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ORIGINAL ARTICLE

Male Infertility

An examination of predictive markers for successful sperm extraction procedures: a linear model and systematic review

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The authors performed a comprehensive review of current literature to create a model comparing commonly evaluated variables in male factor infertility, for example, follicle-stimulating hormone (FSH), testicular volume (TV), and testosterone (T), to better predict sperm retrieval rate (SRR). Twenty-nine studies were included, 9 with data on conventional testicular sperm extraction (cTESE) for a total of 1227 patients and 20 studies including data on microdissection testicular sperm extraction (mTESE) for a total of 4760 patients. A weighted-means value of SRR, FSH, T, and TV was created, and a weighted linear regression was then used to describe associations among SRR, type of procedure, FSH, T, and TV. In this study, weighted-means values demonstrated mTESE to be superior to cTESE with an SRR of 51.9% *vs* 40.1%. Multiple weighted linear regressions were created to describe associations among SRR, procedure type, FSH, T, and TV. The models showed that for every 1.19 mIU ml^{-1} increase in FSH, there would be a significant decrease in SRR by 1.0%. Seeking to create a more clinically relevant model, FSH values were then divided into normal, moderate elevation, and significant elevation categories (FSH <10 mIU ml^{-1}, 10–19 mIU ml^{-1}, and >20 mIU ml^{-1}, respectively). For an index patient undergoing cTESE, the retrieval rates would be 57.1%, 44.3%, and 31.2% for values normal, moderately elevated, and significantly elevated, respectively. In conclusion, in a large meta-analysis, mTESE was shown to be more successful than cTESE for sperm retrievals. FSH has an inverse relationship to SRR in retrieval techniques and can alone be predictive of cTESE SRR.

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INTRODUCTION

Infertility is a medical condition affecting couples worldwide. Currently, infertility is described as the inability of a heterosexual couple, after 12 months of regular and unprotected intercourse, to conceive a child. Nearly 15.0% to 20.0% or 1:6 of all couples worldwide meet this criterion for infertility.[1] Infertility continues to be a very challenging reality for both males and females.[2] The inability to conceive an offspring can be related to female factor, male factor, or a combination of both. Male factor infertility is estimated to affect 30.0%–50.0% of all infertile couples and is becoming more common as sperm counts continue to decline worldwide.[3,4] In addition, male factor infertility has been associated with reduced life expectancy and heavy financial burden, potentially causing excessive strain within personal relationships of those who suffer from the condition.[5–7]

In male patients who undergo a complete male factor workup, nonobstructive azoospermia (NOA) is found to be the diagnosis in about 10.0% of cases.[8] The development of intracytoplasmic sperm injection (ICSI) technique in 1992 was a significant advance in reproductive technology and allowed men with NOA to have a chance at genetic offspring. Testicular sperm aspiration (TESA) was originally developed and used by practitioners for men with NOA to obtain sperm directly from the seminiferous tubules to allow the cells to be utilized for fertilization. Multiple techniques have since been developed and refined to obtain the sperm directly from the testicle for the ICSI procedure.[9,10] The most common technique is conventional testicular sperm extraction (cTESE) due to its more straightforward approach and lower cost. Microdissection testicular sperm extraction (mTESE) was further developed in 1999 as a more targeted way of retrieving sperm from the testicle and causing less microvascular damage.[11,12] The reported sperm retrieval (SR) rates (SRRs) in studies comparing mTESE to cTESE vary; however, on average, SRRs are shown to be 30.0%–35.0% and 43.0%–57.0% for cTESE and mTESE, respectively.[13–15]

There is much debate over deciding the appropriate SR technique. In general, mTESE is more successful in obtaining enhanced SRR over cTESE but also comes with added costs, increased operative time, additional embryology staff, as well as specialized training on the part of the practitioner. Numerous articles have attempted to describe correlations between multiple variables and chances of success for successful SR when using these techniques such as follicle-stimulating hormone (FSH) levels, mean testicular volume (TV),

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and testosterone (T) levels.[16–18] In this comprehensive systematic literature review and meta-analysis, there was an emphasis placed on the development of an improved understanding of the different successes of SRR for cTESE *vs* mTESE with respect to a patient's unique hormonal profile. This effort is designed to help guide clinicians in offering patients the most efficacious SR procedure while reducing unnecessary costs and degree of invasiveness.

MATERIALS AND METHODS

Literature search

Articles published in the English language that compared cTESE with mTESE regarding their SRRs in patients with NOA were sought after. Papers published between January 2000 and December 2018 were searched electronically via search engines such as PubMed, Google Scholar, and ScienceDirect by the two authors (NM and KRE). The computer-based search terms are demonstrated in **Table 1**.

Study selection

The study included articles for consideration if they pertained to SRR in men with NOA, compared the performance of at least one other SR method to mTESE, and reported patient-related variables concerning their SR method. For the purpose of this study, NOA was defined as the lack of sperm in the ejaculate due to the failure of spermatogenesis. Studies that did not include mTESE, NOA, and SRR and did not compare different SR methods to mTESE were not included. Similar articles that reduplicated studies on the same populations were limited, and only the most recent articles were selected. Other studies that were excluded pertained to those listing SRR from men with obstructive azoospermia that could not be separated from the SRR of men with NOA, as well as those studies that serially employed the use of multiple comparative techniques that were dependent upon one another. Studies were analyzed for bias using the Newcastle–Ottawa scale and were preferentially selected if they were found to be of "good quality". After a review of the abstracts of 43 articles, 29 articles were selected for employment within this meta-analysis.[12–15,17–41] Of the 29 studies, 9 studies contributed data on 1227 patients who received cTESE[12,13,15,17,19,22,24,30,32] and 20 studies contributed a total of 4760 patients who received mTESE[14,18,20,21,23,25–29,31,33–41] (**Figure 1**).

Data collection

The information used in this meta-analysis and systematic review was independently extracted by the same two authors using a standardized methodology to collect points of data. These categories included publication year, sample size, mean patient age during the time of surgery, demographics, SRR, mean TV, T, FSH, LH, estradiol, inhibin b, and histopathology. While articles that produced data for each of the above categories were sought after, the selected articles that did not have all the categories were not excluded from the analysis. The availability of extractable values for FSH, T, and TV was limited. Of note, SRR was defined as the success rate of procurement of at least a single viable sperm cell to be preserved or used in ICSI or *in vitro* fertilization.

Data synthesis

Studies that were included in this paper were analyzed for the values of the variables listed above and compared with each other. To perform statistical analysis and table creation, SPSS (version 21, SPSS Statistics, Chicago, IL, USA) and Microsoft Excel (Microsoft, Redmond, WA, USA) were employed. Clinical values that were extracted from employed articles were scrutinized as arithmetic means weighted by study sample size. A random effects model was employed to perform the meta-analysis, and a weighted linear regression model was used to describe the association between collected data values. This paper described statistical significance as a two-tailed $P < 0.05$.

Table 1: Search terms used to find articles from PubMed, ScienceDirect, and Google Scholar

Number	*Individual search term*
1	MicroTESE
2	Microdissection TESE
3	Micro-dissection TESE
4	Microdissection testicular sperm extraction
5	Micro-dissection testicular sperm extraction
6	cTESE
7	Conventional testicular sperm extraction
8	TESE
9	Testicular sperm extraction

TESE: testicular sperm extraction; cTESE: conventional TESE

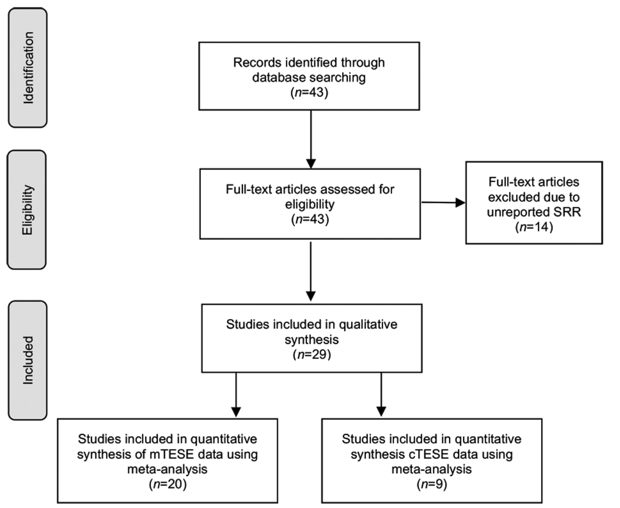

Figure 1: PRISMA flow diagram to outline selection process for studies included for analysis. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SRR: sperm retrieval rate; TESE: testicular sperm extraction; cTESE: conventional testicular sperm extraction; mTESE: microdissection testicular sperm extraction.

RESULTS

The criterion for article inclusion in this meta-analysis was applied to all 43 papers under review, in which 29 were retained. Nine of these studies contributed data on 1227 patients undergoing cTESE, while 20 studies provided data from 4760 patients who received mTESE. Certain characteristics of interest were queried from within each study, including patient demographics, SRRs, and study averages for T (in ng dl^{-1}), TV (in ml), FSH (in mIU ml^{-1}), and LH (in mIU ml^{-1}), as shown in **Table 2**. A weighted-means average was calculated for all 29 studies to reveal an average participant number of 338 with an average age of 34.8 years. The analysis also found a mean TV of 10.5 ml, T level of 398.2 ng dl^{-1}, FSH level of 21.0 mIU ml^{-1}, and LH level of 9.2 mIU ml^{-1}.

Weighted-means analysis comparing mTESE to cTESE was performed for each study's average SRR, FSH (in mIU ml^{-1}), T (in ng ml^{-1}), and TV (in ml). cTESE was found to be less effective than mTESE with an SRR of 40.1% (95% confidence interval [CI]: 34.8%–45.5%) compared to 51.9% (95% CI: 46.1%–57.7%), respectively. **Table 3** demonstrates direct comparisons between mTESE and cTESE with respect to average FSH, T, and TV.

Table 2: Description of included studies with total nonobstructive azoospermia participant averages of overall sperm retrieval rate and age

Reference	*Region*	*Overall SRR (%)*	*Mean TV (ml)*	*T (ng dl⁻¹)*	*FSH (mIU ml⁻¹)*	*LH (mIU ml⁻¹)*	*Total number of patients*	*Average age (year)*
Bernie *et al.*[17] 2015	Various	52 (mTESE) 35 (cTESE)	13.5	373	20.5	-	1890	34.4
Spahovic *et al.*[19] 2017	Bosnia/Herzegovia	42	10.8	404	17.5	7.2	21	36.5
Eken and Gulec[20] 2018	Turkey	65.5	10.4	368	19	9.4	145	33.4
Salehi *et al.*[12] 2017	Iran	48.8	-	430	16.8	8.7	170	32.6
Hussein *et al.*[21] 2012	Egypt	57	14.5	700	13.2	-	612	26.7
Sacca *et al.*[22] 2016	Italy	47.6	-	450	17.8	6.5	97	37.3
Kalsi *et al.*[23] 2015	UK	46.5	-	381	19.4	-	58	39
Ghalayini *et al.*[24] 2011	Jordan	56.9 (mTESE) 38.2 (cTESE)	11.85	410	18.2	11.05	133	35.1
Yildirim *et al.*[25] 2014	Turkey	54.55	-	-	-	-	131	37.7
Enatsu *et al.*[26] 2016	Japan	29.5	10.9	430	22.5	8.9	329	33.9
Alfano *et al.*[27] 2017	Italy	49	10	370	18.3	7	47	38
Xu *et al.*[28] 2017	China	38.5	8.05	373.5	22.25	7.5	52	33.15
Binsaleh *et al.*[18] 2017	Saudi Arabia	43.9	13	369.5	19.7	8.7	255	35.8
Ozer *et al.*[29] 2018	Turkey	20	5	265	32.7	16	110	32.7
Caroppo *et al.*[30] 2017	Italy	44.3	7.9	-	19.6	-	356	36.8
Cissen *et al.*[31] 2016	The Netherlands	43.7	-	404	22.1	9	1371	34.3
Okada *et al.*[32] 2002	Japan	44.6 (mTESE) 16.7 (cTESE)	-	-	-	-	146	
Ramasamy *et al.*[13] 2005	US	58 (mTESE) 32 (cTESE)	-	309.5	22	12	435	37
Colpi *et al.*[41] 2009	Italy	46.8	-	-	-	-	154	36.7
Ramasamy *et al.*[14] 2009	US	60	8.5	-	32.7	-	792	36.25
Turunc *et al.*[33] 2010	Turkey	43.9	12.9	-	17.9	-	335	35.2
Ando *et al.*[34] 2013	Japan	42.3	12.6	463	18.6	6.9	52	34.3
Schwarzer *et al.*[35] 2013	Germany	58.2	-	-	-	-	220	
Bryson *et al.*[36] 2014	US	56	-	-	31	-	1127	34.1
Aydin *et al.*[37] 2015	Turkey	58.6	-	316	16.4	10.2	111	31.8
Tsujimura *et al.*[15] 2006	Japan	44.85	8.7	325	28	9.1	180	34.45
El-Haggar *et al.*[40] 2008	Egypt	54	9.91	-	18.7	-	100	30.4
Ramasamy and Schlegel[38] 2007	US	44.8	-	-	22.1	-	311	35
Ravizzini *et al.*[39] 2008	Brazil	57.1	9.25	424	18.7	9.6	53	37.3

Study means were included for TV, T, FSH and LH. TV: testicular volume; T: testosterone, FSH: follicle-stimulating hormone; LH: luteinizing hormone; SRR: sperm retrieval rate; TESE: testicular sperm extraction; cTESE: conventional TESE; mTESE: microdissection TESE; -: not analysis

Table 3: Weighted-means values of sperm retrieval rate, testosterone value, and testicular volume for the 29 studies

Weighted-means variables	*mTESE (n), mean (95% CI)*	*cTESE (n), mean (95% CI)*
SRR (%)	20, 51.9 (46.1–57.7)	9, 40.1 (34.8–45.5)
FSH (mIU ml⁻¹)	13, 16.6 (8.8–24.6)	3, 16.4 (14.8–17.9)
T (ng ml⁻¹)	13, 455 (291–620)	3, 385 (189–581)
Mean TV (ml)	11, 12.3 (10.2–14.4)	2, 9.2 (–1.4–19.8)

n is the number of observations used for the mean value calculation. FSH: follicle-stimulating hormone; TESE: testicular sperm extraction; cTESE: conventional TESE; mTESE: microdissection TESE; CI: confidence interval; SRR: sperm retrieval rate; TV: testicular volume; T: testosterone

Weighted linear regression models were then used to describe the association between SRR and type of extraction, FSH level, T level, and TV. The number of available records was insufficient to identify statistically significant differences for some of the variables, including T level and TV. The analysis showed that using mTESE as compared to cTESE may be expected to add 11.8% to the SRR ($P < 0.05$). In addition, it was demonstrated that for each 1.19-point increase in the mean FSH across a population, the SRR may be expected to decrease by 1.0%, regardless of the retrieval technique utilized ($P < 0.05$).

To define a more clinically useful model, FSH was divided into three distinct ranges with SRR calculated for each. The ranges were normal (FSH levels <10 mIU ml^{-1}), moderate elevation (FSH levels: 10–19 mIU ml^{-1}), and significant elevation (FSH levels >20 mIU ml^{-1}). The model demonstrated that for a patient undergoing cTESE, SRRs would be 57.1%, 44.3%, and 31.2% for values of FSH categorized as normal, moderately elevated, and significantly elevated, respectively ($P < 0.05$; **Table 4**). A similar model for mTESE was unable to be constructed due to insufficient data.

DISCUSSION

Azoospermia has been observed in 1.0% of the entire population and is shown to be the underlying etiology of 10.0%–12.0% of all cases of infertility. Nearly 60.0% of men with azoospermia have NOA, but with improvements in assisted reproductive technology (ART), fertility has been made possible. Achieving fertility has also been assisted by the development of multiple SR techniques, including cTESE and mTESE.[2] The increasing rates of male factor infertility thus require fertility specialists to be equipped not only with an advanced skill set but also with the knowledge of SRR using different techniques given a patient's hormonal makeup.

Table 4: Efficacy of cTESE in an index patient by analyzing its sperm retrieval when FSH levels are divided into three clinical categories based on total amount

FSH clinical category	*cTESE SRR (%)*
Normal FSH: <10 mIU ml^{-1}	57.1
Moderate FSH elevation: 10–19 mIU ml^{-1}	44.3
Significant FSH elevation: >20 mIU ml^{-1}	31.2

TESE: testicular sperm extraction; cTESE: conventional TESE; FSH: follicle-stimulating hormone; SRR: sperm retrieval rate

This comprehensive systematic review and meta-analysis is one of the largest of its kind and was designed to create a model to evaluate the preoperative hormonal profile of a patient before undergoing cTESE or mTESE based on pooled data from previously published literature. We also created a clinically useful predictive model for SRR success based upon FSH levels. After compiling 29 studies that met our inclusion criteria, we were able to determine that some variables, such as FSH and SR technique, could be predictive of SRR. Other variables, such as T and mean TV, were unable to be assessed for their predictivity of SRR due to lack of data across examined studies. With the increased usage of ICSI, there has also been an associated increase in usage of SR techniques. This underscores the need for examination of unique patient factors as a means for a more cost-effective solution to SR.[42]

Using weighted-means values, it was found that mTESE outperformed cTESE with an average SRR of 51.9% *vs* 40.1%, respectively. This was an expected outcome and has been previously established in the literature and other studies. While SRR is higher when using mTESE, so are other factors such as additional staff, equipment, operative time, and specialized training, which all need to be factored into the clinical decision-making process.[12] Weighted linear regression was then utilized to describe associations between SRR, type of procedure, FSH, T, and mean TV. The weighted linear regression demonstrated that FSH can be used as a predictor of SRR. The model found that for each increase of FSH by 1.19 mIU ml^{-1}, there would be a decrease in SRR of 1.0%, but this would be difficult to apply in a clinical setting. We simplified the modeling by dividing FSH values into clinically meaningful categories to help better predict SRR. The model was only computed for cTESE due to limited data regarding average FSH levels and other hormonal values reported in studies examining mTESE. FSH was categorized as three clinically meaningful categories: normal (FSH levels <10 mIU ml^{-1}), moderate elevation (FSH levels: 10–19 IU ml^{-1}), and significant elevation (FSH levels >20 mIU ml^{-1}). The analysis demonstrated that in men with NOA who had a normal FSH, their chance of SR success would be 57.1%. Similar men with moderate FSH elevations would have a 44.3% chance, and those with the highest elevations would only have a 31.2% SRR. These findings have been understudied, yet have the potential to be beneficial in helping to counsel patients appropriately before undergoing a costly SR procedure. By continuing to understand the hormonal influence of positive SRR data, appropriate and realistic expectations can be offered to patients for enhanced shared decision-making.

This review is unique in that the different type of analysis and modeling employed strives to provide a clinically relevant framework to assist physicians in better counseling patients who are weighing the value of undergoing a cTESE *vs* mTESE. This study is the largest identifiable analysis of the hormonal impact to successful cTESE and mTESE procedures, which is often limited due to its retrospective nature. The data sets that were included were often incomplete and/or insufficient for a thorough analysis to help complete the model that was attempted to be created. Due to the small number of studies included in this meta-analysis, results may be subject to selection bias as well as aggregation bias due to the use of the mean population values in the descriptive models. In addition, the FSH model could only be created for cTESE due to limited data.

Due to the multiple pathologies associated with patients undergoing both cTESE and/or mTESE, there exists the potential for increased heterogeneity within this study, possibly a limiting factor. Future studies would ideally prospectively collect data to compare FSH levels and success with mTESE or cTESE to construct improved predictive models. Preferably, a multicenter study should be enlisted to help obtain significant numbers to better guide practitioners in counseling their patients.

CONCLUSIONS

This meta-analysis found mTESE to have a statistically significant higher SRR as compared to cTESE. Performing mTESE on a patient is shown to have an 11.8% increase in SRR over a predicted SRR from cTESE in the same patient. Data analysis also suggested an inverse relationship between FSH levels and SRR when performing either SR technique. Further investigation found that by classifying a patient's FSH levels alone can be predictive of SRR with cTESE; therefore, this information can be used to help educate patients on possible outcomes to avoid unnecessary costs and hardships.

AUTHOR CONTRIBUTIONS

MR was involved in project development and formed the hypothesis that drove this study. NM drafted the manuscript and helped craft overall study design and coordination. NM and KRE screened articles and performed data collection. NM, KRE, and MR were involved in data analysis, as well as manuscript editing. KS was involved in data analysis with statistical software. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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