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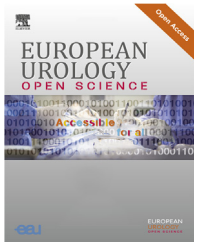

European Association of Urology

Review – Andrology

Role of Follicle-stimulating Hormone, Inhibin B, and Anti-Müllerian Hormone in Predicting Sperm Retrieval from Men with Nonobstructive Azoospermia Undergoing Microdissection Testicular Sperm Extraction: A Systematic Review and Meta-analysis

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Abstract

Background and objective: No clear-cut markers for predicting positive sperm retrieval (+SR) at microdissection testicular sperm extraction (mTESE) have been identified thus far. Our aim was to conduct a systematic review and meta-analysis to evaluate the ability of follicle-stimulating hormone (FSH), inhibin B (InhB), and anti-Müllerian hormone (AMH) to predict +SR in men with nonobstructive azoospermia (NOA) undergoing mTESE.

Methods: We performed a search in the PubMed, EMBASE, Web of Science, and Scopus databases according to the Preferred Reporting Items for Systematic Review and Meta-analysis statement. Thirty-four publications were selected for inclusion in the analysis.

Key findings and limitations: Overall, the mean +SR rate was 45%. Pooled standardized mean difference (SMD) values revealed significant hormonal differences between the +SR and −SR groups, with lower FSH (SMD −0.30), higher InhB (SMD 0.54), and lower AMH (SMD −0.56) levels in the +SR group. Pooled odds ratios (Ors) revealed no significant prediction of +SR by either FSH (OR 1.03, 95%

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confidence interval [CI] 1.00–1.06) or InhB (OR 1.01, 95% CI 1.00–1.02), despite variations in baseline levels and study heterogeneity. Conversely, AMH had significant predictive value (OR 0.82, 95% CI 0.73–0.92), with lower baseline levels in the +SR group. InhB and FSH levels were higher in the +SR group, while InhB exhibited the opposite trend.

Conclusions and clinical implications: Despite study heterogeneity, our meta-analysis findings support the ability of AMH to predict +SR for men with NOA undergoing mTESE.

Patient summary: We conducted a review and analysis of results from previous studies. Our findings show that for men with an infertility condition called nonobstructive azoospermia, blood levels of anti-Müllerian hormone can predict successful extraction of sperm using a microsurgical technique. Levels of two other hormones did not predict successful sperm extraction.

1. Introduction

Surgical testicular sperm extraction (TESE) is a crucial technique for sperm retrieval (SR) in men with nonobstructive azoospermia (NOA) [1–3]. Two primary TESE techniques are commonly used for SR: conventional TESE (cTESE) and microdissection TESE (mTESE) [1,2,4]. The latter has seen a surge in adoption among surgeons owing to its higher SR success rates and lower level of excisional damage in comparison to cTESE [5]. Nonetheless, a significant challenge persists owing to the absence of reliable clinical biomarkers to predict the likelihood of successful SR at mTESE in men with NOA [6,7]. While several studies have presented data on positive SR (+SR) rates in this setting, ranging from 30% to 60%, mTESE remains an unsuccessful and unnecessary procedure for a notable proportion of men with NOA [6,8,9]. Consequently, the decision to undergo mTESE often involves a delicate balance, considering the probabilities of success and failure as indicated by scientific literature or the specifics of the individual case. This uncertainty weighs heavily on both physicians and patients, causing unnecessary physical and emotional strain, further exacerbating the already challenging workup of male infertility. Over the years, many attempts have been made to identify adequate predictors of +SR [6]. The potential of various hormones as predictors of +SR, including follicle-stimulating hormone (FSH), inhibin B (InhB), and anti-Müllerian hormone (AMH), has been explored. The rationale behind the predictive capabilities of these hormones in SR is underscored by their pivotal involvement in spermatogenesis and their function as markers of Sertoli cell maturation [10]. Despite this rationale, conflicting results have emerged over the years. For instance, some studies identified FSH as a predictor of SR outcomes in men with NOA [8,11], whereas others failed to confirm this association [12–14]. Similar conflicting results have been observed for InhB [13–16]. More recently, serum AMH has emerged as a promising predictor of SR, with particular potential in cases of idiopathic NOA (iNOA), for which the underlying cause of azoospermia remains unknown [13]. Given these findings and recent insights, a systematic review and meta-analysis summarizing these studies is necessary to provide a higher level of evidence [13]. Thus, we conducted a systematic review and meta-analysis to investigate the role of FSH, InhB, and AMH in predicting SR in men with NOA undergoing mTESE.

2. Methods

2.1. Search strategy

We performed a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Fig. 1) [17]. The search was performed in the PubMed, EMBASE, Web of Science, and Scopus databases, querying studies up to July 30, 2023. The search string used was: ((“azoospermia” OR “azoospermic” OR “infertile men” OR “male infertility” OR “infertility” OR “ICSI” OR “intracytoplasmic sperm injection” OR “IVF” OR “in vitro fertilization” OR “ART” OR “assisted reproductive technology”) AND (“AMH” OR “anti-Mullerian Hormone” OR “FSH” OR “follicle stimulating hormone” OR “LH” OR “luteinizing hormone” OR “sexual hormones” OR “gonadotropins” OR “testosterone”)) AND (“mTESE” OR “micro-testicular sperm extraction” OR “TESE” OR “testicular sperm extraction”) AND (“sperm retrieval” OR “sperm recovery” OR “semen retrieval” OR “semen recovery”). Review articles, commentaries, editorials, non–peer-reviewed articles, and non-English studies were excluded. The systematic review and meta-analysis protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42023444202).

2.2. Study quality

The Newcastle and Ottawa Scale (NOS) was used to evaluate the risk of bias in nonrandomized studies. The NOS is designed to assess the quality of nonrandomized studies, particularly cohort and case-control studies. A star system is used to rate three broad categories: selection of study

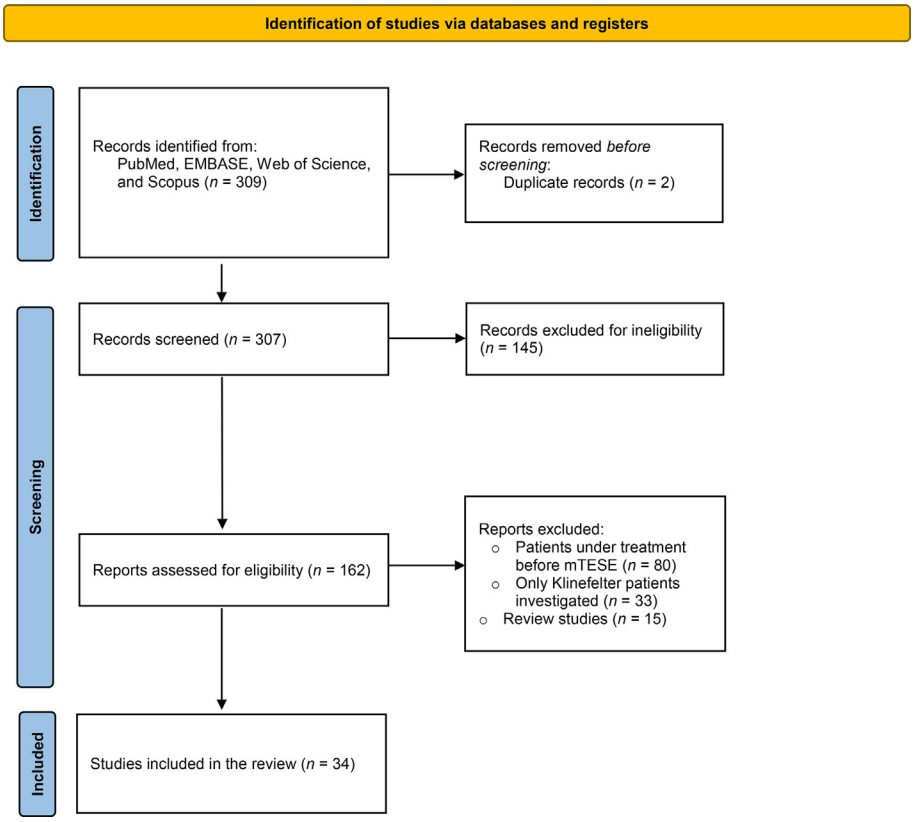

Fig. 1 – Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow chart showing the study selection process with inclusion and exclusion criteria for the studies reviewed.

groups, comparability of groups, and ascertainment of the outcome of interest (Supplementary Table 1).

2.3. Study selection criteria

Four authors (E.P., C.C., F.B., and A.B.) independently selected the studies for inclusion. Discrepancies were resolved via consensus among all co-authors. The study selection process followed specific inclusion and exclusion criteria. Studies were included if they assessed the role of serum FSH, InhB, and AMH in predicting SR outcomes in patients with NOA undergoing either cTESE or mTESE. Studies not published in English or not available in full-text form were excluded, as were studies that used preoperative hormonal treatment or provided data on salvage cTESE/mTESE or performed mTESE on men with Klinefelter syndrome. Studies reporting outcomes after cTESE were also excluded.

2.4. Variables and outcome definitions

The data collection process was structured using a predefined pro forma spreadsheet to gather essential information. This information included study population, age, type of surgery, SR outcomes, and preoperative levels of FSH, InhB, and AMH. Data on the birth rate were also gathered when reported. In addition, unadjusted odds ratios (ORs) and the corresponding confidence intervals (CIs) for SR prediction using FSH, InhB, and AMH were collected. The primary objectives of the study were to explore differences in preoperative hormone levels (FSH, InhB, and AMH) between the groups with positive (+SR) and negative (−SR) SR outcomes, and to investigate the predictive role of these hormones for SR.

To achieve these objectives, the study was designed using the PICOTS framework:

1. Population: men with NOA.
2. Intervention: mTESE.
3. Comparison: There was no comparison group in this study.
4. Outcome: association between preoperative levels of FSH, InhB, and AMH and +SR and their predictive ability for +SR at mTESE.
5. Timing: Not applicable.
6. Setting: Hospital setting.

2.5. Publication bias

Publication bias was assessed using contour-enhanced funnel plots, Begg's test, and Egger's test. When considering pooled standardized mean difference (SMD) values for preoperative hormone levels, heterogeneity and τ^2 results indicated differing levels of variability among the studies analyzed. FSH showed high heterogeneity and a substantial τ^2 value, suggesting significant variation in effect sizes and potential publication bias. By contrast, InhB and AMH exhibited moderate heterogeneity and lower τ^2 values, indicating less variability, but cautious interpretation is still

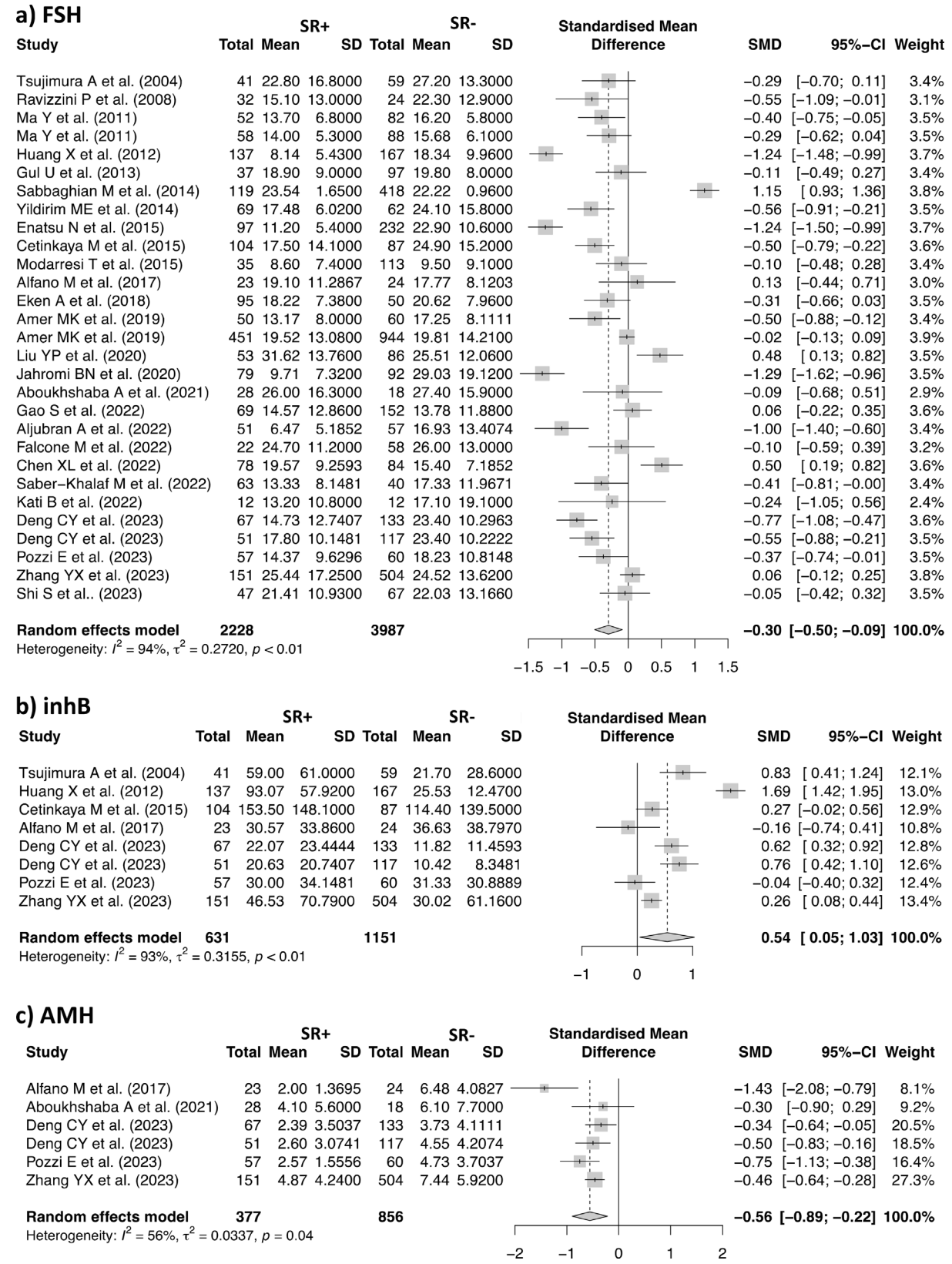

Fig. 2 – Pooled standardized mean difference (SMD) in preoperative (A) follicle-stimulating hormone (FSH), (B) inhibin B (InhB), and (C) anti-Müllerian hormone (AMH) levels between successful (SR+) and unsuccessful (SR-) sperm retrieval via microdissection testicular sperm extraction in patients with nonobstructive azoospermia. CI = confidence interval; SD - standard deviation.

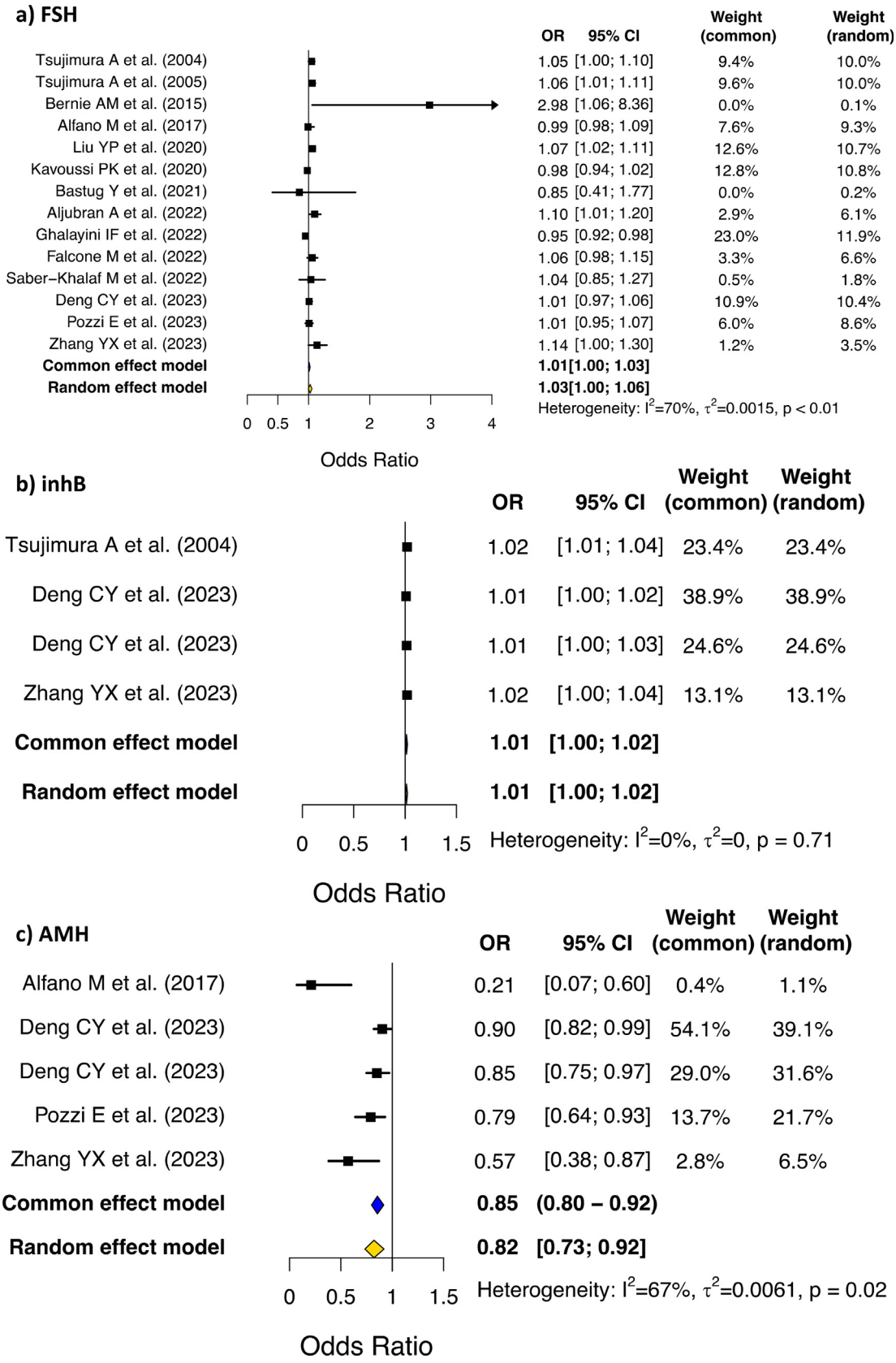

Fig. 3 – Pooled odds ratio (OR) from studies reporting the association between preoperative levels of (A) follicle-stimulating hormone (FSH), (B) inhibin B (InhB), and (C) anti-Müllerian hormone (AMH) and successful sperm retrieval via microdissection testicular sperm extraction in patients with nonobstructive azoospermia. CI = confidence interval.

required because of potential publication bias (Fig. 2). Pooled ORs from forest plots for preoperative hormone levels also revealed varying degrees of heterogeneity and potential publication bias. ORs for FSH and AMH showed considerable heterogeneity, suggesting potential publication bias, while ORs for InhB showed no heterogeneity, indicating little evidence of publication bias (Fig. 3). Lastly, contour plots demonstrated moderate publication bias among the studies included in our analysis, suggesting that the findings were partially influenced by selective reporting (Supplementary Fig. 1).

2.6. Statistical analysis

The statistical analysis consisted of several steps. First, descriptive data were collected to summarize the key characteristics of the studies. Specifically, data on patient age and preoperative hormone levels (FSH, InhB and AMH) were collected in terms of the mean and standard deviation (SD). In cases for which direct mean (SD) values were not available, transformation was applied to convert the median and interquartile range to the mean and SD, using the methods described by Wan et al [18]. Our aim with this systematic approach was to maintain uniformity in reporting pooled effect sizes for continuous variables. Second, we used unadjusted logistic multivariate analysis to confirm the findings. This involved extraction of estimated ORs and their respective CIs from each study for each hormone (FSH, InhB, and AMH). We also computed the standard error (SE) to quantify the magnitude of effect size using the 95% CI reported [19]. Forest plots of the relevant SMD or ORs and CIs from each study were generated as a visual representation of the effect size for each study and the overall pooled effect size for the continuous variables. To analyze the degree of heterogeneity for our primary outcome, we used the I^2 statistic. Given the limited number of studies reporting our parameters of interest, we opted for random-effects models and presented them alongside the common effect model for all the ORs analyzed. Lastly, we assessed publication bias using contour-enhanced funnel plots, Begg's test, and Egger's test to evaluate potential asymmetry and publication bias in the studies [20].

3. Results

3.1. Study selection and quality assessment

The search strategy identified a total of 309 studies from the PubMed and EMBASE databases. After excluding duplicates and applying the inclusion and exclusion criteria, 34 studies were selected for the meta-analysis (Table 1). Of these studies, 29 provided data on mean (SD) FSH levels, while the OR and 95% CI for the association of FHS with +SR was available

Table 1 – Data from the studies included in the systematic review and meta-analysis

Study	Year	Population	Sample size	SR (%)	Birth rate (%)
Tsujimura [22]	2004	NOA	100	41	–
Tsujimura [11]	2005	NOA	100	41	–
Ravizzini [37]	2008	NOA	56	57	28
Ma [38]	2011	NOA	134	39	–
Ma [39]	2011	NOA	146	40	–
Huang [40]	2012	NOA	304	45	–
Gul [41]	2013	NOA	134	28	51
Sabbaghian [42]	2014	NOA	537	22	3
Yildirim [43]	2014	NOA	131	53	53
Modarresi [44]	2015	NOA	148	24	9
Bernie [45]	2015	NOA	211	78	44
Cetinkaya [46]	2015	NOA	191	55	–
Enatsu [47]	2015	NOA	329	29	–
Alfano [12]	2017	NOA	47	49	–
Eken [48]	2018	NOA	145	66	–
Amer [49]	2019	NOA	1395	32	–
Amer [50]	2019	NOA	110	46	–
Jahromi [51]	2020	NOA	171	46	–
Kavoussi [24]	2020	NOA	72	71	25
Liu [23]	2020	NOA	139	38	–
Bastug [25]	2021	NOA	159	62	–
Aboukhshaba [52]	2021	NOA	46	61	–
Saber-Khalaf [29]	2022	NOA	103	61	–
Chen [53]	2022	NOA	162	48	67
Falcone [28]	2022	NOA	80	28	–
Aljubran [26]	2022	NOA	108	47	29
Ghalayini [27]	2022	NOA	134	60	–
Kati [54]	2022	NOA	24	50	–
Gao [55]	2022	iNOA	221	31	–
Deng [14]	2023	iNOA	168	30	–
Shi [56]	2023	iNOA	114	41	–
Deng [31]	2023	NOA	200	34	–
Zhang [30]	2023	NOA	655	23	–
Pozzi [13]	2023	iNOA	117	49	–

NOA = nonobstructive azoospermia; iNOA = idiopathic NOA; SR = sperm retrieval.

in only 14 studies. Eight studies included mean (SD) data for InhB, and four studies also provided OR (95% CI) data. Data on mean (SD) AMH values were available in six studies, with the OR (95% CI) assessed in five of these. Overall, the studies included a total of 6981 men (mean cohort size 203, range 24–1395), with a mean +SR rate of 45% (range 22–78%). The overall mean birth rate was 34% (range 9–67%). Results for quality assessment using the NOS indicate that the studies were generally of moderate to high quality, with a mean NOS score of 6 stars out of a maximum of 9 stars (Supplementary Table 1).

3.2. Synthesis of results

3.2.1. Follicle stimulating hormone

Pooled analysis revealed that preoperative FSH levels were significantly lower in the +SR group than in the −SR group (SMD −0.30, 95% CI −0.50 to −0.09; Fig. 2). However, the pooled OR of 1.03 (95% CI 1.00–1.06) did not confirm FSH as a predictor for +SR in men with NOA at mTESE (Fig. 3). Substantial heterogeneity was observed for the SMD (I^2 = 94%), indicating a high level of variability among the studies. The values of τ^2 = 0.2720 and p < 0.01 indicate significant heterogeneity. Moderate heterogeneity was observed for the pooled OR for FSH (I^2 = 70%), with τ^2 = 0.0015 and p < 0.01 indicating significant variation among the studies.

3.2.2. Inhibin B

No studies classified InhB as a predictor of +SR during mTESE for NOA. Baseline InhB were higher in the +SR group than in the −SR group (SMD 0.54, 95% CI 0.05–1.03; Fig. 2). However, the pooled OR (1.01, 95% CI 1.00–1.02) for the association between InhB and +SR failed to reach statistical significance (Fig. 3). Substantial heterogeneity was observed for the SMD (I^2 = 93%). The values of τ^2 = 0.3155 and p < 0.01 suggest a high level of variation among the studies. By contrast, minimal heterogeneity was observed for the OR for InhB (I^2 = 0%), indicating that the studies are relatively consistent in their findings. The values of τ^2 = 0 and p = 0.71 also suggest low heterogeneity.

3.2.3. Anti-Müllerian hormone

Analysis of AMH as a predictor of +SR yielded significant results. Baseline AMH was significantly lower in the +SR group than in the −SR group (SMD −0.56, 95% CI −0.89 to −0.22; Fig. 2). The pooled OR (0.82, 0.73–0.92) confirmed that AMH is a strong predictor for +SR (Fig. 3). Moderate heterogeneity was observed for the SMD (I^2 = 56%) and the OR (I^2 = 67%).

4. Discussion

Over the past 20 yr, surgical techniques for SR have significantly changed, leading to improvement +SR rates and minimization of testicular damage in men with NOA [5]. mTESE has emerged as a leading technique adopted by most fertility specialists owing to its overall superior benefits over cTESE. Despite the advantages of mTESE, SR is unsuccessful in a non-negligible proportion of NOA patients undergoing mTESE. Therefore, considerable efforts have been made to identify reliable predictors of successful SR in men with NOA [6]. Compelling evidence has accumulated from investigations of key hormones involved in spermatogenesis, such as FSH, InhB, and more recently, AMH. It is well established that spermatogenesis involves a complex interplay of hormones, among which FSH, InhB, and possibly AMH play a crucial role [10]. The causative factors encompass not only hormonal dynamics but also genetic disorders, including Y chromosome microdeletions and conditions such as Klinefelter syndrome [21]. For a notable subset of NOA cases, namely men with iNOA, there is no specific known etiology, further complicating understanding and prediction of SR at surgery [12,13]. This heterogeneity of causes has led to different and sometimes conflicting results among research groups trying to find predictors of +SR with cTESE and/or mTESE, which is further complicated by the rarity of the condition. Thus, study outcomes have been inconclusive for many years, highlighting the complexity of NOA.

Numerous studies have investigated the predictive potential of FSH [8,11–14,22–30]. Given that FSH directly stimulates Sertoli cells within the testes to initiate spermatogenesis, the hypothesis emerged that FSH levels might serve as an indicator of testicular function and thus of the success of SR at mTESE [10,21]. Conflicting results have emerged over time. For instance, Tsujimura et al [11,22] found that FSH was the most influential preoperative factor, together with InhB and total testosterone, in predicting SR. Aljubran et al [26] found that patient age and baseline serum FSH were independently associated with +SR among men with NOA undergoing mTESE. Conversely, more recent studies have found the opposite. For instance, Deng et al [14] found that FSH was not associated with SR at mTESE, and Pozzi et al [13] demonstrated a similar finding for iNOA cases. In this context, our meta-analysis of the pooled SMD revealed significantly higher preoperative FSH levels in the +SR group than in the −SR group (Fig. 2); however, the pooled OR did not confirm a significant association between FSH and +SR in men with NOA at mTESE (Fig. 3).

InhB has also been the focus of extensive research [14,22,30,31]. InhB is secreted by Sertoli cells and inhibits the secretion of FSH. It was initially hypothesized that InhB could offer a more precise representation of Sertoli cell function and thus spermatogenesis [10,21]. However, as for FSH, conflicting results for InhB as a predictive marker of +SR during mTESE have been obtained [14,22,30,31]. Our review identified no studies that classified InhB as a predictor of +SR at mTESE in men with NOA. However, pooled analysis for these studies revealed that men with +SR had lower InhB at baseline than men with −SR (Fig. 2). However, the pooled OR for the association between InhB and +SR did not reach statistical significance, reaffirming the need for more comprehensive research on InhB in this specific context (Fig. 3).

AMH has been the focus of increasing attention regarding its potential role in predicting successful SR at mTESE for men with either NOA or iNOA [12–14,30,31]. AMH is produced by Sertoli cells and is crucial for testicular development and function [32]. The role of AMH in adult males is not completely understood, but it is believed to correlate with spermatogenesis. As for InhB, AMH may be considered

as a marker of Sertoli cell maturation, whereby more immature cells produce more AMH than less immature cells, possibly reflecting the degree of spermatogenesis [21,33–36]. This led to the hypothesis that AMH levels could predict SR at mTESE. In 2017, Alfano et al [12] demonstrated for the first time that higher serum AMH levels and an elevated AMH/testosterone ratio could reflect depletion of the germ cell reservoir within the testis in men with iNOA. Specifically, serum levels of AMH and the AMH/total testosterone ratio emerged as more reliable biomarkers of +SR at mTESE, offering insights for future research. Studies by Deng et al [14] and Zhang et al [30] confirmed these findings. Notably, their investigations focused on the predictive role of AMH in iNOA and NOA more broadly. This underscores the potential of AMH to reflect spermatogenesis across a wider range of NOA etiologies. A recent multicenter collaborative study confirmed the role of AMH in predicting +SR in men with iNOA undergoing mTESE and the lack of predictive capability of FSH and InhB in this setting [13]. Our meta-analysis using the pooled SMD revealed that baseline AMH was significantly lower in the +SR group than in the −SR group (Fig. 2). In addition, the pooled OR confirmed AMH as a strong predictor for +SR (Fig. 3).

These findings have significant clinical implications for counseling of men with NOA regarding mTESE outcomes. Our meta-analysis provides solid evidence that AMH could be a valuable component in the diagnostic pathway for men with NOA. However, to firmly establish its utility and a more comprehensive understanding, further studies are needed for cross-validation and expansion of these promising results, possibly across different ethnicities and NOA subgroups. It is important to emphasize that our study deliberately excluded genetic causes of NOA, such as Y chromosome microdeletions and Klinefelter syndrome. We firmly believe that these specific categories warrant dedicated and focused research studies. The rarity of these conditions further highlights the challenge of conducting comprehensive research in these specific settings.

Our study is not devoid of limitations. First, despite excluding possible genetic-related causes, the notable heterogeneity in NOA etiologies represents a significant challenge. This heterogeneity arises from a variety of factors, including genetic mutations, environmental exposures, and other underlying conditions that contribute to the complexity of NOA. The diverse array of causative factors may have introduced variability into our results, making it challenging to draw definitive conclusions about the influence of FSH and InhB. Moreover, the different NOA etiologies make it difficult to pinpoint a single underlying cause, and this complexity might have affected the consistency of our findings. Second, the diversity in data reporting across the studies (Supplementary Table 1) might have influenced our findings. It is worth noting that some studies in our analysis did not report any genetic analysis results for their cohorts, potentially introducing significant biases in their results and ultimately in the pooled analysis. The lack of standardized reporting across these studies could have led to inconsistencies in the data, making it more challenging to synthesize the results effectively. The absence of genetic analysis in some studies further complicates the interpretation of the findings, as it is known that genetic factors play a significant role in NOA. Third, it is important to acknowledge potential variations in laboratory techniques used for hormone detection across the studies analyzed. Variability in hormone assay methods, reagents, and equipment used by different laboratories can introduce measurement errors, affecting the reliability and comparability of the data. These technical differences may have impacted the accuracy and consistency of our results, particularly concerning measurements of FSH, InhB, and AMH. Furthermore, the operator-dependent nature of mTESE must be considered, for which surgical skills could significantly influence mTESE outcomes. The expertise and experience of the surgeon performing mTESE are critical factors that can affect the SR success rate. Variations in surgical technique, skills, and intraoperative decision-making may have contributed to the heterogeneity in outcomes related to FSH and InhB. Therefore, it is essential to consider the potential influence of the surgeon's proficiency in future research, as this parameter could provide valuable insights into the variability in outcomes among patients with NOA.

Despite these limitations, this is the first systematic review and meta-analysis attempting to provide solid evidence regarding predictors of successful SR among men with NOA undergoing mTESE. Our findings offer valuable insights into the role of FSH, InhB, and AMH as potential predictors of successful SR despite the challenges posed by the complex and heterogeneous nature of NOA. Future research should aim to address these limitations and further investigate the impact of genetic, technical, and surgical factors on SR outcomes in men with NOA to enhance our understanding and clinical management of this condition.

5. Conclusions

The overall +SR rate at mTESE was 45%. Our systematic review and meta-analysis provide evidence that serum AMH is a predictor of +SR in men with NOA undergoing mTESE. Conversely, serum FSH and InhB did not predict +SR. While these results should be validated in more specific NOA subgroups for greater precision and applicability, it is important to note that this may not be feasible, as many studies did not adequately specify or investigate the factors that could have been used to categorize the NOA cohorts. In addition, there was variability among the selected studies, so our findings should be interpreted with caution.

Author contributions: Edoardo Pozzi and Christian Corsini had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Pozzi, Corsini
Acquisition of data: Pozzi, Corsini, Belladelli, Bertini
Analysis and interpretation of data: Pozzi, Corsini, Salonia
Drafting of the manuscript: Pozzi, Corsini
Critical revision of the manuscript for important intellectual content: Colecchia, Ramasamy, Montorsi, Alfano, Salonia.

Statistical analysis: Pozzi, Corsini.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2024.05.001.

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