Recovery of spermatogenesis after hormone therapy: what to expect and when to expect it

Administration of exogenous sex steroids suppresses spermatogenesis through estrogen and androgen receptor-mediated feedback inhibition of hypothalamic and pituitary function. This results in an acquired variant of hypogonadotropic hypogonadism (HH) characterized by extremely low or undetectable serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), atrophic testes, and severe oligozoospermia or azoospermia. This clinical picture has become common in clinical practice with the increasing prevalence of testosterone therapy, which is prescribed to tens of thousands of reproductive-aged men in the United States annually. Many of these men (and their doctors) are not aware of the well-established reproductive toxicity of testosterone therapy. Azoospermia induced by the administration of exogenous sex steroids is also encountered in men who abuse anabolic steroids and in male-to-female transgendered patients on estrogen-based therapies who desire biological children or who wish to cryopreserve sperm before orchiectomy for gender reassignment.

Most of what we know about recovery of spermatogenesis after hormone therapy comes from large, well-designed clinical trials of relatively short-duration hormonal male contraception in healthy men with normal baseline fertility. These studies have clearly demonstrated the severe impact of exogenous androgen administration on sperm production and semen quality. They also have reassuringly reported that the overwhelming majority of men recover fertility after cessation of hormone administration in a time-dependent manner. However, recovery without medical therapy to stimulate endogenous testicular function is slow. The best available data come from a 2006 integrated multivariate analysis of 30 previously published clinical trials, which reported that the probabilities of recovery to 20 million sperm/mL at 6, 12, and 24 months were 67%, 90%, and 100%, respectively (1).

Rather than simply waiting for spermatogenesis to recover after cessation of hormone therapy, which can take up to 2 years, medical therapy to promote endogenous testicular function has been used to expedite recovery in affected men. The armamentarium of available therapies includes agents that promote pituitary gonadotropin production by reducing estrogen receptor-mediated negative feedback (selective estrogen receptor modulators such as clomiphene citrate and tamoxifen, aromatase inhibitors such as anastrazole and letrozole), and gonadotropin replacement therapy with human chorionic gonadotropin (hCG, bioequivalent to LH) and recombinant or urine-derived FSH.

The vast majority of our knowledge about the efficacy of therapy to expedite recovery of spermatogenesis after hormone therapy is extrapolated from the body of literature that has described outcomes of gonadotropin-replacement therapy in men with congenital or acquired hypogonadotropic hypogonadism. A 2014 meta-analysis reported the detection of sperm in the ejaculate of 75% of previously azoospermic men after gonadotropin therapy (2). The mean sperm concentration achieved was 6 million/mL, and the spontaneous pregnancy rate was 30%. The treatment regimens used in the included studies were highly variable and nonstandardized, but mostly used hCG monotherapy or hCG with various forms of FSH. The patient populations were also heterogeneous and predominantly comprised of men with congenital HH rather than men with acquired HH resulting from exogenous hormone therapy.

Although the data describing spontaneous recovery of spermatogenesis after male hormonal contraception and the data that have reported on outcomes of gonadotropin therapy in men with HH are valuable, they are not necessarily directly applicable to azoospermic or severely oligozoospermic men with exogenous sex-steroid-induced HH. These men represent a large and unique patient cohort. By definition, most of them have baseline testicular dysfunction that required testosterone therapy, so the prevalence of baseline pretreatment subfertility would be expected to be higher than in the healthy population. Moreover, many of these men have been on longer-term hormone therapy than participants in the male hormonal contraception clinical trials. To date, very few studies have been published that have reported outcomes of medical therapy to expedite recovery of spermatogenesis in this specific population of patients.

The report from Dr. Lipshultz's group, "Age and Duration of Testosterone Therapy Predict Time to Return of Sperm Count after Human Chorionic Gonadotropin Therapy" (3), is thus an important contribution to the literature. This article expands on this same group's prior report that recovery of spermatogenesis in severely infertile men with testosterone-induced HH is first seen on average 4.6 months after initiation of combination therapy (hCG with either a selective estrogen receptor modulator or aromatase inhibitor) (4). Their present study of 66 men is the largest study to date that specifically describes the outcomes of medical therapy to promote recovery of endogenous testicular function in severely infertile men with testosterone therapy-induced HH. By using the clinically meaningful end point of total motile sperm count >5 million, these authors have provided data that are practical, useful, and can be immediately incorporated into clinical practice. Affected couples can be counseled that the overall likelihood of achieving sufficient spermatogenesis for intrauterine insemination within 12 months is 70%. Furthermore, individualized probabilities of recovery can be calculated using the patient's age and prior duration of testosterone therapy, which were both determined to be independently predictive of recovery (3).

We still have a lot to learn about the optimal treatment of men who have been rendered severely infertile by hormone therapy. What we do know, however, has been advanced by the Lipshultz group's work, which should be very useful in counseling affected couples. Azoospermic or severely oligozoospermic patients with exogenous sex-steroid-induced HH should be counseled that (1) their prognosis for recovery is excellent but not guaranteed, (2) recovery begins on average 4 to 5 months after initiation of medical therapy

but can take up to 2 years, (3) semen quality will be sufficient for intrauterine insemination in 70% of men within 12 months of medical therapy to promote spermatogenesis, and (4) older men who have been on testosterone for longer durations are less likely to recover.

For some younger couples who are not actively or urgently trying to conceive, the slow timeline of expected recovery without medical therapy may be sufficient. For other couples who want to conceive in the short or medium term, 6 to 12 months of medical therapy to promote endogenous testicular function followed by attempts at natural conception or intrauterine insemination may be appropriate. Other couples, such as those affected by concomitant female factors, may elect to pursue medical therapy to induce spermatogenesis and attempt in vitro fertilization–intracytoplasmic sperm injection as soon as any sperm become detectable in the ejaculate. Regardless of the specific clinical situation, detailed knowledge about the natural history, treatment, and prognosis of sex-steroid-induced HH can empower clinicians and patients to work together to make personalized treatment decisions.

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