The beneficial effects of toremifene administration on the hypothalamic-pituitary-testicular axis and sperm parameters in men with idiopathic oligozoospermia

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Objective: To evaluate whether toremifene, a selective estrogen receptor modulator (SERM), has a beneficiary effect on all three main sperm parameters.
Design: Prospective interventional clinical study.
Setting: University hospital.
Patient(s): One-hundred subfertile men with idiopathic oligozospermia.
Intervention(s): Toremifene (60 mg daily) was administered to all men for 3 months. At baseline and at the end of each month, serum concentrations of follicle-stimulating hormone (FSH), testosterone, inhibin B, and sex hormone–binding globulin (SHBG) were measured. At baseline and at the end, semen analysis was performed and sperm concentration, spermatozoal motility and normal sperm forms were determined.
Main Outcome Measure(s): Gonadotropin, testosterone, inhibin-B levels, total sperm count, sperm morphology and motility.
Result(s): Toremifene administration resulted in a significant increase in FSH, testosterone, SHBG, and inhibin B levels, as well as in sperm concentration, percentage motility and normal sperm forms. Twenty-two men's partners achieved pregnancy within 2 months of the end of treatment. At the end of the third month, serum FSH levels were significantly higher in the men whose partners did not achieve pregnancy, and total sperm count and normal sperm forms were significantly lower compared with the group of men whose partners achieved pregnancy.
Conclusion(s): Toremifene administration for a period of 3 months in men with idiopathic oligozoospermia is associated with significant improvements of sperm count, motility, and morphology, mediated by increased gonadotropin secretion and possibly a direct beneficial effect of toremifene on the testes. The above findings are also indicative of a better testicular exocrine (improved sperm parameters) response to treatment in men whose partners achieved pregnancy compared with those who did not. Further randomized, placebo-controlled trials should be conducted to determine whether this particular selective estrogen receptor modulator can be useful as an initial approach in men with oligozoospermia. (Fertil Steril® 2007;88:847–53. ©2007 by American Society for Reproductive Medicine.)

Key Words: Toremifene, oligozoospermia, male infertility, SERM

A selective estrogen receptor modulator (SERM) is a compound that can act as an estrogen agonist or antagonist, depending on the specific target tissue (1). At present, four SERMs are approved for clinical use: clomiphene, raloxifene, tamoxifen, and toremifene. Three of these compounds belong to the triphenylethylene family: clomifene, tamoxifen, and toremifene. Raloxifene belongs to the benzothiophene family (2).

Most of the unique pharmacology of SERMs can be explained by three interactive mechanisms. The first is differential estrogen-receptor expression in a given target tissue. The second consists of the differential estrogen-receptor conformation on ligand binding. The third is the differential expression and binding to the estrogen receptor of coregulator proteins (3).

In women, at least three SERMs have been shown to increase circulating levels of gonadotropin. The exact mechanism for this effect is based on the estrogen antagonistic properties of SERMs at the hypothalamic and pituitary level (4). In addition, SERMs have been shown to increase sex hormone–binding globulin (SHBG) levels, which can be attributed to the estrogen agonist activity of SERMs in the liver (2, 3).

There have been relatively few studies of SERMs in males. Clomiphene citrate and tamoxifen have been proposed for the management of male factor infertility (1). Tamoxifen citrate was introduced 30 years ago as an empiric treatment for idiopathic oligozoospermia because of its stimulatory action on gonadotropin secretion and its postulated direct effects on Leydig cell function and 5α-dihydrotestosterone production in seminiferous tubules and epididymis (5). The main effect

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of tamoxifen on spermatogenesis is stimulatory, resulting in a twofold increase in spermatozoa concentration. Such an increase in spermatozoa concentration may be important because a change of this magnitude at the low range of spermatozoa concentrations found in oligozoospermic men has been associated with disproportionately higher fecundity. However, this particular SERM has not been shown to induce any marked changes in motility and morphology (6, 7).

The effect of treatment with tamoxifen citrate on cumulative achievement of pregnancy over a long period of time is similar to that of assisted reproductive techniques (ART) (8, 9). On the basis of these results (6, 10, 11), tamoxifen citrate was proposed by a World Health Organization working committee as the first line of treatment for idiopathic oligozoospermia (12).

Because tamoxifen increases spermatozoa concentration but has no marked effect on spermatozoa motility and morphology, this study was designed to evaluate whether another SERM, toremifene, has a beneficiary effect on all three main semen parameters. To the best of our knowledge, no previous data have been reported concerning the effect of this specific SERM on the hypothalamic-pituitary-testicular axis and semen parameters in men with idiopathic abnormalities in one or more of the three main semen parameters.

MATERIALS AND METHODS

Patients

One hundred subfertile men with idiopathic oligozoospermia, mean (± SEM) age 20 to 47 years (33.53 ± 0.5 years), were consecutively recruited from the fertility center of our department. All of the men were characterized as subfertile because they had been unsuccessful in achieving pregnancy with their partners for 12 months, although their partners did not show any of the known causes of female subfertility.

Idiopathic oligozoospermia was defined as quantitative and/or qualitative aberrations of sperm variables according to World Health Organization criteria (12). Men with known or demonstrable causes of oligozoospermia (varicocele, infections, autoimmunity, stress, chromosomal abnormalities, environmental factors, or epididymitis) were excluded.

Careful clinical examination showed that all of the men had complete development of the secondary sex characteristics, with a mean (± SEM) right testicular volume of 18.45 ± 0.39 cm^3 and mean (± SEM) left testicular volume 17.80 ± 0.41 cm^3 (mean testicular volume 18.14 ± 0.39 cm^3). Total testicular volume was assessed by comparison with a standard value on orchidometry. None of the men had received any medication during the 6-month period preceding the study.

Study Protocol

All of the men received toremifene as monotherapy at a dose of 60 mg daily for a period of 3 months. At baseline, and at the end of the first, second, and third month of treatment, blood samples were collected at 9 AM after an overnight fast.

All samples were centrifuged immediately, and serum was stored at −70°C until assayed for FSH, testosterone, inhibin B, and SHBG. Sperm was examined at baseline and at the end of the third month of treatment. All participants were properly informed about the purpose of the study and gave informed written consent. The study was approved by the ethics committee of the hospital.

Hormonal Measurements

We measured FSH (IU/L) using the FSH IRMA kits from Biosource Technologies (Vacaville, CA). Total testosterone (ng/dL) was measured by enzyme-linked immunosorbent assay (ELISA; testosterone enzyme immunoassay test kit, LI7603; Linear Chemicals). The serum levels of SHBG (nmol/L) were measured by ELISA (SHBG ELISA, MX 520 11; IBL, Hamburg, Germany). Inhibin B levels were measured using ELISA kits from Oxford Bio Innovation DSL Ltd (Upper Heyford, Bicester, Oxfordshire, United Kingdom).

Semen Analysis

Semen was collected by masturbation into sterilized glass containers after a 3- to 6-day abstinence. After evaluation of liquefaction and measurement of viscosity and volume, motility was measured, at room temperature (22° to 25°C), 1 hour after ejaculation, as previously described elsewhere (12–15).

Sperm morphology was evaluated from Papanicolaou-stained smears, and the classification of abnormal sperm forms was made according to the guidelines of the WHO (12). One hundred spermatozoa were studied from each semen specimen, and the same individual (D.P.) evaluated all smears. The percentage of motile spermatozoa was measured by the subjective method at room temperature (22° to 25°C), and sperm concentration was determined in an undiluted semen specimen with the use of Makler's Counting Chamber (16, 17).

Statistical Analysis

Statistical analysis was performed with SPSS statistical software, v. 13.0 (SPSS Inc, Chicago, IL). Two-tailed statistical significance was set at 5%. Categorical parameters (smoking status) were compared with Fischer's exact test. The normality of distribution was assessed with the Kolmogorov-Smirnov test (K-S) test. Values that did not fit the normal distribution were log-transformed.

Mean was compared at baseline with Student's *t*-test and during treatment with general linear model–based two-way repeated measures of analysis of variance (ANOVA); time (treatment) was set as the within-groups factor and achievement of pregnancy as the between-subjects factor. Within-groups post hoc analysis was performed after Bonferroni adjustment for multiple comparisons. Between groups post hoc analysis was based on model parameter estimates.

For those parameters where statistically significant or borderline differences or interactions between the men whose