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Misuse of testosterone replacement therapy in men in infertile couples and its influence on infertility treatment

Seung-Hun Song[1], Suye Sung[2], Young Sun Her[2], Mihee Oh[2], Dong Hyuk Shin[2], Jinil Lee[2], Jeongwon Baek[2], Woo Sik Lee[3], Dong Suk Kim[1]

[1]Department of Urology, Fertility Center, CHA Gangnam Medical Center, CHA University, Seoul; [2]Fertility Center of CHA Gangnam Medical Center, Seoul; [3]Department of Obstetrics and Gynecology, Fertility Center of CHA Gangnam Medical Center, CHA University, Seoul, Korea

Objective: We investigated the clinical characteristics of men with testosterone replacement therapy (TRT)-induced hypogonadism and its effect on assisted reproductive technology (ART) in infertile couples.
Methods: This study examined the records of 20 consecutive male patients diagnosed with azoospermia or severe oligozoospermia ($<5\times10^6$/mL) who visited a single infertility center from January 2008 to July 2018. All patients were treated at a primary clinic for erectile dysfunction or androgen deficiency symptoms combined with low serum testosterone. All men received a phosphodiesterase 5 inhibitor and TRT with testosterone undecanoate (Nebido®) or testosterone enanthate (Jenasteron®). Patients older than 50 years or with a chronic medical disease such as diabetes were excluded.
Results: The mean age of patients was 37 years and the mean duration of infertility was 16.3±11.6 months. At the initial presentation, eight patients had azoospermia, nine had cryptozoospermia, and three had severe oligozoospermia. Serum follicle-stimulating hormone levels were below 1.0 mIU/mL in most patients. Three ongoing ART programs with female factor infertility were cancelled due to male spermatogenic dysfunction; two of these men had normal semen parameters in the previous cycle. After withholding TRT, serum hormone levels and sperm concentrations returned to normal range after a median duration of 8 months.
Conclusion: TRT with high-dose testosterone can cause spermatogenic dysfunction due to suppression of the hypothalamic-pituitary-testicular axis, with adverse effects on infertility treatment programs. TRT is therefore contraindicated for infertile couples attempting to conceive, and the patient's desire for fertility must be considered before initiation of TRT in a hypogonadal man.

Keywords: Azoospermia; Hypogonadism; Male infertility; Testosterone

Introduction

Testosterone replacement therapy (TRT) has long been the standard treatment for men with symptomatic hypogonadism. Current clinical guidelines recommend testosterone supplementation for men who are symptomatic and have low testosterone levels. The benefits of TRT include increased growth of body hair, energy, muscle mass and stamina, overall confidence, and motivation [1]. The diagnosis of hypogonadism and its treatment with TRT has become more common in recent years because of the availability of new forms of supplements, direct-to-consumer advertising, and the successful alleviation of symptoms for many men receiving this treatment. Recent studies have reported that TRT has become one of the largest growing health care markets over the last 5 years [2,3].

Infertility, a serious social issue in many industrialized countries, is

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Corresponding author: **Dong Suk Kim**
Department of Urology, Fertility Center, CHA Gangnam Medical Center, CHA University, 566 Nonhyeon-ro, Gangnam-gu, Seoul 06135, Korea
Tel: +82-2-3468-3413 Fax: +82-2-3468-3449 E-mail: dskim100@chamc.co.kr

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commonly associated with sexual dysfunction. Male partners in infertile couples complain more about poor sexual function and satisfaction, and have higher rates of androgen deficiency type complaints than male partners in fertile couples [4]. Thus, these men may also benefit from TRT for their symptoms of hypogonadism. The potential adverse effects of TRT, including cardiovascular disease, prostate cancer, obstructive sleep apnea, and erythrocytosis, have been well reported [5]. The impact of TRT on fertility has only rarely been considered, because traditionally, the candidates for TRT were middle-aged or older men. However, testosterone usage has become increasingly common in young men. Recently, there have been warnings about the potential negative effect of TRT on fertility when used by men of reproductive age due to suppression of the hypothalamic-pituitary-testicular (HPT) axis by a negative feedback mechanism [6,7]. However, this issue is not familiar to all primary care physicians and patients. We investigated the clinical characteristics of TRT-induced hypogonadism in men in infertile couples, and its effect on infertility treatment programs such as assisted reproductive technology (ART).

Methods

This retrospective study examined the records of 20 consecutive male patients diagnosed with azoospermia or severe oligozoospermia ($<5\times10^6$/mL) who visited a single infertility center (CHA Gangnam Medical Center, Seoul, Korea) from January 2008 to July 2018 (Table 1). The study was approved by our Institutional Review Board (IRB No. GCI-19-07). The fertility evaluation consisted of a thorough personal and family history, physical examination (body mass index, testicular volume, palpation of vas deferens, and presence of varicocele), semen analysis (sperm concentration, motility, and morphology), and laboratory tests including reproductive hormone profiles (follicle-stimulating hormone [FSH], luteinizing hormone, testosterone, and prolactin levels). Testis volume was measured using an orchidometer. All patients were treated at a primary clinic for erectile dysfunction or androgen deficiency symptoms combined with low serum testosterone. These men received TRT with multiple injections of testosterone undecanoate Nebido® (Bayer HealthCare AG, Leverkusen, Germany) or testosterone enanthate Jenasteron® (EVER Pharma Jena GmbH, Jena, Germany) intramuscularly, in addition to phosphodiesterase 5 inhibitors for sexual dysfunction. Patients older than 50 years or with a chronic medical disease such as diabetes were excluded. None of the patients had a history of genital infection, varicocele, cryptorchidism, or gonadotoxin exposure.

Semen parameters including sperm concentration, motility, and morphology were assessed as previously described [8]. All semen samples were obtained by masturbation into a wide-mouthed plastic container in a separate room after 2 or more days of sexual abstinence, and were allowed to liquefy for at least 20 minutes at 37°C before further analysis. If sperm were not detected through a conventional microscopic Makler chamber evaluation, the semen sample was centrifuged at $1,500\times g$ for 10 minutes to detect any viable sperm. Azoospermia was determined by analyzing centrifuged specimen at least two different occasions. IBM SPSS ver. 23.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. A nonparametric analysis was performed using the Wilcoxon signed-rank test, and *p*-values less than 0.05 were considered to indicate statistical significance.

Table 1. Patient characteristics

Clinical characteristics	Value
No. of patients	20
Age (yr)	37.0 (31–47)
BMI (kg/m^2)	23.5 ± 2.8
Right testicular volume (mL)	16.3 ± 3.5
Left testicular volume (mL)	16.2 ± 3.6
Infertility duration (mo)	16.3 ± 11.6
Azoospermia (case)	8
Cryptozoospermia (case)	9
Severe oligozoospermia (case)	3

Values are presented as mean (range) or mean ± standard deviation.
BMI, body mass index.

Results

The mean age of the patients was 37 years (range, 31–47 years) and the mean duration of infertility was 16.3 ± 11.6 months. Semen analysis at initial presentation indicated that eight patients had azoospermia, nine had cryptozoospermia, and three had severe oligozoospermia (Table 1). None of the patients had any previous history of genital infection, varicocele, cryptorchidism, or gonadotoxin exposure. Physical examinations showed that all patients had normal-sized testes (≥ 14 mL). The serum FSH level was below normal (< 1.0 mIU/mL) in most patients.

An analysis of patients' histories showed that all 20 patients re-

Table 2. Changes in semen parameters and hormone levels during follow-up

Variable	Initial visit	Last follow-up	*p*-value
Semen volume (mL)	2.5 ± 1.1	2.9 ± 1.2	0.14
Sperm concentration ($\times10^6$/mL)	1.5 ± 3.1	49.8 ± 30.5	< 0.05
Sperm motility (%)	13.7 ± 20.9	38.7 ± 11.6	< 0.05
Sperm morphology (%)	3.8 ± 1.8	4.3 ± 0.9	0.44
Serum FSH (mIU/mL)	0.6 ± 0.4	5.2 ± 2.8	< 0.05
Serum testosterone (ng/mL)	4.8 ± 2.1	4.0 ± 1.3	0.12

Values are presented as mean ± standard deviation.
FSH, follicle-stimulating hormone.

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Table 3. Changes of semen parameters in eight patients with azoospermia during follow-up

Variable	Initial visit	Last follow-up
Semen volume (mL)	1.9 ± 0.2	3.1 ± 1.3
Sperm concentration (× 10^6/mL)	0	32.9 ± 18.9
Sperm motility (%)	NA	40.9 ± 13.2
Sperm morphology (%)	NA	4.7 ± 1.0

Values are presented as mean ± standard deviation.
NA, not available.

ceived TRT at primary clinics because of erectile dysfunction and had low levels of serum testosterone. TRT consisted of multiple injections of testosterone undecanoate (Nebido) or testosterone enanthate (Jenasteron) for a median duration of 8 months (range, 4–12 months). Three ongoing ART programs with female factor infertility were cancelled due to male spermatogenic dysfunction; two of these men had normal semen parameters in the previous ART cycle.

A thorough evaluation of the patients indicated that all 20 patients were suspected to have iatrogenic hypogonadism because of external testosterone supplementation. They were advised to return for subsequent fertility testing, with hormone and semen analysis, after cessation of TRT. After a median duration of 8 months (range, 2–11 months), serum hormone levels and sperm concentrations (≥ 15 × 10^6/mL) returned to normal range in all 20 patients. There were significant differences in the sperm concentration, sperm motility, and serum FSH levels between the initial presentation and last follow-up (Table 2). The eight patients with azoospermia at the initial presentation also showed a similar recovery pattern (Table 3).

Discussion

TRT has long been the standard treatment for men with symptomatic hypogonadism. The well-known benefits of TRT include increased growth of body hair, energy, muscle mass and stamina, overall confidence, and motivation. Testosterone usage is increasing secondary to new forms of supplementation, partly due to consumer advertising and symptomatic improvement for many men receiving this treatment in recent years [1,2]. Our study showed that TRT aggravated male fertility in infertile couples and had a clear negative impact on infertility treatment programs. Three ongoing ART programs with female factor infertility were cancelled due to the husband's spermatogenic dysfunction. Two patients among our cases had normal semen parameters in the previous cycle. ART refers to treatments used to help an infertile couple achieve pregnancy by manipulation of eggs, sperm, and/or embryos outside the body. It includes procedures such as *in vitro* fertilization (IVF) and intracytoplasmic sperm injection. Because an ART program does not always lead to successful pregnancy, an infertile couple may require multiple ART cycles to achieve pregnancy. In each IVF cycle, the female partner usually receives a high-dose hormonal supplement to stimulate ovulation, and an invasive oocyte aspiration procedure under anesthesia. IVF programs are expensive, and also have the potential to cause ovarian hyperstimulation syndrome [9,10].

When an IVF cycle fails, infertile couples may try to conceive naturally through timed intercourse during the ovulation period before another IVF cycle. We previously reported that many male partners in infertile couples report significantly greater stress, including erectile dysfunction, during fertile periods [11]. It is not uncommon for young men undergoing a fertility evaluation to have a low or borderline serum testosterone levels. Therefore, the possibility exists that the male partner might be treated with exogenous testosterone to improve his sexual function. However, the fertility issues associated with TRT in men have been rarely mentioned because traditionally, the candidates for TRT were middle-aged or older men [5]. All patients in this study received injections of testosterone undecanoate (Nebido) or testosterone enanthate (Jenasteron) due to poor sexual function or low libido while trying to conceive a baby. However, none of the patients were informed that TRT could reduce fertility, and all 20 men experienced spermatogenic dysfunction, although it was reversible. The authors previously reported a similar finding for TRT with testosterone undecanoate (Nebido) only [12]. These results highlight the need for more proper education of urologists and primary care clinicians who care for patients with hypogonadal symptoms.

Testosterone plays essential roles in the development and maturation of the male reproductive system and in spermatogenesis. However, administration of exogenous high-dose testosterone can cause infertility due to suppression of the HPT axis and decreased production of FSH, leading to decreased spermatogenesis [6]. In fact, because of this effect, some researchers consider testosterone to be a potentially promising contraceptive [13]. Despite the deleterious effect of TRT on male fertility, more men of reproductive age appear to be taking testosterone in recent years, either because of a lack of knowledge regarding its contraceptive effects or because of a misconception that it may increase male fertility. This misconception is not limited to non-urologists. A survey of the American Urological Association found that as many as 25% of respondents had used testosterone as an empirical treatment for male infertility [14].

Previous studies have described the recovery pattern of spermatogenesis after discontinuation of TRT. Our study patients experienced recovery to normal serum hormone levels and sperm concentrations (≥ 15 × 10^6/mL) at 7.9 ± 2.1 months after cessation of TRT (Table 2). A previous study reported recovery of 67% at 6 months, 90% at 12 months, 96% at 16 months, and 100% at 24 months [15]. Insufficient recovery has also been reported. Kohn et al. [16] studied the recovery

of spermatogenesis in 66 men who received TRT and reported that 30% of them were unable to achieve a total motile sperm count of more than 5 million after 12 months. They suggested that failure of recovery had positive correlations with patients' age and TRT duration. In most cases, gonadotropin replacement therapy is not required for the recovery of TRT-induced hypogonadism. However, if a patient wants to accelerate the recovery, gonadotropin agents similar to those used for patients with hypogonadotropic hypogonadism may be helpful [17].

The major limitation of this study is its small number of subjects, with the possibility of substantial selection bias. Nevertheless, our results clearly show that male infertility must be considered as a serious side effect of TRT. Use of TRT by men with hypogonadal symptoms is generally safe, but numerous reports have documented other adverse effects of TRT, such as cardiovascular disease, prostate cancer, obstructive sleep apnea, and erythrocytosis [18-20]. However, only a few recent studies have documented the deleterious effect of TRT on male fertility [6,7]. Considering the current widespread use and easy availability of TRT, this negative effect on male fertility should be stressed as a potentially serious side effect of TRT. Clinicians should be more informed of this adverse effect, and should use caution when initiating TRT in men of reproductive age. TRT with high-dose testosterone is definitely contraindicated for couples attempting to conceive.

TRT with high-dose testosterone can cause spermatogenic dysfunction due to suppression of the HPT axis, adversely affecting infertility treatment programs. TRT is therefore contraindicated for infertile couples attempting to conceive, and the patient's desire for fertility must be considered before initiation of TRT in a hypogonadal man.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

ORCID

Seung-Hun Song https://orcid.org/0000-0003-4649-9129
Suye Sung https://orcid.org/0000-0002-4581-3182
Young Sun Her https://orcid.org/0000-0003-3678-2801
Mihee Oh https://orcid.org/0000-0002-2880-5738
Dong Hyuk Shin https://orcid.org/0000-0002-9789-237X
Jinil Lee https://orcid.org/0000-0001-5102-3278
Jeongwon Baek https://orcid.org/0000-0003-2686-6358
Woo Sik Lee https://orcid.org/0000-0002-2329-1774
Dong Suk Kim https://orcid.org/0000-0001-7350-0303

Author contributions

Conceptualization: SHS, SS, WSL, DSK. Data curation: YSH, MO, DHS, WSL, JB. Formal analysis: SHS, DSK. Funding acquisition: SHS. Methodology: SHS, JL. Project administration & Visualization: SHS. Writing - original draft: SHS, DSK. Writing - review & editing: SHS.

References

1. Corona G, Sforza A, Maggi M. Testosterone replacement therapy: long-term safety and efficacy. World J Mens Health 2017;35:65-76.
2. Layton JB, Li D, Meier CR, Sharpless JL, Sturmer T, Jick SS, et al. Testosterone lab testing and initiation in the United Kingdom and the United States, 2000 to 2011. J Clin Endocrinol Metab 2014;99:835-42.
3. Handelsman DJ. Global trends in testosterone prescribing, 2000-2011: expanding the spectrum of prescription drug misuse. Med J Aust 2013;199:548-51.
4. O'Brien JH, Lazarou S, Deane L, Jarvi K, Zini A. Erectile dysfunction and andropause symptoms in infertile men. J Urol 2005;174:1932-4.
5. Traish A. Testosterone therapy in men with testosterone deficiency: are we beyond the point of no return? Investig Clin Urol 2016;57:384-400.
6. Patel AS, Leong JY, Ramos L, Ramasamy R. Testosterone is a contraceptive and should not be used in men who desire fertility. World J Mens Health 2019;37:45-54.
7. Kolettis PN, Purcell ML, Parker W, Poston T, Nangia AK. Medical testosterone: an iatrogenic cause of male infertility and a growing problem. Urology 2015;85:1068-73.
8. World Health Organization. WHO laboratory manual for the examination and processing of human semen. 5th ed. Geneva: WHO Press; 2010.
9. Madill JJ, Mullen NB, Harrison BP. Ovarian hyperstimulation syndrome: a potentially fatal complication of early pregnancy. J Emerg Med 2008;35:283-6.
10. Han AR, Kim HO, Cha SW, Park CW, Kim JY, Yang KM, et al. Adverse pregnancy outcomes with assisted reproductive technology in non-obese women with polycystic ovary syndrome: a case-control study. Clin Exp Reprod Med 2011;38:103-8.
11. Song SH, Kim DS, Yoon TK, Hong JY, Shim SH. Sexual function and stress level of male partners of infertile couples during the fertile period. BJU Int 2016;117:173-6.
12. Bang JK, Lim JJ, Choi J, Won HJ, Yoon TK, Hong JY, et al. Reversible infertility associated with testosterone therapy for symptomatic hypogonadism in infertile couple. Yonsei Med J 2013;

54:702-6.
13. Ly LP, Liu PY, Handelsman DJ. Rates of suppression and recovery of human sperm output in testosterone-based hormonal contraceptive regimens. Hum Reprod 2005;20:1733-40.
14. Ko EY, Siddiqi K, Brannigan RE, Sabanegh ES Jr. Empirical medical therapy for idiopathic male infertility: a survey of the American Urological Association. J Urol 2012;187:973-8.
15. Liu PY, Swerdloff RS, Christenson PD, Handelsman DJ, Wang C; Hormonal Male Contraception Summit Group. Rate, extent, and modifiers of spermatogenic recovery after hormonal male contraception: an integrated analysis. Lancet 2006;367:1412-20.
16. Kohn TP, Louis MR, Pickett SM, Lindgren MC, Kohn JR, Pastuszak AW, et al. Age and duration of testosterone therapy predict time to return of sperm count after human chorionic gonadotropin therapy. Fertil Steril 2017;107:351-7.
17. McBride JA, Coward RM. Recovery of spermatogenesis following testosterone replacement therapy or anabolic-androgenic steroid use. Asian J Androl 2016;18:373-80.
18. Coward RM, Simhan J, Carson CC 3rd. Prostate-specific antigen changes and prostate cancer in hypogonadal men treated with testosterone replacement therapy. BJU Int 2009;103:1179-83.
19. Tan RS, Salazar JA. Risks of testosterone replacement therapy in ageing men. Expert Opin Drug Saf 2004;3:599-606.
20. Elsherbiny A, Tricomi M, Bhatt D, Dandapantula HK. State-of-the-art: a review of cardiovascular effects of testosterone replacement therapy in adult males. Curr Cardiol Rep 2017;19:35.