Testicular versus percutaneous epididymal sperm aspiration for patients with obstructive azoospermia: a systematic review and meta-analysis

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Background: Intracytoplasmic sperm injection (ICSI) is a popular treatment for male infertility due to obstructive azoospermia (OA). Testicular sperm aspiration (TESA) and percutaneous epididymal sperm aspiration (PESA) are two common sperm retrieval approaches for ICSI among men with OA. However, the comparative efficacies of TESA and PESA have been debated for more than a decade and there has been no synthesis of the available evidence. This meta-analysis compared fertility outcomes between TESA and PESA among men with OA undergoing ICSI.

Methods: We searched Embase, PubMed, ScienceDirect, and Web of Science to identify studies comparing the effectiveness of TESA and PESA for ICSI. Study quality was assessed using the Newcastle-Ottawa scale. Data were pooled using a random-effects model. Outcomes were fertilization rate, implantation rate, pregnancy rate, and miscarriage rate. Results are expressed as odds ratio (OR) with 95% confidence intervals (CIs). Study heterogeneity was evaluated by the I-square (I^2) statistic.

Results: Of 2,965 references retrieved, eight studies met eligibility criteria. These studies included 2,020 men receiving 2,060 ICSI cycles. The pooled results showed no significant differences in pregnancy and miscarriage rates between TESA and PESA groups, but TESA yielded a significantly higher implantation rate than PESA (OR =1.58, P=0.02, I^2=24%).

Conclusions: TESA and PESA yielded similar pregnancy and miscarriage rates for couples receiving ICSI because of OA, but each demonstrated unique advantages and disadvantages. Further studies are required to evaluate safety outcomes and efficacy for specific clinical groups.

Keywords: Obstructive azoospermia (OA); intracytoplasmic sperm injection (ICSI); testicular sperm aspiration (TESA); percutaneous epididymal sperm aspiration (PESA)

Introduction

Obstructive azoospermia (OA) is one of the major causes of infertility in men (1), and is particularly frequent in men with vasectomy, reproductive tract trauma, or congenital absence of the vas deferens but normal spermatogenesis. The clinical management of OA depends on etiology but usually includes either (I) surgery to resolve obstruction or (II) sperm retrieval for intracytoplasmic sperm injection (ICSI) (1). Although the former method permits natural fertilization, the reproductive tract may be difficult to approach or reconstruct in some cases. Thus, ICSI may be the more feasible solution for these patients. First applied in 1992 (2), ICSI has evolved to become a reliable therapy for the majority of male reproductive tract deficiencies (3). However, numerous paternal and maternal factors can influence ICSI outcome. A major paternal factor is the source of sperm. Percutaneous epididymal sperm aspiration (PESA) and testicular sperm aspiration (TESA) are two common sperm retrieval approaches for ICSI in men with severe OA (1), but the more appropriate choice for sperm retrieval is still debated.

Several studies have directly compared ICSI outcomes between PESA and TESA treatment groups but results have not been unanimous. A retrospective study from a private fertility center in Brazil found no significant difference in pregnancy rate between these two procedures but did report non-similarity in other outcomes (4). Another large-scale retrospective study from Egypt also reported that the source of sperm used for ICSI treatment of OA did not affect fertilization, pregnancy, or miscarriage rates (5). Alternatively, one report found a higher fertilization rate in the PESA group among OA cases (6). Despite debate for more than 15 years, whether PESA or TESA yields better ICSI outcomes for OA remains unresolved. Some of these studies included patients with non-OA (NOA) and OA in the same group; however, the etiologies of NOA and OA are entirely different (7), so it is more reasonable to compare ICSI outcomes separately for these two types of azoospermia. Further, these data were gathered from single centers, which may the applicability of the results to the general OA population. Hence, our study aimed to compare ICSI outcomes between PESA and TESA among patients with OA across centers by meta-analysis.

Methods

Our systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (8). This synthesized study was exempted from institutional review board approval because it used published data. An experienced researcher (YN Kang) and a urologist (CC Wu) coordinated the study (9-11).

Inclusion and exclusion criteria

Study eligibility criteria were established prior to literature search and selection. The inclusion criteria were (I) men with OA, (II) undergoing ICSI, and (III) comparing TESA to PESA. The exclusion criteria were as follows: (I) mixed data of OA with other conditions without stratified analysis; (II) book contents, meeting reports, or news articles; (III) gray literature without details; (IV) no report of relevant outcomes (fertilization rate, implantation rate, pregnancy rate, miscarriage rate, complications/adverse events). Two reviewers (YN Kang and PY Shen) individually identified the relevant studies according to the criteria. Disagreements were resolved through discussion with a third author (CC Wu).

Data sources and search strategy

Four electronic databases were searched for potential references: Embase, PubMed (including MEDLINE), ScienceDirect, and Web of Science. The primary search strategy was established in PubMed using common terms, medical subject headings, and abbreviations related to OA and ICSI. Synonyms were combined by the Boolean operator "OR" and the concepts of OA and ICSI were combined using the Boolean operator "AND". The search strategy included no restrictions on publication date or language to include studies from countries across the globe. The final searches were completed before 28 June 2019 (Supplementary file 1).

Evidence selection

After potential references were identified, two investigators (PY Shen and YN Kang) independently selected eligible studies in two steps. First, the title and abstract were screened for relevance. Articles appearing relevant according to title and abstract review were then subjected to full review. The two investigators excluded articles unrelated to OA, ICSI, and TESA according to eligible criteria, and then retrieved full-texts of the remaining articles for further

review. The two investigators removed ineligible studies without details on patient condition or predefined study endpoints. A senior urologist made the final judgment in case of disagreement.

Data extraction

Two investigators (PY Shen and YN Kang) independently extracted the following information and outcome data from the included studies: first author, publication year, study design, number of patients, study period, paternal mean age, maternal mean age, mean number of ICSI cycles, and outcomes (including fertilization rate, implantation rate, pregnancy rate, and miscarriage rate). The outcomes were usually reported as event rates. If the original report presented outcomes as percentages, they were converted to event rates. If the original report only showed mean ± standard deviation, we cannot convert in event rates because of no denominator.

Quality assessment

Most of the included studies were retrospective, so two authors (PY Shen and KW Shih) independently appraised study quality using the Newcastle-Ottawa Quality Assessment Scale. When a given study was rated differently, a third investigator (YN Kang) critically reviewed risk of bias for the disagreement and made the final rating.

Statistical analysis

We used a pairwise meta-analysis for statistical synthesis. Odds ratio (OR) was chosen to express pooled results because the outcomes were binary data and most studies were retrospective. To overcome the variability among study populations and treatments, quantitative syntheses were conducted using a random-effects model. Moreover, to compare rare events, the Mantel-Haenszel method was employed. The results of this meta-analysis are presented as forest plots including events, total numbers, and ORs with [95% confidence intervals (CIs)].

According to the Cochrane Handbook for Systematic Reviews of Interventions, a pooled result may be influenced by heterogeneity across studies and by publication bias. Thus, heterogeneity and small study effects should be examined (12). Usually, heterogeneity is tested and presented as tau-square and I-square (I^2) values, so we calculated these two values and judged heterogeneity of pooled results according to I^2 and P values for tau-square. I^2, the most common statistics for heterogeneity across studies, represents the proportion of total variation among studies due to heterogeneity (with $I^2>75\%$ considered highly heterogeneous). Pooled results were also deemed highly heterogeneous when the P value for tau-square was lower than 0.10 (12). Funnel plots were constructed and assessed by Egger's test for publication bias. Pooled results were considered biased by publication when Egger's test reached statistical significance.

We also conducted subgroup analyses according to paternal age group for all outcomes because paternal age is an important factor determining ICSI success. According to a previous study (13), paternal age was stratified into three subgroups: <30 years old, 30–35 years old, and >35 years old. In addition, maternal age is an important factor in human reproduction, so we also conducted subgroup analyses according to maternal mean age. Based on available data and previous work (13,14), we used <30 years old, 30–35 years old, and >35 years old for subgroup stratification. To clarify the effect of sperm aspiration technique on miscarriage, we further stratified data by number of ICSI cycles because there appears to be a cumulative increase in risk (14).

Pairwise meta-analyzes were completed in Review Manager (version 5.3, The Cochrane Collaboration, Oxford, UK), and the small study effects were detected using Comprehensive Meta-Analysis (version 2) for Microsoft Windows 10.

Results

Literature search results

The initial literature search retrieved a total of 2,965 references from Embase (n=1,097), PubMed (n=715), ScienceDirect (n=344), and Web of Science (n=809). Of these, 1,018 duplicates were removed, and 1,934 were excluded as unrelated documents (n=37), for not enrolling OA patients (n=1,314), for not using ICSI (n=119), for having no PESA treatment group (n=428), or having no TESA treatment group (n=36) according to title and abstract screening. Full-text review of the remaining 13 references excluded five publications, one review, two studies without comparison of PESA versus TESA, and two gray literature documents without the required details (15,16). Finally, seven retrospective studies and
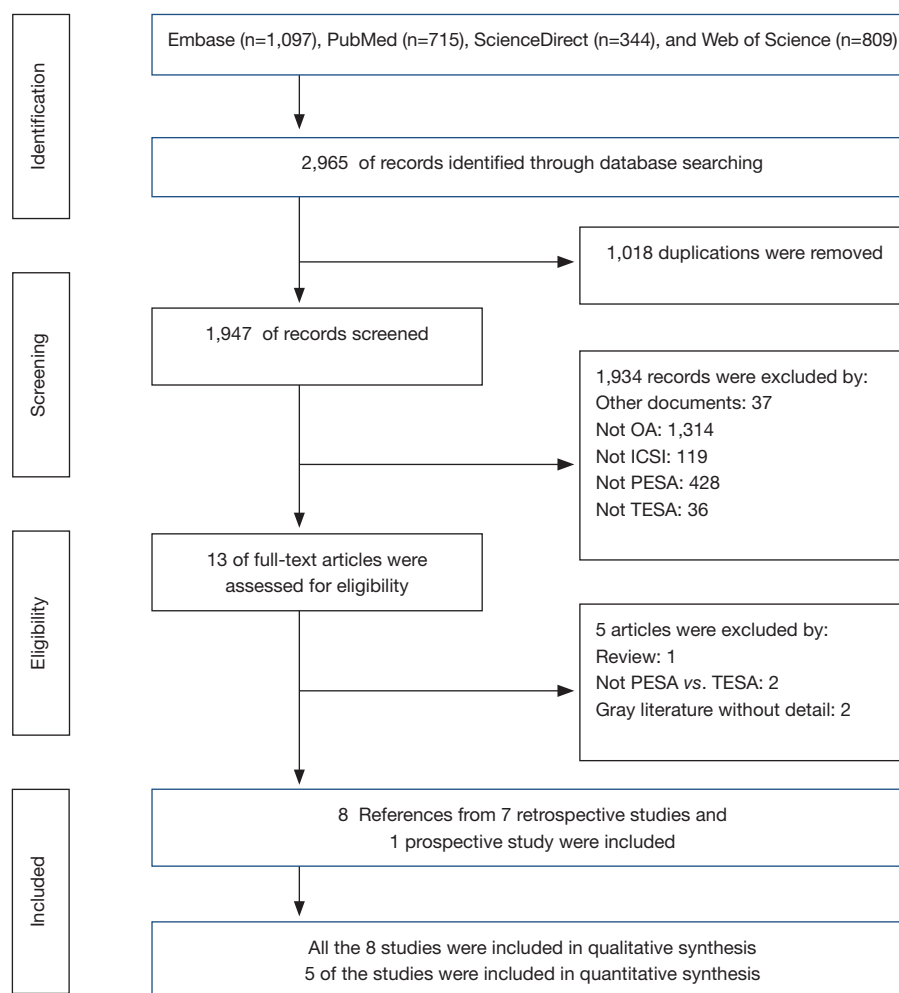
634

Shih et al. TESA versus PESA for OA

Figure 1 Flow diagram of evidence selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. OA, obstructive azoospermia; ICSI, intracytoplasmic sperm injection; TESA, testicular sperm aspiration; PESA, percutaneous epididymal sperm aspiration.

one prospective study were included in the qualitative and quantitative synthesis (5,6,13,17-21). *Figure 1* shows the process of study selection for this comprehensive review.

Overview of the included studies

The included studies involved 2,020 men receiving 2,060 ICSI cycles. *Table 1* summarizes basic study characteristics including first author surname, publication year, study design, number of patients, study period, paternal mean age, maternal mean age, and mean number of ICSI cycles. These studies covered the period from the early 1990s to 2015 and thus included those from the early years of TESA and PESA application to near present day. The studies were conducted

in Brazil (6,17,18,20), China (13,21), Egypt (5), and the USA (19). According to the available information, paternal mean age ranged from 30 to 47 years and maternal mean age from 28 to 35 years. Seven of the 8 included studies provided adequate information on study design, although results may still be influenced by bias due to differences in clinical processes. The other (retrospective) study presented limited information on methodology and bias control (21). Complete information on quality assessment is presented in *Table S1*.

Fertilization

Three of the eight studies, including 420 men receiving

Table 1 Characteristics and risk of bias of included studies

Author and publication year	Study type	Patients	Included years	Mean paternal age (y)		Mean maternal age (y)		ICSI cycles	
				TESA	PESA	TESA	PESA	TESA	PESA
Borges *et al.* (2009)	Retrospective study	73	2006.1–2007.7	44.3	46.7	32.6	31.9	24	49
Dozortsev *et al.* (2006)	Retrospective study	185	2000.2–2003.12	33	32.8	Not reported	Not reported	42	143
Glina *et al.* (2003)	Retrospective study	58	1996.8–2000.12	Overall: 45		Overall: 34		14	64
Kamal *et al.* (2010)	Retrospective study	1,121	1994–2006	39.73	38.25	31.05	30.53	790	331
Levine *et al.* (2003)	Retrospective study	112	1995.8–2001.7	39.8	37.1	35.5	32.1	18	94
Semião-Francisco *et al.* (2010)	Retrospective study	274	1997.1–2007.3	46.2	47.8	34.3	33	103	171
Wang *et al.* (2006)	Prospective cohort study	20	2001.9–2002.11	30.27	30.27	29.22	29.22	20	20
Yu *et al.* (2017)	Retrospective study	177	2011–2015	Stratified without mean age		29.48	28.14	71	106

ICSI, intracytoplasmic sperm injection; TESA, testicular sperm aspiration; PESA, percutaneous epididymal sperm aspiration.

440 ICSI cycles, reported data on fertilization rate (6,13,18). The pooled estimate indicated that TESA led to significantly lower fertilization rate than PESA (OR =0.63, 95% CI: 0.44–0.92, P=0.02) with moderate heterogeneity among studies (I^2=38%; P=0.17) (*Figure S1*). However, subgroup analysis did not reveal significant differences in fertilization rates between TESA and PESA treatment arms, although there was a favorable trend for greater PESA success among the subgroup with mean paternal age from 30 to 35 years old. In this subgroup, TESA yielded a lower fertilization rate than PESA but without statistical significance (OR =0.45, 95% CI: 0.18–1.12, P=0.09). There was also substantial heterogeneity among studies (I^2=55%; P=0.13).

Implantation

Two studies including 362 patients receiving 362 ICSI cycles reported implantation rates (6,13). Pooled results showed that TESA yielded a significantly higher implantation rate than PESA (OR =1.58, 95% CI: 1.08–2.31, P=0.02) and

heterogeneity was low (I^2=24%; P=0.27) (*Figure 2*). In one of these studies (13), significantly higher implantation rates were found in the TESA subgroups 30–35 years (OR =1.62, 95% CI: 1.05–2.49, P=0.03) and older than 35 years (OR =2.95, 95% CI: 1.13–7.75, P=0.03), but not in the younger than 30 years subgroup (OR =1.10, 95% CI: 0.56–2.14, P=0.79).

Pregnancy

A total of five studies including 1,541 men receiving 1,673 ICSI cycles presented data on pregnancy rates (5,6,13,18,19). The pooled results revealed no significant difference between TESA and PESA (OR =1.14, 95% CI: 0.82–1.57, P=0.43) and heterogeneity was low (I^2=20%; P=0.28) (*Figure 3*). Similar trends were also found in subgroups of paternal mean age between 30 and 35 years old (OR =1.26, 95% CI: 0.55–2.86, P=0.59) and greater than 35 years old (OR =1.23, 95% CI: 0.75–2.02, P=0.41). Moreover, no significant differences in pregnancy rates between TESA and PESA were observed among maternal subgroups stratified by
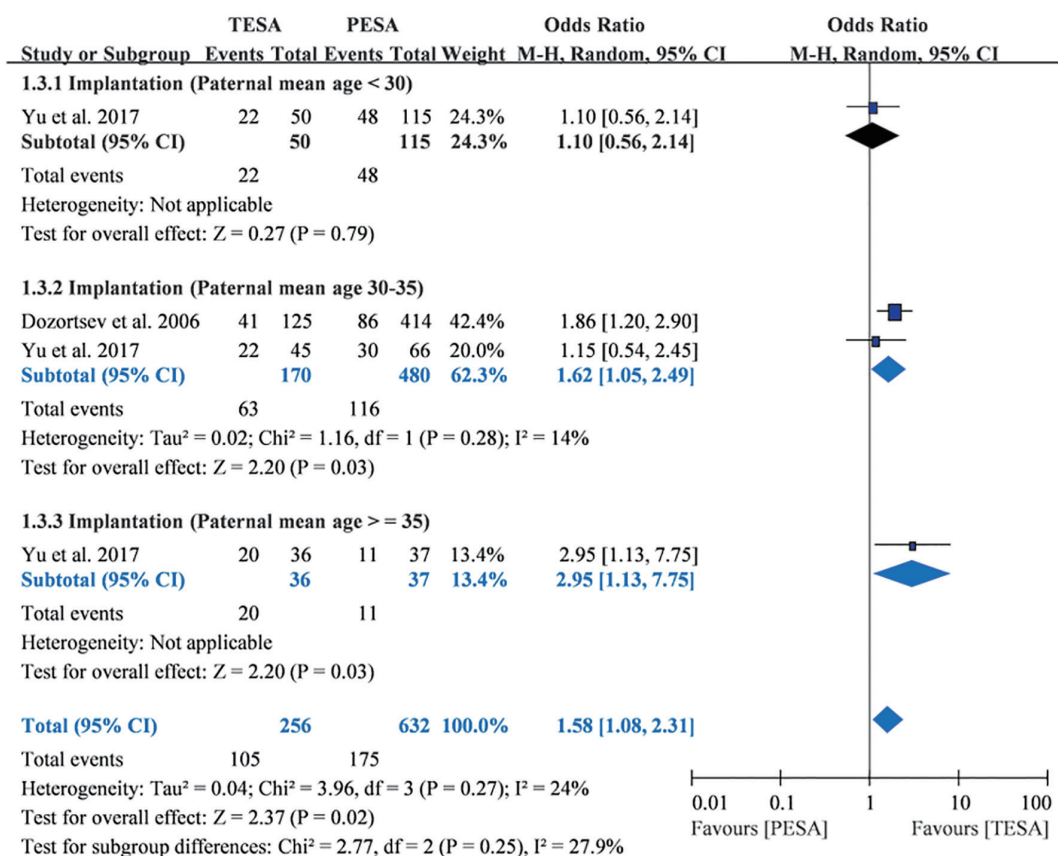
636

Shih et al. TESA versus PESA for OA

Figure 2 Forest plot of implantation rates. TESA, testicular sperm aspiration; PESA, percutaneous epididymal sperm aspiration; CI, confidence interval.

mean age (*Figure S2*).

Miscarriage

Only two studies involving 243 men receiving 263 ICSI cycles reported miscarriage rates (6,18), and pooled estimates indicated no significant difference between TESA and PESA (OR =1.08, 95% CI: 0.68–1.73, P=0.74) (*Figure S3*).

Publication bias

Pregnancy rate was the target outcome for publication bias testing as it was reported most frequently. The funnel plot showed no substantial asymmetry (*Figure S4*); moreover, Begg and Mazumdar rank correlation (tau =0.50, z-value =1.22, P=0.22) and Egger's test (intercept =0.89, *t*-value =0.85, P=0.46) revealed no evidence of publication bias.

Discussion

The present synthesis identified eight studies comparing ICSI outcomes between TESA and PESA for men with OA. Reported outcomes included fertilization rate, implantation rate, pregnancy, and miscarriage rate. There were no significant differences in pregnancy and miscarriage rates between TESA and PESA treatment groups, although fertilization rate was slightly higher using PESA and implantation rate numerically higher using TESA. Thus, the choice of TESA or PESA for men with OA does not appear to influence pregnancy or miscarriage rate after ICSI, although each approach has unique advantages and disadvantages for fertilization and implantation.

In addition to yielding similar pregnancy rates, TESA and PESA share several advantages, including simplicity of the procedure. However, TESA uses a 22-G butterfly needle to penetrate into the testis with suction for fluid aspiration, and
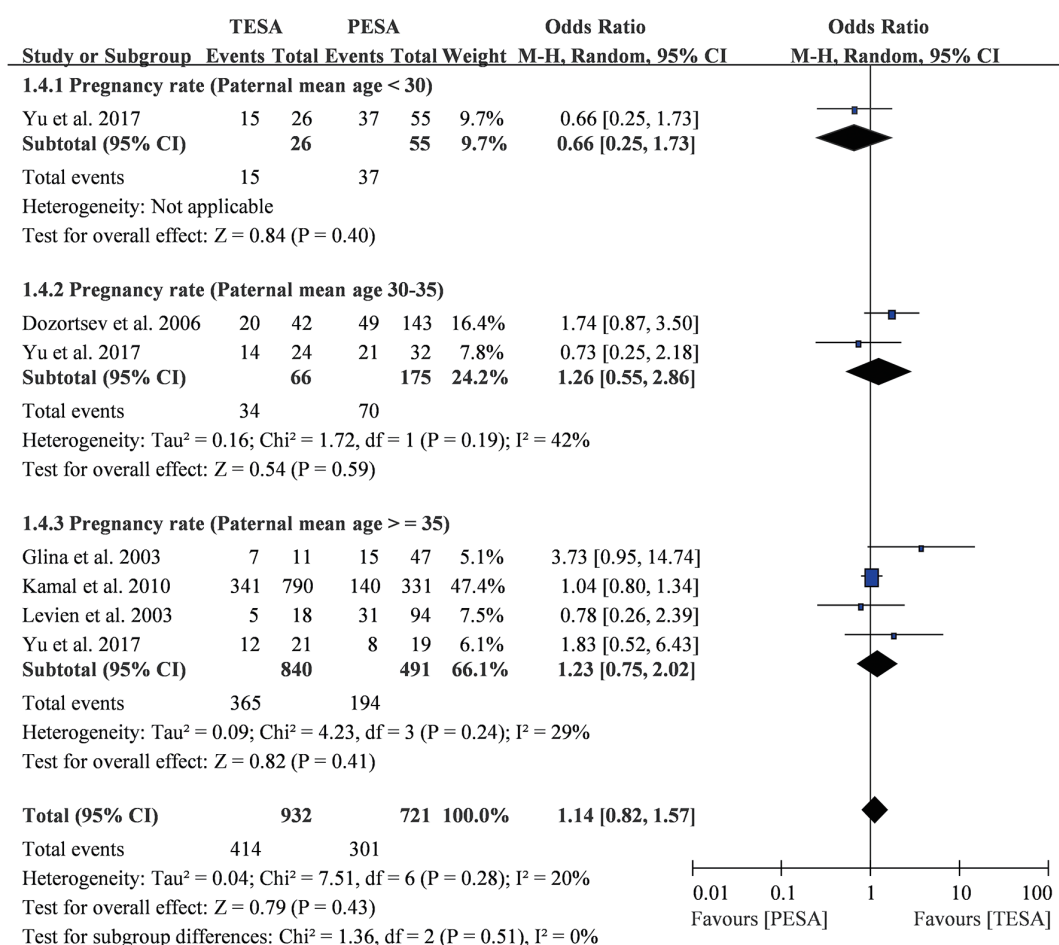
Figure 3 Forest plot of pregnancy rates. TESA, testicular sperm aspiration; PESA, percutaneous epididymal sperm aspiration; CI, confidence interval.

it is easier to retrieve sperm as TESA targets the main source. This ease of access may also influence quality and quantity. The quality of sperm may differ among reproductive regions in older males. In particular, the quality and quantity of sperm from the distal end of the testis may be inferior to sperm in the testis. This may account for the higher implantation rate using TESA compared to PESA. Furthermore, Color Doppler ultrasonography is an effective support tool for TESA guidance to avoid blood vessels and reduce hematoma formation (22). However, TESA causes testicular damage due to multiple needle penetrations, and may lead to intra-testicular hemorrhage. Other disadvantages of TESA include tunical vessel puncture and hematocele formation (23).

In contrast, PESA is usually performed using a 26-G needle to puncture directly into the epididymal ductule with suction force. The syringe is then rotated and advanced in a different direction with suction to extract fluid from the epididymis. This procedure may be repeated several times as PESA is conducted blind and depends on palpation by the surgeon to find the epididymis. Alternatively, PESA is an easy approach to repeat the sperm retrieval procedure and has been confirmed as highly effect for ICSI treatment of OA regardless of etiology (24). Sperm retrieval appears to be more effective in men with OA than testicular failure as evidenced by higher pregnancy rate and live birth rate (25). The main disadvantage of PESA is that the puncture site cannot be precisely controlled, and so the needle may miss the sperm-containing ductile. In addition, hematoma due blood vessel puncture and contamination of the sample with red blood cells have been observed (26).

Several studies have reported higher incidences of developmental impairment and congenital diseases due to DNA abnormities in children born through ICSI, whether sperm was retrieved from the testicle or epididymis (27). There is also evidence that mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) are of better quality in testicular sperm than epididymal sperm (28), which may provide another explanation for the higher implantation rate using TESA. This in turn implies that PESA should be accompanied by longer-term follow-up. Open epididymal sperm aspiration is an alternative to PESA in which the puncture site is better controlled (29). However, we did not find evidence indicating that children born through TESA-ICSI demonstrate better development during long-term follow-up than those born through PESA-ICSI.

This meta-analysis supports the conclusion of a previous synthesis in the Cochrane Database that there is little evidence for the superiority of TESA or PESA (30). Our synthesis revealed compatible outcomes using TESA or PESA, although TESA yielded higher implantation rates than PESA in men older than 35 years. A previous meta-analysis also found a trend showing that paternal age may be a factor affecting ICSI using different retrieval techniques, although that synthesis focused on cryptozoospermia (14). On the contrary, our synthesis revealed a lower fertilization rate using TESA compared to PESA. Therefore, the present evidence cannot provide guidance for choosing TESA over PESA or vice versa for ICSI among men with OA. As these two sperm retrieval techniques have similar efficacy, we suggest that future studies should focus instead on safety outcomes. Clinicians may then be better able to choose the superior technique based on benefit-risk assessment.

There are some limitations of our meta-analysis. First, we did not compare efficacy for future pregnancies or miscarriage rate following PESA or TESA failure. Both procedures can damage tissue, and there is no guarantee of success even though sperm aspiration is a route technique for artificial reproduction. Thus, OA patients may receive either PESA or TESA multiple times. In this light, it may also be valuable to compare PESA to TESA for cost and post-operation pain. Second, our quantitative syntheses are based on only eight studies (at most) because we rejected those reporting percentages without the denominator. Moreover, some outcome analyzes were based on only two or three studies, although there was no serious bias in these cases. Third, some of the included studies did not report maternal age, an important factor influencing ICSI success. Therefore, we could not examine how maternal age affects pooled implantation and miscarriage rates following PESA and TESA. Another potential problem is that two studies were from the same institute in Brazil and had a partially overlapping in study period. However, they reported different outcomes, and no data of them can be pooled together. Therefore, our results were not biased by overlapping cohorts.

Conclusions

The pooled evidence in this meta-analysis confirms that TESA and PESA have similar efficacy for men with OA, with both yielding implantation rates higher than 80%. On the other hand, the two approaches may have different risks in clinical practice. TESA is the bigger target for sperm aspiration but may be more harmful than PESA. Alternatively, while PESA is less damaging, it may have to be performed several times as the epididymal ductule is much smaller than the testis. Thus, doctors should base the decision on whether to use TESA or PESA for sperm retrieval according to accessibility and risk of damage.

Acknowledgments

Footnote

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Supplementary file 1 Data source and search strategy

Primary search strategy

1. Obstructive azoospermia;
2. OA;
3. #1 OR #2;
4. Intracytoplasmic sperm injection;
5. ICSI;
6. Vitro fertilization;
7. IVF;
8. #4 OR #5 OR #6 OR #7;
9. #3 AND #8.

Embase

('obstructive azoospermia'/exp OR 'obstructive azoospermia' OR oa) AND ('intracytoplasmic sperm injection'/exp OR 'icsi' OR 'injection, intracytoplasmic sperm' OR 'intracytoplasmic sperm injection' OR 'sperm injections, intracytoplasmic' OR 'vitro fertilization' OR 'ivf'/exp OR ivf)

PubMed

((obstructive azoospermia OR OA) AND (((intracytoplasmic sperm injection OR ICSI) OR vitro fertilization) OR IVF))

ScienceDirect

(obstructive azoospermia OR OA) AND (intracytoplasmic sperm injection OR ICSI OR vitro fertilization OR IVF)

Web of Science

Topic: (obstructive azoospermia OR OA) AND Topic: (intracytoplasmic sperm injection OR ICSI OR vitro fertilization OR IVF)

Table S1 Risk of bias

Item	Borges Jr *et al*. (2009)	Dozortsev *et al*. (2006)	Glina *et al*. (2003)	Kamal *et al*. (2010)	Levine *et al*. (2003)	Semião-Francisco *et al*. (2010)	Wang *et al*. (2006)	Yu *et al*. (2017)
Selection								
Representative ness of the exposed cohort	★	★	★	★	★	★	★	★
Selection of the non-exposed cohort	★	★	★	★	★	★	★	★
Ascertainment of exposure	★	★	★	★	★	★	★	★
Demonstration that outcome of interest was not present at start of study	★	★	★		★	★	★	★
Comparability								
Comparability of cohorts on the basis of the design or analysis controlled for confounders	★★	★★	★★	★★	★	★★	–	★★
Outcome								
Assessment of outcome	★	★	★	★	★	★	★	★
Was follow-up long enough for outcomes to occur	★	★	★	★	★	★	★	★
Adequacy of follow-up of cohorts	★	★	★	★	★	★	★	★

Figure S1

Study or Subgroup	TESA Events	TESA Total	PESA Events	PESA Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Fertilization (Paternl mean age < 30)						
Yu et al. 2017	192	194	454	462	5.3%	1.69 [0.36, 8.04]
Subtotal (95% CI)		194		462	5.3%	1.69 [0.36, 8.04]
Total events	192		454			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
1.1.2 Fertilization (Paternal mean age 30-35)						
Dozortsev et al. 2006	222	329	746	966	46.7%	0.61 [0.46, 0.81]
Yu et al. 2017	171	182	209	212	7.4%	0.22 [0.06, 0.81]
Subtotal (95% CI)		511		1178	54.1%	0.45 [0.18, 1.12]
Total events	393		955			
Heterogeneity: Tau² = 0.28; Chi² = 2.25, df = 1 (P = 0.13); I² = 55%						
Test for overall effect: Z = 1.71 (P = 0.09)						
1.1.3 Fertilization (Paternal mean age >= 35)						
Glina et al. 2003	94	153	397	587	38.9%	0.76 [0.53, 1.10]
Yu et al. 2017	127	132	109	109	1.6%	0.11 [0.01, 1.94]
Subtotal (95% CI)		285		696	40.6%	0.49 [0.09, 2.50]
Total events	221		506			
Heterogeneity: Tau² = 0.87; Chi² = 1.78, df = 1 (P = 0.18); I² = 44%						
Test for overall effect: Z = 0.86 (P = 0.39)						
Total (95% CI)		990		2336	100.0%	0.63 [0.44, 0.92]
Total events	806		1915			
Heterogeneity: Tau² = 0.06; Chi² = 6.49, df = 4 (P = 0.17); I² = 38%						
Test for overall effect: Z = 2.38 (P = 0.02)						
Test for subgroup differences: Chi² = 2.13, df = 2 (P = 0.34), I² = 6.1%						

Favours [PESA]   Favours [TESA]
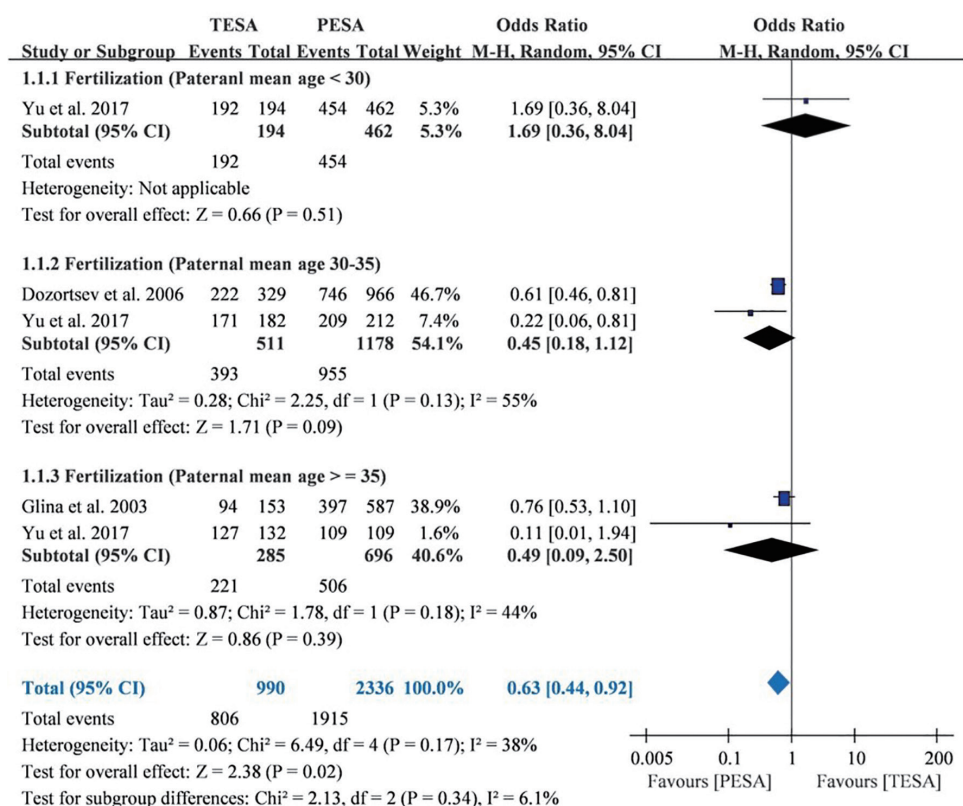(0.005   0.1   1   10   200)

Figure S1 Forest plot of fertilization rates. TESA, testicular sperm aspiration; PESA, percutaneous epididymal sperm aspiration; CI, confidence interval.

Figure S2

Study or Subgroup	TESA Events	TESA Total	PESA Events	PESA Total	Weight	Odds Ratio IV, Random, 95% CI
1.5.1 Pregnancy rate (maternal mean age < 30)						
Yu et al. 2017 (a)	15	26	37	55	9.8%	0.66 [0.25, 1.73]
Yu et al. 2017 (b)	14	24	21	32	7.8%	0.73 [0.25, 2.18]
Subtotal (95% CI)		50		87	17.6%	0.69 [0.34, 1.43]
Total events	29		58			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.00 (P = 0.32)						
1.5.2 Pregnancy rate (maternal mean age >= 30)						
Levien et al. 2003	5	18	31	94	7.4%	0.78 [0.26, 2.39]
Kamal et al. 2010	341	790	140	331	64.0%	1.04 [0.80, 1.34]
Yu et al. 2017	12	21	8	19	6.0%	1.83 [0.52, 6.43]
Glina et al. 2003	7	11	15	47	5.0%	3.73 [0.95, 14.74]
Subtotal (95% CI)		840		491	82.4%	1.23 [0.75, 2.02]
Total events	365		194			
Heterogeneity: Tau² = 0.09; Chi² = 4.23, df = 3 (P = 0.24); I² = 29%						
Test for overall effect: Z = 0.82 (P = 0.41)						
Total (95% CI)		890		578	100.0%	1.04 [0.76, 1.43]
Total events	394		252			
Heterogeneity: Tau² = 0.02; Chi² = 5.60, df = 5 (P = 0.35); I² = 11%						
Test for overall effect: Z = 0.26 (P = 0.79)						
Test for subgroup differences: Chi² = 1.65, df = 1 (P = 0.20), I² = 39.4%						

Favours [PESA] Favours [TESA]
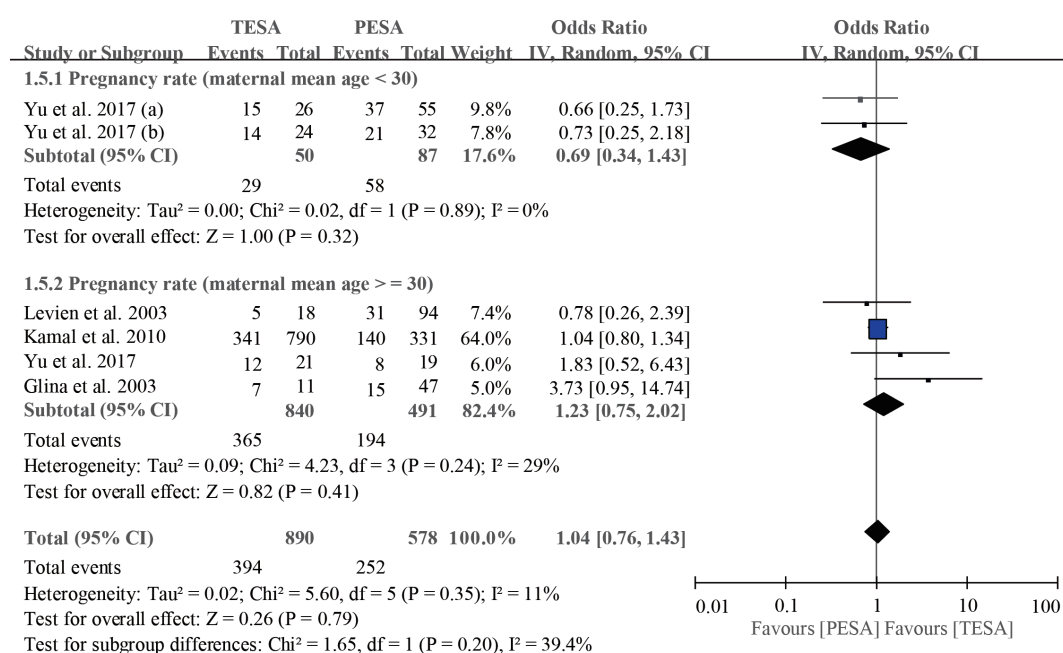(0.01   0.1   1   10   100)

Figure S2 Forest plot of pregnancy rates (stratified by maternal mean age). TESA, testicular sperm aspiration; PESA, percutaneous epididymal sperm aspiration; CI, confidence interval.
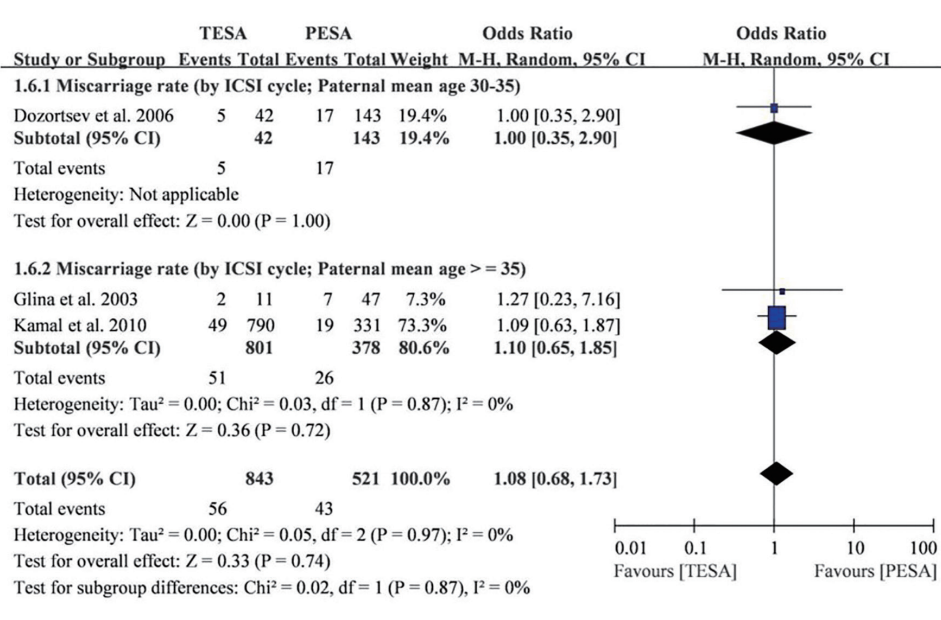
Figure S3 Forest plot of miscarriage rates. TESA, testicular sperm aspiration; PESA, percutaneous epididymal sperm aspiration; CI, confidence interval.
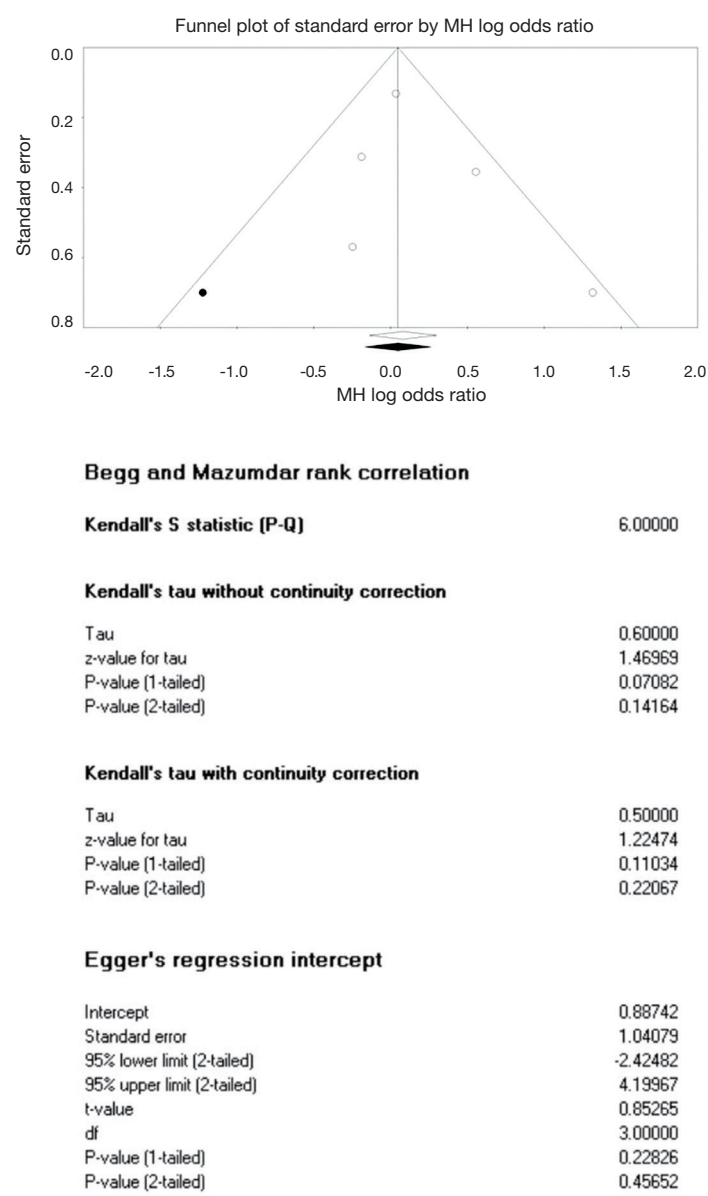

Figure S4 Small study effect test.