difference in time to sperm recovery based on type of testosterone supplementation previously used. Nineteen men (40%) achieved a clinically documented pregnancy during the mean 14 months of follow-up, with no significant difference by type of previous testosterone therapy or supplemental therapy used with hCG. No men discontinued therapy because of adverse effects [23].

Some experts treat with hCG alone for three to six months because many cases will demonstrate improvement in semen parameters during this time. In those without adequate spermatogenesis other agents including clomiphene, anastrozole, or recombinant FSH can be used to ensure both LH and FSH activity is present to optimize fertility potential [23,36]. The major limitations to this approach include the requirement for multiple pharmaceutical agents, costs of medications, and potential need for sperm extraction despite trying different medications.

34.7 Management of Hypogonadal Men Interested in Starting Testosterone Therapy and Maintaining Fertility

Both the AUA and the Endocrine Society published guidelines in 2018 that recommend against the use of exogenous testosterone in men wishing to preserve fertility [1,39]. However, there are patients who may be interested in starting testosterone therapy for hypogonadal symptoms while simultaneously maintaining fertility potential. There are emerging strategies that could allow for continued use of testosterone therapy when paternity is not a short-term goal.

34.7.1 Testosterone Therapy and hCG

In 2005, researchers demonstrated that exogenous testosterone caused ITT levels to drop by 94% in otherwise healthy, reproductive-aged men. In these men, adding hCG ranging from 250 IU to 500 IU every other day to testosterone therapy regimens maintained ITT levels [34]. However, this three-week study was too short to evaluate semen parameters or determine the short-term impact on spermatogenesis. A retrospective study in 2013 served to establish the idea of maintaining fertility while on exogenous testosterone. Twenty-six men initiating testosterone replacement therapy who desired fertility were simultaneously started on hCG. These men received 500 IU of hCG every other day while on different formulations of exogenous testosterone. Mean serum testosterone levels before initiating testosterone replacement and hCG were 207 ng/dL compared to 1,056 ng/dL on both agents. Mean pretreatment sperm concentration was 35 ± 30 million/mL. No differences in semen analysis parameters were observed during greater than one year of follow-up on testosterone and hCG. There were also no differences noted between sperm concentrations for men

https://doi.org/10.1017/9781009197533.035

using different types of testosterone formulations [40]. Nine (35%) of these men achieved pregnancy at one year of follow-up. Of note, pregnancy information was incomplete as not all men were actively pursuing pregnancy during the study period.

More work is needed in this area to understand differences in outcomes across different testosterone formulations, varying duration of testosterone therapy, and impact on fertility potential based on semen parameters and pregnancy rates. The existing data suggests testosterone combined with hCG can address hypogonadal symptoms while maintaining fertility potential. The major limitations to this approach include potential for side effects of high testosterone levels, such as erythrocytosis; requiring two pharmaceutical agents and comfort with injection therapy; as well as costs of hCG and testosterone formulations that may not be covered by insurance.

34.7.2 Testosterone Therapy and hCG-Based Combination Therapy

In addition to maintaining ITT levels with hCG, some men will require Sertoli cell stimulation with FSH. Clomiphene citrate has been suggested as first-line combination therapy with hCG [41]. In three to six months, repeat semen analysis and hormonal evaluation should be performed to decide whether other oral agents or recombinant FSH should be used. Anastrozole should be employed instead of clomiphene if testosterone-to-estradiol ratio is less than 10:1. Finally, if little or no improvement in semen parameters and low FSH persists despite hCG-based combination therapy, then recombinant FSH every other day should be used for its direct gonadotropin action [16,42].

There are no studies summarizing the effect of testosterone and hCG-based combination therapy but physiologically these regimens should help promote spermatogenesis through simultaneous stimulation of Leydig and Sertoli cells. The major limitations to this approach include potential for side effects from multiple pharmaceutical agents, comfort with injection therapy, costs of medications, a lack of data for patient selection and counseling, and need for additional interventions despite maximal pharmaceutical therapy. Future studies should aim to evaluate impact on hormonal profile of these patients including testosterone, estradiol as well as long-term effects on spermatogenesis and pregnancy rates.

34.8 Recommended Treatment Algorithms

34.8.1 Our Recommended Pathway for Restoring Fertility

First, if a patient desires pregnancy within six months and has not yet started testosterone, they should abstain from initiating testosterone therapy until a pregnancy has been achieved. Otherwise, men who are actively trying for a pregnancy should stop taking testosterone and follow the recovery regimen detailed in Figure 34.1. After stopping testosterone, men can choose any of the management options already described through shared decision-making with their physician.

Men desiring the most efficient and data-driven management option should start a regimen consisting of 2,000–3,000 IU hCG every other day [42]. Clomiphene citrate 25 mg every day or 50 mg every other day should also be incorporated to help promote FSH production and pituitary function [23]. Repeat SA and hormonal evaluation should be repeated every three months. If pregnancy is not achieved and neither FSH levels or SA parameters show improvement, clomiphene should be discontinued and recombinant FSH 75–150 IU every other day should be added [42–44]. If this fails, testicular sperm retrieval with possible microdissection should be offered in conjunction with in vitro fertilization as a final chance for biologic paternity. Once pregnancy has been achieved, reinitiation of testosterone should be discussed with special consideration to future fertility goals [16].

34.8.2 Our Recommended Pathway for Maintaining Fertility While Initiating Exogenous Testosterone Therapy

All men wishing to preserve fertility should have a baseline SA prior to initiation of testosterone therapy. If a planned pregnancy is desired within the 6–12 month time frame, patient can be offered exogenous testosterone supplemented with hCG 500 IU every other day (Figure 34.2) [42]. Clomiphene citrate or anastrozole should be considered as optional throughout this time.

When planning for pregnancy in more than 12 months, testosterone therapy with adjuvant 500 IU hCG can be offered. These patients should be cycled off testosterone every six months given the increased risk of impaired fertility with prolonged, uninterrupted courses of exogenous testosterone [21]. Each off-cycle can involve a four-week cycle of 3,000 IU of hCG every other day and clomiphene citrate [21]. During any of these above regimens, anastrozole may be added and titrated in dose to address elevations in estradiol (Figure 34.3).

34.9 Future Directions

The idea of "fertility sustaining" testosterone therapy remains in its infancy and continues to be studied and refined. There are promising developments that may help with monitoring responses to therapy aimed at maintaining fertility as well as new therapeutic strategies.

34.9.1 17-hydroxyprogesterone as a Marker of Preserved Spermatogenesis

The changes in ITT levels with exogenous testosterone have historically relied on the association between preserved ITT and improvement in SA parameters. In the 2005 study already described, invasive testicular biopsies/aspiration were used to measure changes in ITT while on exogenous testosterone compared to the preservation of ITT with simultaneous testosterone and hCG administration [34]. Intratesticular steroids are comprised of approximately 70% testosterone, 20% 17-hydroxyprogesterone (17-OHP), and smaller percentages of other

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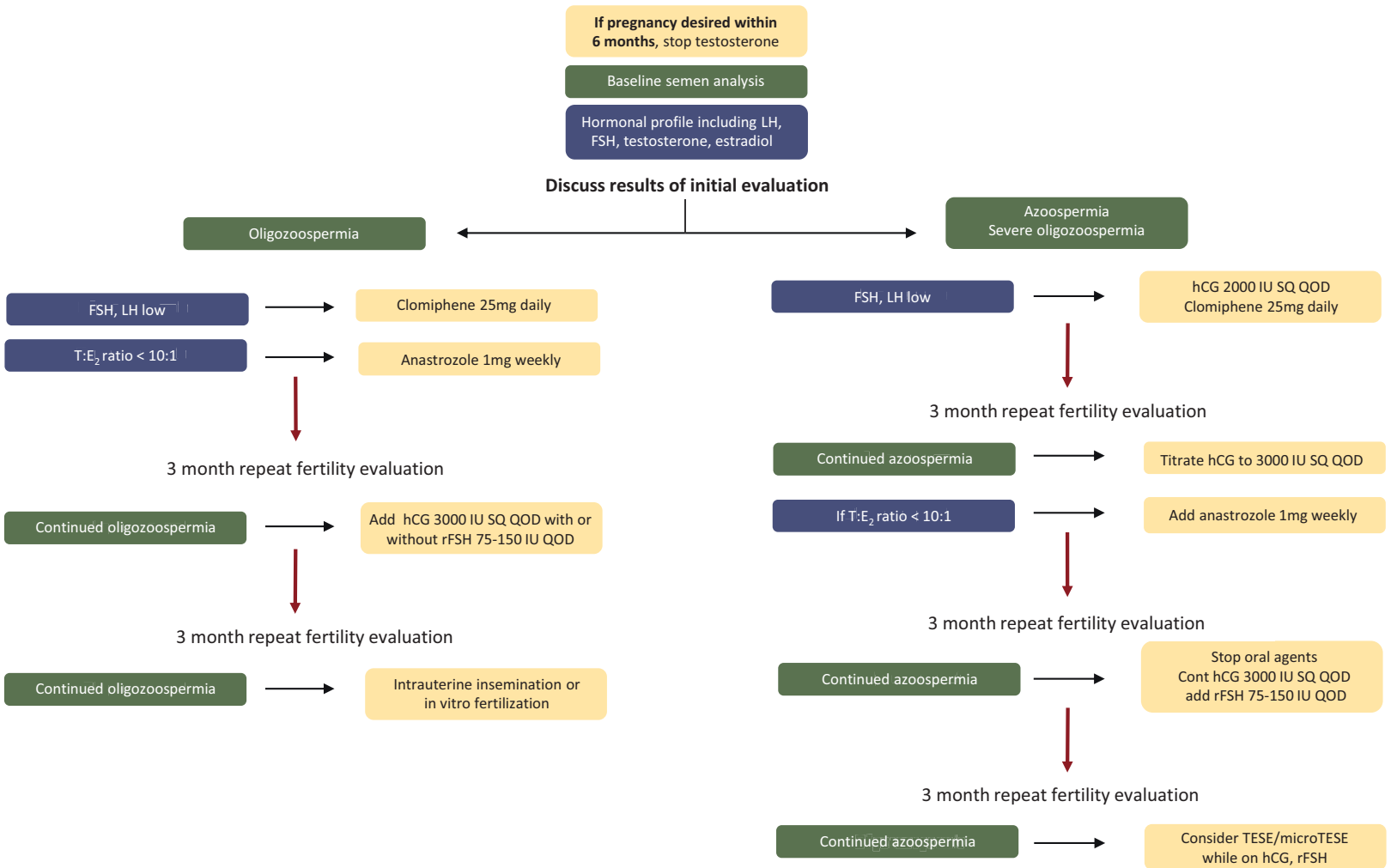

Figure 34.1 Pathway for restoring fertility after testosterone therapy

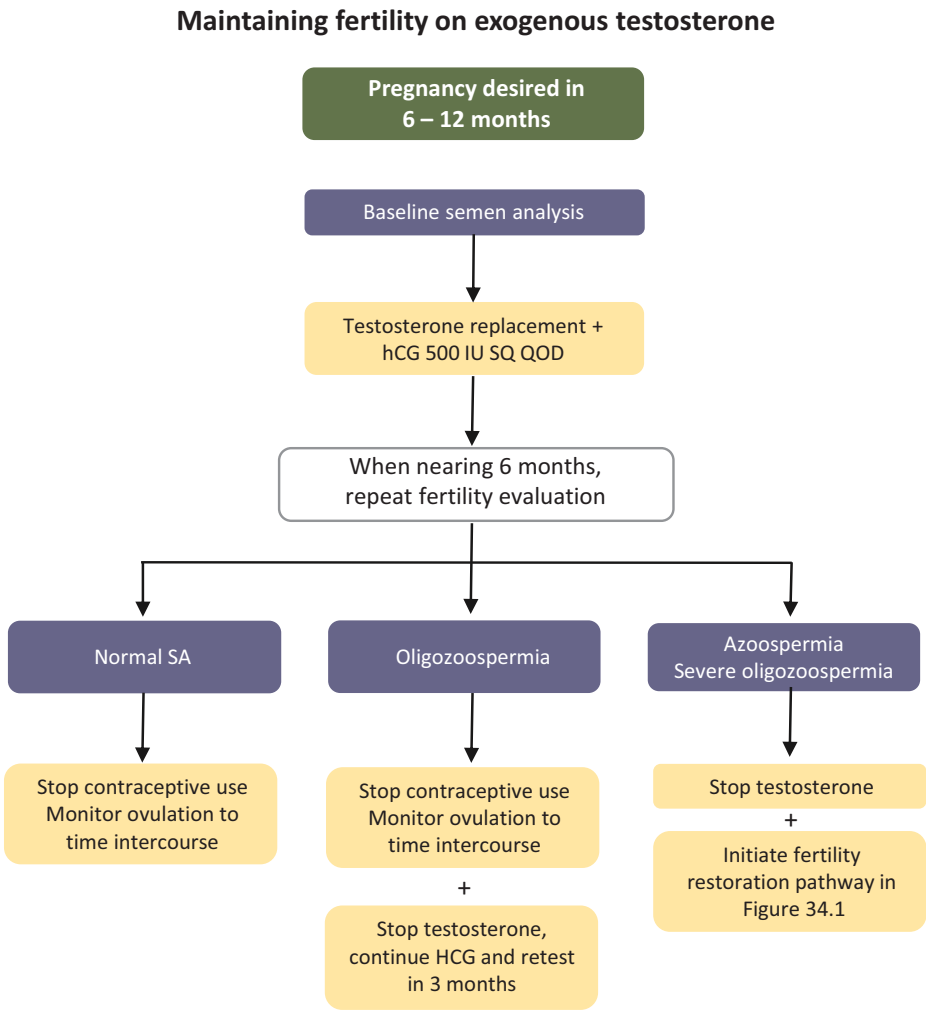

Figure 34.2 Maintaining fertility on exogenous testosterone

hormones. This intratesticular production contributes to the majority of serum testosterone and 17-OHP levels [45]. In 2018, Amory and colleagues found that serum 17- OHP decreased with exogenous testosterone, increased with hCG, and was strongly associated with end-of-treatment ITT levels [45,46]. They also found that other androgens such as androstenedione or dehydroepiandrosterone did not have this association.

17-OHP has the potential to function as a clinical biomarker used for counseling patients, tracking responses to therapy, and managing medications that support Leydig cell function and increase ITT. Future investigations should aim to identify minimal and optimal concentrations of ITT and 17-OHP for spermatogenesis.

34.9.2 Short-Acting Testosterone

Long-acting testosterone preparations including injections, topical gels, patches, and pellets suppress the HPG axis, reduce gonadotropin levels, and suppress ITT and spermatogenesis [7]. However, recent studies of an FDA-approved, short-acting testosterone nasal gel suggest that short-acting formulations of testosterone may not have the same impact on spermatogenesis [47].

A single-center, open-label, single-arm trial evaluated the effect of testosterone nasal gel on serum testosterone levels and semen parameters. A total of 38 out of 44 men (86.4%) and 30 out of 33 men (90.9%) achieved testosterone levels greater than 300 ng/dL at three and six months, respectively [47]. All men had normal FSH and LH levels prior to treatment. Fourteen (32.6%) and 16 (38.1%) men had levels of FSH and LH below normal levels at three months, respectively, while 6 (18.2%) and 9 (27.3%) were below lower limit of normal for FSH and LH at six months, respectively. At three and six months, there was no statistically significant difference in sperm concentration with mean difference of −4.1 million/mL at three months ($p = 0.193$) and −5.5 million/mL at six months ($p = 0.081$); similarly, there was no change in mean total motile sperm count. Of note, one patient (1.7%) developed azoospermia and three patients (5%) had SA with severe oligozoospermia [47].

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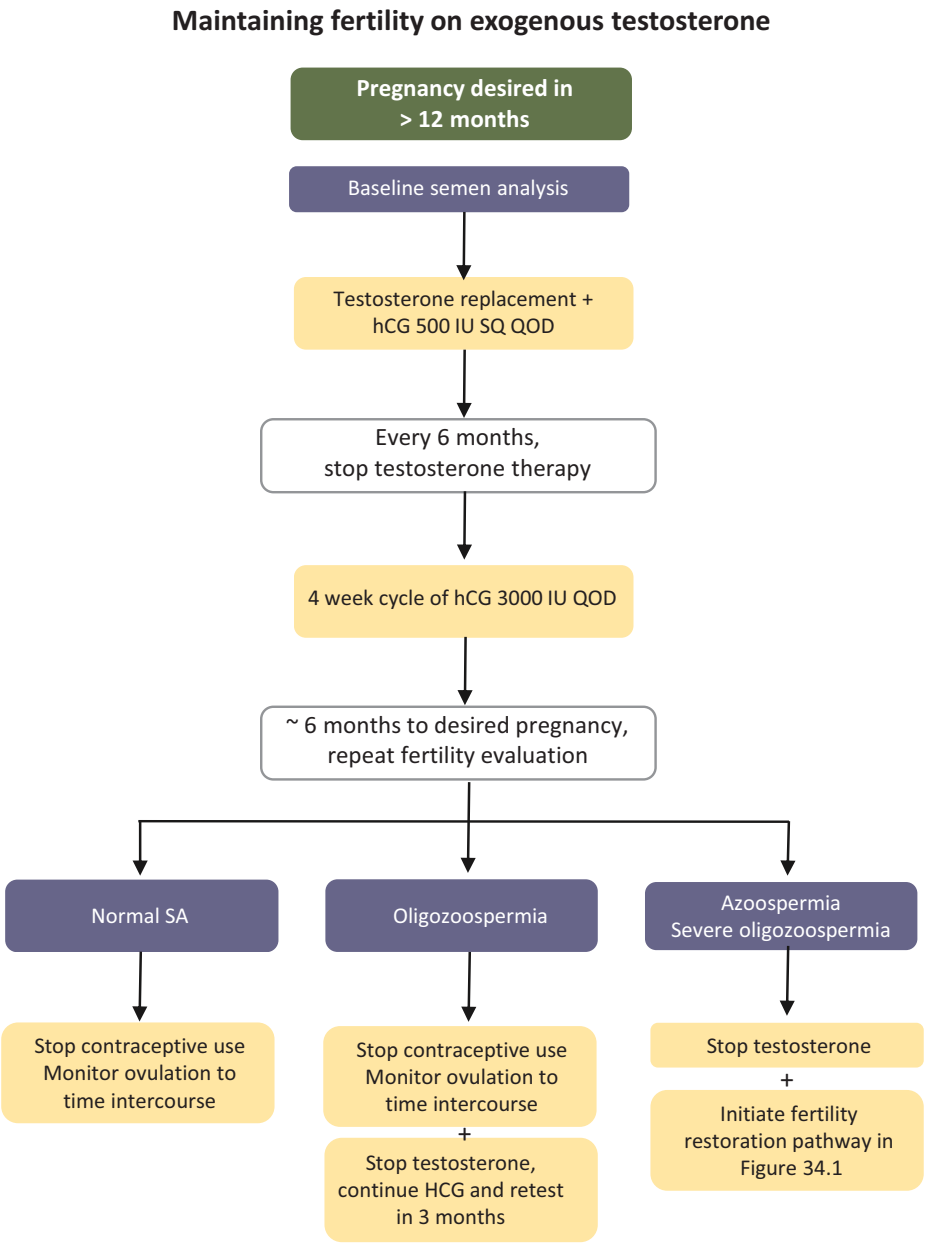

Figure 34.3 Maintaining fertility on exogenous testosterone

This early data is promising and short-acting testosterone formulations may offer hypogonadal symptom management with a less deleterious effect on fertility potential. However, while not statistically significant, the data suggests a possible decrease in sperm concentration over six months of follow-up. Long-term studies will be essential to determine whether this formulation can sustain spermatogenesis or result in quicker recovery of sperm concentration when stopping testosterone.

34.9.3 Leydig Stem Cell Injection

Animal models are now promising nonpharmacologic strategies for restoring testosterone without suppression of the HPG axis and its downstream effects on spermatogenesis. A 2019 study of castrate mice demonstrated that autografting of Leydig stem cells – a combination of Leydig, Sertoli, and peritubular smooth muscle cells – increased serum testosterone while simultaneously maintaining the production of FSH and LH [48]. This experiment was the first to show that ectopic grafting of Leydig stem cells in subcutaneous tissue resulted in testosterone production while preserving the HPG axis. However, this was a short study of four-week duration and the increase in testosterone was modest at best. Additional work will be required to determine the viability and sustainability of this approach and whether serum and ITT levels can be restored to eugonadal ranges.

https://doi.org/10.1017/9781009197533.035

This is not the only application of ectopic grafting of autologous tissues to address fertility concerns. In the same year, Fayomi and colleagues demonstrated successful autografting of cryopreserved prepubertal testicular tissues in Rhesus macaques with production of testosterone, spermatogenesis, and graft-derived sperm resulting in the birth of a healthy female macaque baby [49]. Testicular tissue grafting may be the next frontier in reproductive medicine that leverages native tissues to support Leydig and Sertoli cell function.

34.10 Conclusion

Over time, more men will need help managing hypogonadal symptoms while still wanting the option for future paternity. When these men present for evaluations, one of the most important aspects of the evaluation is the timing for desired pregnancy. For those interested in a pregnancy within six months, testosterone therapy should be stopped, and adjuncts should be used to stimulate Sertoli and Leydig function. For patients who have a longer timeline before pregnancy is desired, testosterone can be continued with hCG to support ITT levels and spermatogenesis.

In the future, improved serum biomarkers may help urologists monitor responses to therapy and predict pregnancy outcomes. New testosterone formulations may preserve spermatogenesis or lead to quicker recoveries in sperm counts. Finally, tissue grafting has the potential to revolutionize the management of male infertility.

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