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Review Article

Klinefelter Syndrome: Review of the Literature Comparing TESE and mTESE, Sperm Retrieval and Pregnancy Rate -

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ABSTRACT

Purpose: To review the Testicular Sperm Extraction (TESE) with and without microscopy on patients with Klinefelter Syndrome (KS).

Method: A literature search was conducted for studies comparing TESE and mTESE efficacy for men with KS. The efficacy was measured by using the SRR and PR following Intracytoplasmic Sperm Injection (ICSI). The studies used were divided into two groups: large studies with 40 or more patients, and small studies with fewer than 40 patients.

Results: Our review results demonstrate among 1,070 KS patients treated by ICSI the SRR was 46.3% and PR was 21% with mTESE and 45.6% SRR and 44.4% PR with TESE. The SRR was 9.5% higher in large studies but PR was higher for small studies by 7.8%. Higher pregnancy rates demonstrated by TESE although the sperm retrieval rate was similar in both techniques. Among 1070 patients with KS, treated by ICSI the SRR was 46.3% and PR was 21% with mTESE and 45.6% SRR and 44.4% PR with TESE.

Conclusions: mTESE seems to have no advantages in SRR and PR as compared to standard TESE. Our results and recent meta-regression analysis publication findings of similar SRR with TESE and mTESE and similar or even better PR by TESE merits further investigation by a prospective randomized study. Parameters predicting sperm retrieval in KS patients are missing. This review's findings of similar SRR with TESE and mTESE and similar or even better PR by TESE merits further investigation by a prospective randomized study.

Keywords: Klinefelter syndrome; Azoospermia; Male infertility; Testicular sperm extraction; TESE; Mtese

INTRODUCTION

The majority of males with Klinefelter Syndrome (KS) are azoospermic and have historically been considered sterile. Today, Testicular Sperm Extraction (TESE) and Intracytoplasmic Sperm Injection (ICSI) enable 37% of KS couples to have a child [1]. Despite this observed improvement, solid parameters to identify patients with KS who have fertilization potential and a chance of fatherhood are still lacking. Investigators have attempted to correlate serum testosterone, FSH and testicular volume with positive sperm retrieval outcomes. Thus far, the results have varied widely among the different studies conducted.

FSH level appears to be the most predictive variable for sperm recovery via TESE. In 2015 Guler et al. demonstrated this phenomenon in their study where they analyzed the impact of testicular histopathology on ICSI from patients with Non Obstructive Azoospermia (NOA). They classified the histopathologies into categories as follows: normal spermatogenesis, hypospermatogenesis, maturation arrest, Sertoli cells only, and peritubular hyalinization/tubular atrophy. It was observed that higher FSH was associated with lower PR in the "maturation arrest" group [2]. Sperm Retrieval Rates (SRR) and Fertilization Rates (FR) were found to be significantly different among all testicular histological groups of NOA. FSH found to be the best predictor of a successful TESE and testicular histology significantly influenced SRR and FRs but not PR and LBR in NOA [2]. More favorable SRR after mTESE has been reported, especially in histological patterns with focal spermatogenesis like in Sertoli cell only syndrome. In patients with uniform maturation arrest the outcome of mTESE was less favorable [3]. However, retrieval of motile spermatozoa may be sufficient to disregard predictive factors and hope of ICSI fertilization and pregnancy [4].

In contrast, a recent review's meta-regression analysis showed that age, testis volume, FSH, LH and testosterone levels did not affect the final SRR. They also reported that there was no difference between unilateral and bilateral sperm extractions [5]. Other studies looked at the effect of early hormonal therapy on sperm retrieval rates in KS patients. Once again, the results varied between different studies. Preoperative testosterone levels that were close to or within normal range were associated with a higher predicted chance of sperm extraction. This held true both for untreated patients as well as those treated with hormonal therapies such as aromatase inhibitors,

clomiphene citrate or hCG [6-10]. Out of all variables investigated, most studies agreed that age is the best predictive factor for SRR in patients with KS. Higher SRR is seen in men less than 30 years of age [7,11]. Accordingly, hormonal treatment should be considered, if indicated at all, for patients over 30 years, before opting for surgical management.

There are few randomized clinical trials comparing mTESE with conventional TESE in NOA. Conducting more of these trials will help to elucidate what factors could potentially be predictive of chances of obtaining spermatozoa in these patients. More data about testicular histology patterns, FSH levels, testicular volume and method of TESE need to be investigated. In particular, the use of microscopy to magnify the operative field has been expected to significantly aid the extraction process. Studies are needed to either validate or disprove these theories, and to explore whether or not mTESE also helps to decrease complications. The standard TESE has been associated with complications including immune system reactions within the seminal tubes and blood, as well as testis hematomas during the procedure.

METHOD

The aim of this review was to collect and analyze the available data from studies comparing the use of TESE versus mTESE in non-mosaic KS patient populations. A review of the literature was performed by searching Medline, PubMed, Embase and Cochrane library for articles. The following key words were used: mTESE, TESE, ICSI and PR in patients with non-mosaic Klinefelter Syndrome. Only studies with more than 9 patients, clearly reported methodology and results on PR and/or SRR were included in this review. The collected data and papers are presented in the table 1 and 2. Statistical analysis of the data was done using a two-tailed hypothesis, with a significance level set at 0.05.

RESULTS

Information on fertility outcome after ICSI treatment of patients with KS was available in 29 studies. In 6 studies, the methodology and results were not clear and these were excluded from the review. Fourteen articles reported both SRR and PR, and 8 articles reported only the SRR. The articles that did not report PR are designated with asterisk in table 1 and were not included in the PR calculation (Tables 1 and 2).



The differences in sperm retrieval rate and pregnancy rate between mTESE and TESE techniques are presented in table 1. Collectively, 462 patients were treated with mTESE and 608 with TESE. The SRR was 46.3% and PR was 21% with mTESE compared to 45.6% SRR and 44.4% PR with TESE. The articles were further divided into groups according to large cohort sizes of 40 patients or more and small cohort sizes of less than 40. The SRR was 9.5% higher in large studies but PR was higher for small studies by 7.8%. The overall number of patients was much lower in small studies by a difference of 29.5% for SRR and 21% for PR as compared to the overall number of patients in the large studies.

DISCUSSION

SRR was similar in both sperm retrieval techniques, however, higher PRs were found in TESE compared to mTESE couples (Table 1). Our results are consistent with the meta-regression analysis by Corona et al. reporting 44% SRR with TESE and 43% with mTESE. Among 1,248 NOA patients, treated by ICSI the PR and LBR were 43% for both techniques and results were independent of any clinical or biochemical parameters tested [5]. In our view, during the last 15 years, factors that may have influenced the above results are: a) the introduction and use of new culture media in the market, b) manufacturers failure to state the detailed ingredients of the culture media on the label, important for quality control, c) limited experience and lack of training with sperm retrieval techniques, d) the increased number of IVF laboratories and the rare incidence of KS patients permits few patients to be treated in each center, e) the transition period of sperm retrievals being performed initially only by urologists, and later by both gynecologists and urologists.

Table 2 was created to assess the differences in outcomes between small versus large studies, and TESE vs mTESE. The large studies showed a 7% higher SRR, yet an 8.8% lower PR in comparison to the smaller studies. This demonstrates that a higher sperm count after completion of harvesting is not the key to successfully achieving a pregnancy. Although it has been claimed that with the use of mTESE, the chances of picking up sperm is higher, our analysis of the literature indicates that this is not true. When comparing all studies, TESE and mTESE had a statistically insignificant difference in SRR, however the PR was much higher with TESE. An important question to be answered, then, is why mTESE yields a much lower PR? It is possible that this difference can be explained by the techniques and protocols used.

Polarized light microscopy has been used to visualize sperm since 1937 and spindle dynamics from the 1950s-1970s, verifying that the technique is compatible with live cells. Microscopy remains the primary tool enabling the morphological assessment of gametes and embryos, for IVF laboratories [12]. Concern has been raised about the potential detrimental effects during handling and analysis, during which time they are also exposed to considerable amounts of light. Studies indicate that short wavelength visible light exposure, primarily from an incandescent microscope light bulb, can impair embryo development in rodent species [13]. Visible light exposure on mouse and rabbit gametes reportedly resulted in decreased cell division and increased DNA fragmentation [14,15]. Collection of 1-cell hamster embryos using a light microscope or with fluorescent light (370-760 nm) impaired subsequent development, even when the fluorescence was used for as little as three minutes [16]. Similar results were found after exposure of hamster and mouse zygotes to fluorescent light [17]. This same phenomenon could potentially be explained these observations about mTESE.

Table 1: Sperm Retrieval Rate (SRR %) and Pregnancy Rate (PR%) after mTESE and TESE techniques. (* = No pregnancy data available and was not calculated in total PR).

Reference	Pts ¹	Sperm Retrieval (SRR %)	G ²	Pregnancy Rate (PR %)
Published studies with mTESE				
Ishikawa et al. 2016 [21]	48	25/48 (52.1%)	10	10/48(20.83%)
Ozveri et al. 2015 [22]	9	6/9 (66.6%)	1	1/9 (11.11%)
Sabbaghian et al. 2014 [23]	134	38/134 (28.4%)	5	4/134 (2.98%)
Ando et al 2013 [24]	35	14/35 (42.4%)	*	*
Greco E et al. 2013 [25]	10	1/10 (10%)	*	*
Bakircioglu et al. 2011 [11]	106	50/106 (47%)	29	23/106 (21.69%)
Ramaswamy et. al. 2009 [9]	68	45/68 (66%)	28	28/68 (41%)
Okada et. al. 2005 [26]	10	6/10 (60%)	4	4/10 (40%)
Schiff et. al. 2005 [27]	42	29/42 (69%)	18	18/42 (43%)
TOTAL	462	214/427 (46.32%)	88	88/417 (21.03%)
Published studies with TESE				
Vicdan et al. 2016 [28]	83	35/83(42.1%)	33	22/41(52.7%)
Cetinkaya et al. 2015 [29]	191	104/191 (54.5%)	*	*
Madureira et al. 2014 [30]	65	25/65 (38.5%)	17	17/65(26.1%)
Greco E et al. 2013 [25]	28	14/28 (50%)	15	15/28 (53.57%)
Selice et al. 2010 [31]	24	9/24 (38%)	*	*
Yarali et al. 2009 [32]	39	22/39 (56%)	15	15/39 (39%)
Kyono et. al. 2007 [6]	17	6/17 (35%)	9	7/17 (41%)
Vernaev et al. 2004 [33]	50	24/50 (48%)	*	*
Seo et al. 2004 [34]	25	4/25 (16%)	*	*
Westlander et. al. 2003 [35]	19	4/19 (21%)	2	2/19 (20%)
Madgar et al. 2002 [8]	20	9/20 (45%)	*	*
Friedler et. al. 2001 [36]	12	5/12 (42%)	8	4/12 (33%)
Levron et. al 2000 [37]	20	8/20 (40%)	9	5/20 (25%)
Tournaye et al. 1996 [38]	15	7/15 (47%)	*	*
TOTAL	608	276/608 (45.39%)	87	87/196 (44.38%)

¹Pts: patients

²G: Gravidas / pregnancies

Note: All above studies patients did not receive any medical treatment prior to sperm retrieval except in 2 studies of Ramaswamy et al. 2009, and Schiff et al. 2005 that patients were treated with TRT, hCG, cc, aromatase inhibitors prior to mTESE

During microscopy increased local temperature of the area in focus, has been a concern since prolonged exposure might affect gamete and embryo development [18,19] However, the modern microscopes used in the clinical setting for real-time imaging in IVF laboratories, have undergone numerous modifications to ensure the safety of the gametes and embryos [20]. The microscopes used for mTESE are usually the same as those used in neurosurgery without any calibration for the spermatozoa. Using polarized light microscopy for testicular tissue dissection and sperm extraction should be calibrated appropriately and validated for the gametes safety [12]. Additionally, the sperm identification and collection procedure should be completed quickly to reduce the time of tissue exposure to room temperature and microscope light. Exposure time and room conditions are another important detail that is not typically reported in the studies currently published.

Table 2: Difference in Sperm Retrieval Rate (SRR %) and Pregnancy Rate (PR%) in large and small studies with non-mosaic Klinefelter Syndrome patients treated by ICSI.

	Small studies < 40 patients	Large studies > 40 patients	Z-score	P-value*
SRR	(115/283) 40.60%	(375 / 787) 47.60%	-2.0309	0.04236
PR	(38/115) 33.0%	(122 / 504) 24.20%	1.9532	0.05118
	All studies TESE	All studies mTESE	Z-score	P-value
SRR	(276/608) 45.40%	(214 / 462) 46.32%	-0.3010	0.76418
PR	(87/241) 36.10%	(88 / 417) 21.10%	5.9531	0

*Two tailed hypothesis, Significance Level: 0.05.

The outcome of mTESE versus TESE in NOA was also investigated by a systematic review published in 2014. Seven out of 62 identified studies were included in the final analysis. SRR was significantly higher in the mTESE group (42.9-63%) in comparison with TESE (16.7-45%) [3]. In another retrospective cohort study among 714 men with NOA, 40.5% had successful sperm retrieval at their first TESE. In total, 261 couples had 444 ICSI cycles and 48 frozen embryo transfer cycles, leading to 129 pregnancies and 96 live birth deliveries. The expected cumulative delivery rates after six ICSI cycles were 78%. Authors indicated the intrinsic limitations related to the retrospective cohort study design [1]. Fewer complications were observed on ultrasound examination after mTESE procedure [3].

CONCLUSIONS

Our review results demonstrate among 1,070 KS patients treated by ICSI the SRR was 46.3% and PR was 21% with mTESE and 45.6% SRR and 44.4% PR with TESE. Parameters predicting sperm retrieval in KS patients are missing. This review's findings of similar SRR with TESE and mTESE and similar or even better PR by TESE merits further investigation by a prospective randomized study.

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