Finasteride and Fertility: Case Report and Review of the Literature

Giuseppe Ricci MD,[a,b] Monica Martinelli BS,[a] Stefania Luppi PhD,[a] Leila Lo Bello MD,[b] Michela De Santis MD,[b] Kristina Skerk MD,[b] and Gabriella Zito MD[b]

[a]Assisted Reproduction Unit, Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste, Italy
[b]University of Trieste, Trieste, Italy

ABSTRACT

Although millions of men have taken or are taking finasteride, there are no documented cases of successful pregnancy in the literature after discontinuation of the drug. Early studies did not show significant influence of finasteride on semen parameters, whereas some recent observations have suggested that in subfertile patients, the effects of the drug might be amplified. Therefore, counseling is particularly difficult for men taking finasteride and planning pregnancy. We report the case of a couple whose male partner had used finasteride for approximately 10 years and who presented for primary infertility. The first semen analysis, carried out 3 months after finasteride cessation, revealed severe oligospermia. One month later, sperm concentration increased, and the following month, the couple spontaneously conceived. A healthy baby was delivered at full term. To the best of our knowledge, this is the first case of successful full-term pregnancy and live birth after long-term use of finasteride, which suggests that treatment with finasteride, even after several years, does not prevent normal conception. However, caution should be advised with the use of finasteride in male partners of couples who are attempting to become pregnant.

J Drugs Dermatol. 2012;11(12):1511-1513.

INTRODUCTION

Finasteride is a specific and potent inhibitor of the type 2, 5α-reductase enzyme that inhibits the conversion of testosterone to dihydrotestosterone.[1] The US Food and Drug Administration (FDA) approved finasteride's use in men with androgenic alopecia (AGA) in December 1997, and currently, finasteride is widely utilized by dermatologists for the treatment of this condition.[2]

Since 30% of men are affected by AGA by the age of 30 years[3] and finasteride influences the metabolism of androgens, concerns have been raised about its adverse effects, especially in men of reproductive age. A recent review including 9 randomized controlled trials (n=3,570) has concluded that the only adverse effect associated with finasteride therapy was erectile dysfunction (ED), suggesting that 1 in every 80 patients treated will experience ED.[4] Unfortunately, the studies included in this review did not consider finasteride's effects on fertility. Only 2 randomized studies have addressed this issue.[5,6] Overstreet et al[5] found that at the FDA-approved dose for AGA (1 mg daily), finasteride does not adversely affect sperm parameters. Instead, a significant influence on motility was observed in a randomized controlled trial where men received 5 mg of finasteride daily, the dose approved by the FDA for the treatment of benign prostatic hyperplasia.[6] However, both studies involved potentially fertile men and did not provide any data about finasteride's effects on conception. To date, no full-term pregnancy or live birth during use of or after cessation of finasteride therapy has been documented.

We report the case of a patient who presented to our center for primary infertility and demonstrated severe oligospermia. The patient had taken finasteride for approximately 10 years. We reviewed the literature on finasteride's effects on male fertility, searching in the Ovid/Medline, PubMed, and Google Scholar databases for all articles published in English, French, German, and Italian between January 1950 and December 2011. The following terms were used: *finasteride, male fertility, infertility, spermatozoa, semen,* and *pregnancy*. We also reviewed all the references cited in those papers.

CASE REPORT

Approval to report this case was obtained from the institutional review board of the Institute for Maternal and Child Health IRCCS Burlo Garofolo in Trieste, Italy.

A couple presented to our Assisted Reproduction Unit for primary infertility of 18 months' duration. The woman, aged 36 years, had no history of ovulation disorders, endometriosis, pelvic inflammatory disease, pelvic surgery, or other conditions potentially interfering with fertility. Her menstrual cycles were regular. Pelvic examination and transvaginal ultrasound did not reveal any pathology. The man, aged 37 years, was a nonsmoker and nondrinker. He had no history of occupational exposure to heat, radiation, or chemicals. He had previously undergone surgery for hiatal hernia repair as well as saphenectomy. He was being treated with 15 mg of oral lansoprazole daily for a

gastroesophageal reflux disease and sporadically with 2 mg of bromazepam for mild generalized anxiety disorder. He had used minoxidil topical solution for hair loss for approximately 4 years, until 1999. He then continued with 1 mg of oral finasteride daily for an additional 10 years, which he had discontinued 3 months before our evaluation.

The patient had no history of sexual dysfunction, and physical examination was unremarkable. The first semen analysis showed severe oligospermia: volume 4.2 mL; sperm count 3.5 x 10^6/mL, and 30% progressive motility. Color Doppler ultrasound showed no varicocele and revealed only a mild decrease in left testicular volume. Serum hormonal levels were: follicle-stimulating hormone 6.6 mIU/mL, luteinizing hormone 4.2 mIU/mL, estradiol 16 pg/mL, prolactin 8 ng/mL, testosterone 6 ng/mL, free testosterone 15.5 pg/mL, and dehydroepiandrosterone sulfate 133 ng/mL. The patient was advised not to resume finasteride therapy.

A second semen analysis was performed 1 month later, and an increase in sperm concentration was found: volume 4.2 mL, sperm count 12 x 10^6/mL, and 29% progressive motility. The couple was counseled to undergo assisted reproduction treatment, but they conceived spontaneously 1 month later. The pregnancy was uneventful, and fetal growth was regular. A spontaneous labor with normal vaginal delivery occurred at full term.

At birth, the male child weighed 3,455 g and was in good health. Postnatal growth was normal. At 1-year follow-up, the development of the child was regular, and the semen analysis of the patient confirmed moderate oligospermia: volume 2.3 mL, sperm count 9 x 10^6/mL, and 32% progressive motility.

DISCUSSION

To the best of our knowledge, this is the first reported case of a successful full-term pregnancy and live birth in a couple whose male partner had a history of long-term treatment with finasteride. Finasteride (1 mg daily) is widely used for the treatment of men with AGA, many of whom are of reproductive age.

Scant data are available on the effects of finasteride on semen parameters. We have reviewed the literature on finasteride's effects on male fertility and have identified very few randomized studies and some case reports. A double-blind, placebo-controlled study of 181 healthy men showed that daily treatment with 1 mg of finasteride for 48 weeks did not significantly affect semen parameters.[5] Although an early study showed no influence on spermatogenesis in 47 men taking a higher dose of finasteride (5 mg daily),[7] a more recent randomized, double-blind, placebo-controlled study of 99 healthy men found that finasteride 5 mg or dutasteride 0.5 mg once daily for 1 year had only mild effects on semen parameters.[6] The authors observed a decrease in semen volume, sperm concentration, and sperm motility at the end of treatment, but no change in sperm morphology. At 24-week follow-up, there was nearly complete recovery for total sperm count and semen volume, but not for sperm motility, which was significantly reduced.[6] It should be noticed that these randomized studies enrolled only healthy men with no history of infertility or difficulty conceiving[5] or those with normal semen parameters.[6] Therefore, counseling for men taking finasteride and planning pregnancy is particularly difficult.

Recently, some authors have suggested that in subfertile patients, the negative effects of finasteride therapy might be amplified.[8-10] Glina et al[8] first reported 3 cases of young patients with very poor semen quality during daily treatment with 1 mg of finasteride. Semen parameters improved considerably after cessation of the drug. Liu et al[9] described 2 cases of azoospermia and severe oligospermia in men using 1 mg of finasteride. There was significant improvement in semen parameters and reverse of azoospermia 6 months after the cessation of the finasteride. Another case of azoospermia during treatment with 1 mg of finasteride was described by Chiba et al.[10] The patient had been diagnosed with oligospermia 5 years earlier. A significant improvement of semen quality was observed after the discontinuation of finasteride, which allowed the patient to try obtaining pregnancy by intrauterine insemination.

> "This case indicates that treatment with finasteride, even after several years, does not prevent normal conception."

In order to investigate the potential submicroscopic sperm alterations induced by finasteride, Collodel et al[11] evaluated sperm morphology by transmission electron microscope, sperm chromosomal abnormalities by fluorescence in situ hybridization and the presence of Y-chromosome microdeletions by polymerase chain reaction in a single patient with azoospermia and in 2 patients with severe asthenozoospermia. Alterations of morphology consistent with necrosis and elevated diploidy and sex chromosome disomy frequencies were found. A significant improvement of semen parameters was observed 1 year after discontinuation of finasteride therapy, whereas the frequency of chromosomal abnormalities was unchanged.

Tu and Zini[12] found an elevated sperm DNA fragmentation index (DFI) in a patient receiving 1 mg of finasteride daily who presented for secondary infertility of 4 years' duration. The couple had had 4 consecutive spontaneous abortions. A significant progressive reduction of sperm DFI was observed 3 and 6 months after finasteride discontinuation. The authors

hypothesized that low-dose finasteride might negatively influence the DNA integrity of sperm, resulting in increased pregnancy losses.[12] None of these studies described full-term pregnancy or live birth during use of or after cessation of finasteride therapy.

The case reported here describes a spontaneous pregnancy that occurred 5 months after discontinuation of finasteride therapy. The pregnancy resulted in a healthy baby, who showed regular development at age 1 year. Since the patient's semen quality was unknown before finasteride treatment, this case cannot support the hypothesis that the effects of finasteride might be amplified in patients with subfertility.[8-10] It cannot be excluded that semen changes were independent from finasteride administration and that pregnancy was simply coincidental. However, this case indicates that treatment with finasteride, even after several years, does not prevent normal conception. We retain that this observation is relevant because there are no documented cases of successful pregnancy currently available in the literature, although millions of men have taken or are taking finasteride.[13]

In conclusion, caution should be advised for the use of finasteride in male partners of couples who trying to conceive. Furthermore, finasteride discontinuation, particularly in subjects with impaired semen analysis, should be considered, until adequate studies are available that report on the drug's effects of the drug on conception.

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

REFERENCES

1. Rasmusson GH, Liang T, Brooks JR. A new class of 5a-reductase inhibitors. In: Roy AK, Clark JH, eds. *Gene Regulation by Steroid Hormones II*. New York, NY: Springer-Verlag; 1983:311-334.
2. Sawaya ME, Shapiro J. Androgenetic alopecia. New approved and unapproved treatments. *Dermatol Clin*. 2000;18(1):47-61.
3. Ellis JA, Sinclair R, Harrap SB. Androgenetic alopecia: pathogenesis and potential for therapy. *Expert Rev Mol Med*. 2002;4(22):1-11.
4. Mella JM, Perret MC, Manzotti M, Catalano HN, Guyatt G. Efficacy and safety of finasteride therapy for androgenetic alopecia: a systematic review. *Arch Dermatol*. 2010;146(10):1141-1150.
5. Overstreet JW, Fuh VL, Gould J, et al. et al. Chronic treatment with finasteride daily does not affect spermatogenesis or semen production in young men. *J Urol*. 1999;162(4):1295-1300.
6. Amory JK, Wang C, Swerdloff RS, et al. The effect of 5alpha-reductase inhibition with dutasteride and finasteride on semen parameters and serum hormones in healthy men. *J Clin Endocrinol Metab*. 2007;92(5):1659-1665.
7. Lewis RW, Lieber MM, Hellstrom WJ, et al. The effect of finasteride on semen production and sexual function in normal males. *J Urol*. 1992;147(5):398A.
8. Glina S, Neves PA, Saade R, Netto NR Jr, Soares JB, Galuppo AG. Finasteride-associated male infertility. *Rev Hosp Clin Fac Med Sao Paulo*. 2004;59(4):203-205.
9. Liu KE, Binsaleh S, Lo KC, Jarvi K. Propecia-induced spermatogenic failure: a report of two cases. *Fertil Steril*. 2008;90(3):849.e17-e19.
10. Chiba K, Yamaguchi K, Li F, Ando M, Fujisawa M. Finasteride-associated male infertility. *Fertil Steril*. 2011;95(5):1786.e9-e11.
11. Collodel G, Scapigliati G, Moretti E. Spermatozoa and chronic treatment with finasteride: a TEM and FISH study. *Arch Androl*. 2007;53(4):229-233.
12. Tu HY, Zini A. Finasteride-induced secondary infertility associated with sperm DNA damage. *Fertil Steril*. 2011;95(6):2125.e13-e14.
13. Schweiger ES, Boychenko O, Bernstein RM. Update on the pathogenesis, genetics and medical treatment of patterned hair loss. *J Drugs Dermatol*. 2010;9(11):1412-1419.

AUTHOR CORRESPONDENCE

Giuseppe Ricci MD
E-mail:.....ricci@burlo.trieste.it