

## ORIGINAL RESEARCH ARTICLE

# Follicle-stimulating hormone and Inhibin B as predictors of successful sperm retrieval in men undergoing testicular sperm extraction: A review of 44 cases and meta-analysis

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## Abstract

The aim of the study and meta-analysis was to evaluate the predictive value of follicle-stimulating hormone (FSH) and inhibin B in sperm retrieval in men with non-obstructive azoospermia (NOA). A total of 44 patients with a mean age of 36.1 years (SD=±6.17) was included. We had 19 patients with successful sperm retrieval and 25 with failure. All patients had a normal karyotype. There was no difference between groups regarding patients mean age, prolactin or FSH. Patients with successful sperm retrieval had a significantly higher inhibin B level (134.62(±64.35) vs. 72.36(±67.78), p=0.006) and, paradoxically a higher body weight (92.38(±11.38) vs. 83.76(±11.90), p=0.027). The forest plots showed that a higher FSH level was significantly correlated with a negative success rate. A higher Inhibin B level was associated with a higher successful sperm retrieval (p=0.00001 respectively, p=0.0002). Surgical sperm retrieval could be, in some cases, the only chance to have a biological offspring. (*Afr J Reprod Health* 2023; 27 [6]: 51-59).

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**Keywords:** Inhibin B, FSH, azoospermia, meta-analysis, TESE

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## Résumé

Le but de notre étude et méta-analyse a été d'évaluer la valeur prédictive de l'hormone folliculo-stimulante et de l'inhibine B dans la récupération de sperme chez les hommes avec NOA. Un total de 44 patients avec un âge moyen de 36,1 ans (SD=±6,17) a été inclus. Nous avons 19 patients avec un prélèvement de sperme réussi et 25 avec un échec. Tous les patients avaient un caryotype normal. Il n'y avait pas de différence entre les groupes concernant l'âge moyen des patients, la prolactine ou la FSH. Les patients dont la récupération de sperme a réussi avaient un taux d'inhibine B significativement plus élevé (134,62 (±64,35) contre 72,36 (±67,78), p = 0,006) et paradoxalement un poids corporel plus élevé (92,38 (±11,38) contre 83,76 (±11,90), p=0,027). Les graphiques en forêt ont montré qu'un niveau de FSH plus élevé était significativement corrélé à un taux de réussite négatif, tandis qu'un niveau d'inhibine B plus élevé était associé à une récupération de sperme plus réussie (p=0,00001 respectivement p=0,0002). Le prélèvement chirurgical de sperme pourrait être dans certains cas la seule chance d'avoir une progéniture biologique. (*Afr J Reprod Health* 2023; 27 [6]: 51-59).

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**Mots-clés:** Inhibine B, FSH, azoospermie, méta-analyse, TESE

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## Introduction

Although it is not a life-threatening condition, male infertility is recognised as a worldwide health problem. The definition of infertility by the World Health Organisation is the inability of a couple to conceive after at least 12 months of regular, unprotected sexual intercourse. According to Sun *et al.*, the prevalence of infertility increased annually by 0.291% in men between 1990

and 2017<sup>1</sup>. Couple infertility due to male factor ranges from 20% to 70%, according to Agarwal *et al.*, and the prevalence of infertile men ranges from 2.5% to 12% depending on the geographical area, with the highest in Africa and Central/Eastern Europe<sup>2</sup>. Before 1995, there was no medical solution for infertile couples in which the male partner was diagnosed with non-obstructive azoospermia (NOA). The introduction of new surgical techniques such as testicular sperm

extraction (TESE), micro-dissection testicular sperm extraction (mTESE) or microsurgical epididymal sperm aspiration (MESA) combined with subsequent intracytoplasmic sperm injection, allowed many couples with male factor infertility to have their own biological offsprings. Even with the advances in assisted reproductive techniques, in men with NOA a surgical sperm retrieval technique could be necessary. No technique could guarantee success, and because of this, it is important to identify predicting factors for sperm retrieval rate before surgery. Although widely studied, there is still no consensus regarding the efficacy of these factors. The hypothalamic-pituitary-gonadal axis significantly regulates the formation and maturation of sperm. Inhibin B, anti-Mullerian hormone (AMH), and testosterone are secreted from the testes when the hypothalamic gonadotropin-releasing hormone stimulates the anterior pituitary's production of gonadotropins, specifically follicle stimulating hormone releasing hormone and luteinizing hormone. Males' hypothalamic-pituitary-gonadal axis is significantly controlled by the dimeric glycoprotein hormone inhibin B, secreted by the testicular support cells. In adult males, serum Inhibin B levels were inversely associated with follicle-stimulating hormone (FSH), functioning as a negative-feedback on FSH. Although research has shown that serum inhibin B and AMH are more sensitive predictors of testicular spermatogenesis than serum FSH, their role as sensitive predictors of successful testicular sperm retrieval in NOA is still debated. Our meta-analysis aimed to evaluate the predictive value of follicle-stimulating hormone (FSH) and inhibin B in sperm retrieval in men with NOA.

## Methods

We have included patients referred to two infertility centres between January 2019 and August 2021. Patients had been diagnosed with infertility for at least a year. All patients had azoospermia in at least two spermograms and underwent TESE. All patients had a normal karyotype and no mutations in the CFTR gene. Tissue extraction was bilateral, taking six fragments from each testicle. Processing was performed on MHM-C medium (90166, Irvine Scientific), followed by mechanical maceration, centrifugation and microscopic examination by an

experienced embryologist. Depending on the outcome of the procedure, they were divided into two groups: Group A- patients with successful sperm retrieval after TESE and Group B- patients in which TESE failed to retrieve spermatozoa. We compared the age, body weight, FSH, prolactin, and Inhibin B levels between groups. For the dosing of the markers, the blood was collected in the morning on fasting patients. FSH and Prolactin were dosed by the immunochemical method with detection by electrochemiluminescence and Inhibin B by ELISA. Considering that the compared data were numerical and we had two groups, the statistical analysis was performed using the t-Student, a p-value of  $< 0.05$  was considered statistically significant. The SPSS.16 software was used.

## Ethical consideration

The Declaration of Helsinki's guiding principles are applied to data collecting. By completing an informed consent form, each patient consented to provide anonymous data and tissue samples for forthcoming research. The Ethics Committee approval was not requested, considering that it was a retrospective, non-interventional study. Before the trial began, all patients provided their written informed permission. Prior to analysis, all patient data was de-identified and anonymized.

## Meta-analysis

We performed this meta-analysis using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines. A systematic Medline and Embase databases were performed, using the following words: 'Inhibin B' [MeSH Terms] AND ('azoospermia' [All Fields] OR 'male infertility' [All Fields]) AND ('FSH' [All Fields]) AND ('azoospermia' [MeSH Terms] OR 'male infertility' [All Fields]). We excluded non-English language articles and those in which the full-text was unavailable. The main search, as well as screening for eligibility of titles, abstracts and full-text articles, was completed independently by two authors and any discrepancies were solved by consensus. We included articles where a sperm retrieval technique was used in men with NOA. Articles that included patients with diseases known to be responsible for male infertility (e.g.:

Klinefelter syndrome, Kartagener's syndrome, and history of chemotherapy) were excluded.

Heterogeneity in sperm retrieval rate was assessed using  $I^2$  statistics. To calculate the individual odds ratios (OR) and individual and pooled mean differences with corresponding 95% CI we used Review Manager (RevMan) [Computer program], Version 5.4, The Cochrane Collaboration, 2020. To calculate the mean difference, we compared the outcomes after sperm retrieval with inhibin B and FSH levels before sperm retrieval. We applied a random effect model standardly. Considering that all of the included studies are observational, we assessed the risk of bias using the Newcastle - Ottawa quality assessment scale.

## Results

A total of 44 patients aged between 26 and 59 years, with a mean age of 36.1 years (SD= +/- 6.17) was included. We had 19 patients in Group A and 25 in Group B. All patients had a normal karyotype. There was no difference between groups regarding patients mean age, prolactin or FSH. Patients with successful sperm retrieval had a significantly higher inhibin B level and paradoxically a higher body weight. The clinical and paraclinical features are shown in Table 1.

## Meta-analysis

Out of the 3980 results of the search, only 16 articles have been selected. The flowchart of selection is shown in Figure 1. The selected studies were published between 2000 and 2020, and included a total of 1837 patients with NOA. FSH level was solely studied in 4 articles (25%), inhibin B in 6 (37.5%) and both hormones in 6 (37.5%), as shown in Table 2.

We noticed an inverse relationship between FSH and Inhibin B serum level and spermatozoa retrieval rate. As shown in figure 2 and 3, a higher FSH level was significantly correlated with a negative success rate. In comparison, a higher Inhibin B level was associated with a higher successful sperm retrieval ( $p=0.00001$  respectively  $p=0.0002$ ). In our meta-analysis, the selected studies had a high heterogeneity ( $I^2=89\%$  respectively  $96\%$ ). Out of the 1837 patients, in 806

(43.87%) cases, successful sperm retrieval was reported. The risk of bias total score, assessed by the Newcastle-Ottawa scale, varied between 5 and 8, the mean risk of bias being 6.12, resulting in an average level of study quality.

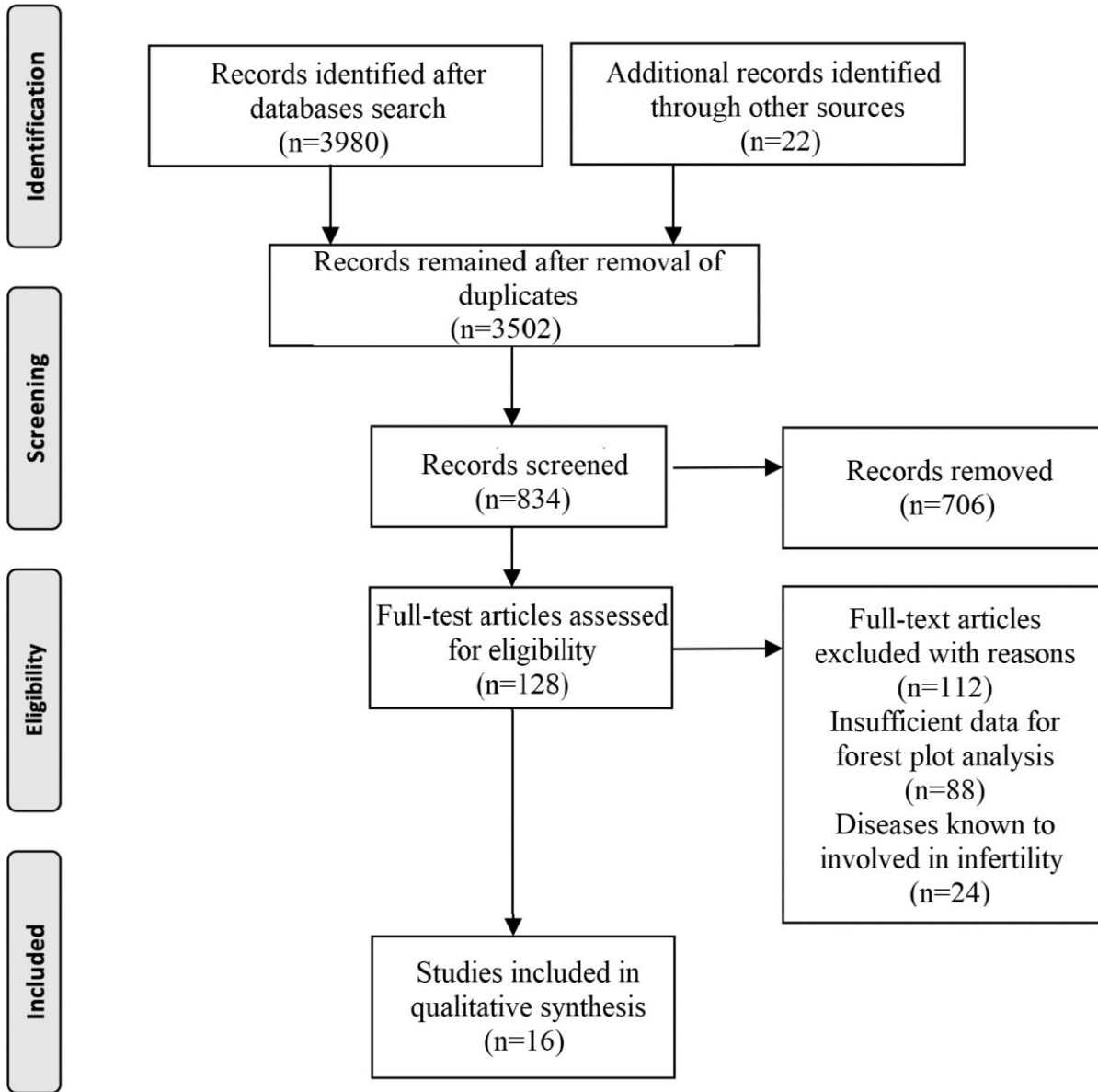
## Discussion

Spermatogenesis is a complex process and involves spermatogenesis-related genes and a neuroendocrine system for its regulation. Disturbances of any of these myriad of factors could lead to impairment of spermatogenesis and in some cases, it would result in azoospermia (absence of spermatozoa in the ejaculate). If this occurs, surgical sperm retrieval could be the only chance for the affected male to have a biological offspring. Although it could be considered a minor surgery, these procedures can lead to some complications like postoperative hypogonadism, haematoma, inflammation, or even devascularization. Besides genetic studies, some hormones could be prognostic makers for successful sperm retrieval, which would enable the identification of successful cases, thus avoiding unnecessary surgery. According to Meeker *et al.* inhibin B and FSH could be markers of spermatogenesis in patients with NOA<sup>19</sup>. The authors suggested that measuring the two hormones in serum could serve as a substitute for measuring semen quality. Inhibin B, of which normal values in males are between 120 and 400 ng/L, is a heterodimeric glycoprotein produced only by the testis. The production is stimulated by the secretion of FSH and it has negative feedback on FSH secretion<sup>20</sup>.

There is still a lack of consensus in the data from the literature regarding the efficacy of the two hormones. There is no clear low level of inhibin B for men considered fertile. In a group of 55 fertile men and 85 patients referred for infertility, Myers *et al.*, reported a mean "normal" value of 138 pg/mL, while Sikaris *et al.*, in a cohort of 124 healthy men with normozoospermia calculated a mean value of 180 pg/mL<sup>21,22</sup>. In a very large Chinese cohort of 25 481 with normal spermogram, Wang *et al.*, established a normal value of inhibin B between 87.42-299.93 pg/mL. The authors also noticed an association between inhibin B level and patient's age. Although the difference was not statistically significant, men  $\leq 20$  years had much

**Table 1:** Characteristics of included patients

Parameter	Group A	Group B	p
Mean age (years)( +/-SD)	36.74 +/-7.59	35.55 +/-4.74	0.27
Weight (kg) (+/-SD)	92.38 +/-11.38	83.76 +/-11.90	<b>0.027</b>
Prolactin (µg/L) (+/-SD)	107.89 +/-154.41	238.54 +/-439.44	0.20
FSH (mIU/mL) (+/-SD)	9.69 +/-6.95	11.91 +/-7.69	0.11
Inhibin B (ng/L) (+/-SD)	134.62 +/-64.35	72.36 +/-67.78	<b>0.006</b>



**Figure 1:** Flowchart of the study selection

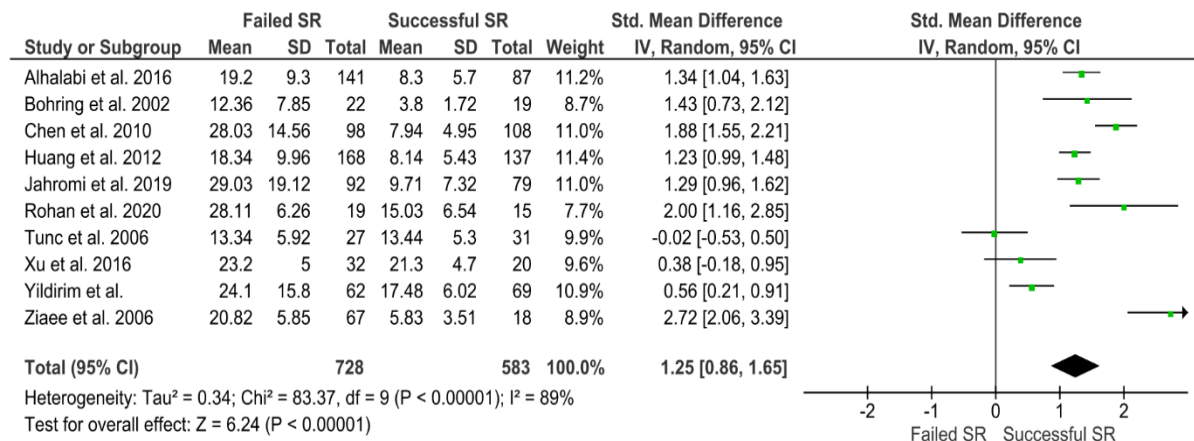
higher inhibin B levels compared to those >50 years old<sup>23</sup>. A reason for this discrepancy, according to Myers *et al.*, was the different assay protocols. One technique use treatment simultaneous with sample

incubation, and another one uses an extensive boiling pre-treatment process<sup>21</sup>.

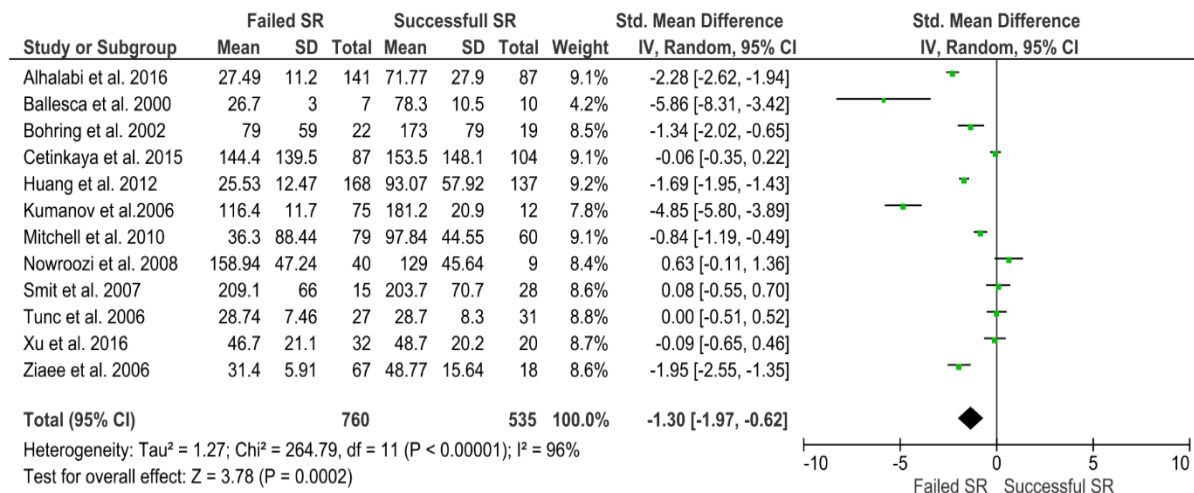
The FSH level in males is important because it is involved in Sertoli cell proliferation,

**Table 2:** Characteristics of included studies

Author	Year	Study type	Hormone studied	No. patients	Retrieval technique
Alhalabi et al. <sup>3</sup>	2016	Prospective	FSH, Inhibin B	228	TESE/FNA
Ballesca et al. <sup>4</sup>	2000	Prospective	Inhibin B	17	TESE
Bohring et al. <sup>5</sup>	2002	Prospective	FSH, Inhibin B	41	TESE
Cetinkaya et al. <sup>6</sup>	2015	Retrospective	Inhibin B	191	mTESE
Chen et al. <sup>7</sup>	2010	Prospective	FSH	206	Masturbation
Huang et al. <sup>8</sup>	2012	Prospective	FSH, Inhibin B	305	TESE
Jahromi et al. <sup>9</sup>	2020	Prospective	FSH	171	mTESE
Kumanov et al. <sup>10</sup>	2006	Prospective	Inhibin B	87	Masturbation
Mitchell et al. <sup>11</sup>	2010	Prospective	Inhibin B	139	mTESE
Nowroozi et al. <sup>12</sup>	2008	Prospective	Inhibin B	49	TESE
Rohan et al. <sup>13</sup>	2020	Retrospective	FSH	34	mTESE
Smit et al. <sup>14</sup>	2007	Retrospective	Inhibin B	43	MESA
Tunc et al. <sup>15</sup>	2006	Retrospective	FSH, Inhibin B	58	mTESE
Xu et al. <sup>16</sup>	2016	Prospective	FSH, Inhibin B	52	mTESE
Yildirim et al. <sup>17</sup>	2014	Retrospective	FSH	131	mTESE
Ziaee et al. <sup>18</sup>	2006	Retrospective	FSH, Inhibin B	85	TESE



**Figure 2:** Forest plot showing the correlation between FSH level and sperm retrieval rate



**Figure 3:** Forest plot showing the correlation between inhibin B level and sperm retrieval rate

and through a largely unclear mechanism, in spermatogenesis. In patients with hypogonadotropic hypogonadism, sperm parameters fertility could be improved by restoration of FSH levels. According to Santi *et al.*, proposed the administration of exogenous FSH in order to overstimulate spermatogenesis<sup>24</sup>. Although in animal models, exogenous FSH had increased the number of spermatogonia, in humans the improvement of spermatogenesis of this type of treatment was never clearly demonstrated. Nevertheless, a Cochrane meta-analysis of seven studies, showed an increased rate of spontaneous pregnancies in couples in which exogenous FSH was administered to the male partner<sup>24</sup>.

Many other factors have been studied in order to predict the outcome of TESE. According to Qi *et al.*, age, body-mass index, prolactin, luteinizing hormone, or total testosterone are not reliable predictors<sup>25</sup>. Although it is the main hormone produced by the testis and is believed to be involved in some stages of spermatogenesis, testosterone is not a good marker for successful sperm retrieval. In a cohort of 421 patients with NOA, Althakafi *et al.*, failed to demonstrate a significant correlation between the outcome of mTESE and serum testosterone levels<sup>26</sup>.

Although considering the  $I^2$  value, the articles we selected had a high heterogeneity rate. The authors used different sperm retrieval techniques. The majority used TESE or mTESE. Despite that the two procedures are quite similar the result could be different. Deruyver *et al.* compared the outcomes of the two procedures in a meta-analysis of 7 studies<sup>26</sup>. In the group of conventional TESE, sperm retrieval rate ranged from 16.7 to 45%, while in the mTESE group from 42.9 to 63%. The difference being significant in 5 out of the seven studies. There were also differences from the testicular histology point of view. In patients with Sertoli cell-only syndrome, mTESE provided superior results, with a sperm retrieval rate between 22.5 and 41% compared to 6.3-29% in the case of conventional TESE<sup>27</sup>. According to Maglia *et al.*, age could influence the outcome of the two techniques. In a cohort of 145 patients, the authors did not find a significant outcome between the two procedures (49.0% vs. 41.7%,  $p = 0.40$ ). Still, they noticed a significantly higher sperm retrieval rate in patients older than 35 years who underwent

mTESE compared to conventional TESE ( $p = 0.03$ )<sup>28</sup>.

The pathogenesis of NOA can be affected by genetic factors. According to Matzuk *et al.*, there are almost 473 genes that could impair spermatogenesis<sup>29</sup>. Nowadays, in patients with NOA, genetic tests like polymerase chain reaction analysis for azoospermia factor and chromosomal karyotype assays for Klinefelter syndrome are currently used. According to Tharakan *et al.*, excepting azoospermia factor microdeletion, with a 3–10% prevalence in patients with NOA, the incidence of monogenic mutations is too low to justify routine clinical testing<sup>30</sup>. This means that hormone levels could be the cornerstone for preoperative evaluation of men with NOA.

Spermatogenesis is a complex process in which other biomarkers can be involved. Another hormone generated by Sertoli cells, AMH, is present in high concentrations in the seminal plasma due to preferential apical outflow towards the seminiferous lumen. According to Zarezadeh *et al.*, an agreement has been reached in the literature on the prediction of surgical sperm recovery based on seminal levels of AMH. The existence of neither spermatozoa nor germ cells in the testicular tissues of NOA subjects who had TESE surgery has therefore been found to be predicted by seminal levels of AMH. Similar investigations also showed no disparaging remarks regarding effective TESE results for seminal AMH. Furthermore, a significant number of patients had seminal AMH readings that were undetectable, preventing its use in clinical practice. Seminal AMH cannot be regarded as a predictive biomarker for successful sperm extraction<sup>31</sup>.

Rat testes germ cells, particularly mature spermatocytes, contain the protein survivin, which can control apoptosis. A reduction in survivin expression may cause spermatogenesis disorders. Additionally, seminal survivin was found in 24 NOA males who underwent successful TESE but not in 13 NOA men who underwent unsuccessful TESE, suggesting that seminal survivin was linked to successful sperm retrieval in NOA men<sup>32</sup>. The spermatogenic epithelium's liquid releases clusterin, which is then deposited on the membranes of elongated sperm cells and mature sperm. Clusterin is produced by Sertoli cells. The SP-clusterin levels of nine NOA patients who had

successful micro-TESE and 19 patients who underwent unsuccessful micro-TESE did not differ statistically significantly, according to Fukuda *et al.*<sup>33</sup>. But it's important to remember that their univariate analysis revealed SP-clusterin as an SSR predictor. Spermatogenesis and leptin have been connected. With a cut-off value of 2.9 ng/mL (sensitivity of 43.1% and specificity of 75.0%), Ma *et al.* found a significant difference in SP-leptin levels between positive and negative sperm retrieval groups<sup>34</sup>. However, using artificial neural networks to combine leptin and other markers can significantly increase the prediction accuracy of sperm retrieval in NOA patients.

Our meta-analysis has some limitations: first, the studies are pretty heterogenous, the authors come from different continents, and the number of patients varied from 17 to 305. Not all patients in our included studies underwent the same type of intervention. Although in our meta-analysis, the FSH levels were inversely associated with successful sperm retrieval, in our patients, the difference was not significant as some data from the literature. We conclude that the best endocrine measure of spermatogenesis in sub-fertile males is inhibin B. According to our findings, serum inhibin B and FSH levels have limited clinical value for specific individuals, necessitating more research. A new direction of research would be the prior administration of treatment to patients with NOA. As we showed in a previous study, some substances can positively influence sperm count<sup>35</sup>.

## Conclusion

As the prevalence of male infertility increases, more patients with NOA will require a surgical sperm retrieval procedure. Inhibin B and FSH are good markers of spermatogenesis. The majority of studies showed that a higher inhibin B level and a lower FSH concentration are related to successful sperm retrieval. Nevertheless, we should consider that no perfect marker and cannot replace testicular biopsy as a diagnostic and treatment tool in patients with NOA. The decision of a sperm retrieval procedure should be taken after the patient was been informed about the risks and benefits, not forgetting that surgical sperm retrieval could be, in some cases the only chance to have a biological offspring.

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## Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contribution

CP, DP assessed the authenticity of raw data. DR, VJ and DP conceived and designed the study. DR, DP were involved with performing the surgery and other procedures. CP, AM, VJ, and DP collected, analysed and interpreted the data. DP and DR drafted the manuscript, CP, AM, and VJ revised the manuscript. All authors have read and approved the final version of the manuscript.

## Competing interests

The authors declare that they have no competing interests.

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