JOMH

Systematic Review

Journal of Men's Health

Reproductive outcomes of testicular and ejaculated sperm for ICSI in patients with previous ICSI failures: a systematic review and meta-analysis

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Abstract

This systematic review aims to compare and evaluate the outcome of using either testicular sperm (Testi-ICSI) or ejaculated sperm (Ejac-ICSI) in intracytoplasmic sperm injections in patients with recurrent ICSI failure. The Cochrane Library, MEDLINE, EMBASE, and PubMed were used to search for relevant papers up till October 2020. Four cohort studies and two case series studies were included. Four studies investigated males with high sperm DNA fragmentation (SDF) and were classified as ''high SDF'', which included 247 couples and 2712 injected oocytes. The other three studies provided paired data to an unselected population of infertile men with either untested SDF or when anomalous SDF was not used as the basis for deciding to use Testi-ICSI, and were classified as ''noclassify'' in this study. This subgroup consisted of a total of 290 couples and 1061 injected oocytes. There was a higher level of clinical pregnancy rates (CPRs) in the "high SDF" subgroup when Testi-ICSI was used as compared to Ejac-ICSI, at 43.4% and 20.8% respectively, with a pooled odds ratio (OR) of 2.87 (95% confidence interval (CI) 1.44–5.71; P = 0.003). Furthermore, in the "high SDF" subgroup, Testi-ICSI use was associated with better take home baby rates (38%) as compared to Ejac-ICSI (16%), with a pooled OR of 3.24 (95% CI 1.20–8.76; *P* = 0.02). In the ''noclassify'' group, there was no statistically significant difference in the CPRs and take home baby rates of Testi-ICSI and Ejac-ICSI, although there was a trend of better CPRs and take home baby rates with Testi-ICSI use. Utilization of Testi-ICSI in recurrent ICSI failure couples, where males were confirmed to have high SDF in their ejaculated sperm, were correlated with greater CPRs and take home baby rates. However, Testi-ICSI may not result in better ICSI outcomes among men with untested SDF or when anomalous SDF was not the main factor influencing the decision to utilize Testi-ICSI.

Keywords

Intracytoplasmic sperm injection; Male infertility; Sperm retrieval; Testicular spermatozoa; Sperm DNA fragmentation

1. Introduction

About 40% of couples seeking assisted reproductive technology (ART) tend to have repeated miscarriages and implantation failures [1]. Sperm DNA fragmentation (SDF) may contributes to fertilization capacity and embryo development [2]. However, as there is a lack of evidence on the relationship between SDF and reproductive outcomes, the American Society of Reproductive Medicine (ASRM) does not encourage the routine use of SDF assays in patients who are considering ART [3]. In contrast, recent evidence supports the role of SDF in ART: in infertile males with SDF \geq 30%, the use of intracytoplasmic single sperm injection (ICSI) may result in better fertility outcomes than in vitro fertilization (IVF) [4]. The threshold of SDF \geq 20% is also a useful guideline for diagnosing male infertility and predicting pregnancy rates following ART treatment [5].

Testicular sperm extraction (TESE), microscopic TESE (microTESE), or testicular sperm aspiration (TESA) are methods commonly utilized to harvest testicular sperm. When the non-obstructive azoospermia leading to infertility occurs, and sperm donor assistance is refused, testicular retrieved sperm are conventionally used [6]. During the course of an ART cycle, the source of sperms could possibly influence SDF levels [7]. In addition, previous systematic reviews have shown that testicular sperm had lower SDF levels as compared to ejaculated sperm, and the using of testicular sperm for ICSI was more likely to lead to better results [7, 8]. Hence, once the presence of high SDF is confirmed in ejaculated sperm, testicular sperm DNA is considered to be more complete than ejaculated sperm.

However, testicular sperm extraction is invasive, and complications such as bleeding, infection, and irreversible testicular tissue damage may potentially occur during the operation [9]. Hence a careful evaluation should be made as to whether testicular sperm should be used. This study thus aims to collect and summarize the evidence on whether couples with recurrent ICSI failure will benefit more from Testi-ICSI as compared to Ejac-ICSI. Clinical Pregnancy Rates (CPRs) and take home baby rate were defined as the primary outcomes, and the fertilization rate was used as the secondary outcome.

2. Materials and methods

As the present study involved no human intervention, the Preferred Reporting Items for Systematic Reviews and Metaanalysis (PRISMA) statement was adhered to in reporting the results. The study was also registered with PROSPERO (registry number: CRD42021225964).

2.1 Literature search

The Cochrane Library, Google Scholar, and Pubmed, were used to identify all relevant studies until October 2020. The search combined terms related to "testicular sperm", "ejaculate", "ICSI failure OR ART failures", and "intracytoplasmic sperm injection", combined with the filter "human" in any language and article types. Finally, references of included articles were also manually searched to identify relevant studies.

2.2 Eligibility criteria and selection of studies

Studies that evaluated the effect of Testi-ICSI and Ejac-ICSI among couples with history of ICSI failure were included, with or without SDF test in the ejaculate sperm. Exclusion criteria included the following: (1) Diagnosis of azoospermia or cryptozoospermia; (2) Review articles; (3) Use of other therapeutic strategies (medication, varicocelectomy) before baseline; (4) Missing outcome data. Abstracts were independently evaluated by two authors (YHL and XWY), and full manuscripts were retrieved if they met the selection

2.3 Data extraction

Data was extracted independently by two authors (XYZ and YHL). For each study, specific information were identified and extracted as follows: (1) Population characteristics (history of ICSI failure); (2) Participants' semen analysis profile; (3) Study design; (4) Sperm extraction method; (5) Age of participants; (6) Outcome data (fertilization rates, CPRs, and take home baby rates. Nonrandomized studies were also assessed for the risk of bias [10] as shown in **Supplemental Table 1**.

2.4 Sensitivity analysis and risk of bias

The leave-one-out approach was used for sensitivity analyses. When individual studies were excluded in turn, there was lead no significant change in summarized conclusion. This signifies that the results were reliable. Funnel plot asymmetry tests were not conducted for the assessment of publication bias as the number of included trials were too small.

2.5 Statistical analysis

Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was utilized to conduct statistical analyses. For dichotomous variables, odds ratio (OR) and the 95% confidence interval (CI) were calculated whereas for continuous variables, the standardized mean difference (SMD) and 95% CI were used. Q-test or I^2 was utilized to quantify heterogeneity among different trials. A random effect model was utilized because of the limited number of studies [11].

3. Results

After the initial identification of 198 studies, 4 cohort studies [12-15] and 2 case series studies [16, 17] published between 2005 and 2020 were included in the final analysis (Fig. 1). The pertinent characteristics of each study are shown in Table 1 (Ref. [12-17]). The two subgroups of "high SDF" and "noclassify" are presented in the forest plots as previously mentioned.

3.1 Fertilization rates

Fertilization rates were provided in 6 studies, with a total of 3773 injected oocytes. In both subgroups of "high SDF" and "noclassify" there was no heterogeneity. In the "high SDF" subgroup, fertilization rate was 59.1% for Testi-ICSI and 58.5% for Ejac-ICSI, with a pooled OR of 1.04 (95% CI 0.89–1.21; $I^2 = 0$; P = 0.66; Fig. 2). In the "noclassify" subgroup, fertilization rates of testicular versus ejaculated sperm were 66.2% and 61.5% respectively, with a pooled OR of 1.16 (95% CI 0.90–1.50; $I^2 = 0$; P = 0.25; Fig. 2). There was no significant changes in the pooled result with the removal



FIG. 1. Trial identification and selection process.

	Testicular sperm		Ejaculated sperm			Odds Ratio	Odds Ratio	
Study or Subgroup	Events	<u>rents Total Events Total</u>		Weight M-H, Random, 95% Cl		M-H, Random, 95% Cl		
1.1.1 Noclassify								
Gilman 2018	18	32	44	86	2.7%	1.23 [0.54, 2.78]		
Herrero 2019	335	501	281	442	24.7%	1.16 [0.88, 1.51]	,	
Subtotal (95% CI)		533		528	27.4%	1.16 [0.90, 1.50]	•	
Total events	353		325					
Heterogeneity: Tau ² =	: 0.00; Chi² = 0).02, df=	1 (P = 0.89);	l² = 0%				
Test for overall effect:	Z=1.16 (P=	0.25)						
1.1.2 High SDF								
Alharbi 2020	311	536	263	438	27.0%	0.92 [0.71, 1.19]		
Arafa 2017	229	479	218	469	27.4%	1.05 [0.82, 1.36]		
Greco 2005	140	187	131	185	8.5%	1.23 [0.78, 1.94]		
Pabuccu 2017	147	198	156	220	9.6%	1.18 [0.77, 1.82]	- +- -	
Subtotal (95% CI)		1400		1312	72.6%	1.04 [0.89, 1.21]	•	
Total events	827		768					
Heterogeneity: Tau ² =	= 0.00; Chi ² = 1	l.73, df=	3 (P = 0.63);	l² = 0%				
Test for overall effect:	Z=0.44 (P=	0.66)						
Total (95% CI)		1933		1840	100.0%	1.07 [0.94, 1.22]	•	
Total events	1180		1093					
Heterogeneity: Tau ² =	= 0.00; Chi ² = 2	2.33, df=	5 (P = 0.80);	l² = 0%				긢
Test for overall effect:	Z = 0.98 (P =	0.33)		U.UI U.I I 1011	00			
Test for subaroun diff	ferences [.] Chi ²	ravours (experimental) ravours (control)						

FIG. 2. Forest plot demonstrating relative risk for fertilization rates with intracytoplasmic sperm injection (ICSI) when using testicular or ejaculated sperm.

	Patients included	Male an	e (Vear)	Females	ige (Vear)					
Author (year)						Sperm	Design C	Outcome measures	Previous ICSI failures	
	Semen parameters	Mean \pm SD/range		Mean \pm SD/range		extraction				
		E-ICSI	T-ICSI	E-ICSI	T-ICSI					
Greco 2005 [17]	High SDF: (TUNEL)	28-	-55	24	-35	TESE	Case-control study	м А, В	\geq 2 ICSI failure with ejaculated sperm	
	SDF rates in neatsemen >15%									
Pabuccu 2017 [15]	High SDF: (TUNEL)	40.1 ± 5.5	40.5 ± 6.2	36.8 ± 3.4	36.7 ± 3.9	TESA	Case-control study	A, B, C	\geq 2 ICSI failure with ejaculated sperm	
	Normozoo spermic with SDF ${>}30\%$									
	High SDF: (SCD)	47.5 ± 11.4	38.4 ± 12.2	30.6 ± 5.3	31.6 ± 5.2	TESA	Case-control study	A, B, C	At least 1 ICSI failure with ejaculated sperm	
Arafa 2017 [16]	Normozoo spermic with SDF ${>}30\%$									
Gilman 2018 [12]	Noclassify; (mean)	40.6 ± 5.83	42.9 ± 5.59	38.1 ± 3.67	$\textbf{38.0} \pm \textbf{3.79}$	Micro-TESE	Retrospectivecoho	rt A, B, C	1 ICSI failure with ejaculated sperm	
	Sperm conc (M/mL): 29.6									
	Sperm motility (%): 25.5									
	Sperm morphology: 3									
Herrero 2019 [14]	Noclassify; (mean)	40.1 ± 5.5	40.5 ± 6.2	36.8 ± 3.4	36.7 ± 3.9	TESE	Case-control study	A, B, C	\geq 2 ICSI failure with ejaculated sperm	
	Sperm conc (M/mL): 37.6									
	Sperm motility (%): 23.5									
	Sperm morphology: 4.2									
Alharbi 2020 [13]	High SDF:	37.0 ± 6.6	$\textbf{38.9} \pm \textbf{5.9}$	33.5 ± 4.8	34.4 ± 3.7	TESA	Retrospectivecoho	rt A, B, C	At least 1 ICSI failure with ejaculated sperm	
	Normozoo spermic with SDF ${>}30\%$									

TABLE 1. Characteristics of included studies.

E-ICSI, ICSI using ejaculated sperm; ICSI, intracytoplasmic sperm injection; SCD, sperm chromatin dispersion; TESA, testicular sperm aspiration; TESE, testicular sperm extraction; T-ICSI, ICSI using testicular sperm; TUNEL, transferase-mediated dUTP nick-end labeling. A: Fertilization rates; B: Clinical pregnancy rate; C: Take home baby rate.

	Testicul a r sperm		Ejaculated sperm			Odds Ratio	Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight M-H, Random, 95% Cl		M-H, Rande	om, 95% Cl	
2.1.1 Noclassify									
Alharbi 2020	18	37	27	56	20.7%	1.02 [0.44, 2.34]		—	
Gilman 2018	4	18	9	54	10.2%	1.43 [0.38, 5.36]		•	
Herrero 2019	20	64	12	61	21.0%	1.86 [0.81, 4.23]	-	-	
Subtotal (95% CI)		119		171	51.9%	1.39 [0.81, 2.37]	-		
Total events	42		48						
Heterogeneity: Tau ² =	0.00; Chi ² = 1	.02, df=	2 (P = 0.60);	l² = 0%					
Test for overall effect:	Z=1.20 (P=)	0.23)							
2.1.2 High SDF									
Alharbi 2020	18	37	12	31	16.7%	1.50 [0.57, 3.95]		-	
Arafa 2017	14	36	5	36	12.7%	3.95 [1.24, 12.56]			
Greco 2005	8	18	1	18	4.0%	13.60 [1.48, 125.31]			→
Pabuccu 2017	13	31	8	40	14.7%	2.89 [1.01, 8.28]			
Subtotal (95% CI)		122		125	48.1%	2.87 [1.44, 5.71]			
Total events	53		26						
Heterogeneity: Tau ² =	0.12; Chi ² = 3	.90, df=	3 (P = 0.27);	I² = 23%					
Test for overall effect:	Z = 3.01 (P = 1	0.003)							
Total (95% CI)		241		296	100.0%	1.96 [1.24, 3.11]		◆	
Total events	95		74						
Heterogeneity: Tau ² =	0.09; Chi ² = 7	.77, df=	6 (P = 0.26);	I² = 23%					
Test for overall effect:	Z = 2.86 (P = 1	0.004)		1U Foveure feentrel	100				
Test for subaroup diffe	erences: Chi²	- 2.69.	df = 1 (P = 0.1	0). I ² = 6	2.8%		r avours (experimental)	ravours (control)	

FIG. 3. Forest plot demonstrating relative risk for Clinical Pregnancy Rates with Testi-ICSI and Ejac-ICSI.

of particular studies during sensitivity analyses.

3.2 Clinical pregnancy rates

CPRs were provided in 6 studies, over 465 cycles. For the "noclassify" subgroup, CPRs were 35.3% and 28.1% for Testi-ICSI and Ejac-ICSI respectively, with a pooled OR of 1.39 (95% CI 0.81–2.37; $I^2 = 0$; P = 0.23; Fig. 3). In the "high SDF" subgroup, CPRs was significant higher in Testi-ICSI group than Ejac-ICSI group, at 43.4% for Testi-ICSI and 20.8% for Ejac-ICSI, with a pooled OR of 2.87 (95% CI 1.44–5.71; $I^2 = 23$; P = 0.003; Fig. 3). Sensitivity analyses showed that this result was reliable.

3.3 Take home baby rates

Five studies reported take home baby rates, over a total of 484 couples. Take home baby rates were much higher among Testi-ICSI couples as compared to Ejac-ICSI couples in the "high SDF" subgroup, at 38% and 16% respectively, with an a pooled OR of 3.24 (95% CI 1.20–8.76; $I^2 = 52\%$; P = 0.02; Fig. 4). In the "noclassify" subgroup, the Testi-ICSI and Ejac-ICSI groups had a comparable take home baby rate with a pooled OR of 1.61 (95% CI 0.87–2.98; $I^2 = 0\%$; P = 0.13; Fig. 4). The removal of any individual study did not have a disproportionate effect on the results.

4. Discussion

Many meta-analyses and systematic reviews have compared between the use of testicular sperm (Testi-ICSI) and ejaculated sperm (Ejac-ICSI) in intracytoplasmic sperm injection in patients without azoospermia [18], with high SDF [7, 8] and cryptozoospermia [19–21]. None of these meta analyses focused on the benefits of Testi-ICSI in couples who experienced previous ICSI failures, except for Esteves *et al.* [7]

who evaluated the benefits of Testi-ICSI among males with high SDF. In addition, only two articles provided data on a subgroup of participants with "repeat ICSI failure", which was used by Esteves *et al.* for further analyses. Since the publication of these meta-analyses, additional studies have been published [12–14, 16], which provide new information with regards to the use of Testi-ICSI and Ejac-ICSI.

Studies have shown ART outcomes tends to be negatively affected by impaired sperm, although some couples can have successful pregnancies even when using abnormal sperm [22, 23]. For men with higher SDF levels in their ejaculated sperm, the use of Testi-ICSI was associated with a higher rates of implantation and pregnancy than Ejac-ICSI, as testicular sperm tends to have a lower SDF as compared to ejaculated sperm [7, 24]. This may possibly be due to the difference in SDF between testicular and ejaculated sperm, as infertile men were more likely to have abnormal SDF levels, even within normal semen parameters [25, 26].

As opposed to ejaculated sperm, this possibly hints at the ability of testicular sperm, in achieving more favorable reproductive outcomes in couples who have experienced previous ICSI failures. To our knowledge, the present study is the first to focus mainly on the use of Testi-ICSI in couples with recurrent ICSI failure. Our results show that if ejaculated sperm was found to have high levels of SDF, Testi-ICSI was associated with higher CPRs and take home baby rates. However, in an unselected population of infertile men, with untested SDF, Testi-ICSI may not result in better ICSI outcomes. This is consistent with a previous meta-analysis which examined men with cryptozoospermia, and found that Testi-ICSI did not result in a better outcome than Ejac-ICSI, where there was insufficient sperm to detect SDF levels [19].

The failure of fail one or several IVF cycles does not predict failure in subsequent cycles [27]. Some researchers insist that the conclusion of Testi-ICSI leads to better reproductive

	Testicular sperm		Ejaculated sperm			Odds Ratio	Odds Ratio		
Study or Subaroup	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl	M-H, Random, 95% Cl		
3.1.1 Noclassify									
Alharbi 2020	12	33	16	48	21.8%	1.14 (0.45, 2.89)	}_		
Gilman 2018	3	18	6	54	10.9%	1.60 [0.36, 7.19]	_		
Herrero 2019	15	64	7	61	20.4%	2.36 [0.89, 6.27]			
Subtotal (95% CI)		115		163	53.1%	1.61 [0.87, 2.98]	►		
Total events	30		29						
Heterogeneity: Tau ² =	0.00; Chi ^z = 1	.11, df=	2 (P = 0.57);	P= 0%					
Test for overall effect:	Z = 1.52 (P =	0.13)							
3.1.2 High SDF									
Alharbi 2020	12	33	9	30	18.5%	1.33 [0.46, 3.83]			
Arafa 2017	14	36	3	36	12.8%	7.00 [1.80, 27.24]			
Pabuccu 2017	12	31	5	40	15.7%	4.42 [1.35, 14.44]			
Subtotal (95% CI)		100		106	46.9%	3.24 [1.20, 8.76]			
Total events	38		17						
Heterogeneity: Tau ² =	0.40; Chi ² = 4	l.19, df=	2 (P = 0.12);	P= 52%					
Test for overall effect	Z = 2.31 (P =	0.02)							
Total (95% CI)		215		269	100.0%	2.21 [1.27, 3.83]			
Total events	68		46						
Heterogeneity: Tau ² = 0.14; Chi ² = 7.09, df = 5 (P = 0.21); P = 30%									
Test for overall effect	Z = 2.81 (P =	0.005)					Eavoure (experimental) Eavoure (control)		
Test for subaroup diff	erences: Chiª	= 1.36.	df = 1 (P = 0.2	4). I² = 2	6.7%				

FIG. 4. Forest plot demonstrating relative risk for take home baby rates with Testi-ICSI and Ejac-ICSI.

outcomes in recurrent ICSI failure unreliable, as the Testi-ICSI cycle was compared with those of the first failed Ejac-ICSI cycle for the same patient in the case series studies. Furthermore, couples who achieved pregnancy with Ejac-ICSI were excluded [17]. The use of case-control studies have solved this problem, because Testi-ICSI cycles are not compared with previous Ejac-ICSI failure cycle within the same patient, but with Ejac-ICSI cycles in other couples with comparable conditions.

Some researchers disagree with the use of Testi-ICSI in nonazoospermic men due to the possible surgical complications [9]. In addition, while Moskovtsev *et al.* [28] showed that aneuploidy rates were 2 to 3 times higher in testicular sperm than ejaculated sperm, others found that testicular and ejaculated sperm had similar aneuploidy rates [29]. Currently available aneuploidy studies tend to be conducted with a smaller sample size, thus the question of whether testicular sperm truly has a higher rate of aneuploidy remains inconclusive.

The most common assays, terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), sperm chromatin dispersion (SCD), Comet-single cell gel electrophoresis, and sperm chromatin structure assay (SCSA) were mainly used to detect SDF clinically [30]. Most of the studies included in our meta-analysis used the TUNEL method, with the threshold set at 15% [17] and 30% [15], whereas another article used the SCD method, and set the threshold as 30% [16]. In Esteves et al.'s [7] study, 29% was deemed to be the threshold of SDF, where Testi-ICSI becomes more beneficial. Due to the lack of standardized programs and the different measurement methods used, the sensitivity, specificity, and cut-off rate of each method varies. In addition, the type of sperm DNA detection and threshold that should be used remains controversial [30, 31]. This problem also exists in the present study, which may weaken the strength of the conclusions drawn. Therefore, the use

of reliable SDF measurements and effective thresholds are essential, and the limitations of SDF testing and the possible benefits to clinical results should be taken into account when considering the use of Testi-ICSI.

Our study aimed to evaluate the influence of the source of sperm (testicular or ejaculated) used for ICSI on ICSI results for couples with history of ICSI failure. Thus, factors concerning the female, such as her age, AMH, BMI should be comparable between the different experimental groups to prevent bias. In our study, two of included studies investigated the outcome of subsequent Testi-ICSI cycles for couples who failed their initial Ejac-ICSI [16, 17]. For the rest of the included studies, only one study clearly stated that couples with an older female (>40 years) and female factors were excluded [13]. Although females were matched only in terms of age but not other female factors related to ICSI outcomes, such as mean oocytes retrieved, and mean MII in other studies, there was no significant difference between the experimental groups. This suggests that the contribution of female factors to ICSI outcomes was balanced and comparable between the included articles [12, 14, 15].

The present study has limitations. Firstly, a number of the included studies had small sample sizes and all studies were retrospective in nature. Secondly, certain factors that could have influenced ICSI outcomes were not reported in all studies, such as the lifestyle patterns of participants, presence of varicoceles, and medication use, along with other relevant male factors. Furthermore, different detection methods and cutoff values were used to determine the percentage of sperm with fragmented DNA. In addition, the definition of recurrent ICSI failure differs among the included studies; Finally, a potential confounder was identified in Herrero *et al.*'s [14] study, where the Testi-ICSI group had a significantly higher SDF than the Ejac-ICSI group's SDF. Although sensitivity analyses showed no change in results, the presence of such confounders may result in bias. In this article, we evaluated whether the outcomes of Testi-ICSI were superior to that of Ejac-ICSI in recurrent ICSI failure couples. The analyses showed that the use of Testi-ICSI in recurrent ICSI failure couples, where the ejaculated sperm of males had high levels of SDF, was related to better CPRs and LBRs. However, when Testi-ICSI was used in an unselected population of infertile men with either untested SDF or when their decision to use Testi-ICSI was not based on anomalous levels of SDF, treatment with Testi-ICSI may not result in better outcomes. When genomics, epigenetics, proteomics, and metabolomics are better understood in the future, it may then be possible to answer the question of whether sperm in the testis is truly better than sperm from the ejaculate.

5. Conclusions

Currently, there is limited research on Testi-ICSI use in couples with recurrent ICSI failures. The present study suggests that Testi-ICSI use was correlated with higher CPRs and LBRs only in males with confirmed high SDF levels in their ejaculated sperm. However, when Testi-ICSI was used in an unselected population of infertile men with either untested SDF or when their decision to use Testi-ICSI was not based on anomalous levels of SDF, treatment with Testi-ICSI may not result in better outcomes.

Abbreviations

ART, assisted reproductive treatment; CIs, confidence interval; CPRs, Clinical Pregnancy Rates; ICSI, intracytoplasmic single sperm injection; IVF, in vitro fertilization; ORs, Odds ratios; SDF, Sperm DNA fragmentation; SMD: standardized mean difference; Testi (Ejac)-ICSI, testicular sperm (ejaculated sperm) intracytoplasmic single sperm injection.

Author contributions

QW and XWY designed and instructed the writing of this article. YHL and XYZ researched and assessed the literature. QW, XYZ and XWY extracted the data from each article and drew the Tables and Figures of the review. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Research involving human participants or animals were not conducted by any of the authors. The study was also registered with PROSPERO (registry number: CRD42021225964).

Acknowledgment

Thanks to all the peer reviewers for their opinions and suggestions.

Funding

Study on the effect of oxLDL on progesterone production by HIF pathway on infertility in obese women-Jilin Provincial Finance Department (JLSCZD2019-040).

Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://oss.jomh.org/ jomh/article/1402519669519073280/attachment/ Supplemental%20Table2ROBINS-I.docx.

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