Effect of rejuvenation hormones on spermatogenesis

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Objective: To review the current literature for the effect of hormones used in rejuvenation clinics on the maintenance of spermatogenesis.
Design: Review of published literature.
Setting: Not applicable.
Patient(s): Men who have undergone exogenous testosterone (T) and/or anabolic androgenic steroid (AAS) therapies.
Intervention(s): None.
Main Outcome Measure(s): Semen analysis, pregnancy outcomes, and time to recovery of spermatogenesis.
Result(s): Exogenous testosterone and anabolic androgenic steroids suppress intratesticular testosterone production, which may lead to azoospermia or severe oligozoospermia. Therapies that protect spermatogenesis involve human chorionic gonadotropin (hCG) therapy and selective estrogen receptor modulators (SERMs). The studies examining the effect of human growth hormone (HGH) on infertile men are uncontrolled and unconvincing, but they do not appear to negatively impact spermatogenesis. At present, routine use of aromatase inhibitors is not recommended based on a lack of long-term data.
Conclusion(s): The use of hormones for rejuvenation is increasing with the aging of the Baby Boomer population. Men desiring children at a later age may be unaware of the side-effect profile of hormones used at rejuvenation centers. Testosterone and anabolic androgenic steroids have well-established detrimental effects on spermatogenesis, but recovery may be possible with cessation. Clomiphene citrate, human growth hormone (HGH)/insulin-like growth factor-1 (IGF-1), human chorionic gonadotropin (hCG), and aromatase inhibitors do not appear to have significant negative effects on sperm production, but quality data are lacking. (Fertil Steril® 2013;99:1814–20. ©2013 by American Society for Reproductive Medicine.)
Key Words: Hormones, rejuvenation, spermatogenesis

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In 1970, fewer than 15% of all men fathering children were over 35 years of age. Today, that percentage has risen to almost 25%. Likewise, the number of men in the 50 to 54 age group has seen a notable increase in fatherhood (1). Not only is the male population aging and reproducing later, but many men are also searching for the fountain of youth. A 2009 article in the *Chicago Tribune* by Bruce Jaspen (2) reported that the sale of anti-aging products sales in the U.S. alone has exceeded $50 billion annually. Many of these products are hormones that are being prescribed in antiaging centers known as rejuvenation clinics. Because of the off-label illicit use of these medications and the unregulated nature of this industry, little is known about the effect of these hormones on male fertility. This article reviews common antiaging hormones used in rejuvenation clinics and their mechanism of effect on spermatogenesis (Table 1).

MATERIALS AND METHODS

A PubMed literature search was conducted for the time period of 1984–2012, focusing on 45 studies examining the effect of hormones used for rejuvenation on semen analysis, pregnancy outcomes, and time to recovery of spermatogenesis. Those publications representing level 1 evidence were marked with the annotation (LOE 1). Six hormones were reviewed: exogenous testosterone, anabolic steroids, human growth hormone (HGH), clomiphene citrate (CC), human chorionic gonadotropin (hCG), and aromatase inhibitors (AI). These hormones were selected based on clinical experience and information publicly promoted by rejuvenation centers. There were insufficient published quality data for a meta-analysis, so a systematic review was performed for all hormones. Institutional review board approval was not necessary for a review paper.

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TABLE 1

Overview of the effect(s) of rejuvenation hormones on spermatogenesis.

Hormone	Mode of action	Mechanism of effect on spermatogenesis
Testosterone	Negative	Suppression of the HPG axis results in decreased ITT concentration, which decreases spermatogenesis.
Anabolic androgenic steroids (AAS)	Negative	Suppression of the HPG axis results in decreased ITT concentration, which decreases spermatogenesis.
Clomiphene citrate (CC)	Neutral/positive	This SERM increases testicular testosterone production, which may be beneficial for spermatogenesis.
Growth hormone/Insulin-like growth factor (HGH/IGF-1)	Neutral/positive	HGH stimulates IGF-1 formation, which may improve sperm maturation in a paracrine-autocrine manner.
Aromatase inhibitor (AI)	Neutral	This cytochrome P450 enzyme blocks the conversion of androgens to estrogen, consequently increasing serum levels of LH, FSH, and testosterone and may stimulate spermatogenesis.
Human chorionic gonadotropin (hCG)	Neutral/positive	This LH analog stimulates Leydig cell production of testosterone, which can initiate and maintain spermatogenesis in hypogonadotropic hypogonadal men.

Note: FSH = follicle-stimulating hormone; HPG = hypothalamic-pituitary-gonadal; ITT = intratesticular testosterone levels; LH = luteinizing hormone; SERM = selective estrogen receptor modulator.

Moss. Rejuvenation hormones and spermatogenesis. Fertil Steril 2013.

EXOGENOUS TESTOSTERONE

Background

Exogenous testosterone therapy is approved by the US Food and Drug Administration (FDA) for the treatment of symptomatic hypogonadism. Exogenous testosterone is one of the most common therapies used for the purpose of male rejuvenation. Examples of exogenous testosterone include topical gels, subcutaneous testosterone pellets, and intramuscular injectable testosterone. Over the past 5 years, there has been an increase in testosterone prescriptions by 170%. This correlates with the recent introduction of newer commercial products and an increased public awareness of androgen deficiency syndromes (3). It is estimated that more than 13.8 million men $\geq$45 years of age visiting a primary care doctor in the United States have symptomatic androgen deficiency (4). Importantly, many testosterone users/abusers and clinicians are unaware that exogenous testosterone suppresses the hypothalamic-pituitary-gonadal (HPG) axis and may result in infertility. In a recent survey of U.S. urologists, Ko et al. (5) observed that approximately 25% have used exogenous testosterone to treat low testosterone levels associated with male infertility.

Mechanism of Action

Exogenous testosterone inhibits spermatogenesis by suppressing the HPG axis. Specifically, testosterone therapy results in negative feedback on the HPG axis. It inhibits gonadotropin-releasing hormone (GnRH), thereby inhibiting the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (Fig. 1). Suppression of gonadotropins results in a decrease in intratesticular testosterone levels (ITT) and overall testosterone production. Normally, ITT concentrations are approximately 50 to 100 times serum levels. As exogenous testosterone therapies suppress ITT production, spermatogenesis can be dramatically compromised (6). Intratesticular testosterone is an absolute prerequisite for normal spermatogenesis, and its inhibition can result in azoospermia (7, 8).

Clinical Evidence

Exogenous testosterone supplementation decreases sperm production. However, when it was evaluated as a male contraceptive agent, studies showed that most men have a return to normal sperm production within 1 year after discontinuing testosterone supplementation (LOE 1) (Table 2) (9). For example, a study by the World Health Organization (WHO) Task Force evaluated 271 men who had received 200 mg of testosterone enanthate weekly (LOE 1) (10). After 6 months, 157 (65%) of the men were azoospermic, and the mean time to azoospermia was 120 days. After 6 months of treatment, the patients entered the recovery phase where exogenous testosterone was discontinued. 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.

Gu et al. (11) administered testosterone 500 mg monthly of undecanoate for 30 months to a group of 855 Chinese men (LOE 1). Using a primary outcome of pregnancy rate, 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. Ninety-five percent of men achieved azoospermia or severe oligozoospermia ($<1 \times 10^6$ sperm/mL), and the median time to onset of azoospermia or severe oligozoospermia was 108 days. The median time to recovery of spermatogenesis calculated from the beginning of the recovery phase was 196 days. 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. Additionally, the use of testosterone therapy in a broad population of men may have varying results.

A significant limitation of the published literature concerning this topic is a lack of pregnancy outcome data. The published literature represents the best available evidence to date regarding the recovery of spermatogenesis after testosterone supplementation, but it is largely limited to male contraceptive studies. This situation may not be