Aromatase inhibitors for male infertility

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Some men with severely defective sperm production commonly have excess aromatase activity, reflected by low serum testosterone and relatively elevated estradiol levels. Aromatase inhibitors can increase endogenous testosterone production and serum testosterone levels. Treatment of infertile males with the aromatase inhibitors testolactone, anastrazole, and letrozole has been associated with increased sperm production and return of sperm to the ejaculate in men with non-obstructive azoospermia. Use of the aromatase inhibitors anastrazole (1 mg/day) and letrozole (2.5 mg/day) represent off-label use of these agents for impaired spermatogenesis in men with excess aromatase activity (abnormal testosterone/estradiol [T/E] ratios). Side effects have rarely been reported. Randomized controlled trials are needed to define the magnitude of benefit of aromatase inhibitor treatment for infertile men. (Fertil Steril® 2012;98:1359–62. ©2012 by American Society for Reproductive Medicine.)

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Spermatogenesis is dependent on maintenance of high levels of intratesticular testosterone as well as Sertoli cell stimulation with FSH (1). For men with idiopathic infertility, there are no reliable treatments to enhance fertility. However, increased sperm production or motility has been associated with empiric medical therapy using estrogen receptor modulators such as clomiphene citrate or tamoxifen citrate. Such medical therapy to improve spermatogenesis has primarily focused on enhancement of intratesticular testosterone levels and stimulation of FSH production. Unfortunately, use of estrogen receptor modulators results in increased estrogen levels as well as increased testosterone production. Aromatase is a cytochrome P-450 enzyme that converts testosterone to estradiol and androstenedione to estrone. In addition to the female reproductive tract and adipose tissue, aromatase can be found in the testis, liver, and brain, among other tissues. In the testis, aromatases are localized to Leydig and Sertoli cells and are found in germ cell tumors (2). Aromatase inhibitors have the ability to increase endogenous testosterone production without the associated increase in circulating estrogens seen with estrogen receptor modulators (3).

Recent studies have identified a potential specific endocrine defect in men with severe male factor infertility (3). Some men with severely impaired sperm production have a relative excess of estrogen to testosterone, quantitatively measured as an increased testosterone/estradiol (T/E) ratio. Pavlovich et al. (3) characterized men with severe male infertility as having a T/E ratio of 6.9, whereas men with normal spermatogenesis had a mean T/E ratio of 14.5. Based on these observations, they proposed a cut-point of 10 as the lower limit of normal T/E ratios in men (calculated using T in ng/dL, and estradiol as pg/mL). Clinical studies of aromatase inhibitors have focused on men with defective spermatogenesis associated with low serum testosterone levels and abnormal T/E ratios.

Animal studies have found that local expression of aromatase is essential for spermatogenesis, suggesting a role of estrogen in male germ cell development (4). Estrogens are a critically important factor in the reabsorption of fluid within the rete testis. With the very high level of sperm production in rodents, there is an associated obligate reabsorption of fluid in the rete testis. Inhibition of fluid reabsorption (similar to the effects of efferent duct ligation) can cause such increase in intratesticular fluid and intratesticular pressure that testis atrophy occurs in rodent testes (5). For the rodent model, it can be difficult to separate the adverse effects of decreasing efferent duct fluid reabsorption from any beneficial effects on spermatogenesis. Without a model of impaired rodent spermatogenesis, aromatase inhibitor studies in animals have been limited. Estrogens may also have direct adverse effects on the germinal epithelium. High estrogen levels, perhaps in combination with low androgen levels, have been shown to impair spermatogenesis (6).

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Clinical use of aromatase inhibitors have been applied to idiopathic infertility with the intent of reducing estrogenic effects on the male reproductive system, especially by reducing feedback inhibition of the HPG axis. Since males detect testosterone levels by the pituitary primarily by estrogen levels rather than testosterone alone, inhibition of estrogen production by an aromatase inhibitor can be a potent stimulant for increased LH production and hence intratesticular and circulating testosterone levels (7). For men with a low serum testosterone and low T/E ratio, treatment with an aromatase inhibitor to increase sperm production would be more rational than treatment with a selective estrogen receptor modulator.

CLINICAL TRIALS

Medical therapy with aromatase inhibitors has been reported in a series of clinical trials and case reports. A PubMed search was carried out using the search terms "aromatase inhibitor male infertility" to identify these studies, and review of the references in the identified articles was performed as well.

Aromatase inhibitors are available in steroidal and nonsteroidal oral formulations. In some trials, treatment was applied for male infertility patients without selection based on hormonal abnormalities, whereas in other reports, only patients with low testosterone and abnormal T/E ratio were selected for therapy. The outcome of these trials may well result from the selection of patients for treatment. If an aromatase inhibitor specifically benefits only those patients with excess aromatase activity, then it may not demonstrate benefit in a small trial of men with idiopathic infertility. Unfortunately, many trials were not controlled; results during treatment were compared to those of the same patients at baseline. Whereas hormonal changes are detected in all of these trials and suggest therapeutic benefit (at least in enhancing endogenous testosterone production), it is not always clear that patients had improved fertility from this therapy. A summary of these reports is provided below, based on the agents used.

Testolactone

Testolactone, a steroidal inhibitor that is no longer clinically available in the United States, has been studied in several trials for idiopathic male infertility. A randomized, controlled cross-over trial reported in 1989 investigated the use of testolactone in men who have idiopathic infertility (8). Twenty-five men were assigned randomly to testolactone, 2 g/d, or placebo for 8 months followed by crossover to the other treatment arm for another 8 months. Oddly, estradiol and testosterone levels did not change with treatment during the trial. Sex hormone–binding globulin, however, decreased by 30%, and free testosterone increased by 36% with treatment. There was not a statistically significant change in free estradiol levels reported in this study. The increase in serum levels of LH, FSH, and 17-hydroxyprogesterone was 15%, 20%, and 90%, respectively. No improvement in semen parameters was noted, and no pregnancies occurred in either group. This relatively high dose of testolactone may have resulted in a suppression of testosterone production, a known side effect of high dose testolactone therapy.

A study by Pavlovich and colleagues (3), using a much lower dose of testolactone, noted a statistically significant increase in the T/E ratio as well as improvement in sperm parameters when men with severe male infertility were treated with testolactone. In this study, the treatment group was selected for low testosterone (<300 ng/dL) with T/E ratio <10 and compared to an age-matched, fertile control reference group. In this study, no side effects requiring cessation of medical therapy were reported, but transient liver function test abnormalities were noted in 8 of 45 men (6 with enzymatic abnormalities within two times the normal levels and indirect hyperbilirubinemia in 2). All abnormalities returned to normal after therapy. Raman et al. (9) also noted improved hormonal response to testolactone (vs. anastrazole) in the subset of patients with Klinefelter syndrome, again selected for treatment based on low testosterone and abnormal T/E ratios.

Anastrazole

Raman and Schlegel (9) evaluated the effects of anastrozole, a more selective aromatase inhibitor, on hormonal and semen parameters of infertile men who had abnormal T/E ratios. This was not a study of empiric treatment, because it did not focus on patients who had idiopathic nonobstructive azoospermia and normal testosterone levels; some of the patients had other male-factor diagnoses such as Klinefelter's syndrome and varicoceles and all treated patients had low testosterone levels reflective of hypogonadism. The study included 140 infertile men who had abnormal T/E ratios. Seventy-four patients were given 50 to 100 mg of testolactone twice daily for a mean duration of 6 months, and 104 men were given 1 mg of anastrozole daily for a mean duration of 4.7 months. No untreated group was included. Subgroup analyses were performed on overweight patients, patients who had Klinefelter's syndrome, and those who had past or current varicoceles. All treatment groups had a statistically significant increase in T/E ratios, and improved semen parameters were noted in those who underwent semen analyses before and after treatment. Interestingly, the obese patients did not have a greater benefit of treatment than other patients, even though aromatase from adipose tissue could increase aromatase activity. This observation may reflect our hypothesis that most aromatase activity comes from the testis, not peripheral conversion (Peter N. Schlegel, personal communication, October 2012).

In men treated with testolactone, the T/E ratio increased from 5.3 ± 0.2 to 12.4 ± 1.1 (mean ± standard error of the mean) ($P<.001$). Sperm concentration increased from 5.5 to 11.2 million sperm per mL ($P<.01$), motility increased from 14.7% to 21.0% ($P<.05$), morphology increased from 6.5% to 12.8% ($P<.05$), and the motility index increased from 606.3 to 1,685.2 million motile sperm per ejaculate ($P<.05$). Similarly, in men treated with anastrozole, the T/E ratio increased from 7.2 ± 0.3 to 18.1 ± 1.0 ($P<.001$). Sperm concentration increased from 5.5 to 15.6 million sperm per mL ($P<.001$), and the motility index increased from 833 to 2,931 million motile sperm per ejaculate ($P<.005$). The men who had Klinefelter's syndrome did not improve during anastrozole therapy, perhaps because anastrazole does not inhibit adrenal steroid. Pregnancy rates were not evaluated, because

many men had nonobstructive azoospermia; this clinically important outcome may be addressed in future randomized, controlled trials.

Side effects were rare during anastrazole treatment. Raman et al. (9) found that less than 5% of men reported changes in libido and 7.4% of men had transient and clinically insignificant alterations in liver function tests. Routine testing of liver function tests are no longer carried out at our center during treatment based on these observations.

Letrozole

Letrozole is a more potent aromatase inhibitor than anastrazole and has been applied clinically for treatment of males in several trials. Investigators from Toronto (10) reported a single case with induction of spermatogenesis, documented on testis biopsy, for a man treated with letrozole 2.5 mg/day for 4 months. The increase in spermatogenesis was associated with a marked increase in serum testosterone from 14 nmol/L (pretreatment) to 28 nmol/L, associated with a marked increase in FSH levels as well. Since the patient was subsequently found to have epididymal obstruction, correlative semen parameters were not evaluable.

A follow-up study by Cavallini et al. (11) reported on four patients with FSH levels <10 IU/L and non-obstructive azoospermia who all had sperm return to the ejaculate during letrozole therapy (2.5 mg/d). Mean FSH levels increased markedly during treatment, and serum testosterone went from 331 to 1,117 ng/dL during treatment. All hormone levels returned to baseline levels within a week of terminating treatment. Of note, males with nonobstructive azoospermia will often have rare sperm seen on a subsequent semen analysis despite the absence of sperm on several semen specimens. This may occur because of better detection of sperm with extended sperm preparation (12) or small variations in sperm production over time.

Saylam et al. (13) treated a total of 27 infertile male patients who had low serum testosterone levels and T/E ratios <10. Of the ten oligospermic men, increased sperm concentration, motility, and morphology were observed, with 2 of 10 males contributing to pregnancies without further intervention. Of the 17 azoospermic males, 4 of 17 (24%) had sperm return to the ejaculate during treatment, associated with increased serum testosterone levels for all treated patients. As expected, mean serum estradiol levels decreased. There were no control patients in this study.

Gregoriou et al. (14) treated 29 men with low T/E ratios (<10) using anastrazole or arimidex in a poorly controlled clinical study (alternate allocation of enrolled patients.) The patients were treated with 6 months of letrozole 2.5 mg/d, as in the other studies, and followed for hormonal changes as well as changes in semen parameters. Very similar increases in total testosterone levels and decrease in serum estradiol were seen for each of the treatment groups. Increases in sperm concentration, motility, and morphologically normal sperm and ejaculate were seen for patients treated with either letrozole or anastrazole. The magnitude of increase in sperm concentration was numerically greater for patients treated with anastrazole, but the benefit did not appear to be statistically significant.

In the Cavallini et al. study (11), a loss of libido was reported by all 4 men treated, with nervousness in 1 and rash in 2 cases. In the Saylam et al. study (13), 2 of 27 men reported mild headaches, not requiring cessation of therapy with no other side effects identified. Gregoriou et al. (14) reported only mild side effects in all of the 29 men treated with letrozole or anastrazole, again with transient liver enzyme abnormalities in <10% of men during therapy.

SUMMARY

Men with impaired sperm concentration appear to commonly have excess aromatase activity, reflected by relatively increased serum T/E ratio, especially in men with nonobstructive azoospermia. Our observations of men who have had T/E levels evaluated during both endogenous testosterone production and subsequent exogenous testosterone replacement strongly suggest that the source of excess aromatase activity is the testis, likely from excess Leydig cell conversion of testosterone to estrogens (Peter N. Schlegel, personal communication, October 2012). In addition, the observation of impaired sperm production in men with excess aromatase activity (associated with increased multi-repeat sequences involving the nucleotides TTTA in the aromatase gene [TTTAn] repeats) suggests that excess aromatase may cause male infertility and be specifically treatable (15). Unfortunately, rodent models of this condition of impaired spermatogenesis associated with excess aromatase activity have not been explored to-date. Such a model could allow better insight into the pathogenesis and treatment options for these men.

Treatment of infertile men with low serum testosterone levels using aromatase inhibitors is rational, and has been associated with improved semen parameters as well as increased total serum testosterone levels as well as suppressed estradiol. Controls have typically been matched observed patients, in the clinical trials where controls were even included in the studies. Semen parameters are highly variable biological measures, so changes in semen parameters associated with medical therapy may not have been caused by the medication used. The observation of improvements in semen parameters is especially common when patients are selected for study based on low semen parameters, where regression to the mean will result in higher semen parameters during treatment.

Obviously, randomized controlled trials of aromatase inhibitors would be helpful to better define the potential role of these agents in treatment of male infertility. We have estimated that the trial size required to evaluate the benefit of aromatase inhibitors in improving sperm retrieval for males with non-obstructive azoospermia would require enrollment of over 700 patients. This would require a multi-year or multi-center study that may not be feasible in the foreseeable future. Until such definitive studies are available, the off-label use of aromatase inhibitors for male infertility patients with low serum testosterone and abnormal T/E ratios is rational and appears to be markedly increasing.

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