Is semen analysis necessary prior to the commencement of testosterone supplementation therapy in men of reproductive age?

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Male hypogonadism is a clinical syndrome characterized by symptoms (i.e., fatigue, low energy) in conjunction with decreased serum testosterone levels.[1] Hypogonadism is diagnosed in about 5% to 40% of men, partially due to decreased serum testosterone levels from various causes, including chronic diseases, obesity, and smoking.[2] In the face of increasing awareness of hypogonadism, more men are being treated with testosterone supplementation therapy (TST). Indeed, the yearly initiation rate in the United States increased from 20.2/10 000 person-years to 75.5/10 000 person-years from 2000 to 2011.[3] Among the men prescribed testosterone, 12.4% of them were under 40 years of age,[3] illustrating the fact that a large cohort of men given TST are of reproductive age.

Although TST is effective at treating hypogonadism with high rates of satisfaction,[4-6] it is not without side effects. Of particular concern in these young men of reproductive age is that exogenous testosterone suppresses the hypothalamic-pituitary-gonadal axis, leading to testicular atrophy and inhibition of spermatogenesis.[7,8] Coupled with the fact that prior anabolic steroid use is common in young men seeking treatment for symptomatic hypogonadism,[9] the potential for decreased spermatogenic capacity and compromised reproductive function in young, hypogonadal men is possible.

It is also important to remember that these concepts are not limited to young men. More men are having children later in life due to career and educational aspirations, as well as improved life expectancies.[10] This trend is highlighted by the fact that the age of married fathers has gradually increased and men of advanced paternal age (APA) now account for >15% more births than they did 10 years ago.[11] Currently, the mean paternal age is 27 years and there is no accepted universal definition for advanced paternal age, but the most frequently cited number is 40.[10] Advanced paternal age has also been associated with autism, schizophrenia, bipolar disorder, achondroplasia, as well as increased rates of infant death from congenital malformations.[10-12]

It is important to understand that the theoretical risk of exogenous TST potentially leading to permanent azoospermia (or lack of sperm in the ejaculate) can affect males of any age. Therefore, the idea of future fertility must be discussed early in the counselling process with all men and the assessment of reproductive potential confirmed prior to the commencement of any exogenous TST. Currently, no standards exist as to how to best manage this clinical scenario.

Obtaining a semen analysis prior to initiating TST would be beneficial for a multitude of reasons. First, a pre-TST semen analysis would rule out pre-existing azoospermia or compromised reproductive capacity prior to treatment. Secondly, the pre-TST semen analysis would serve as a baseline measurement of reproductive function. Given the inevitable decline in sperm counts following TST, initial semen parameters would provide an unbiased baseline prior to the effects of testosterone. This would yield an appropriate target for men who are interested in initiating a pregnancy with their partner post-TST.

It is also critical that men remain aware that the potential duration for the recovery of spermatogenesis can vary between 111 and 182 days.[13,14] While these rates are based on contraceptive studies, the variable duration and quantity of TST in hypogonadal males could be higher. As such, men with escalated doses of TST should be advised of the longer durations of recovery.

Spermatogenesis secondary to TST can be successfully recovered by simple discontinuation of TST. However, this approach is not without side effects and results in a significant hypogonadal state, while the patient slowly regains his capacity to generate sufficient levels of intrinsic testosterone. The addition of a selective estrogen receptor modulators, such as clomiphene citrate as well as recombinant follicle stimulating hormone (FSH), are also options in situations where the natural initiation of spermatogenesis does not occur.[15] Alternatively, low-dose human chorionic gonado-

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tropin (HCG) administered alone or concomitantly with TST can preserve spermatogenesis[16] and maintain intratesticular testosterone[17] in hypogonadal men on TST. By obtaining a baseline semen analysis, the effectiveness of these treatments can be measured, and patient expectations can be established. Furthermore, given the theoretical possibility of complete azoospermia following TST, a semen analysis identifying pre-treatment azoospermia would negate any possible liability that exogenous testosterone contributed to the lack of sperm in the ejaculate.

Taken together, a semen analysis before staring TST should be performed on all men of reproductive age, as well as in men who desire fertility. A baseline semen analysis has numerous benefits, including the ability to unmask occult azoospermia, act as a baseline measure of reproductive function, and provide a recovery target for management of TST-induced testicular dysfunction. Physicians treating men of reproductive age with TST should incorporate semen analysis as part of their initial treatment protocol.

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