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Non-mosaic Klinefelter Syndrome Successful Conception after TESE/ICSI-A Report of the First Egyptian Case

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Abstract

Klinefelter syndrome patients are mostly clinically azoospermic, and before the era of testicular sperm extraction (TESE) were unable to father genetically own offspring, particularly the non-mosaic ones. Non-mosaic Klinefelter (NMK) patients have chances of fatherhood once sperm is harvested from the epididymal seminiferous tubules and further injected in the ovarian cytoplasm. We report a case of 36 yrs old NMK patient, treated for 3 months with supportive and hormonal medication achieving a pregnancy after testicular sperm extraction/Intracytoplasmic sperm injection (TESE/ICSI). This is the first published case of successful conception in a couple with a non-mosaic Klinefelter father in Egypt using TESE/ICSI. Review of the literature for any advantages of micro-TESE (mTESE) over TESE and conception demonstrated higher pregnancy rates by TESE although the sperm retrieval rate was similar in both techniques. Non-mosaic Klinefelter patients should no longer be considered sterile. mTESE seems to have no advantages in sperm recovery rate (SRR) and pregnancy rate (PR) compared to TESE.

Keywords

Klinefelter syndrome; Azoospermia; Male infertility; TESE; ICSI

Introduction

Klinefelter syndrome (KS) is the most common chromosomal disorder in men. It was first described in 1942 by Harry Klinefelter [1]. The estimated prevalence of KS is 0.2% in the general population, 3% among infertile men, and up to 11% in men with non-obstructive azoospermia [2]. Yet, KS remains frequently underdiagnosed, because of the wide phenotypic variation among affected individuals, and the lack of established screening programs. Only 25% of men with KS are diagnosed during their lifetime, with fewer than 10% being diagnosed before puberty [3]. The disorder is categorized by X-chromosome polysomy, with X-disomy (47,XXY) being the most common variant representing about 80%-90% of the cases. Characteristic features of KS include small testes, hypogonadism, and infertility [4]. Higher grades of X chromosome polysomy are associated with a more severe clinical presentation, whereas genetic mosaicism (46,XY/47,XXY) usually results in a milder phenotype [5].

Since the introduction of intracytoplasmic sperm injection (ICSI) [6] and testicular sperm extraction (TESE) [7], a considerable number of men with Klinefelter syndrome have been able to father genetically own offspring. Looking at the three of the more recent published studies, (i) in 2015-Ozveriet al. [8] confirms that sperm retrieval is possible in azoospermatic Klinefelter Syndrome patients, and recommends the use of assisted reproductive technology (ART) for those wishing to conceive; (ii) in 2016-Ishikawaet al. [9] concluded that the use of mTESE to extract motile sperm is vital in the use of Klinefelter Syndrome cases in order to maximize the chances of achieving a clinical pregnancy and embryological development; (iii) in 2016-Vicdanet al. [10] concluded that with regards to the use of fresh versus cryopreserved sperm in ICSI cycles demonstrated an equal chance of success.

In this case report a successful conception and delivery of a healthy baby in an azoospermic non-mosaic Klinefelter father using a combined TESE-ICSI protocol is highlighted.

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Case Presentation

A 36 year old Egyptian male of rural origin presented to our fertility clinic complaining of primary infertility for 9 years. He enjoyed a good sex life, without any concern regarding libido, erection, intercourse and ejaculation. His wife was 10 years younger and her menstrual history was unremarkable. General examination diagnose well developed secondary male sexual characteristics, 187 cm tall and weight of 82 Kg. Genital examination revealed an average sized penis with normal male pubic hair pattern and two small firm testicles. Both vas were palpable and showed no abnormality. Repeated spermograms in 3 months intervals and 3 days of abstinence diagnose total azoospermia. The second result was a duplicate of the first one and the results of the hormonal assay showed a hypergonadotrophic hypogonadism state (Table 1). Karyotyping followed after the clinical data raised suspicion of Klinefelter Syndrome, reporting a nonmosaic Klinefelter (Figure 1).

Although the value of treatment of cases with hypergonadotrophic hypogonadism is controversial, the patient was treated for 3 months with combined hormonal and non-hormonal supplement therapy prior to TESE (Table 2). An attempt to enhance the harvest of the scheduled testicular sperm extraction and improving ICSI chances of fertilization.TESE was performed and multiple sections were retrieved from both testes. Primary scanning of the surgical harvest revealed azoospermia. After processing, the left testis showed motile sperms from 2 tissue cores, allowing for ICSI as well as a cryopreservation vial for future interest. The operation was uneventful. Postoperatively mild left orchitis was diagnosed which subsided after a 10-day course of quinolones, anti-inflammatory drugs and scrotal elevation.

The wife was treated with long GnRH (gonadotrophin-releasing hormone) agonist regimen, pituitary down-regulation with Triptorelin 0.1 mg once daily SC injection (Decapeptyl; Ferring), commenced in the mid-luteal phase of the menstrual cycle and continued for 2 weeks. This was followed by estradiol blood level and trans-vaginal ultrasound confirmation of down-regulation, recording the leading follicle diameter and antral follicular count (AFC). Human menotropin, gonadotropin injections at a dose of 225 IU/day (Menogon;Ferring) initiated and continued until leading follicle reach 24 mm maximum diameter, within high range estradiol level and low progesterone level. The human chorionic gonadotrophin (hCG) injection (Choriomon 5000 IU/day; IBSA; Egypt) was administered when at least three follicles reach R17 mm in diameter. Vaginal egg collection was scheduled 36 hours following hCG triggering. TESE was performed before oocyte retrieval in order to confirm a positive retrieval of sperms.

Hormone	Result	Reference Range
FSH*	25.82 mIU/mL	1.5-12.4
LH*	21.78 mIU/mL	1-9.3
Testosterone	191 ng/dL	300-1000
Prolactin	5.85 ng/mL	2.58-21.4
Estradiol (E2)	34.5 pg/mL	7.63-52
AMH*	0.23 ng/mL	1.5-10.6
TSH*	1.08 mIU/mL	0.27-4.2

*FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; AMH: Anti-Müllerian Hormone; TSH: Thyroid Stimulating Hormone

Table 1: The hormonal assay of the patient

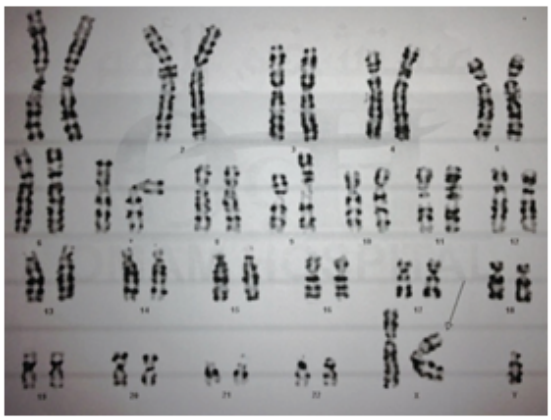

Figure 1: The Karyotyping of our patient. Notice the arrow pointing out the extra X chromosome

Drug	Dose
Follitropin alfa	75 IU subcutaneous 3 times weekly
hCG*	500 IU subcutaneous 3 times weekly
Vitamin E	400 IU per day
Relora	250 mg per day
Vitamin C	200 mg per day
Lycopene	100 mg per day
Zinc	70 mg per day
L-Methionine	25 mg per day
Vitamin A	5000 IU per day
Folic acid	1000 mcg per day
Selenium	250 mcg per day
Vitamin B12	15 mcg per day

*hCG: Human chorionic gonadotropin

Table 2: Details of our 3 month regimen prescribed to our patient prior to TESE

Discussion

Historically, men with KS were considered infertile. However, it is now well accepted that isolated foci of spermatogenesis can exist in the testes of patients with KS [11]. This discovery, along with advances in assisted reproductive technologies (ART) during the past two decades, have made paternity possible for men with KS. Surgical sperm retrieval and intracytoplasmic sperm injection (ICSI) have dramatically improved the fertility potential of men with KS. Tournaye et al. [12] first reported on successful sperm retrieval in men with KS using TESE in 1996. The first pregnancies achieved using ICSI of ejaculated and testicular sperm were reported 2 years later [13]. Since then, there have been reported 101 children born to fathers with nonmosaic KS [14]. With the use of microdissection TESE, sperm retrieval rates in patients with KS are considered equivalent to those in men with non- obstructive azoospermia.

Mehta et al. [15] published a systematic review/meta-analysis in 2012 to investigate the effect of early hormonal therapy (HR) on sperm retrieval rates in patients with Klinefelter Syndrome (KS). Although the studies varied in their conclusions as to predictors of sperm retrieval, positive predictors included young age and preoperative Testosterone levels close to or within the normal range, either at baseline or with hormonal therapy (aromatase inhibitors, clomiphene citrate, or hCG) [16,17]. 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 [17,18]. The age of the reported patient was 36 years who does not fit with most the studies age predictor for successful retrieval. However, his testosterone level was low and the treatment before surgery might have had a positive impact upon successful sperm retrieval.

The very recent review reporting that performing TESE/micro-TESE in KS patients, results in SRRs, pregnancy rates (PRs) and live birth rates (LBRs) of close to 50%, with the results being independent of any clinical or biochemical parameters tested justifies our

management with TESE/ICSI [19].

Conclusion

The vast majority of 47,XXY males are azoospermic and considered sterile until the introduction of TESE/ICSI. Solid parameters to distinguish patients with KS and fertilization potential and chance of fatherhood are missing. The literature review findings of similar SRR and PR with TESE and mTESE encourages the much lower cost option of TESE.

Conflicts of Interests

The authors declare no conflicts of interests.

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