Successful Fertility Treatment for Klinefelter's Syndrome

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Abbreviations and Acronyms

FSH = follicle-stimulating hormone

hCG = human chorionic gonadotropin

ICSI = intracytoplasmic sperm injection

IVF = in vitro fertilization

KS = Klinefelter's syndrome

LH = luteinizing hormone

SRR = sperm retrieval rate

TESE = testicular sperm extraction

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Study received Weill Cornell Medical College institutional review board approval.

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Purpose: We examined preoperative factors that could predict successful microdissection testicular sperm extraction in men with azoospermia and nonmosaic Klinefelter's syndrome. We also analyzed the influence of preoperative hormonal therapy on the sperm retrieval rate.

Materials and Methods: A total of 91 microdissection testicular sperm extraction attempts were done in 68 men with nonmosaic Klinefelter's syndrome. Men with serum testosterone less than 300 ng/dl received medical therapy with aromatase inhibitors, clomiphene or human chorionic gonadotropin before microdissection testicular sperm extraction. Preoperative factors of patient age and endocrinological data were compared in those in whom the procedure was and was not successful. The sperm retrieval rate was the main outcome. Clinical pregnancy (pregnancy with heartbeat) and the live birth rate were also calculated.

Results: Testicular spermatozoa were successfully retrieved in 45 men (66%), representing 62 (68%) attempts. Increasing male age was associated with a trend toward a lower sperm retrieval rate ($p = 0.05$). The various types of preoperative hormonal therapies did not have different sperm retrieval rates but men with normal baseline testosterone had the best sperm retrieval rate of 86%. Patients who required medical therapy and responded to that treatment with a resultant testosterone of 250 ng/dl or higher had a higher sperm retrieval rate than men in whom posttreatment testosterone was less than 250 ng/dl (77% vs 55%). For in vitro fertilization attempts in which sperm were retrieved the clinical pregnancy and live birth rates were 57% and 45%, respectively.

Conclusions: Microdissection testicular sperm extraction is an effective sperm retrieval technique in men with Klinefelter's syndrome. Men with hypogonadism who respond to medical therapy may have a better chance of sperm retrieval.

Key Words: testosterone, testis, sperm retrieval, Klinefelter syndrome, pregnancy

KLINEFELTER'S syndrome is the most common form of male hypogonadism and chromosome aneuploidy with a reported prevalence of 0.1% to 0.2% in the general population, and up to 3.1% in infertile males and 10% in men with azoospermia.[1,2] The genotypic abnormality results from a meiotic nondisjunction event, causing a 47,XXY genotype in most cases, although up to 3% of men with KS are mosaic 46,XY/47,XXY.[3] Almost all men with KS are azoospermic but rarely spontaneous paternity has been reported.[4,5] Before the introduction of ICSI[6] the fertility outlook in most of these patients was hopeless. ICSI offers the opportunity for reproduction even when spermatozoa are present only in the testis. In 1996 successful recovery of spermato-

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zoa by TESE in men with azoospermia and KS was reported[7] with the first pregnancies reported in 1997.[8] Surgical sperm retrieval has revealed spermatozoa in up to half of patients with nonmosaic KS.[9] This recovery rate is similar to that in all men with nonobstructive azoospermia.[10]

Controversy surrounds the preoperative factors that can predict sperm retrieval success using microdissection TESE in men with KS. The predictive value of testicular volume, baseline testosterone and the testosterone response to the hCG test were suggested by some investigators[11] but not by others.[10,12] Age was proposed as a limiting factor for sperm retrieval in some studies[13,14] and used to promote the concept of earlier sperm retrieval. Hence, we evaluated the effect of age and endocrinological parameters on sperm retrieval in our study group. We also analyzed the influence of medical therapy in men with low testosterone in this patient population.

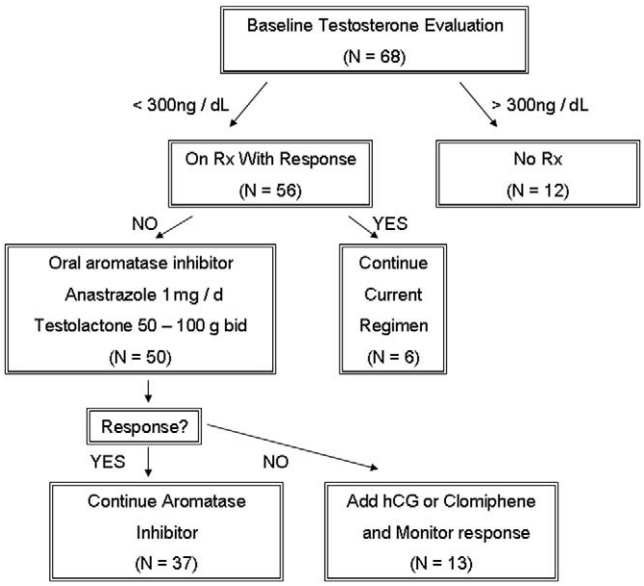

Figure 1. Medical therapy (*Rx*) in patients with KS at our institution. *g*, gm. *d*, day. *bid*, twice daily.

MATERIALS AND METHODS

Patient Selection

We retrospectively analyzed the records of all consecutive patients who presented between March 1999 and June 2008 with nonobstructive azoospermia and nonmosaic KS, and underwent microdissection TESE. The 47,XXY karyotype was confirmed by analysis of peripheral lymphocytes with at least 50 cells cytogenetically analyzed per patient. Azoospermia was confirmed by analysis of at least 2 centrifuged semen specimens according to WHO guidelines.[15] An additional semen sample was confirmed to be azoospermic on the day of planned microdissection TESE. Testicular volume was measured by physical examination using an orchidometer and the volume of the larger testis was used for analysis. Hormonal evaluation included testosterone, estradiol, FSH and LH measurement. Pretreatment testosterone was determined at least 6 months off any hormonal replacement. Clinical pregnancy in female partners was defined by identifying the gestational sac with a fetal heartbeat on transvaginal ultrasound 7 weeks after embryo transfer. Confirmation of live birth was made by telephone interviews of couples who were identified with clinical pregnancy. All patients seeking help at our institution were offered professional genetic counseling, including the options of prenatal diagnosis and preimplantation genetic diagnosis. The karyotype after ICSI in all tested embryos was 46,XY or 46,XX. The study protocol was approved by the Weill Cornell Medical College institutional review board.

Medical Therapy Before Microdissection TESE

Men with serum testosterone less than 300 ng/dl[16] (10.4 nmol/l) were treated with aromatase inhibitors (50 to 100 mg testolactone orally twice daily or 1 mg anastrozole daily),[17] hCG or clomiphene for at least 2 to 3 months before surgery (fig. 1). In patients primarily evaluated at our institution initial therapy was provided with an oral aromatase inhibitor. Men who did not respond to initial oral aromatase inhibitor therapy with normal testosterone after 1 month were subsequently also treated with hCG injections. Treatment with hCG was initiated at a dose of 1,500 IU twice weekly and titrated upward until a response in serum testosterone was achieved or a maximum dose of 2,500 IU 3 times weekly was reached. In patients previously on other hormonal therapy except exogenous testosterone before referral to our center, eg clomiphene, recombinant FSH etc, with normal serum testosterone the previous treatment was maintained. In patients receiving exogenous testosterone the therapy was discontinued before initiating medical treatment at our institution. Medical therapy was continued until the time of TESE. All patients on exogenous testosterone had that treatment stopped for at least 6 months before TESE.

Microdissection TESE

The microdissection TESE procedure was described previously.[18] Sperm retrieval was typically attempted on the day before oocyte retrieval. Briefly, a midline incision was made in the scrotum and the testis with the spermatic cord was preferentially delivered from the side with the larger testis. The tunica vaginalis was opened and the tunica albuginea was visualized. Under an operative microscope the tunica albuginea was widely opened in an equatorial plane around approximately 270 degrees of the circumference of the testis with preservation of the subtunical vessels.

After the tunica albuginea was opened direct examination of the testicular parenchyma was performed at between 12× and 18× magnification under an operating microscope. Examination included as much of the testicular parenchyma as possible until spermatozoa were found. Small samples (1 to 15 mg) were excised by teasing out larger, more opaque tubules from surrounding Leydig cell nodules in the testicular parenchyma. Excised samples were examined immediately for testicular spermato-