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Pregnancy Outcomes with Paternal Exposure to Finasteride, a Synthetic 5-Alpha-Reductase Inhibitor: A Case Series

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Abstract

Finasteride (a synthetic 5-alpha-reductase inhibitor) is used for the treatment of male pattern baldness and benign prostatic hyperplasia. There have been few reports on pregnancy outcomes after paternal exposure to finasteride either prior to or during pregnancy. Nineteen cases with documented paternal exposure to finasteride either prior to or during pregnancy were identified through the Korean Motherisk program. Detailed patient histories were obtained and each patient was followed from pregnancy through abortion or delivery. Of the 19 patients, 13 (68.4%) gave birth to normal full-term babies. The other six cases (31.6%) resulted in either spontaneous (n=3) or artificial (n=3) abortions. These results are consistent with previous animal studies demonstrating an increase in adverse outcomes with paternal exposure to finasteride.

Keywords Paternal exposure; Finasteride

Introduction

Finasteride is an inhibitor of 5-alpha reductase, an enzyme that converts testosterone to dihydrotestosterone (DHT). Since DHT is the active androgen in many male genital tissues, finasteride acts as an androgen antagonist. Androgen antagonists are effective for the treatment of conditions caused by excessive DHT, such as male pattern baldness and benign prostatic hyperplasia [1]. The most common type of hair loss, androgenic alopecia, is caused by high levels of DHT.

Male pattern baldness is known to affect many men in their prime reproductive years. In the United States, 30% of the male population over 30 years of age and about 50% of men over the age of 50 are known to have this condition [2]. In Korea, one-fifth of the general male population has reported experiencing hair-loss and the rate has increased ten-fold over the last decade. Therefore, it is not surprising that 48.8% of Koreans with alopecia are in their twenties and thirties (Korean National Health Insurance Services, n.d.).

One of the drugs currently marketed for the treatment of this condition is Propecia (finasteride 1 mg, Merck & Co., Inc.). The manufacturer provides a cautionary statement that women who are pregnant or who may become pregnant should not handle crushed or broken Propecia tablets as exposure to the active ingredient might cause abnormalities in a male offspring's sex organs. It also mentions possible side effects for men. Clinical studies have shown that a small number of men experience sexual side effects such as a decrease in the amount of semen and difficulty in achieving an erection. In addition, it notes that the side effects disappear upon discontinuation of finasteride. Such statements are based on a number of case reports where subjects taking finasteride were also experiencing oligospermia or azoospermia. A common finding in these case reports was the significant improvement in semen concentration following cessation of the drug. The improvements were significant enough to allow subjects to continue with less-invasive fertility therapy [3,4]. Although there have been studies with seemingly meaningful correlations, the lack of an overall understanding of fetal safety with paternal exposure to finasteride renders no definitive advice for patients. Therefore, a significant percentage of men who are in their reproductive years and seeking treatment for alopecia are faced with ambiguous information about the drug's effects.

Case series

Nineteen cases of pregnant women where the father had been exposed to finasteride were identified (Table 1). Each case was selected from a pool of women who had received obstetric and teratogen-risk evaluation through the Korean Motherisk Program. Detailed medical and obstetric histories were obtained from the subjects and each woman was followed until either spontaneous/artificial abortion or delivery.

The subjects were between the ages of 28 and 36 with a varied obstetric history. Eighteen of the 19 pregnant subjects had a male partner with a uniform indication of hair loss. In one case, the partner reported using the medication for prostate gland hypertrophy. The starting and ending points of finasteride use in relation to pregnancy and the duration of treatment varied greatly among the subjects. Of the 19 cases, seven reported that exposure occurred prior to conception; the other 12 reported that paternal exposure to the

medication continued after conception. The medication was usually terminated as the couples had noticed the possible adverse effects of the drug on the fetus. In addition, a review of the mothers' medication histories revealed that a number of subjects had been simultaneously exposed to other drugs. Further, one subject was reported to have been consuming alcohol and smoking cigarettes. None of the subjects had experienced any obstetric complications.

Case	Maternal age (year)	Gravidity	Parity	Indication for treatment	Time of exposure	Co-exposure	Pregnancy outcomes
1	30	a	a	Hair loss	Preconception		Normal full-term delivery
2	31	1	0	Hair loss	Up to 14 weeks	Alcohol, Smoking	Normal full-term delivery
3	39	4	3	Hair loss	3 months pre-conception to 5^{+1} weeks		Normal full-term delivery
4	31	2	1	Benign prostatic hyperplasia	2 months pre-conception to 6 weeks		Normal full-term delivery
5	a	1	1	Hair loss	Preconception		Normal full-term delivery
6	36	2	1	Hair loss	2 years pre-conception to 5 weeks	Diazepam, Metoclopramide	Spontaneous abortion
7	28	1	1	Hair loss	Preconception		Normal full-term delivery
8	36	2	1	Hair loss	1 year pre-conception to 12 weeks		Normal full-term delivery
9	33	3	2	Hair loss	4 months pre-conception to 7 weeks		Elective abortion
10	31	2	a	Hair loss	1 year pre-conception to 6 weeks		Elective abortion
11	32	1	0	Hair loss	Up to 4 weeks	Smoking	Elective abortion
12	35	6	0	Hair loss	Preconception		Normal full-term delivery
13	29	1	0	Hair loss	Up to 29 weeks		Normal full-term delivery
14	28	6	1	Hair loss	Up to 24 weeks		Normal full-term delivery
15	29	2	1	Hair loss	Preconception		Normal full-term delivery
16	28	2	1	Hair loss	Up to 10^{+1} weeks		Normal full-term delivery
17	32	2	0	Hair loss	Up to 13^{+4} weeks		Normal full-term delivery
18	31	1	0	Hair loss	Preconception		Spontaneous abortion
19	31	1	a	Hair loss	Up to $7+^{3}$ weeks		Spontaneous abortion
[a]Unknown							

Table 1: Nineteen cases with paternal exposure to finasteride.

Among the 19 cases, 13 women gave birth to normal full-term babies. The other six pregnancies resulted in abortions: three were spontaneous and three were artificial. The first subject to have a spontaneous abortion was a 36-year-old woman who had experienced a previous miscarriage and also had a living child. Her partner had been taking finasteride from pre-conception until 5 weeks into pregnancy. She had also been taking diazepam (a drug belonging to FDA class D, which means there is positive evidence of human fetal risk based on adverse reaction data from clinical trials; however, potential benefits may warrant use of the drug in pregnant women despite potential risks) and metoclopramide. The missed abortion occurred at 7+4 weeks. A second case of spontaneous abortion

occurred at 9+3 weeks. The subject in this case was a 31-year-old woman whose husband had taken finasteride for androgenic alopecia prior to conception. The third case of spontaneous abortion occurred in a 31-year-old woman at 9+2 weeks, in which exposure had continued until 7+3 weeks.

Discussion

Although earlier research studies have suggested that finasteride's effect on infertility is insignificant, a number of recent studies and case reports have shown otherwise. A study by Garcia et al. showed that finasteride-exposed rats experienced deterioration in fertility parameters due to changes in morphology and epididymal and sperm function. The authors explained that finasteride caused an acceleration of sperm transport through the epididymis, which compromised maturation, thereby resulting in decreased fertility [5].

In addition to a negative influence on sperm parameters, a case report by Tu et al. (2011) showed that discontinuation of finasteride resulted in an improved sperm DNA fragmentation index (DFI), an estimate of breaks in sperm DNA. The authors hypothesized that a high sperm DFI of 30% had caused previous recurrent pregnancy losses. They noted that the current literature had focused primarily on finasteride's effect on sperm parameters such as volume and concentration, and that more studies are needed on the relationship between finasteride and sperm DNA integrity [6].

Despite an insufficient knowledge of parental factors in spontaneous abortion, a correlation between sperm DFI and miscarriage aligns with current knowledge of how chromosomal abnormalities in sperm are associated with early pregnancy loss [7]. In addition, more than 80% of abortions occur in the first trimester (first 12 weeks) of pregnancy, and half of these result from chromosomal anomalies. Both the abortion rate and the incidence of chromosomal anomalies decrease after the first trimester [8].

In understanding the results of the present study, it is essential to understand the maternal factors that influence the incidence of spontaneous abortion. An increase in spontaneous abortion has been linked to age and parity of the mother. Tobacco and alcohol use, as well as excessive caffeine intake, are also considered to have a potential association with an increased rate of miscarriages [8].

The rate of abortion (18.75%, 3 of 16) in our data doesn't necessarily mean that finasteride is a definite cause of early pregnancy loss. The data show that paternal use of finasteride is another potential hazard associated with early pregnancy complications even in a preconception time. These results are clinically meaningful to physicians and couples who plan a pregnancy. Nonetheless, the absence of paternal sperm quality data is a limitation in the present study. This was due to a retrospective study design primarily involving verbal interviews with subjects. The sperm quality data would have contributed to a more thorough evaluation of the influence of finasteride on pregnancy outcomes. Further investigation in future prospective cohort studies with a larger sample size is needed. Considering a large number of men suffering from baldness and prostatic hyperplasia, a clearer understanding of the correlation between finasteride use and spontaneous abortion may have a huge impact to pregnancy outcomes. In our opinion, men who prepare to become a father should reconsider finasteride use until the drug safety related to pregnancy is established.

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