

# The treatment of hypogonadism in men of reproductive age

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**Objective:** To review the mechanisms of T replacement therapy's inhibition of spermatogenesis and current therapeutic approaches in reproductive aged men.

**Design:** Review of published literature.

**Setting:** PubMed search from 1990–2012.

**Patient(s):** PubMed search from 1990–2012.

**Intervention(s):** A literature review was performed.

**Main Outcome Measure(s):** Semen analysis and pregnancy outcomes, time to recovery of spermatogenesis, serum and intratesticular T levels.

**Result(s):** Exogenous T suppresses intratesticular T production, which is an absolute prerequisite for normal spermatogenesis. Therapies that protect the testis involve hCG therapy or selective estrogen receptor (ER) modulators, but may also include low-dose hCG with exogenous T. Off-label use of selective ER modulators, such as clomiphene citrate (CC), are effective for maintaining T production long term and offer the convenience of representing a safe, oral therapy. At present, routine use of aromatase inhibitors is not recommended based on a lack of long-term data.

**Conclusion(s):** Exogenous T supplementation decreases sperm production. Studies of hormonal contraception indicate that most men have a return of normal sperm production within 1 year after discontinuation. Clomiphene citrate is a safe and effective therapy for men who desire to maintain future potential fertility. Although less frequently used in the general population, hCG therapy with or without T supplementation represents an alternative treatment. (Fertil Steril® 2013;99:718–24. ©2013 by American Society for Reproductive Medicine.)

**Key Words:** Hypogonadism, selective estrogen receptor modulator, male fertility

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In a recent survey of US urologists, Ko et al. (1) observed that approximately 25% have used exogenous T to treat low T levels associated with male infertility. Because of the potential of T therapies to decrease spermatogenesis and of the increasing number of men receiving hormone replacement therapy, this practice pattern is concerning. Although Food and Drug Administration labeling

for T therapies indicates that treatment may result in azoospermia or impairments of spermatogenesis, there is a distinct absence of expert recommendations on the topic of hormone replacement therapy in men of reproductive age. Regarding the treatment of hypogonadal men of reproductive age, this article will review [1] the extent of the problem, [2] the mechanisms by which T therapy

impairs spermatogenesis, and [3] therapeutic approaches to protect the testis.

## THE EXTENT OF THE PROBLEM

Symptomatic hypogonadism is a common problem (2). It is estimated that more than 6.5 million men in the United States will have symptomatic androgen deficiency by 2025 (3). Between the ages of 20 and 30 years, men experience a decline in T and free T levels by 0.4% and 1.3% per year, respectively (4). Mulligan et al. (5) observed that roughly 39% of men older than 45 years had low serum T levels, defined as less than 300 ng/dL. In addition, 20%–30% of infertile men will be found to have low T or increased LH levels (6).

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Testosterone therapies have been increasingly used in aging men, as well as in men of reproductive age. Compared to the 1970s, men are fathering children at an older age. Combined with the maturation of the Baby Boomer population, it is anticipated that there may be a significant increase in hypogonadal, aging men desiring to father children. The treatment of hypogonadism requires symptomatology, as well as low serum T levels, generally regarded to be around 300 ng/dL. With the recent introduction of several newer commercial T preparations and an increased public awareness of androgen deficiency syndromes, use of hormone replacement therapies has been increasing. During the past 5 years there has been an increase in T prescriptions by 170% (7). However, men desiring to maintain their reproductive potential may not be fully aware of the risks of exogenous T therapy.

Many T users/abusers and clinicians are unaware of the fact that the use of exogenous T has been shown to suppress the hypothalamic-pituitary-gonadal axis and result in infertility. Physicians need to educate their patients about the potentially deleterious effects exogenous T can have on spermatogenesis and on fertility. The use of IM T has been investigated as a male contraceptive agent (8).

## T REPLACEMENT THERAPY INHIBITS SPERMATOGENESIS

### Mechanisms

T inhibits GnRH and gonadotropin secretion. Exogenous administration of synthetic T results in negative feedback on the hypothalamic-pituitary axis, inhibiting GnRH, and, thus, inhibition of the secretion of FSH and LH. Suppression of gonadotropins results in a decrease in intratesticular T (ITT) levels and overall T production. Normally, ITT concentrations are roughly 50–100 times serum levels. Exogenous T therapies can suppress ITT production to such a degree that spermatogenesis can be dramatically compromised at ITT concentrations to less than 20 ng/mL (9). Intratesticular T is an absolute prerequisite for normal spermatogenesis. Complete inhibition of ITT can result in azoospermia (10, 11).

In men using anabolic steroids, despite normal-to-high serum androgen concentrations, ITT concentrations necessary to maintain spermatogenesis may be lacking. Many male users of anabolic steroids develop hypogonadotropic hypogonadism with subsequent testicular atrophy. Anabolic steroid use commonly results in oligozoospermia or azoospermia along with abnormalities of sperm motility and morphology (12, 13).

### Recovery of Spermatogenesis after Exogenous T Use

Rates of success in recovering spermatogenesis after use of exogenous T are generally quite favorable. The first strategy that should be used for the hypogonadal male interested in fathering children is the cessation of use of exogenous T. A study by the World Health Organization Task Force evaluated 271 men who received 200 mg of T enanthate weekly (14). After 6 months, 157 (65%) of the men were azoospermic. The mean time to azoospermia was 120 days. After 6 months of

treatment, the patients entered the recovery phase. Although 84% of men were able to achieve a sperm density >20 million/mL after a median of 3.7 months, only 46% of patients were able to achieve their baseline sperm density.

Mills (15) evaluated the recovery of spermatogenesis after exogenous T administration in 26 men with a recent history of anabolic steroid use. In this relatively small study, all men who discontinued exogenous T usage were treated with hCG 3,000 units IM every other day for a minimum of 3 months. Of the two men who remained azoospermic, one had insufficient follow-up and the other was suspected of continued anabolic steroid use. Men who were using IM T at the time of presentation recovered spermatogenesis in an average of 3.1 months. However, men receiving transdermal T supplementation at the time of presentation took an average of 7.4 months. Mills (15) concluded that impairment of fertility after T replacement therapy suppression is reversible and that the rate of sperm may be related to the delivery system.

The published literature represents the best available evidence regarding the recovery of spermatogenesis after T supplementation. However, the preponderance of the literature reflects results with the use of T therapy as a male contraceptive agent. This situation may very well not be reflective of the hypogonadal male seen in clinical practice. The caveat is that the consistency of spermatogenesis recovery in clinical practice may not be as predictable as seen in contraceptive studies.

### T as a Male Contraceptive

Pharmaceutical companies have tried to develop hormonal male contraceptives with the intent of causing a withdrawal of the gonadotropin support to the testis with resultant suppression of spermatogenesis and ITT (16). Testosterone has been studied alone, as well as in combination with progestagens (16). Testosterone used as a contraceptive agent is a good model to determine the effect and time to recovery with cessation of T treatment. These trials have not examined the use of agents to promote recovery of natural T or spermatogenesis.

A study by Wang et al. (17) found that oligozoospermia induced by exogenous T was associated with normally functioning spermatozoa. Data were analyzed from eight subjects whose sperm concentrations were between 1.3 and  $10 \times 10^6$ /mL at the suppression phase. Testosterone enanthate (200 mg) was administered IM weekly during the suppression and T treatment (efficacy) phases (total 15 months). Sperm function tests were performed during the pretreatment, during suppression (usually after 6–10 weeks of treatment, when sperm concentration was anticipated to decrease to <10 million/mL), and during recovery phases. Investigators found that the sperm concentration was reduced, but sperm motility, motility characteristics, and morphology were not affected by T enanthate treatment. The residual spermatozoa in the ejaculate exhibited normal hyperactivation, could acrosome react, and maintained the capacity to penetrate and fuse with the oocyte. The investigators concluded that suppression of spermatogenesis to moderate oligozoospermia (<10 million/mL) with exogenous T was not associated with impaired sperm function.

In a separate investigation, Gu et al. (18) from China administered T undecanoate (500 mg) monthly for 30 months. Using a primary outcome of pregnancy rate (PR), nine pregnancies were reported in >1,500 person-years of exposure in the 24-month efficacy phase (855 men) for a cumulative contraceptive failure rate of 1.1 per 100 men. Forty-three participants (4.8%) did not achieve azoospermia or severe oligozoospermia ( $<1 \times 10^6$  sperm/mL). Median time to onset of azoospermia or severe oligozoospermia was 108 days. Spermatogenesis returned to the normal fertile reference range in all but two participants. The median time to recovery of spermatogenesis calculated from the beginning of the recovery phase was 196 days. Recovery of sperm concentrations to their own baseline values was 182 days and to normal sperm output ( $>20 \times 10^6$ /mL) was 230 days. Most important, spermatogenesis recovered to normal reference levels (sperm concentration range,  $0\text{--}19 \times 10^6$ /mL) in all but 17 participants who completed the 12-month recovery period, and 15 of those returned to normal reference levels at an extra 3-month follow-up visit. Although this study has a follow-up period of 2.5 years, it is important to note that longer term data are not available in the published literature.

Liu et al. (8) performed an integrated, multivariate analysis of 30 studies published between 1990 and 2005, in which semen analyses were monitored every month until recovery. The primary outcome was the time for the sperm concentration to recover to a threshold of 20 million/mL. Included were 1,549 healthy eugonadal men aged 18–51 years who were treated with either androgens or androgens plus proestrogens. The strength of this large meta-analysis was >1,200 man-years of treatment and >700 man-years of post-treatment recovery. The median times for sperm to recover to thresholds of 20, 10, and 3 million/mL were 3.4 months, 3.0 months, and 2.5 months, respectively. Higher rates of recovery were identified with older age, Asian origin, shorter treatment duration, shorter-acting T preparations, higher sperm concentrations at baseline, faster suppression of spermatogenesis, and lower LH levels at baseline. It should be noted that the contraceptive trials were in men of Chinese ethnicity and that extrapolation of findings to men of non-Chinese ethnicities may not be reliable. In addition, the use of T therapy in a broad population of men may have varying results.

The typical probability of recovery to 20 million/mL was 67% within 6 months, 90% within 12 months, 96% within 16 months, and 100% within 24 months (Table 1). This observed

time to recovery may be helpful for patient counseling. It should be cautioned that return of spermatogenesis may be prolonged for a small number of men, which may be of significant concern with advanced maternal age. This study concluded that hormonal male contraceptive regimens show full reversibility within a predictable time course. It should be noted that a significant limitation of the published literature is a lack of pregnancy outcome data. Also, it is important to emphasize that semen analysis data do not correlate with pregnancy outcomes and that none of the literature assesses time to fecundity.

## THERAPEUTIC APPROACHES

For those hypogonadal men who desire to protect their future fertility, exogenous T should be discouraged. As demonstrated in the contraceptive trials, cessation of T therapy may result in the restoration of baseline serum T levels. However, these hypogonadal men may feel markedly symptomatic and desire higher serum T levels. Rather than continue exogenous T therapy, a more appropriate approach in these patients is to increase their own endogenous T. There are several ways to accomplish this. However, all of these methods, except for hCG injections, are considered off-label uses and should be discussed in detail with our patients. The underlying etiology of hypogonadism, especially regarding modifiable causes needs to be evaluated before starting treatments.

### Selective Estrogen Receptor Modulators: Clomiphene Citrate

Clomiphene citrate (CC) is a selective estrogen receptor (ER) modulator (19). This class of medications competitively binds to ERs on the hypothalamus and pituitary gland (Fig. 1). As a result, the pituitary sees less estrogen (E), and makes more LH, which increases T production by the testes. Common dosing starts at 25 mg orally every other day with upward titration to 50 mg daily, as needed. It is not as effective in increasing serum T levels when LH and FSH levels are already elevated, as seen in primary testis failure. At present, use of hormonal dynamic testing, such as CC or hCG stimulation test, are not well-defined or commonly used. Tamoxifen citrate is another selective ER modulator. Potential side effects include gynecomastia, weight gain, hypertension, cataracts, and acne.

**TABLE 1**

**Model-based probability of spermatogenic recovery to various thresholds.**

**Probability of recovery (%)**

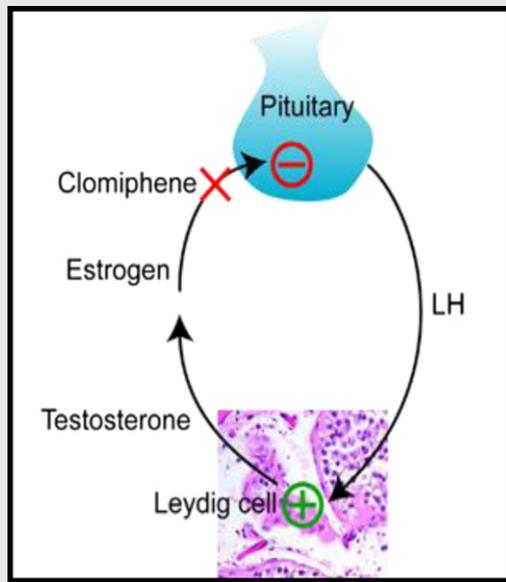
	Within 6 months	Within 12 months	Within 16 months	Within 24 months
Individual baseline value	54 (46–60)	83 (75–89)	95 (89–98)	100 <sup>a</sup>
20 million/mL	67 (61–72)	90 (85–93)	96 (92–98)	100 <sup>a</sup>
10 million/mL	79 (73–83)	95 (92–97)	99 (97–100)	100 <sup>a</sup>
3 million/mL	89 (84–92)	98 (95–99)	100 <sup>a</sup>	100 <sup>a</sup>

Note: Adapted from Liu PY et al. *Lancet* 2006;367:1412–20.

<sup>a</sup> Confidence interval could not be obtained from the model.

Kim. *Hypogonadism therapy in reproductive age men. Fertil Steril* 2013.

FIGURE 1



Clomiphene citrate (CC) works by blocking estrogen (E) at the pituitary. The pituitary sees less E, and makes more LH. More LH means that the Leydig cells in the testis make more T. (Adapted from Craig Neiderberger, M.D. <http://urol.uic.edu/dept/niederberger.php> and used with permission.)

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Clomiphene citrate can be quite effective in increasing serum T levels (20, 21). In a study by Taylor and Levine (22), CC resulted in significant increases in T levels from baseline, with increases similar to those with T gel replacement therapy (TGRT). One hundred four men began CC (50 mg every other day) or TGRT (5 g of 1% gel). Average follow-up was 23 months (CC) versus 46 months (TGRT). Average post-treatment T was 573 ng/dL (baseline, 277 ng/dL) in the CC group and 553 ng/dL (baseline, 221 ng/dL) in the TGRT group. They noted that the monthly cost of CC was about \$190 less than the cost of Testim 1% (5 g daily) at \$270 (Auxilium Pharmaceuticals, Inc.), and AndroGel 1% (5 g daily) at \$265 (Abbott Laboratories). The CC represents a treatment option for men with hypogonadism, demonstrating biochemical and clinical efficacy with few side effects and lower costs than TGRT.

In 2003, Guay et al. (23) observed an increase in free T ( $P < .001$ ) in all 178 men with hypogonadism and erectile dysfunction after treatment with CC for 4 months. Sexual function improved in 75%, with no change in 25%. Responses decreased significantly with aging ( $P < .05$ ), diabetes, hypertension, coronary artery disease, and multiple medication use.

Low-dose CC is also effective in improving the T/E<sub>2</sub> ratio in men with hypogonadism (24). In a small study, Shabsigh et al. (24) administered CC (25 mg daily) to 36 hypogonadal men with a mean age of 39 years. Mean pretreatment T and estrogen levels were  $247.6 \pm 39.8$  ng/dL and  $32.3 \pm 10.9$  ng/dL, respectively. At 4–6 weeks, the mean T level increased to  $610.0 \pm 178.6$  ng/dL ( $P < .00001$ ), whereas the T/E<sub>2</sub> ratio improved from 8.7–14.2 ( $P < .001$ ).

More recently, Katz et al. (3) from the Memorial Sloan-Kettering Cancer Center observed that long-term use of CC was safe and effective in improving serum T levels to normal (Table 2). In this moderately sized analysis, 86 men with hypogonadism (T levels  $< 300$  ng/dL), aged 22–37 years, were evaluated and treated for a mean duration of 19 months. The CC was started at 25 mg every other day and titrated to 50 mg every other day. Target T level was 550 ng/dL. Once desired T levels were achieved, T/gonadotropin levels were measured twice per year. In response to questions on the Androgen Deficiency in Aging Males questionnaire, improvements were reported in every area except for loss of height (Table 3). There was significant improvement in 5 of the 10 variables including decreased libido, lack of energy, decreased life enjoyment, feeling sad/grumpy, and decreased sports performance. During a long-term follow-up, this study demonstrated that CC is an effective and safe alternative to T supplementation therapy in men with hypogonadism.

A randomized, prospective trial of CC for hypogonadal men with normal semen parameters is necessary to validate the recommendation for the use of selective ER modulators for fertility preservation. This study would need to demonstrate that semen profiles are not adversely affected. The CC has been commonly used for the empiric treatment of male infertility, although the effect can be variable and unpredictable.

### Enclomiphene

A recently patented transisomer of clomiphene (Androxal; Repros), potentially able to increase T yet maintain normal semen quality, is currently being tested at 19 US sites (phase 3 trials ZA-301 and ZA-302). Preliminary results have been positive, and this new treatment may be an especially important and safe therapy for men with hypogonadism in their reproductive years.

### Human Chorionic Gonadotropin

Human chorionic gonadotropin is an LH analogue that stimulates Leydig cell production of T and it can be derived from urine as well as recombinant sources. Exogenous hCG increases IIT concentrations and serum T levels. For men with hypogonadotropic hypogonadism from anabolic steroid abuse, administration of IM injections two to three times per week at doses of 2,000–3,000 units for 4 months can initiate spermatogenesis (25).

Human chorionic gonadotropin alone can maintain spermatogenesis for short periods of time. In a small case series by Deebenbusch et al. (26), 13 azoospermic men with hypogonadotropic hypogonadism were initially administered hCG and hMG to induce spermatogenesis. Human chorionic gonadotropin was then administered 500–2,500 IU SC twice weekly alone for up to 2 years (range, 3–24 months). After 12 months, sperm counts decreased gradually but remained present in all patients, except for one who became azoospermic. The decreasing sperm counts indicate that FSH is essential for maintenance of quantitatively normal spermatogenesis.

High doses of hCG are not needed to stimulate and maintain spermatogenesis. Roth et al. (27) induced experimental

TABLE 2

## The effect of clomiphene citrate on serum hormone profiles.

	Baseline, mean ( $\pm$ SD)	After treatment, mean ( $\pm$ SD)	P value
Total T (ng/dL)	192 (B7)	485 (165)	<.01
Free T (pg/mL)	22 (16)	95 (35)	<.01
SHBG (nM/L)	30 (12)	32 (15)	.72
E <sub>2</sub> (pg/mL)	26 (22)	39 (19)	<.05
LH (IU/mL)	2.6 (2.2)	6.8 (2.9)	<.01
FSH (IU/mL)	1.9 (1.7)	7.6 (1.9)	<.01

Note: Adapted from Katz DJ et al. British Journal of Urology 2012;110:573–8. SHBG = sex hormone-binding globulin.

Kim. Hypogonadism therapy in reproductive age men. Fertil Steril 2013.

gonadotropin deficiency in 37 normal men with the GnRH antagonists and randomized them to receive one of four low doses of hCG: 0, 15, 60, or 125 IU SC every other day or 7.5g daily T gel for 10 days. Testicular fluid was obtained by percutaneous aspiration for steroid measurements at baseline, and after 10 days of treatment. The ITT concentrations increased in a dose-dependent manner with very low-dose hCG administration from 77–923 nmol/L in the 0-IU and 125-IU groups, respectively ( $P < .001$ ). In addition, serum hCG was significantly correlated with both ITT and serum T ( $P < .01$ ). They concluded that doses of hCG far lower than those used clinically increase ITT concentrations in a dose-dependent manner in normal men with experimental gonadotropin deficiency. Although hCG injections may be beneficial in increasing serum T levels and preserving fertility, hCG injections can be costly, and the invasive nature of this medication can also be a deterrent.

## hCG + T

Low-dose hCG with IM T enanthate (200 mg/wk) can maintain ITT and serum T levels (28). The use of hCG with IM T was initially studied for the development of a male contraceptive agent. Coviello et al. (28) administered low doses of hCG (0, 125, 250, or 500 IU every other day) to normal men during

TABLE 3

## Alterations in individual symptoms after clomiphene citrate therapy based on the ADAM questionnaire.

	Baseline (%)	After treatment (%)	P value
Decreased libido	72	32	<.01
Lack of energy	65	40	<.01
Decreased strength/endurance	28	21	.18
Lost height	4	5	.45
Decreased life enjoyment	85	40	<.001
Sad/grumpy	60	30	<.01
Erections weaker	12	8	.29
Decreased sports performance	55	25	<.001
Sleep after dinner	34	28	.17
Decreased work performance	45	38	.28

Note: Adapted from Katz DJ et al. British Journal of Urology 2012;110:573–8. ADAM = Androgen Deficiency in Aging Males.

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this 3-week study, and measured serum and ITT levels. Although the administration of T alone resulted in profound decreases in ITT concentrations (94% from baseline in the T enanthate and placebo hCG group), the addition of low-dose hCG resulted in maintenance of the ITT levels. The mean baseline ITT concentration for all 29 participants before treatment ( $1,174 \pm 79$  nmol/L) was approximately 80-fold higher than that of serum T ( $14.1 \pm 1.1$  nmol/L). Although serum T increased from baseline in all groups, ITT remained significantly higher than serum T in all four groups after treatment. Despite supraphysiologic doses of exogenous T, high levels of ITT can be maintained with the low-dose hCG.

Avila et al. (29) studied the effect of hCG administration with T replacement therapy on spermatogenesis. In this small series, 10 men received short-acting T preparations in addition to low doses of hCG. The key finding of this study was that on the basis of semen analyses, spermatogenesis was essentially maintained. Although there was a minimal decline in sperm density, no men developed azoospermia. Low-dose hCG with T supplementation can maintain production of ITT and spermatogenesis. There are no fecundity data. The substantial cost and need for frequent hCG injections are significant barriers to the use of this combination, especially when alternative therapies are available.

## Aromatase Inhibitors (Anastrozole and Letrozole)

Aromatase is a cytochrome P-450 enzyme concentrated in the testes, liver, brain, and adipose tissue and is responsible for the conversion of T to E<sub>2</sub>. Estradiol inhibits gonadotropin secretion and may exert direct effects on ITT production. Aromatase inhibitors function by blocking the conversion of androgens to E, consequently increasing serum levels of LH, FSH, and T and resulting in functional effects similar to those of the anti-Es. This class of drugs has been used to improve male fertility and stimulate spermatogenesis. Specifically, aromatase inhibitors may have greater benefit than anti-Es in men with lower serum T-to-E<sub>2</sub> ratios ( $<10$ ) and in obese patients.

Classically, aromatase inhibitors have been classified as either steroidal or nonsteroidal. The nonsteroidal late-generation aromatase inhibitors, such as anastrozole and letrozole, are very potent and do not block other steroidogenic enzymes, therefore adrenal steroid supplementation is not required. Although aromatase inhibition by these two agents is close to 100%, their administration does not completely suppress E<sub>2</sub> levels in men and actually decreases the plasma E<sub>2</sub>-to-T ratio by 77%. This incomplete suppression may be related to the high levels of circulating T in men and may provide an advantage by limiting the adverse side effect profile.

Aromatase inhibitors have been used to treat men with conditions including idiopathic male infertility, primarily men with lower serum T-to-E<sub>2</sub> ratios ( $<10$ ), and men with hypogonadism, often related to obesity. They also have been used for normalization of serum T levels before microscopic testicular sperm extraction (TESE) in men with Klinefelter syndrome.

Raman and Schlegel (30) reported on infertile men with T-to-E<sub>2</sub> ratios ( $<10$ ) treated with either testolactone or

anastrozole. Men in both treatment groups had significant improvements in their T-to-E<sub>2</sub> ratios, sperm concentration, morphology, and motility. In the small subset of 25 infertile men receiving anastrozole for oligospermia, sperm concentration increased significantly from 5.5–15.6 million/mL, and the total motile sperm concentration (TMSC) per ejaculate increased from 833–2,931 million/mL ( $P < .005$ ). No change was noted in the azoospermic cohort receiving anastrozole, and no PRs were reported for any of the men in the study regardless of semen parameter improvement.

In men with Klinefelter syndrome, aromatase inhibitors have been used to treat hypogonadism before microscopic TESE. Those men who responded to treatment (defined as having a total T of  $>250$  ng/dL) had a higher sperm retrieval rate than men whose T level after treatment was  $<250$  ng/dL (77% vs. 55%) (31).

In a recent study by Cakan et al. (32), when anastrozole was added to the treatment of 127 men with idiopathic oligoasthenospermia who continued to demonstrate low T-to-E<sub>2</sub> ratios after 3 months of therapy with tamoxifen alone, increased sperm concentration and motility. Increased PRs were also noted.

Letrozole, also a nonsteroidal third-generation aromatase inhibitor, was recently shown by Saylam et al. (33) to be effective in infertile men with low serum T-to-E<sub>2</sub> ratios  $<10$ . Of the 10 men with oligospermia, the mean TMSC significantly increased from  $6.4 \pm 2.7$  to  $15.7 \pm 5.01$  million/mL after treatment. Two of the 10 oligospermic men (20%) achieved spontaneous pregnancy and 4 of 17 azoospermic men (23.5%) were noted to have sperm in their ejaculate, with a mean TMSC of  $1.11 \pm 0.69$  million/mL.

Extensive experience with third-generation aromatase inhibitors in postmenopausal women has not revealed major side effects related to their usage. Because elevations in liver enzymes have been described in 7%–17% of patients, caution should be taken in treating patients who have hepatic disease, and liver function tests should be monitored. Other adverse reactions include increases in blood pressure, rash, paresthesias, malaise, aches, peripheral edema, glossitis, anorexia, nausea/vomiting, and, rarely, alopecia that has spontaneously resolved. The prostate-specific antigen assessment may be beneficial in at-risk populations, as any form of therapy for increasing serum T levels has the potential for increasing prostate-specific antigen levels (34, 35). The primary concern associated with aromatase inhibitors in men is that long-term E deficiency may lead to osteopenia or osteoporosis and ultimately have a negative effect on bone density. Although most studies published to date describing use of aromatase inhibitors in men did not appear to be associated with adverse effects on bone, a recent study (36) demonstrated a decrease in spinal bone mineral density after 1 year of anastrozole therapy in hypogonadal older men (mean age, 60 years). Long-term potentially detrimental effects of aromatase inhibitors on bone health continue to be a concern and have limited physician enthusiasm.

In conclusions, exogenous T supplementation decreases sperm production. However, studies of hormonal contraception indicate that most men have a return of normal sperm production within 1 year after discontinuing T supplementa-

tion. If at all possible, exogenous T use should be avoided in men desiring future fertility given the potential for long-term effects on spermatogenesis. Clomiphene citrate, an oral selective ER modulator, is an off-label, but safe and effective therapy for men who desire to maintain future potential fertility. Although less frequently used in the general population, hCG therapy with or without T supplementation represents an alternative treatment. At present, routine use of aromatase inhibitors is not recommended based on a lack of long-term data. Published literature to date is still limited, and this topic will be a fertile area of interest in upcoming years, especially regarding data on pregnancy outcomes.

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