Annals of Medical Research
DOI: 10.5455/annalsmedres.2019.07.373 2019;26(12):2957-60

Original Article

What should be the minimum frequency of micro testicular sperm extraction (m-TESE) in patients with Klinefelter syndrome?

Ahmet Salvarci[1], Mehmet Balasar[2]

[1]Novafertil IVF Centers ,Department of Urology, Konya, Turkey
[2]Necmettin Erbakan Unıversty, Faculty of Medicine, Department of Urology, Konya, Turkey

Abstract

Aim: To investigate whether a second or even a third surgery is required for sperm retrieval in non-mosaic Klinefelter syndrome patients who underwent a successful/failed micro-testicular sperm extraction (m-TESE).

Material and Methods: The patients underwent physical examination, genetic analyses, pathological screening between 2008 and 2018. In the patients, sperm retrieval rates, pregnancy after intracytoplasmic sperm injection (ICSI) and baby take-home rates were examined.

Results: M-TESE was repeated for the second time in thirty-five patients in total, with twenty of that underwent their first m-TESE with a negative result and fifteen with a positive result. In =6/20 patients (30%) who had a negative result with the first m-TESE and in n=9/15 patients (60%) who had a positive result with the first m-TESE, sperm was detected the second time. Pregnancy was achieved in n=2/6 patients (33%) who were negative the first time and positive the second time. Baby take-home was achieved in one patient (16.6%).

Conclusion: In addition to patients from whom sperm could be retrieved previously, sperm could be detected especially in the second and even third redo m-TESE in patients from whom sperm could not be retrieved. Pregnancy occurred and baby take-home was achieved. Despite the presence of a very limited testicular tissue, it is recommended for this procedure to be performed by expert practitioners upon discussing very openly the complications and achievements, to decide accordingly and repeat m-TESE in these patients where possible.

Keywords: Sperm; klinefelter; pregnancy

INTRODUCTION

Klinefelter syndrome is the most frequently seen chromosomal numerical disorder characterized with one or multiple X chromosome(s) in 1/500-1,000 men and leading to azoospermia. Out of these, 80-90% is 47, XXY pure non-mosaic Klinefelter (1). Whereas, 10-20% is 46, XXY/ 46XY mosaic Klinefelter form where sperm may be detected in the ejaculate (2). When the patients were first seen, no diagnosis had been made in 75% of them. Diagnosis is made at an adult age due to azoospermia often leading to hypogonadism and infertility (3). Based on evidence, it is now known that sperm may be detected at a rate of 44-55% in azoospermic Klinefelter patients via micro testicular sperm extraction (m-TESE) and that pregnancy may be achieved at a rate of 20-25% via intracytoplasmic sperm injection performed with the sperms retrieved (4,5). These success rates achieved in Klinefelter patients resemble those achieved in idiopathic azoospermic patients (4). Unfortunately, there is no clinical predictivity value of sperm retrieval via m-TESE in patients with Klinefelter syndrome. Only if the age of the patient is <35 years, which is the critical value, enables the surgeon to be adopt a more positive approach in m-TESE (6,7). The efficacy of medical treatment has not been proven in these patients. The capacity of their testes to produce spermatogenetic activation and testosterone is significantly low. Thus, medical treatments which raise

Received: 08.07.2019 **Accepted:** 31.09.2019 **Available online:** 09.01.2020
Corresponding Author: Ahmet Salvarci, Novafertil IVF Centers ,Department of Urology, Konya, Turkey
E-mail: drsalvarci@hotmail.com

the serum testosterone level to >250 ng/dl and thus enable spermatogenetic activity in some tubules may be recommended. As a matter of fact, it has been recorded that sperm retrieval rates will increase with m-TESE (6,7). Should we apply a redo m-TESE following the first m-TESE in these patients with such a narrow approach not based on evidence? Can we retrieve sperms? Can we achieve pregnancy? This topic will be evaluated. Furthermore, as a different approach, the 2nd m-TESE procedures in patients who results positive in the first m-TESE in addition to those who results negative will be evaluated. Additionally, we will also refer to the group in whom we have applied redo m-TESE for the third time due to various reasons.

MATERIAL and METHODS

The ethical approval for the study was obtained from the local ethics committee of the institution (Decision No. 2019/1930 on 21/06/2019 by the Ethics Committee of the School of Medicine of Necmettin Erbakan University. Following the decision to perform redo m-TESE, it was explained to patients that there is chance for sperm retrieval in the second procedure whether there was any sperm or not. Potential complications were described, and their consent was received.

The anamneses and physical examinations of non-mosaic Klinefelter patients were analyzed. None of them was receiving a medical treatment for infertility. Radiological testicular volumes were retrieved from their files. Serum levels of FSH, luteinizing hormone (LH) and total testosterone were noted (Elecsys 2010; Roche, Mannheim, Germany). Testicular sperms were extracted from a mid-scrotal incision of approximately 1.5 cm under general and/or local anesthesia and redo m-TESE was performed with an optical augmentation of 25x with an equatorial incision. Dark brown, fibrotic and sporadically atrophic tubules were observed microscopically in atrophic patients with m-TESE and brown Leydig cell nodules were identified. The tissues were dissected in a 5–1.0 mL human tubal fluid on a petri dish in the embryology laboratory and checked under a phase contrast microscopy at x40 magnification. The incised segment of tunica albuginea and other layers were closed with sutures of 4/0 rapid Vicryl. Five days of antibiotic prophylaxis (Ofloxacine 400 mg 1x1) and anti-inflammatory therapy (meloxicam 15 mg 2x1 daily) were administered. Ice compression was applied during the first 2 hours after surgery. Serum FSH, LH, testosterone levels and testicular volume between patients with and without successful retrieval were compared statistically. A p value of less than 0.05 was considered statistically significant.

RESULTS

The files of n=71 non-mosaic Klinefelter patients who applied due to azoospermia were assessed between 2008 and 2018. Twenty peripheral blood lymphocytes were diagnosed by using G- and Q-banding techniques. In genetic screenings, rarely occurring AzFa dby, AzFc sy153 partial Y chromosomal micro deletion patients were identified among patients who had a (-) result in their first and second m-TESE in their AzF deletion results. Their average age was 30.4 years (23-43). Their average right and left testicular volumes were 1.9 and 2.3 ml atrophic, respectively.

A second redo m-TESE was performed in n=35 patients with a (+)/(-) results in their m-TESE. N=20 patients had a negative result while n=15 patients had a positive result in their first m-TESE. In the second redo m-TESE, sperm was retrieved with 30% success rate in n=6/20 in patients who had a negative result in the first m-TESE and with 60% success rate in n=9/15 patients who had a positive result in their first m-TESE. Thus, sperm was retrieved with 42.8% in n=15/35 patients who underwent their second m-TESE. M-TESE was performed once in the remaining n=36/71 patients. Sperm was retrieved in eighteen of them, pregnant was achieved in eight patients and baby take-home was achieved in four patients. No sperm was retrieved in the remaining eighteen patients.

Pregnancy was achieved in 31.4% in n=11/35 patients and baby take-home occurred at a rate of 36% in n=4/11 patients who had a (+)/(-) result in their first m-TESE and underwent redo m-TESE for the second time. A pregnancy rate with a success rate of 33% was achieved especially in n=2/6 who had a (-) result in their first m-TESE and (+) result in their second m-TESE. Only one baby take-home could be achieved. As the remaining patients could not come back for follow up or not be reached, their results could not be observed.

The average surgery time was 79.8 minutes (25-141 minutes) in thirty-five patients who underwent redo m-TESE for the second time. The average time in the group in whom no sperm was retrieved the first time and who underwent redo m-TESE for the second time was longer with 122 minutes.

In n=16/35 patients who underwent redo m-TESE, the previous pathology pattern was Sertoli cell-only (SCO) and Leydig cells-only in n=4/30 patients. The others had no pathology. All patients from whom sperm was retrieved in the second redo m-TESE had SCO.

A third redo m-TESE was planned in five patients reported to have undergone the first and second m-TESE previously separately from our group (not included into n=71 patients) and sperm was retrieved in one patient. The suspicion emerging due to the absence of experts who performed m-TESE in their practice and clinics where m-TESE was performed as well as the absence of data indicating whether the patient had undergone m-TESE or testicular biopsy made us hesitate in the group for whom it was very difficult for us to take a decision.

The comparisons of serum FSH, LH, testosterone levels, surgery time and testicular volume between patients with and without successful sperm retrieval did not show any significant difference (Table 1).

Table 1. Age, hormonal values, testicular volumes, surgery time and pathological assessment of n=14 patients from whom sperm could not be retrieved and who underwent redo micro testicular sperm extraction with no resulting sperm again and n=6 patients in the same group from whom sperm could be retrieved

Characteristics	Redo m-TESE (+) (n=6)	Redo m-TESE (-) (n=14)	p-Value
Age (years)	29.9 (26-33)	31.2 (23-43)	
FSH (IU/L)	36.4 (19-61)	36.7 (29-44)	p=0.764
LH (IU/L)	20.6 (12-30)	21.7 (9-36)	p=0.771
Testicular Volume (R)(ml)	2.09 (1.2-2.9)	1.9 (1.8-2.4)	p=0.894
Testicular Volume (L)(ml)	2.01 (1.3-3.0)	2.2 (1.0-2.4)	p=0.755
Total testosterone (ng/ml)	1.7 (0.7-3.0)	1.7(0.9-2.3)	p=0.666
Surgery Time (minute)	122 (111-143)	132 (122-145)	p=0.703

R=Right/L=Left, FSH:Folicule stımulate hormone, LH: Luteotropic hormone, Redo m-TESE: Redoing micro-testicular sperm extraction. n:number, A p value of less than 0.05 was considered statistically significant.

DISCUSSION

It was first reported in 1996 that sperm could be retrieved from the testes in Klinefelter syndrome (KS) patients (8). It was demonstrated two years later that pregnancy could be achieved with ICSI (9). It was reported that high pregnancy rates could be achieved with m-TESE (m-TESE performed on the same day with oocyte retrieval) (10). It was added that it may be necessary in our practice to re-open the testes and re-conduct sperm retrieval in the ICSIs performed with frozen sperms (11).

It was recorded in literature that m-TESE could affect testicular functions negatively and even reduce temporary serum testosterone level, that this could or could not improve in 12-18 months post-surgery (12). It was demonstrated that this clinical picture could lead to low testosterone levels which could not improve even after the 12th month in KS (13). It was recorded in other studies that in addition to the patients in whom serum testosterone level did not improve, there were also patients in whom the serum testosterone level improved by 50% following m-TESE in KS (14). Due to these reasons, because of risk of reduction on serum testosterone level and thus loss of spermatogenetic activity in testicular tissue and the negative effects of previous m-TESE procedures, we strongly recommend the conduct of redo m-TESE by experts upon informing patients (Figure 1). Especially with increased age (>35 years), the chance of sperm retrieval in these patients is very low even in the first m-TESE let alone the second redo m-TESE.

If m-TESE will be repeated, the success rates in m-TESE as well as its potential permanent complications should be clearly discussed with patients. In addition, families with successful sperm retrieval, pregnancy and even baby take-home cases, also patients in whom no result has been achieved should be mentioned. At the end, it is very critical to know both for us and the patients that a limited rate of success has been achieved in a limited number of patients. Due to low testicular volume and thus of tissue in KS patients, surgical experience holds a very important place. In fact, in successful/failed redo m-TESEs, diffuse fibrosis arising from previous surgeries may lead to problems in sperm retrieval in decreased tissues.

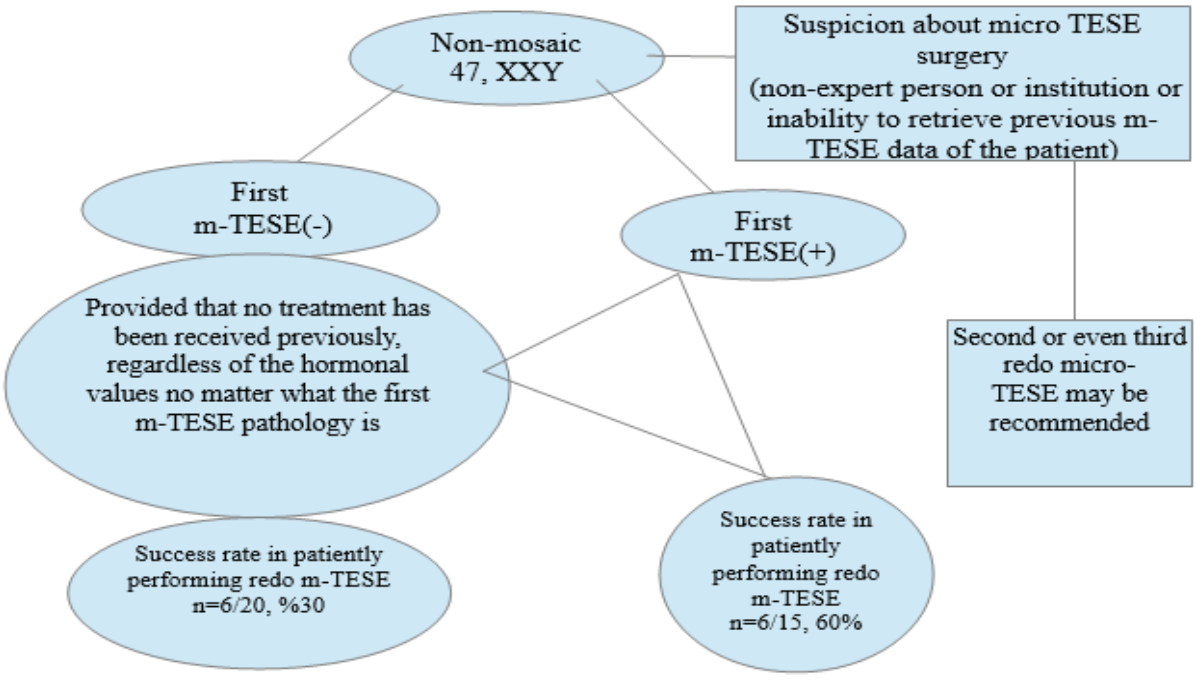

Figure 1. Redo micro TESE procedures performed on patients with non-mosaic Klinefelter syndrome, who obtained a negative result in their micro testicular sperm extraction

These diffuse fibrotic appearances increase the complication rate for the surgeon who performs the second m-TESE and also unveil previous inexperienced approaches. In KS patients with no evidence-based medical treatment, redo m-TESE provides great hopes even if it appears to offer a minimum chance. Considering that the period until the age of 35 is critical for KS in our study, we have noted that it is possible perform the second and even the third m-TESE as we have indicated for suspicious cases (Figure 1) in failed patients and even retrieve sperm. We believe that the conduct of m-TESE by expert practitioners in patients who had a positive and especially negative result in their previous m-TESE will provide good results. We have observed that the pathology results obtained in previous surgeries do not provide guidance for redo procedures. While the time of m-TESE in redo procedures would be shorter due to the reduction in the testicular volume in the previous surgery, it was noticed that they lasted almost as long as those in cases with a normal testicular volume. We believe the underlying reason is caused by the very low testicular volume, diffuse fibrosis left from the previous surgery and slow functioning with the aim to maximally preserve the remaining tissue. Differently in this study, we have noted that there was a higher chance in not only sperm retrieval rates but also the pregnancy rates and baby take-home rates of our patients in the follow-up of our patients.

CONCLUSION

In conclusion, Klinefelter syndrome patients constitute an irreversible patient group with permanent fibrosis and severe hypogonadism risk even if it is the first m-TESE. Furthermore, the addition of patients for whom a second or even third m-TESE is planned like in our series means progression towards serious complications. In the future, there may be testes from which maybe not even stem cells may be retrieved. A close cooperation should be established with the patients for whom a redo m-TESE is considered and it should be ensured that the procedure is performed by very experienced practitioners. Patients should always be followed up for a long period for hypogonadism after surgery. Redo procedures, which have a low chance but provide a major hope, should not be disregarded and should be applied in these patients. Redo m-TESEs should be considered to be applied in non-mosaic Klinefelter syndromes with more results in more series. No one knows what time will bring, but there does not seem to be any other solution for having a baby in KS syndrome patients for the moment.

Competing interests: The authors declare that they have no conflict of interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The ethical approval for the study was obtained from the local ethics committee of the institution (Decision No. 2019/1930 on 21/06/2019 by the Ethics Committee of the School of Medicine of Necmettin Erbakan University.

Ahmet Salvarci ORCID: 0000-0002-5231-2415

Mehmet Balasar ORCID: 0000-0003-4041-9669

REFERENCES

1. Klinefelter HF, Reifenstein EC, Albright F. Syndrome characterized by gynecomastia, aspermatogenesis without a-Leydigism, and increased excretion of follicle-stimulating hormone. Am J Clin Dermatol 1942;2:615- 27.
2. Ferhi K, Avakian R, Griveau JF, et al. Age as only predictive factor for successful sperm recovery in patients with Klinefelter's syndrome. Andrologia 2009;41:84–7.
3. Abramsky L, Chapple J. 47, XXY (Klinefelter syndrome) and, 47, XYY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling. Prenat Diagn 1997;17:363-8.
4. Fullerton G, Hamilton M, Maheshwari A. Should non-mosaic Klinefelter syndrome men be labelled as infertile in 2009? Hum Reprod 2010;25:588-97.
5. Devroey P, Van Steirteghem A. A review of ten years experience of ICSI. Hum Reprod Update 2004;10:19-28.
6. Tuttelman F, Gromoll J. Novel genetic aspects of Klinefelter's syndrome. Mol Hum Reprod 2010;16:386-95.
7. Ramasamy R, Ricci JA, Palermo GD, et al.Successful fertility treatment for Klinefelter's syndrome. J Urol 2009;182:1108-13.
8. Tournaye H, Staessen C, Liebaers I, et al.Testicular sperm recovery in nine 47, XXY Klinefelter patients. Hum Reprod 1996;11:1644-9.
9. Palermo GD, Schlegel PN, Sills ES, et al. Births after intracytoplasmic injection of sperm obtained by testicular extraction from men with nonmosaic Klinefelter's syndrome. N Eng J Med 1998;338:588-90.
10. Seo JT, Park YS, Lee JS. Successful testicular sperm extraction in Korean Klinefelter syndrome. Urology 2004;64;1208-11.
11. Okada H, Shirakawa T, Ishikawa T, et al. Serum testosterone levels in patients with nonmosaic Klinefelter syndrome after testicular sperm extraction for intracytoplasmic sperm injection. Fertil Steril 2004;82:237-8.
12. Ramasamy R, Yagan N, Schlegel PN. Structural and functional changes to the testis after conventional versus microdissection testicular sperm extraction. Urology 2005;65:1190-4.
13. Okada H, Shirakawa T, Ishikawa T, et al. Serum testosterone levels in patients with nonmosaic Klinefelter syndrome after testicular sperm extraction for intracytoplasmic sperm injection. Fertil Steril 2004;82:237-8.
14. Takada S, Tsujimura A, Ueda T, et al. Androgen decline in patients with nonobstructive azoospermia after microdissection testicular sperm extraction. Urology 2008;72:114-8.