

Successful testicular sperm retrieval in adolescents with Klinefelter syndrome treated with at least 1 year of topical testosterone and aromatase inhibitor

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Objective: To evaluate surgical sperm retrieval rates in adolescents with Klinefelter syndrome and testosterone replacement therapy (TRT).

Design: Case series.

Setting: Academic medical center.

Patient(s): Ten patients with Klinefelter syndrome, aged 14–22 years, treated with testosterone replacement and aromatase inhibitor therapy for a period of 1–5 years before surgical sperm retrieval.

Intervention(s): Microsurgical testis sperm extraction with cryopreservation of harvested tissue.

Main Outcome Measure(s): Presence of spermatozoa within testis tissue.

Result(s): Successful sperm retrieval in 7/10 patients (70%).

Conclusion(s): Use of topical TRT did not appear to suppress spermatogenesis in adolescents with KS. It is uncertain whether sperm retrieval rates would be higher or lower without testosterone replacement in these young males. Sperm cryopreservation should be discussed in all KS adolescents who are either receiving or considering initiating TRT. (Fertil Steril® 2013;100:970–4. ©2013 by American Society for Reproductive Medicine.)

Key Words: Klinefelter syndrome, testosterone, hormone replacement, testicular sperm extraction

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Klinefelter syndrome (KS) is the most common chromosomal anomaly in male individuals and is classically associated with small testes, hypergonadotropic hypogonadism, and infertility. Most boys with KS have sufficient levels of circulating testosterone (T) to initiate puberty, but often fail to progress adequately. Testicular size in affected boys briefly increases after the onset of puberty until midpuberty and declines there-

after, accompanied by low serum T and elevated gonadotropin levels (1, 2). In fact, the onset of puberty appears to be associated with accelerated testicular germ cell depletion, which is progressive and irreversible (1).

Historically, men with KS were considered to be infertile. However, successful pregnancies resulting from rare ejaculated sperm in the semen of men with KS have been reported

(3, 4). It is now well accepted that isolated foci of spermatogenesis can exist in the testes of patients with KS (5). This discovery, along with advances in assisted reproductive technology during the past two decades, have made paternity possible for men with KS. Because puberty is associated with a progressive decline in the numbers of spermatogonia within the seminiferous tubules, early sperm retrieval, and semen or testicular tissue cryopreservation, for patients with KS has been recommended by several investigators (6–11).

The use of T replacement therapy (TRT) has been advocated in adolescents with KS to allow for age-appropriate pubertal development and

Received April 5, 2013; revised June 6, 2013; accepted June 7, 2013; published online July 2, 2013.
A.M. has nothing to disclose. A.B. has nothing to disclose. J.R. has nothing to disclose. P.N.S. has nothing to disclose. D.A.P. is a consultant for Eli Lilly and Company.
Supported by the Robert Dow Foundation and Mr. and Mrs. Howard and Irena Laks.
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Fertility and Sterility® Vol. 100, No. 4, October 2013 0015-0282/\$36.00
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<http://dx.doi.org/10.1016/j.fertnstert.2013.06.010>

attainment of secondary sexual characteristics. Benefits of T supplementation include an increase in muscle mass and linear growth, as well as preservation of bone density, all of which have important long-term health implications. However, the impact of TRT on the fertility potential of adolescents with KS is unknown.

Some authors have expressed the concern that exogenous T may further suppress testicular function in the setting of some degree of primary testicular failure. To date, there have been no randomized controlled trials evaluating the impact of TRT on sperm retrieval or reproductive outcomes in men with KS. On average, surgical sperm retrieval rates in men with KS are ~51%, with a range of 28%–69% (11). Lower retrieval rates have been reported in a small subset of KS adults who previously received exogenous T (12, 13), but the nature, duration, and reason for such therapy in these patient subsets are unknown.

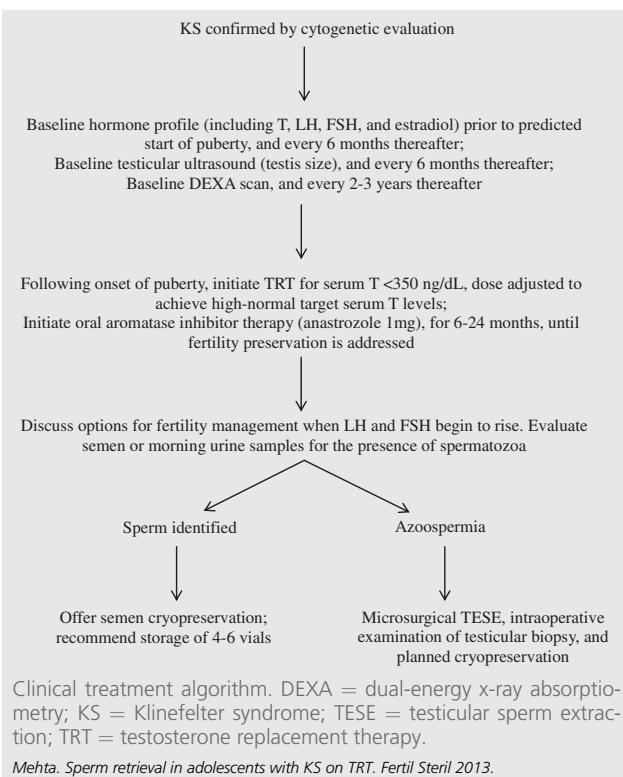
Several authors have identified “young” patient age, usually defined as age <30 years, as being the most consistent positive predictor of sperm retrieval in patients with KS (14–16). With the exception of one case report of testis tissue preservation in an adequately virilized adolescent with KS (7), no studies have investigated the possibility of sperm retrieval in adolescents with KS, especially in the setting of TRT. This is likely due to a combination of factors, including the delayed diagnosis of KS among prepubertal boys (17), limited patient and parent counseling, and concern for exogenous T negatively affecting testicular function.

The aim of the present study was to evaluate surgical sperm retrieval rates in KS adolescents on TRT at a specialized academic center.

MATERIALS AND METHODS

This was a retrospective cohort analysis of adolescents with KS, treated with hormone replacement therapy, who underwent surgical sperm retrieval at our institution. Our clinical algorithm for the management of adolescents with KS is summarized in Figure 1. All patients are followed with serum hormone evaluation, beginning before the predicted onset of puberty, and repeated every 6 months thereafter. Patients with serum T <350 ng/dL are supplemented with topical T therapy, which is dose adjusted for target serum T level >400 ng/dL. Aromatase inhibitor therapy (1 mg anastrozole daily) is initiated concomitantly in all patients on TRT and in all patients who have a serum T:E₂ ratio <10 regardless of whether or not they are receiving TRT. Once initiated, aromatase inhibitors are continued until fertility potential has been addressed, including sperm cryopreservation or surgical sperm retrieval, with a maximum duration of 24 months. Testicular volume is measured by scrotal ultrasound before the initiation of hormone therapy and every 6 months thereafter. In patients who are able and willing to provide an ejaculated semen sample for assessment of their fertility potential, semen evaluation is performed after 30 minutes of centrifugation at 3,000g. The presence of sperm in the ejaculate is investigated on at least two separate occasions for each patient. Microsurgical testicular sperm extraction (TESE) is offered in cases where no sperm is seen under light microscopy.

FIGURE 1



Inclusion criteria for this study consisted of a 47,XXY karyotype, confirmed by cytogenetic evaluation; azoospermia, confirmed by examining two centrifuged semen samples under light microscopy; and ongoing treatment with topical T, with or without an aromatase inhibitor. Patients with mosaicism were excluded. Microdissection TESE was performed as previously described (18), after obtaining informed consent from both patients and parents. All seminiferous tubule tissue obtained during surgery was mechanically processed by the operating surgeon and examined under a light microscope for the presence of sperm (19). The procedure was terminated once the presence of sperm was confirmed.

All consecutive TESE procedures performed from January 1 to November 31, 2012, were analyzed. Demographic data, baseline and pre-operative serum T, FSH, and LH levels, dose and duration of TRT, testicular volumes, testicular histology patterns, and TESE outcomes were collected for each patient. Each TESE specimen was analyzed by two embryologists to verify the findings. The primary outcome measure was the successful retrieval and cryopreservation of sperm.

This study was approved by the Institutional Review Board of Weill Cornell Medical College.

RESULTS

Ten patients meeting the study criteria underwent TESE from January 1 to November 31, 2012. Patient age ranged from 14 to 22 years (mean 15.5). Baseline serum T, LH, and FSH levels ranged from 40 to 350 ng/dL (mean 192), from

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