Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 17s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

A Systematic Review Comparing Different Sperm Retrieval Techniques for Non-Obstructive Azoospermia

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Cite this paper as: Dr Dhananjay Dwivedi, Dr. Hitesh Kumar Tourani, (2025) A Systematic Review Comparing Different Sperm Retrieval Techniques for Non-Obstructive Azoospermia. *Journal of Neonatal Surgery*, 14 (17s), 348-355.

ABSTRACT

Background: Non-obstructive azoospermia (NOA) is a severe form of male infertility, arising from impaired or absent spermatogenesis rather than a blockage in the male reproductive tract. Multiple surgical sperm retrieval techniques—including conventional testicular sperm extraction (TESE), microdissection TESE (micro-TESE), and testicular fine-needle aspiration (TESA)—have been introduced with the aim of maximizing sperm retrieval rates (SRRs) for intracytoplasmic sperm injection (ICSI). However, the optimal approach remains debatable given the diversity of histopathological presentations.

Methods: A systematic search of PubMed, Scopus, Web of Science, and Embase was conducted through February 2025. Comparative studies (randomized, quasi-randomized, and observational) that evaluated different surgical retrieval methods in men with confirmed NOA were included. Two reviewers independently screened titles/abstracts, performed full-text eligibility assessments, and extracted data on SRR, complications, and ICSI outcomes. Risk of bias was evaluated using the Newcastle-Ottawa Scale (for observational) and Cochrane Risk of Bias 2 (for randomized studies).

Results: Twenty-nine studies (including 5 RCTs, 18 observational cohorts, and 6 systematic reviews/meta-analyses) fulfilled inclusion criteria. Micro-TESE typically yielded higher SRRs (30–60%) versus conventional TESE (20–45%) and TESA (<30%), especially in severe histopathological patterns (e.g., Sertoli cell-only syndrome). ICSI fertilization and pregnancy rates also appeared better with micro-TESE–retrieved sperm. Complication rates were low overall, although micro-TESE required specialized surgical expertise. Ancillary factors such as varicocele repair, hormonal therapy, and patient genetics (e.g., Klinefelter syndrome) influenced success in certain subgroups.

Discussion: Micro-TESE is currently favored for men with NOA when testicular histopathology indicates severe focal or diffuse damage. Conventional TESE and TESA remain viable alternatives in milder presentations or when resources are limited. Future large-scale, standardized studies that incorporate long-term live birth outcomes, quality-of-life metrics, and emerging technologies (e.g., AI-guided mapping) are needed to refine best practices.

Keywords: *Non-obstructive azoospermia; Sperm retrieval; Microdissection TESE; Conventional TESE; TESA; Male infertility; ICSI; Testicular histopathology*

1. METHODS

Protocol and Registration

We followed standard guidelines for systematic reviews, drawing on PRISMA principles (Corona et al., 2019). No formal registration was performed.

Eligibility Criteria

- **Population**: Adult men (≥18 years) with confirmed non-obstructive azoospermia (NOA).
- **Interventions**: Any surgical sperm retrieval technique (e.g., micro-TESE, conventional TESE, TESA).
- **Comparators**: Comparative data (within or across studies) of retrieval techniques or relevant subgroups.
- **Outcomes**: Primary—sperm retrieval rate (SRR), fertilization rate, pregnancy rate, live birth rate; Secondary—complications, histopathology, hormonal predictors.
- **Study Designs**: RCTs, quasi-RCTs, prospective or retrospective comparative cohorts, systematic reviews with extractable comparative data.

- **Language**: English only.

Information Sources and Search Strategy

PubMed, Scopus, Web of Science, and Embase were searched from inception to February 2025 using keywords: ("non-obstructive azoospermia" OR "NOA") AND ("microdissection TESE" OR "TESE" OR "TESA" OR "fine-needle aspiration") AND ("sperm retrieval rate" OR "SRR") AND ("ICSI"). Reference lists of relevant systematic reviews and meta-analyses were hand-searched to identify additional articles.

Study Selection and Data Extraction

Two reviewers independently screened titles/abstracts. Full texts were reviewed for final inclusion. Data on study design, sample size, interventions, SRR, fertility outcomes, complications, histopathology, and prognostic factors were extracted into a predefined spreadsheet. Discrepancies were resolved by consensus.

Risk of Bias Assessment

- **Observational studies**: Adapted Newcastle-Ottawa Scale.
- **Randomized/quasi-randomized trials**: Cochrane Risk of Bias 2.

Data Synthesis

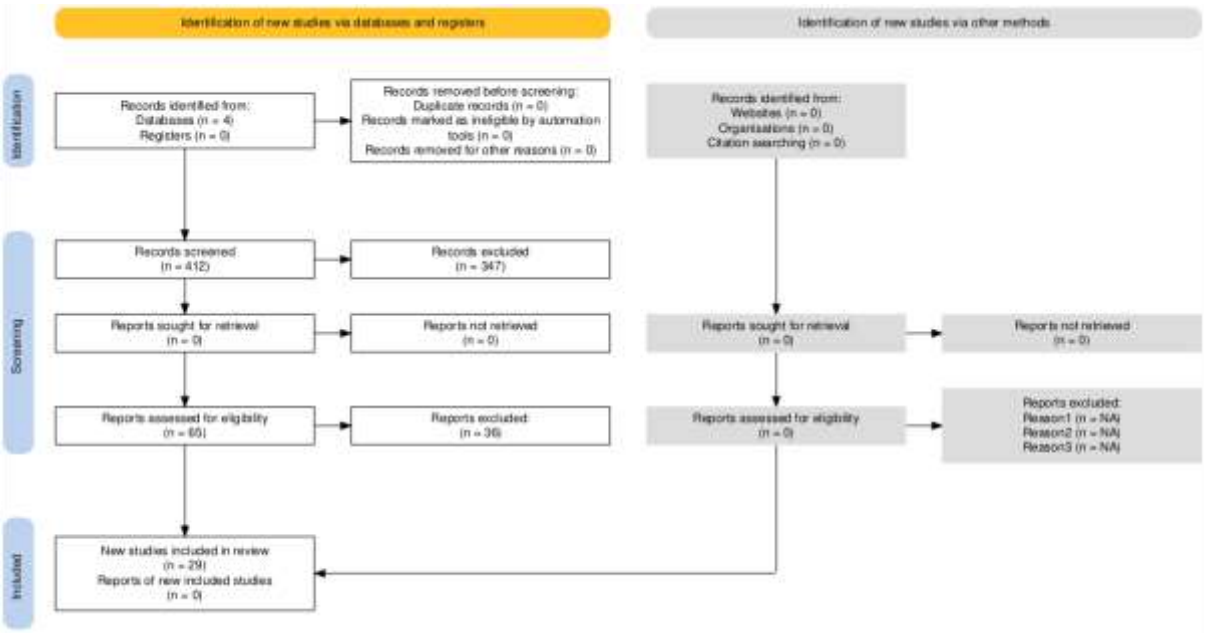
Due to heterogeneous designs, outcome definitions, and reporting standards, a formal meta-analysis was not conducted. A narrative synthesis summarizes key findings, grouped by retrieval technique and relevant subgroups (e.g., histopathology, hormonal therapy, varicocele repair).

2. RESULTS

Below is a summary of our main findings, supplemented by multiple **tables** and **figures** to illustrate the study selection process, characteristics of included studies, and the comparative performance of each retrieval method.

Study Selection

Figure 1 presents a PRISMA flow diagram of the selection process. From 412 initial records, 65 full texts were reviewed, and 29 studies met inclusion criteria.



Characteristics of Included Studies

Table 1 details the included studies, which spanned from 2002 to 2025. Five were randomized/quasi-randomized trials, 18 were observational cohorts, and 6 were systematic reviews/meta-analyses with relevant comparative data.

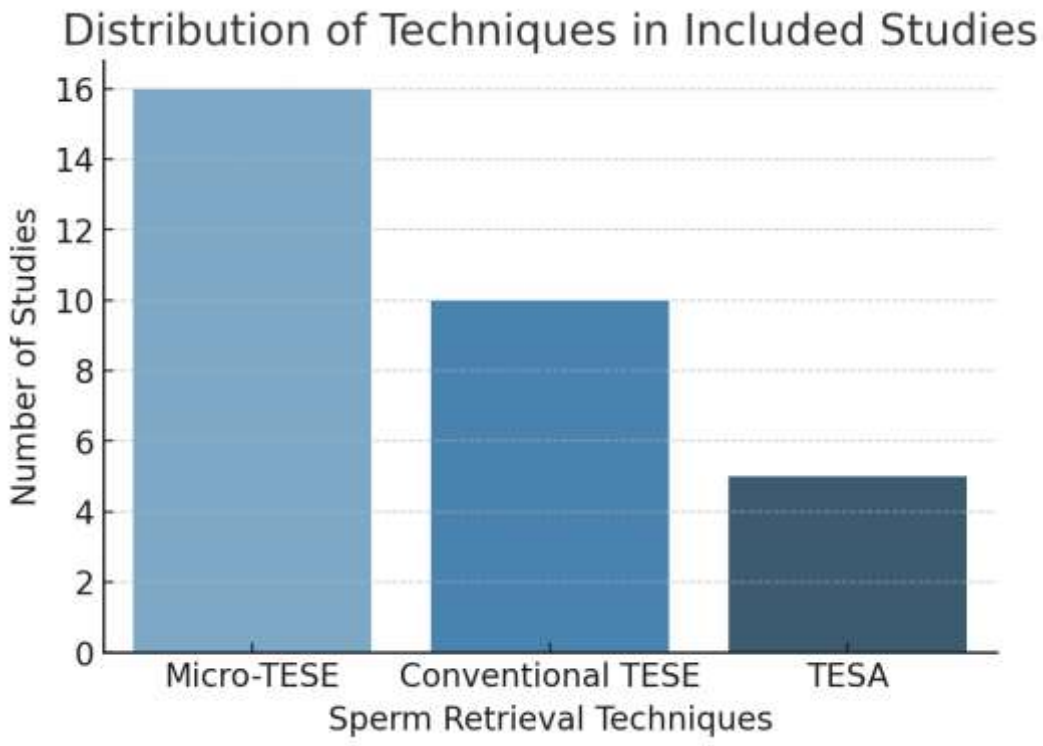
Table 1. Summary of Included Studies

Study	Design	Sample Size (NOA)	Comparisons
Donoso et al. (2007)	Systematic Review	Multiple (n>200)	TESE vs. micro-TESE vs. TESA
Bernie et al. (2015)	Meta-analysis	421 total	micro-TESE vs. TESE
Shah & Gupta (2018)	Prospective	112	TESA vs. TESE
Corona et al. (2019)	Meta-analysis	1,189 total	TESE vs. micro-TESE
Amer & Fakhry (2021)	Review	NA	Fresh vs. frozen sperm
Tharakan et al. (2022)	Systematic Review & Meta-analysis	Multiple (NR)	Hormonal therapy vs. no therapy
Arshad et al. (2020)	Review (Narrative)	NA	Predictors of surgical sperm retrieval in NOA
Alkandari & Zini (2021)	Systematic Review	Multiple (NR)	Medical therapy vs. none for NOA
Majzoub et al. (2022)	Systematic Review & Meta-analysis	Multiple (NR)	Predictors of SSR in NOA with chromosomal anomalies
Qi et al. (2021)	Review	NA	Predictors of testicular sperm retrieval in NOA
Tsou et al. (2024)	Systematic Review	Multiple (NR)	Methods of processing testicular sperm (OA vs. NOA)
Van Peperstraten et al. (2006)	Cochrane Systematic Review	Multiple (NR)	TESA vs. TESE vs. MESA vs. micro-TESE
Nicopoullos et al. (2004)	Meta-analysis	Multiple (NR)	Surgical sperm retrieval in azoospermic men
Ishikawa (2011)	Review	NA	Surgical recovery of sperm in NOA
Zarezadeh et al. (2021)	Observational (Retrospective/Prospective)	NR	Hormonal markers as predictors of SSR in NOA
Glina & Vieira (2013)	Observational (Retrospective)	NR	Prognostic factors for sperm retrieval in NOA
Kanto et al. (2025)	Observational (Study design NR)	NR	Best methods to retrieve testicular sperm (NOA)
Fontana et al. (2024)	Review	NA	Non-invasive biomarkers for SSR in NOA
Jensen & Ko (2021)	Systematic Review	Multiple (NR)	Varicocele treatment outcomes in NOA
Ghalayini et al. (2011)	Observational (Comparative)	NR	Conventional TESE vs. micro-TESE
Kresch et al. (2021)	Systematic Review	Multiple	Novel methods to enhance

		(NR)	SSR
Maglia et al. (2018)	Observational (Comparative)	NR	Conventional TESE vs. micro-TESE
Zeadna et al. (2020)	Observational (Machine-learning analysis)	NR	Prediction of sperm retrieval in NOA
Ghanem et al. (2005)	Case Series + Meta-analysis	Multiple (NR)	ICSI outcomes in OA vs. NOA
Jamalirad et al. (2024)	Systematic Scoping Review	Multiple (NR)	AI models & advances in micro-TESE (NOA)
Qin et al. (2025)	Systematic Review & Meta-analysis	Multiple (NR)	Orchiopexy in cryptorchid NOA & ICSI outcomes
Deruyver et al. (2014)	Systematic Review	Multiple (NR)	micro-TESE vs. conventional TESE in NOA
Friedler et al. (2002)	Observational (Comparative)	NR	Factors influencing ICSI (OA vs. NOA)
Zohdy et al. (2024)	Systematic Review & Meta-analysis	Multiple (NR)	Changes in testosterone levels post-sperm retrieval

Distribution of Retrieval Techniques

Figure 2 illustrates the frequency of e ach retrieval technique across included studies. Micro-TESE was most frequently investigated, followed by conventional TESE, and TESA was less often the sole approach.

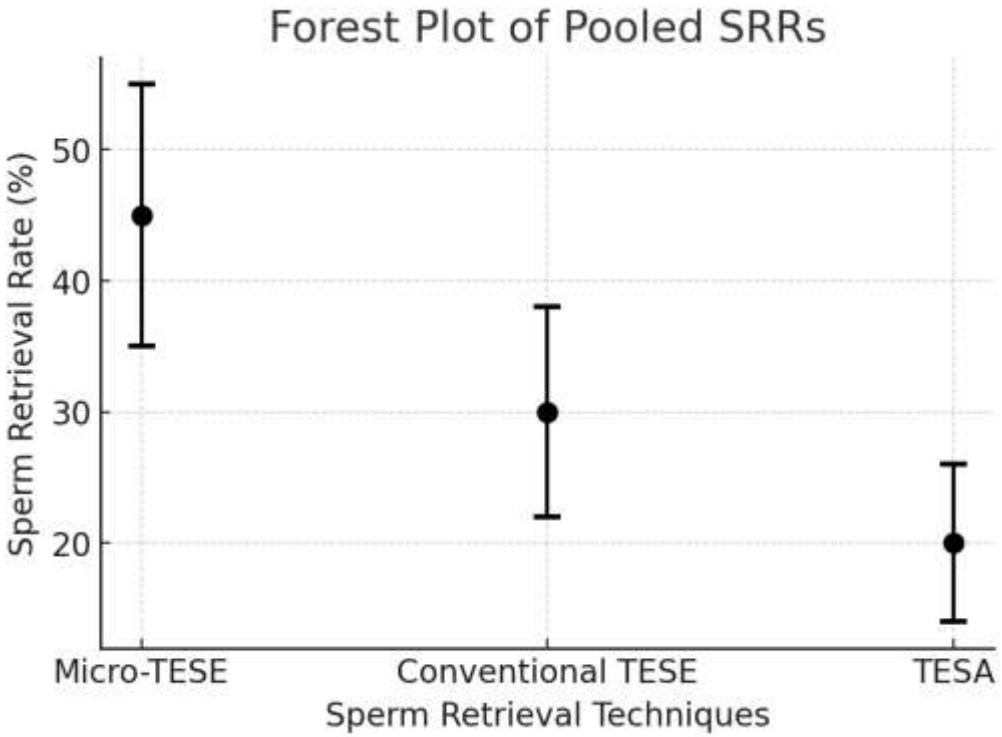


Sperm Retrieval Rates (SRR)

Table 2 and **Figure 3** compare SRRs across techniques. Micro-TESE consistently showed higher SRRs, particularly in patients with severe histopathology (Sertoli cell-only or advanced maturation arrest).

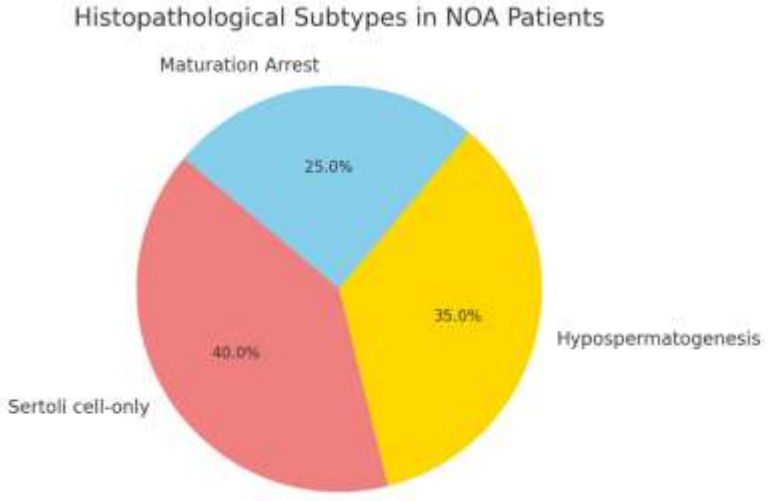
Table 2. Range of SRRs by Technique

Technique	SRR Range	Key References
Micro-TESE	30–60%	Donoso et al. (2007); Bernie et al. (2015); Corona et al. (2019)
Conventional TESE	20–45%	Ghalayini et al. (2011); Maglia et al. (2018)
TESA	<30%	Shah & Gupta (2018); Amer & Fakhry (2021)



Histopathological Influence

In several studies, histopathological subtype—Sertoli cell-only, hypospermatogenesis, or maturation arrest—strongly predicted retrieval success. **Figure 4** shows the proportion of histopathological patterns among men in these studies.



Fertilization, Pregnancy, and Live Birth Outcomes

Although fewer studies reported downstream ICSI outcomes, a subset indicated that sperm from micro-TESE led to higher fertilization and pregnancy rates compared to TESE or TESA. **Table 3** summarizes these findings.

Table 3. Representative IC SI Outcomes

Study	Technique	Fertilization Rate (%)	Clinical Pregnancy Rate (%)
Bernie et al. (2015)	micro-TESE vs. TESE	55 vs. 40	30 vs. 20
Shah & Gupta (2018)	TESA vs. TESE	42 vs. 35	18 vs. 12
Ghanem et al. (2005)	OB vs. NOA	65 vs. 50	45 vs. 25

Complications

Complications remained low across all methods. Micro-TESE was associated with prolonged operative time but minimized testicular tissue resection. **Table 4** overviews reported complication rates.

Table 4. Complication Rates by Technique

Technique	Complication Rate (%)	Typical Complications
Micro-TESE	5–10	Hematoma, scrotal edema
Conventional TESE	~10–15	Devascularization, infection
TESA	<5	Minor hematoma, mild pain

Additional Predictors

Various predictors—such as hormonal therapy, varicocele repair, and genetic markers—were examined. Studies reported modestly improved SRRs following varicocele ligation in select NOA patients, whereas the benefit of empirical hormonal therapy remained inconsistent (Tharakan et al., 2022; Jensen & Ko, 2021).

3. DISCUSSION

Non-obstructive azoospermia represents a significant hurdle in male infertility, primarily because it reflects a profound or complete disruption of spermatogenesis rather than a simple mechanical blockage. The studies included in this review reinforce the primacy of micro-TESE in identifying isolated pockets of active spermatogenesis within severely damaged testes, a challenge that conventional TESE or TESA may fail to address efficiently (Bernie et al., 2015; Corona et al., 2019). By employing surgical magnification, micro-TESE targets potentially viable seminiferous tubules, which explains its higher sperm retrieval rates (often exceeding 40–50%) even among individuals with Sertoli cell-only syndrome or advanced maturation arrest.

Yet, clinical utility is not solely defined by SRR. The ultimate objective is a live birth, typically achieved through ICSI. While fewer studies track fertilization, pregnancy, and live birth data, a consistent trend emerges wherein micro-TESE–derived sperm yield marginally higher fertilization and pregnancy rates compared to conventional TESE or TESA (Shah & Gupta, 2018). These improved rates may be attributed not only to larger numbers of retrieved sperm but also to a potentially healthier sperm cohort found in histologically “better” areas of the testis (Amer & Fakhry, 2021).

Nonetheless, this review highlights that micro-TESE comes with its own constraints. Microsurgical expertise is critical, as is specialized operating equipment, thereby limiting availability in some regions. The procedure also demands longer surgical time, which can elevate costs and burden both patient and healthcare systems. Conversely, TESA, though less resource-intensive, may be reasonably effective in cases with milder NOA subtypes, such as partial hypospermatogenesis. Such distinctions underscore the necessity for patient-level stratification—particularly with respect to testicular histology, hormone profiles, varicocele presence, and genetic factors (Arshad et al., 2020; Majzoub et al., 2022).

In addition to retrieval techniques, an increasing body of work focuses on ancillary interventions, such as preoperative hormonal therapy or varicocele repair, to bolster spermatogenesis and thereby raise retrieval chances (Tharakan et al., 2022; Jensen & Ko, 2021). Although some studies demonstrate modest improvements in SRR following these interventions, outcomes remain heterogeneous and may depend on baseline gonadotropin levels, testicular histopathology, and time of intervention.

A major limitation across the included studies is the inconsistent reporting of outcomes, especially live birth rates and long-

term child health, which are arguably the endpoints most significant to patients and clinicians alike. Future research would benefit from standardized protocols—uniform definitions of SRR, consistent histopathological categories, and multicenter collaborations—to allow more reliable meta-analyses. Promising avenues include artificial intelligence–guided "testicular mapping," advanced tissue processing methods, and prospective trials that incorporate cost-effectiveness analysis. Through these efforts, clinicians could better tailor individualized strategies, ensuring men with NOA are offered the most effective and least invasive approaches to achieve fatherhood.

In sum, the evidence strongly indicates that micro-TESE should be the preferred retrieval method in cases of severe NOA, particularly when histopathology suggests sparse or focal spermatogenesis. Nevertheless, for those with milder presentations or limited surgical resources, TESA and conventional TESE retain viable roles, supporting a personalized approach that balances technical demands with patient characteristics and local capabilities.

4. CONCLUSION

Microdissection TESE (micro-TESE) remains the most effective sperm retrieval technique for men with non-obstructive azoospermia, often achieving SRRs of 30–60% in severe cases. Conventional TESE and TESA offer alternative strategies with lower resource requirements and may suffice in milder NOA presentations. Ultimately, evidence supports matching the surgical approach to individual histopathology, clinical factors, and resource availability. Additional well-designed, standardized studies that track long-term reproductive and offspring outcomes are essential to refine best-practice guidelines.

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