Comparison of microdissection testicular sperm extraction, conventional testicular sperm extraction, and testicular sperm aspiration for nonobstructive azoospermia: a systematic review and meta-analysis

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Objective: To investigate the relative differences in outcomes among microdissection testicular sperm extraction (micro-TESE), conventional testicular sperm extraction (cTESE), and testicular sperm aspiration (TESA) in men with nonobstructive azoospermia.
Design: Systematic review and meta-analysis.
Setting: Outpatient academic and private urology clinics.
Patients(s): Men with nonobstructive azoospermia.
Intervention(s): Micro-TESE, cTESE, or TESA.
Main Outcome Measure(s): Sperm retrieval (SR).
Result(s): Fifteen studies with a total of 1,890 patients were identified. The weighted average age of the patients was 34.4 years, the follicular stimulating hormone level was 20.5 mIU/mL, the T was 373 ng/dL, and the testicular volume was 13.5 mL. In a direct comparison, performance of micro-TESE was 1.5 times more likely (95% confidence interval 1.4–1.6) to result in successful SR as compared with cTESE. Similarly, in a direct comparison, performance of cTESE was 2.0 times more likely (95% confidence interval 1.8–2.2) to result in successful SR as compared with TESA. Because of inconsistent reporting, evaluation of other procedural characteristics and pregnancy outcomes was not possible.
Conclusion(s): Sperm retrieval was higher for micro-TESE compared with cTESE and for cTESE compared with TESA. Standardization of reported outcomes as well as combining all available SR data would help to further elucidate the SRs of these procedures. (Fertil Steril® 2015;104:1099–103. ©2015 by American Society for Reproductive Medicine.)
Key Words: Meta-analysis, microdissection testicular sperm extraction, nonobstructive azoospermia, sperm retrieval, testicular sperm aspiration

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Testicular sperm retrieval (SR) is performed for men with nonobstructive azoospermia (NOA) and is combined with intracytoplasmic sperm injection (ICSI) to allow them to father biological children. Testicular sperm aspiration (TESA) (1, 2),

conventional testicular sperm extraction (cTESE) (3–5), and microdissection-TESE (micro-TESE) (6, 7) are techniques used to retrieve sperm in men with NOA. Sperm retrieval "rates" (i.e., the percentages of postprocedural SR) vary according to the technique used, the patient population, and the skill of the surgeon. Micro-TESE has become popular because spermatogenesis in men with NOA is often only found in small foci (8, 9).

A previously published systematic review compared the outcomes of cTESE with those of micro-TESE but was limited in that it did not include TESA (10). Similarly, many of the other available studies that compared SR techniques often included patients who only underwent a retrieval technique if they had failed a previous attempt with a different technique, thus biasing the data. Although there does exist great heterogeneity in both the patient population that comprises men with NOA as well as in the processing techniques used after SR is performed, to our knowledge no meta-analysis comparing all three of these SR techniques has been performed. To address the shortcomings in the literature, we performed a comprehensive systematic review and meta-analysis comparing all three SR techniques for NOA: TESA, cTESE, and micro-TESE.

MATERIALS AND METHODS

Study Design

This study was a systematic review and meta-analysis. An a priori protocol was written and agreed to by the authors to include study design, search strategy, inclusion and exclusion criteria, primary outcomes, statistical methods, and assessment for bias in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Literature Search

English-language studies reporting on outcomes of TESA or TESE for SR in men with NOA published between 1988 and 2015 were sought by electronic search of MEDLINE, scanning the reference lists of identified articles, and correspondence with study investigators. The computer-based search terms are shown in Supplemental Table 1 (available online).

Study Selection

Studies were eligible for inclusion if they involved SR from men with NOA, performed multiple methods of SR on the same patient as long as the performance of one method was not dependent on the outcome of another, and compared at least two of the three retrieval methods being studied (TESA, cTESE, or micro-TESE). Studies were excluded if they did not compare more than one technique, included men with obstructive azoospermia (OA) who could not be removed from the analysis to only examine the outcomes of men with NOA, or preformed two comparative techniques sequentially (i.e., a man would only get a second procedure if sperm was not retrieved in the first procedure). If multiple publications reporting on the same patient population were identified, only the latest study was included.

Data Collection

The following information was independently extracted by two reviewers from each article using a standardized form: study population (including population source, sampling method used, sample size, and demographic characteristics); geographic location; publication year; mean patient age at the time of surgery; FSH level; total T; testicular volume; definition of SR; and number of patients from whom sperm was retrieved. Of note, these variables were not required for inclusion in the meta-analysis.

Data Synthesis

All analyses were performed using only within-study comparisons to limit possible biases. The mean ages at TESA or TESE reported by each study were combined and summarized using an arithmetic mean weighted by study sample size. Sperm retrievals and 95% confidence intervals (CIs) for the use of TESA, cTESE, or micro-TESE were calculated to summarize the results of each study. Meta-analysis was performed using a random effects model. The consistency of findings across studies was assessed using Cochrane's Q test and the I^2 statistic. Publication bias was assessed by funnel plot. Statistical significance was defined as a two-tailed P value of $<.05$. Analyses were performed using R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Studies Included in the Systematic Review and Meta-analysis

Fifteen studies of 1,890 total patients were identified (Supplemental Fig. 1). The studies were published between 1997 and 2012. Six took place in Asia, four in Europe, three in North America, and two in Africa (Table 1). Reported sample sizes ranged from 14 to 543 patients undergoing TESA, cTESE, or micro-TESE. The weighted average age of the patients was 34.4 years, the FSH level was 20.5 mIU/mL, the T was 373 ng/dL, and the testicular volume was 13.5 mL. When described, a majority of the studies used immediate microscopic examination of the extracted testicular tissue, followed by further analysis to assess for the presence of sperm. The definition of successful SR used by the studies was not explicitly defined in the articles, although on the basis of the language of most studies, a single sperm that could be either preserved or used for IVF/ICSI constituted success.

Meta-analysis

In a direct comparison of cTESE to micro-TESE, the unadjusted SR was 35% for cTESE (95% CI 30%–40%; $\tau^2 = 0.02$; $P=.28$; $I^2 = 19\%$) and 52% for micro-TESE (95% CI 47%–58%; $\tau^2 = 0.04$; $P=.07$; $I^2 = 48\%$) (Fig. 1A). Therefore, performance of micro-TESE was 1.5 times more likely (95% CI 1.4–1.6) to result in successful SR as compared with cTESE. In a direct comparison of cTESE to TESA, the unadjusted SR was 56% for cTESE (95% CI 50%–61%; $\tau^2 = 0.02$; $P=.20$;

TABLE 1

Selected characteristics of the 15 studies included in this systematic review.

First author, year (reference)	Location	Average age of patients (y)	Average FSH (mIU/mL)	Average T (ng/dL)	Average testicular volume (mL)
Friedler, 1997 (11)	Zerifin, Israel	32.7	–	–	–
Ezeh, 1998 (12)	Sheffield, UK	–	18.5	–	30.4
Rosenlund, 1998 (13)	Sweden	–	–	–	–
Schlegel, 1999 (7)	New York, NY	–	–	–	–
Tournaye, 1999 (14)	Brussels, Belgium	–	–	–	–
Amer, 2000 (15)	Giza, Egypt	33.5	15	–	–
Okada, 2002 (16)	Kobe, Japan	–	–	–	–
Tsujimura, 2002 (17)	Osaka, Japan	32.4 in cTESE 33.9 in mTESE	22.6 in cTESE 24.0 in mTESE	440 in cTESE 370 in mTESE	7.2 in cTESE 8.6 in mTESE
Bettella, 2005 (18)	Padova, Italy	37.6	–	–	–
Ramasamy, 2005 (19)	New York, NY	–	22	316 in cTESE, 303 in mTESE	–
Hauser, 2006 (20)	Tel Aviv, Israel	–	–	–	–
El-Haggar, 2008 (21)	Cairo, Egypt	30.4	18.7	–	9.88 in mTESE, s9.94 in TESA
Colpi, 2009 (22)	New York, NY	–	–	–	
Ghalayini, 2011 (23)	Amman, Jordan	35.4 in cTESE, 34.8 in mTESE	–	390 in cTESE, 430 in mTESE	
Nowroozi, 2012 (24)	Tehran, Iran	33	21.7	450	14.8

Bernie. Comparison of micro-TESE, cTESE, and TESA. Fertil Steril 2015.

$I^2 = 31\%$) and 28% for TESA (95% CI 19%–39%; $\tau^2 = 0.27$; $P<.01$; $I^2 = 80\%$) (Fig. 1B). Therefore, performance of cTESE was 2.0 times more likely (95% CI 1.8–2.2) to result in successful SR as compared with TESA. Because of inconsistent reporting, analysis of other patient characteristics and outcomes (e.g., pregnancy) was not possible. As noted above, marked heterogeneity was evident in the meta-analysis of TESA results. Relatively few small study effects were noted by funnel plot comparing reported SRs against study sample sizes (plots would be skewed and asymmetrical if substantial biases were present) (Supplemental Fig. 2).

DISCUSSION

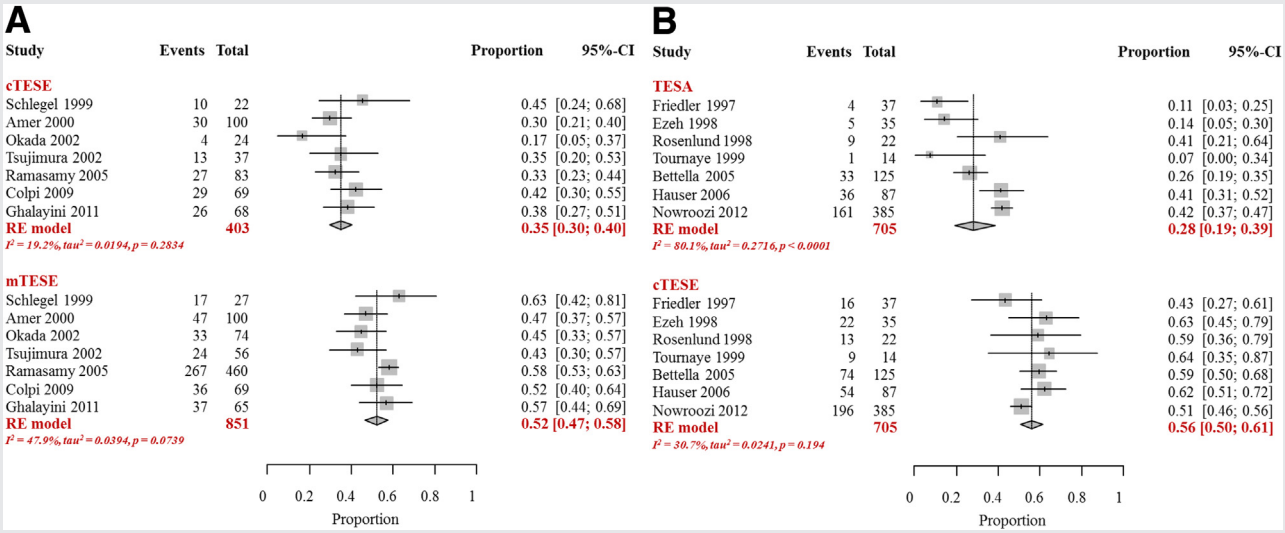
One percent of all men and 10% of men undergoing evaluation for infertility are diagnosed with NOA (25). These facts, combined with increased contemporary exposure and training in SR techniques among urologists, make it likely that more men with NOA will undergo SR followed by IVF/ICSI in the future.

In this systematic review and meta-analysis we found 15 articles that compared SR techniques in men with NOA. Sperm retrievals were higher in in micro-TESE compared with cTESE and in cTESE compared with TESA. Before this meta-analysis, it has generally been assumed in the literature that performing cTESE or micro-TESE in men with NOA would result in a higher SR than TESA, but the extent of this benefit was not certain. Our findings suggest that micro-TESE was 17% better than cTESE in studies that compared the two techniques. Conventional TESE is approximately two times better (or an absolute increase of 28%) than TESA for SR. This SR may actually be artificially lowered by the fact that many men undergoing micro-TESE have failed a previous TESA or cTESE, suggesting that if all men treated with NOA were naïve to a previous procedure, the difference between micro-TESE and cTESE might be even more pronounced.

A strength of our analysis is that we limited our studies to those that made direct comparisons between different SR techniques. Despite this, our meta-analysis has several important limitations. First, there was no way to control for the tissue processing techniques used after SR in the studies analyzed. The embryologist, laboratory, and techniques used to process tissue after SR can lead to an extremely varied success rates. For example, some studies required repeat extended preparation of semen analyses on the day of planned SR that can identify sperm in up to 35% of previously azoospermic men (26). This difference in sperm processing can lead to extremely varied SR outcomes.

Another limitation of this meta-analysis is the patient heterogeneity that exists in the population of men diagnosed with NOA. Depending on the underlying cause of NOA or the pathology present, these patients can have widely varied SR outcomes. Because many of the studies included did not extensively discuss their patient selection methods, we cannot exclude the possibility that the patient populations may have varied between studies. Although we found that micro-TESE and cTESE were both better than TESA in terms of SR in men with NOA, and that micro-TESE was better than cTESE, the

FIGURE 1



(**A**) Meta-analysis of the association of cTESE vs. micro-TESE with SR outcome for men with nonobstructive azoospermia. (**B**) Meta-analysis of the association of TESA vs. cTESE with SR outcome for men with nonobstructive azoospermia.

Bernie. Comparison of micro-TESE, cTESE, and TESA. Fertil Steril 2015.

studies synthesized had heterogeneous populations with varying perioperative characteristics and serum markers. Last, practice patterns and differing surgeon skill levels often make it difficult to know the true differences between the SRs for these procedures. For example, many of the urologists performing TESA as their method of SR may have been doing so because of a lack of training or skill with other techniques. This may cause a falsely lowered SR for TESA, which could actually have more success in the hands of a skilled and highly trained urologist. In summary, although this meta-analysis has provided the most comprehensive coverage of this topic yet, it relies on aggregated published data.

We identified two different SRs for cTESE (56% in the studies that compared it with TESA and 35% in those that compared it with micro-TESE). These results should not be viewed as an absolute determination of treatment success, but rather should be interpreted within the context of the comparisons being made. To determine a truly accurate SR for these techniques, we would need to summarize every study ever published with SR outcomes, not just studies of direct comparisons between procedures.

The choice of SR procedure to perform in a man with NOA is not only dependent on the predicted SR, but also should be guided by previous procedure history, knowledge of testicular pathology, potential for postoperative complications, cost of the procedure, and knowledge and skill of the surgeon. As mentioned, many men undergoing micro-TESE have had previous unsuccessful retrieval procedures. Similarly, if a man has had a previous retrieval procedure or biopsy and is known to have favorable pathology such as hypospermatogenesis, then starting with TESA may be a prudent decision because it can be performed in the office rather than the operating room, with less cost to the patient.

Although micro-TESE provided the highest SR in this analysis, we do not necessarily recommend that this be the only method of SR performed in men with NOA. Because of the heterogeneity that likely exists in both patient population as well as laboratory processing of samples, we recommend that future investigators use prospective analyses and report well-defined preoperative characteristics and serum markers, as well as to delineate how selection of a SR technique was made. Studies with standardized reporting may allow for a better understanding of the true differences in SRs for each technique in men with NOA, as well as help to delineate when it may be reasonable to perform a particular procedure.

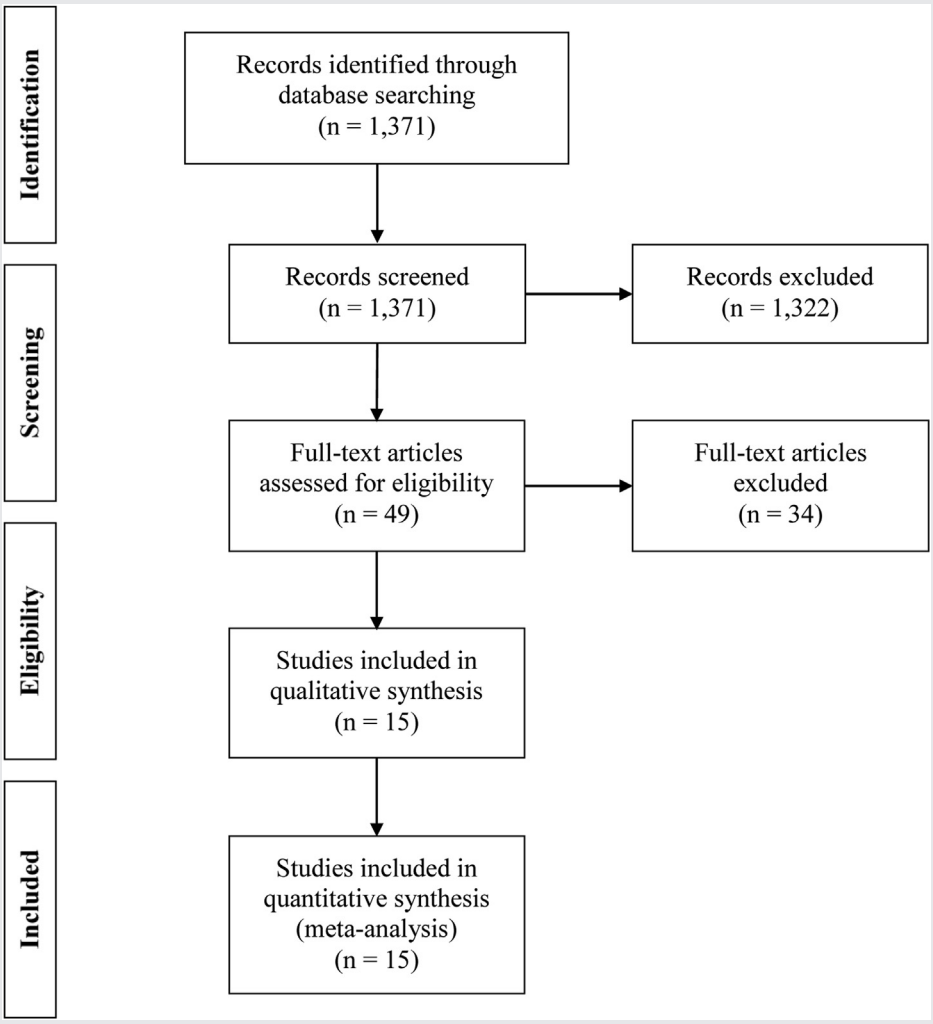
In conclusion, in studies that provided comparative analyses of SR in men with NOA, micro-TESE was superior to cTESE, and cTESE was superior to TESA. Standardization of reported outcomes as well as combining all available SR data available would help to further elucidate the success of each of these procedures.

REFERENCES

1. Craft I, Bennett V, Nicholson N. Fertilising ability of testicular spermatozoa. Lancet 1993;342:864.
2. Lewin A, Weiss DB, Friedler S, Ben-Shachar I, Porat-Katz A, Meirow D, et al. Delivery following intracytoplasmic injection of mature sperm cells recovered by testicular fine needle aspiration in a case of hypergonadotropic azoospermia due to maturation arrest. Hum Reprod 1996;11:769–71.
3. Devroey P, Liu J, Nagy Z, Goossens A, Tournaye H, Camus M, et al. Pregnancies after testicular sperm extraction and intracytoplasmic sperm injection in non-obstructive azoospermia. Hum Reprod 1995;10:1457–60.
4. Schoysman R, Vanderzwalmen P, Nijs M, Segal L, Segal-Bertin G, Geerts L, et al. Pregnancy after fertilisation with human testicular spermatozoa. Lancet 1993;342:1237.

5. Silber SJ, Nagy Z, Liu J, Tournaye H, Lissens W, Ferec C, et al. The use of epididymal and testicular spermatozoa for intracytoplasmic sperm injection: the genetic implications for male infertility. Hum Reprod 1995;10:2031–43.
6. Schlegel PN, Li PS. Microdissection TESE: sperm retrieval in non-obstructive azoospermia. Hum Reprod Update 1998;4:439.
7. Schlegel PN. Testicular sperm extraction: microdissection improves sperm yield with minimal tissue excision. Hum Reprod 1999;14:131–5.
8. Hauser R, Botchan A, Amit A, Ben Yosef D, Gamzu R, Paz G, et al. Multiple testicular sampling in non-obstructive azoospermia–is it necessary? Hum Reprod 1998;13:3081–5.
9. Chan PT, Schlegel PN. Nonobstructive azoospermia. Curr Opin Urol 2000; 10:617–24.
10. Deruyver Y, Vanderschueren D, Van der Aa F. Outcome of microdissection TESE compared with conventional TESE in non-obstructive azoospermia: a systematic review. Andrology 2014;2:20–4.
11. Friedler S, Raziel A, Strassburger D, Soffer Y, Komarovsky D, Ron-El R. Testicular sperm retrieval by percutaneous fine needle sperm aspiration compared with testicular sperm extraction by open biopsy in men with non-obstructive azoospermia. Hum Reprod 1997;12:1488–93.
12. Ezeh UI, Moore HD, Cooke ID. A prospective study of multiple needle biopsies versus a single open biopsy for testicular sperm extraction in men with non-obstructive azoospermia. Hum Reprod 1998;13:3075–80.
13. Rosenlund B, Kvist U, Ploen L, Rozell BL, Sjoblom P, Hillensjo T. A comparison between open and percutaneous needle biopsies in men with azoospermia. Hum Reprod 1998;13:1266–71.
14. Tournaye H. Surgical sperm recovery for intracytoplasmic sperm injection: which method is to be preferred? Hum Reprod 1999;14(Suppl 1):71–81.
15. Amer M, Ateyah A, Hany R, Zohdy W. Prospective comparative study between microsurgical and conventional testicular sperm extraction in non-obstructive azoospermia: follow-up by serial ultrasound examinations. Hum Reprod 2000;15:653–6.
16. Okada H, Dobashi M, Yamazaki T, Hara I, Fujisawa M, Arakawa S, et al. Conventional versus microdissection testicular sperm extraction for nonobstructive azoospermia. J Urol 2002;168:1063–7.
17. Tsujimura A, Matsumiya K, Miyagawa Y, Tohda A, Miura H, Nishimura K, et al. Conventional multiple or microdissection testicular sperm extraction: a comparative study. Hum Reprod 2002;17:2924–9.
18. Bettella A, Ferlin A, Menegazzo M, Ferigo M, Tavolini IM, Bassi PF, et al. Testicular fine needle aspiration as a diagnostic tool in non-obstructive azoospermia. Asian J Androl 2005;7:289–94.
19. 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.
20. Hauser R, Yogev L, Paz G, Yavetz H, Azem F, Lessing JB, et al. Comparison of efficacy of two techniques for testicular sperm retrieval in nonobstructive azoospermia: multifocal testicular sperm extraction versus multifocal testicular sperm aspiration. J Androl 2006;27:28–33.
21. El-Haggar S, Mostafa T, Abdel Nasser T, Hany R, Abdel Hadi A. Fine needle aspiration vs. mTESE in non-obstructive azoospermia. Int J Androl 2008;31: 595–601.
22. Colpi GM, Colpi EM, Piediferro G, Giacchetta D, Gazzano G, Castiglioni FM, et al. Microsurgical TESE versus conventional TESE for ICSI in non-obstructive azoospermia: a randomized controlled study. Reprod Biomed Online 2009; 18:315–9.
23. Ghalayini IF, Al-Ghazo MA, Hani OB, Al-Azab R, Bani-Hani I, Zayed F, et al. Clinical comparison of conventional testicular sperm extraction and microdissection techniques for non-obstructive azoospermia. J Clin Med Res 2011;3:124–31.
24. Nowroozi MR, Ahmadi H, Ayati M, Jamshidian H, Sirous A. Testicular fine-needle aspiration versus testicular open biopsy: comparable sperm retrieval rate in selected patients. Indian J Urol 2012;28:37–42.
25. Su LM, Palermo GD, Goldstein M, Veeck LL, Rosenwaks Z, Schlegel PN. Testicular sperm extraction with intracytoplasmic sperm injection for nonobstructive azoospermia: testicular histology can predict success of sperm retrieval. J Urol 1999;161:112–6.
26. Ron-El R, Strassburger D, Friedler S, Komarovski D, Bern O, Soffer Y, et al. Extended sperm preparation: an alternative to testicular sperm extraction in non-obstructive azoospermia. Hum Reprod 1997;12:1222–6.

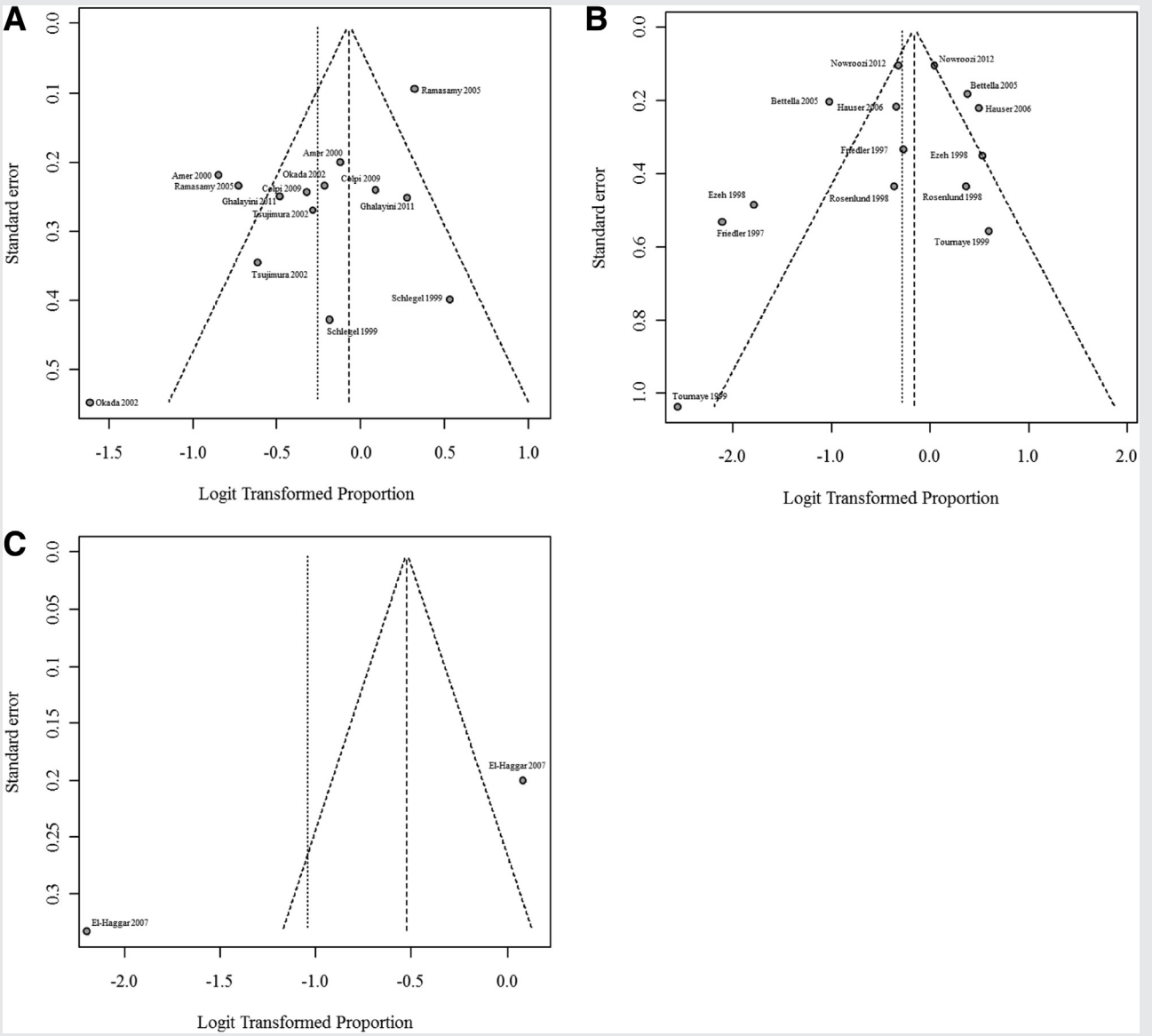
SUPPLEMENTAL FIGURE 1



PRISMA flow diagram of study selection.

Bernie. Comparison of micro-TESE, cTESE, and TESA. Fertil Steril 2015.

SUPPLEMENTAL FIGURE 2



Funnel plot assessment of publication bias.

Bernie. Comparison of micro-TESE, cTESE, and TESA. Fertil Steril 2015.

SUPPLEMENTAL TABLE 1

MEDLINE search strategy used in the present review.

Individual search terms
1. Microdissection TESE
2. Micro-dissection TESE
3. Microdissection testicular sperm extraction
4. Micro-dissection testicular sperm extraction
5. MicroTESE
6. Sperm aspiration
7. Sperm extraction
8. Sperm Retrieval [MeSH]
9. TESA
10. TESE
11. Testicular sperm aspiration
12. Testicular sperm extraction
13. Testicular-sperm aspiration
14. Testicular-sperm extraction

Combined search
15. OR/1–14

Note: MeSH = Medical Subject Heading in MEDLINE.

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