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Changes in Testosterone Levels Following Surgical Sperm Retrieval in Men with Non-Obstructive Azoospermia: Systematic Review and Meta-Analysis

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Purpose: Surgical sperm retrieval (SSR) is used to extract spermatozoa for use with intracytoplasmic sperm injection in men with obstructive and non-obstructive azoospermia (NOA). The procedure may lead to segmental devascularization, postoperative fibrosis, and atrophy with a subsequent decrease in testosterone. The aim of the study is to investigate the impact of SSR on serum levels of total testosterone (TT), follicle-stimulating hormone (FSH), luteinizing hormone (LH) testicular volume, and sexual function in infertile azoospermic men.

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The researchers contributing to this publication are members of the Global Andrology Forum (GAF), based in Moreland Hills, OH, USA. GAF operates under the Global Andrology Foundation, a non-profit organization registered in Innsbruck, Austria.

Materials and Methods: In this systematic review and meta-analysis (SRMA), we searched articles in "PubMed" and "Scopus" exploring the impact of SSR on TT, FSH, LH, and testicular volume. The full-text articles were screened to assess eligibility before data extraction, quality assessment, and meta-analysis.

Results: Seventeen studies meeting the inclusion criteria were finally analyzed and included 1,685 infertile, azoospermic men. Patients underwent SSR and were followed in the postoperative period (one week to 32 months). The analysis showed a significant reduction in TT (mean difference [MD] 3.81 nmol/L, 95% confidence interval [CI] 0.55:7.06; p=0.02) compared to pre-SSR values. We also observed insignificant differences in serum FSH (MD 5.08 IU/L, 95% CI -5.6:15.8; p=0.35), LH (MD -2.96 IU/L, 95% CI -6.31:0.39; p=0.08), and no change in testicular volume (MD 0.07 mL, 95% CI -1.92:2.07; p=0.94) after SSR. Sexual dysfunction was associated with hypogonadism, depression, and anxiety, especially in men with unsuccessful SSR and Klinefelter syndrome.

Conclusions: The results of this SRMA indicate a significant reduction in TT after SSR. Sexual dysfunction after testicular sperm extraction and the potential negative impact of future SSR repeat should be considered during preoperative counseling.

Keywords: Azoospermia; Hypogonadism; Microsurgical testicular sperm retrieval; Sperm injections, intracytoplasmic; Testicular sperm extraction

INTRODUCTION

Surgical sperm retrieval (SSR) helps men with azoospermia to proceed with intracytoplasmic sperm injection (ICSI). There are different SSR methods. The most frequent approaches are conventional testicular sperm extraction (cTESE) [1-3] and microsurgical TESE (mTESE) [4,5]. A few years later, Amer et al [6] minimized the harvested tissues with single tubule biopsies to retrieve a sufficient number of spermatozoa. Testicular sperm aspiration (TESA) was proposed to obtain sperm cells in ejaculatory failure [7], obstructive azoospermia (OA) [8,9], and non-obstructive azoospermia (NOA) [9-11]. Other investigators used a biopsy gun needle to collect spermatozoa for ICSI, cryopreservation, and histology [12,13].

In the TESE procedure, testicular tissue samples are harvested via dissection of testicular tissue followed by tissue resection. In contrast, small pieces of tissue are aspirated in fine needle aspiration (FNA) to extract viable sperm cells. Postoperative complications, such as hematoma, devascularization, and inflammation, have been documented, eventually leading to scars and calcification [5,14,15]. Furthermore, several studies reported a significant reduction in serum testosterone levels after TESE [15,16]. Such reduction can subsequently lead to hypogonadism. The lower the total testosterone values, the more frequently the symptoms of hypogonadism appear [17,18].

Men may undergo a second TESE attempt due to the failure of the first procedure to retrieve viable spermatozoa suitable for ICSI, which occurs in almost 50% of cases [4,5]. mTESE is 1.5 times more likely than cTESE to retrieve sperm (95% confidence interval [CI] 1.4–1.6) [19]. Despite this fact, SSR may fail to harvest spermatozoa suitable for ICSI, and a second TESE procedure could also be offered to these men. The sperm retrieval rate, in this case, ranges between 18.0% and 42.8% [20-24]. The sperm retrieval rate in the third attempt goes as low as 10% [22]. Repeated TESE is also indicated if more sperm are needed for ICSI cycles or if the previously cryopreserved sperm were used up entirely in ICSI cycles [22,25].

A systematic review and meta-analysis (SRMA) indicated a transient but significant drop in testosterone levels referred to as "a temporary hypogonadism" after TESE [26]. The authors noted the challenges clinicians face when counseling patients regarding the clinical symptoms of decreased serum testosterone levels. However, the findings of this SRMA are limited by significant heterogeneity.

The current SRMA aims to explore the impact of SSR on testicular volume, serum levels of total testosterone (TT), follicle-stimulating hormone (FSH), luteinizing hormone (LH), sexual function (loss of desire, erectile dysfunction [ED], and ejaculatory disorders). This data would be instrumental in counseling men before they undergo a cTESE or mTESE procedure.

MATERIALS AND METHODS

This study is conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [27].

This study used a population, exposure, comparator, outcomes, and study design (PECOS) model [28]. The PECOS approach supports conducting a systematic review, including formulating the research question, determining eligibility criteria, presenting outcomes, and wording final recommendations.

1. Inclusion and exclusion criteria

We included studies on azoospermia (irrespective of the cause) in which men were subjected to SSR, including by cTESE, mTESE, TESA, or FNA. However, we confined the meta-analysis to mTESE for NOA because very few articles investigated other approaches to minimize the impact of various techniques on gonadal functions. The outcome measures were serum level of TT, FSH, LH, testicular volume, sexual dysfunctions as assessed by the 5-item questionnaire of the International Index of Erectile Function (IIEF-5), and long-term testicular ultrasound changes following SSR (intraparenchymal hematoma, segmental devascularization, atrophy, and calcifications). The studies included were observational before/after (case-control or cohort).

We excluded articles on SSR for the treatment of anejaculation, high sperm DNA fragmentation, and fertility preservation before cancer therapy. We also ruled out articles on epididymal sperm retrieval, whether percutaneous or microsurgical. Our review did not consider animal studies, pilot studies, literature reviews, abstracts, conference papers, or book chapters.

The PECOS model of the current study is shown in Table 1.

2. Search strategy

A comprehensive systematic search was conducted using Scopus and PubMed. We used a combination of Medical Subject Heading (MeSH) terms and free words. The initial keyword string was created on Scopus and then was adapted to search in other databases as follows:

1) Scopus

TITLE-ABS-KEY ((azoospermia *) AND (" surgical sperm retrieval " OR "TESE" or "TESA" OR "testicular sperm extraction" OR testosterone OR fsh OR "follicle-stimulating hormone" OR lh OR "luteinizing hormone" OR "oestradiol" OR "estradiol" OR "E2" OR "testicular pathology" OR "Johnsen score")) AND (LIMIT-TO (DOCTYPE, "ar"))

2) PubMed

"azoospermia*"[All Fields] AND ("testosterone"[All Fields] OR "testosterone"[MeSH Terms] OR "fsh"[All Fields] OR "follicle stimulating hormone"[All Fields] OR "follicle stimulating hormone"[MeSH Terms] OR "lh"[All Fields] OR "luteinizing hormone"[All Fields] OR "luteinizing hormone"[MeSH Terms] OR "oestradiol"[All Fields] OR "oestradiol"[MeSH Terms] OR "estradiol"[All Fields] OR "E2"[All Fields] OR " testicular pathology "[MeSH Terms] OR "Johnsen score"[MeSH Terms] OR "IIEF" [MeSH Terms]). The databases were searched for

Table 1. Population, Exposure, Comparator, and Outcomes (PECO) model of the current study

	Inclusion	Exclusion
Population	Men with azoospermia (irrespective of the cause)	SSR due to anejaculation, fertility preservation before cancer therapy, high sperm DNA fragmentation
Exposure	cTESE, mTESE, TESA, FNA	Epididymal sperm retrieval
Comparison	Preoperative data	-
Outcome	Change in testicular volume (mL), serum levels of TT (nmol/L), LH (IU/L), FSH (IU/L), IIEF-5 score, and long-term testicular ultrasound changes following SSR (intraparenchymal hematoma, segmental devascularization, atrophy, and calcifications)	Acute complications (bleeding, hematoma, wound complications)
Study design	Before/after, observational studies (case-control or cohort)	Animal studies, pilot studies, reviews, abstracts, conference papers, and book chapters

cTESE: conventional testicular sperm extraction, mTESE: microsurgical TESE, TESA: testicular sperm aspiration, FNA: fine needle aspiration, TT: total testosterone, LH: luteinizing hormone, FSH: follicle-stimulating hormone, IIEF: international index of erectile function, SSR: surgical sperm retrieval.

studies published until March 2023.

3. Data collection and management

1) Selection of studies

The identified articles were divided equally among the research team members. Two independent members screened the retrieved abstracts. The eligibility of the identified abstracts was considered based on the inclusion and exclusion criteria of this review and following the PECOS model of this study. The full-text articles were screened to assess eligibility before data extraction and quality check. An additional search was done to identify narrative and systematic reviews on the same topic, aiming for a manual search for papers quoted in these reviews to check if any papers were missed in our database. We included articles written in English only. Fig. 1 shows the flowchart for identification, screening, and inclusion of the articles.

2) Data extraction

Data extraction was conducted for potentially eligible articles with full-text availability. Extracted information included the following: first author's name, year of publication, Journal, study design, the total number of patients, age of patients, laterality and surgical approach, and testicular pathology (intraoperative), time between SSR and assessment and study outcome parameters (pre- and post-testis size in mL [orchidometer/ultrasound], serum levels of reproductive hormones [TT, nmol/L; FSH, IU/L; LH, IU/L; IIEF-5 score, range from 5 to 25], sexual desire) and long-term ultrasound changes following surgery.

For metric and conversion unit calculation, we used Men's Hormonal health/Metric and conventional unit conversions [29].

4. Quality assessment

The quality of the included studies was assessed using the Cambridge Quality Checklist [30]. Two researchers independently evaluated each study, and a third researcher resolved disagreements.

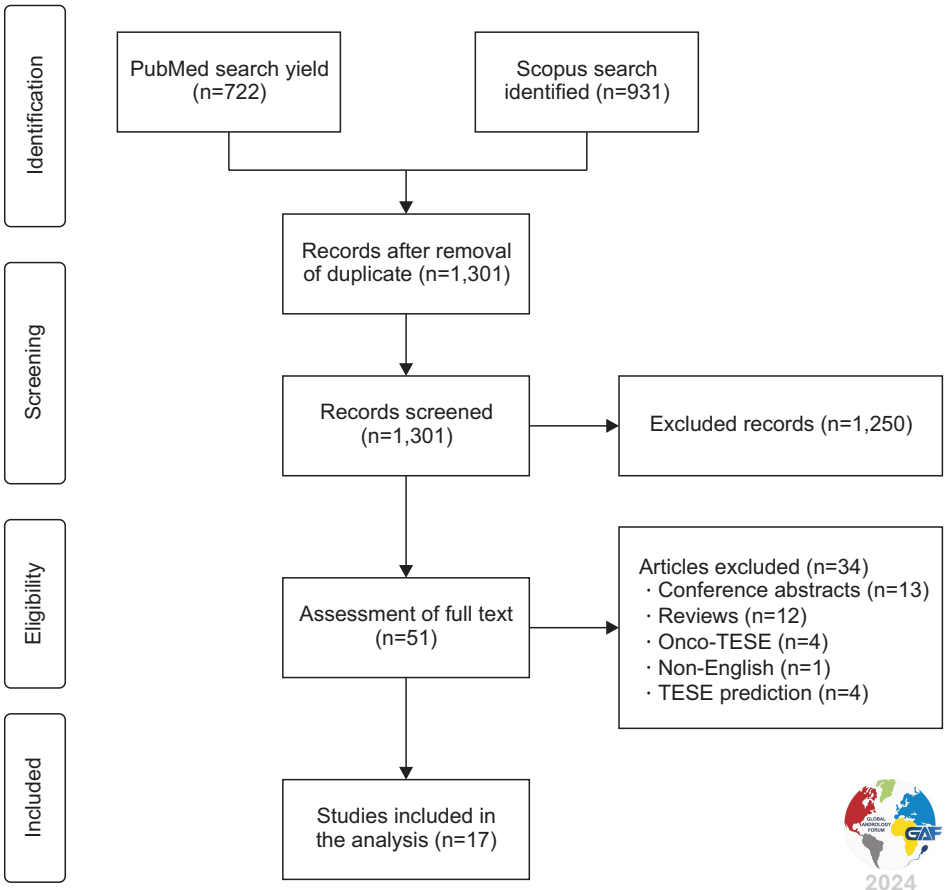

Fig. 1. Study flowchart showing search, screening, eligibility, and inclusion on surgical sperm retrieval-induced hypogonadism. TESE: testicular sperm extraction.

5. Statistical analysis

The I^2 statistic and the Cochrane Q test evaluated the in-between study heterogeneity. Moderate heterogeneity was considered if the I^2 was >40%, and significant heterogeneity is regarded as p-value <0.1. We calculated the mean difference (MD) using the following equation: The pooled mean difference was considered by subtracting the mean outcome after mTESE from the mean outcome before mTESE. The random and fixed effect models were used for high and low heterogeneity. The Restricted maximum-likelihood estimator was used to calculate the in-between study variance (tau2), and the inverse variance method was used to pool the effect size. Publication bias was assessed using the funnel plot. Plot asymmetry was evaluated using Egger's test. Sensitivity analysis was done by excluding one study at a time (leave-one-out method) and observing the changes in the pooled effect size. A study is sensitive when it significantly changes the pooled effect size when removed. The statistical analysis was performed using the R programming language R version 4.1.2 with a p-value of <0.05, considered statistically significant for the overall difference between groups.

RESULTS

Our analysis included 17 articles covering the topic of TESE and its impact on gonadal function in men with azoospermia. The follow-up period ranged between one week and 32 months. A summary of the characteristics and main findings of the included studies are shown in Table 2. The meta-analysis included articles on mTESE only.

1. Change in total testosterone

This analysis included nine studies [31-39]. We removed the article by Steele et al, 2001 [40] because true cut needle biopsy was used in TESE. The follow-up in the included articles ranged between one week (one article) [40] to 14 months [34], with the majority of follow-

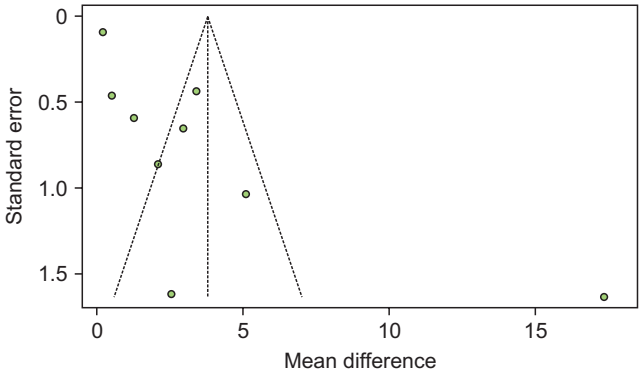

Fig. 3. Funnel plot showing publication bias for the articles on testicular volume (n=9).

Study	Before mTESE Total	Mean	SD	After mTESE Total	Mean	SD	MD [95% CI]
Akbal et al, 2010	36	27.04	6.93	36	9.71	6.93	17.33 [14.13; 20.53]
Altinkilic et al, 2018	78	13.70	5.50	71	11.60	5.00	2.10 [0.41; 3.79]
Binsaleh et al, 2017	255	12.80	5.50	255	9.40	4.30	3.40 [2.54; 4.26]
Eliveld et al, 2023	177	14.67	4.60	177	14.15	4.10	0.52 [−0.39; 1.43]
Herndon et al, 2022	26	15.84	5.48	26	13.31	6.17	2.53 [−0.64; 5.07]
Manning et al, 1998	15	17.20	2.75	15	12.10	2.92	5.10 [3.07; 7.13]
Ozturk et al, 2011	37	14.10	2.70	37	12.83	2.36	1.27 [0.12; 2.43]
Sertkaya et al, 2020	60	13.52	3.81	60	10.57	3.32	2.95 [1.67; 4.23]
Takada et al, 2008	60	9.60	0.50	60	9.40	0.50	0.20 [0.02; 0.38]
Random-effect model	744			737			3.81 [0.55; 7.06]

I^2=96%, τ^2=23.89, p<0.01
Test for overall effect: p=0.02

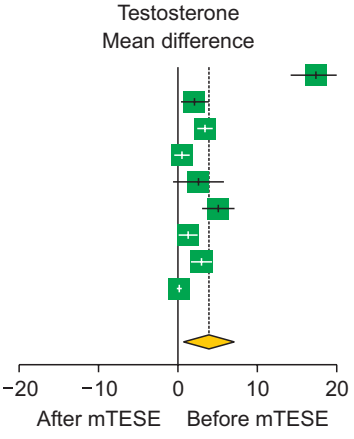

Fig. 2. Forest plot with mean difference (MD) of total testosterone (before and after mTESE; n=9). mTESE: microsurgical testicular sperm extraction, SD: standard deviation, CI: confidence interval.

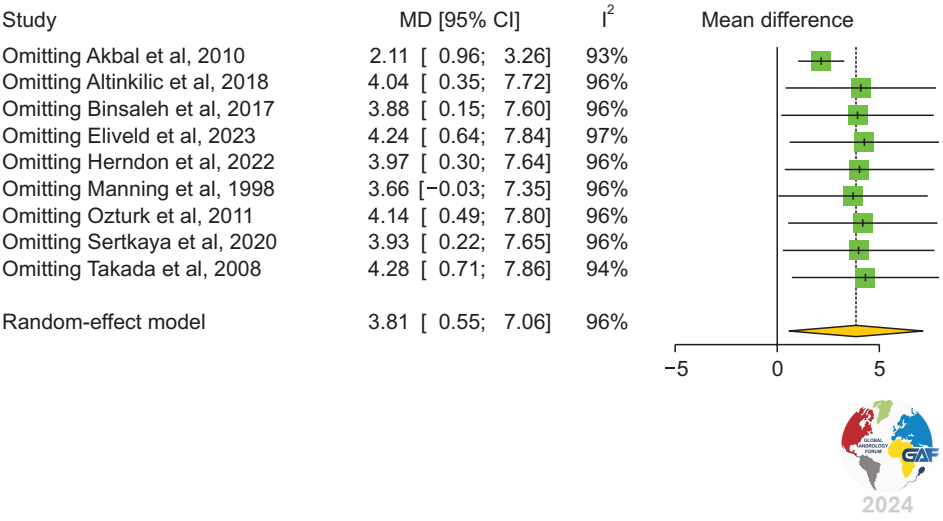

Fig. 4. Sensitivity analysis for total testosterone analysis showing the impact of removal of individual studies on the pooled estimate. MD: mean difference, CI: confidence interval.

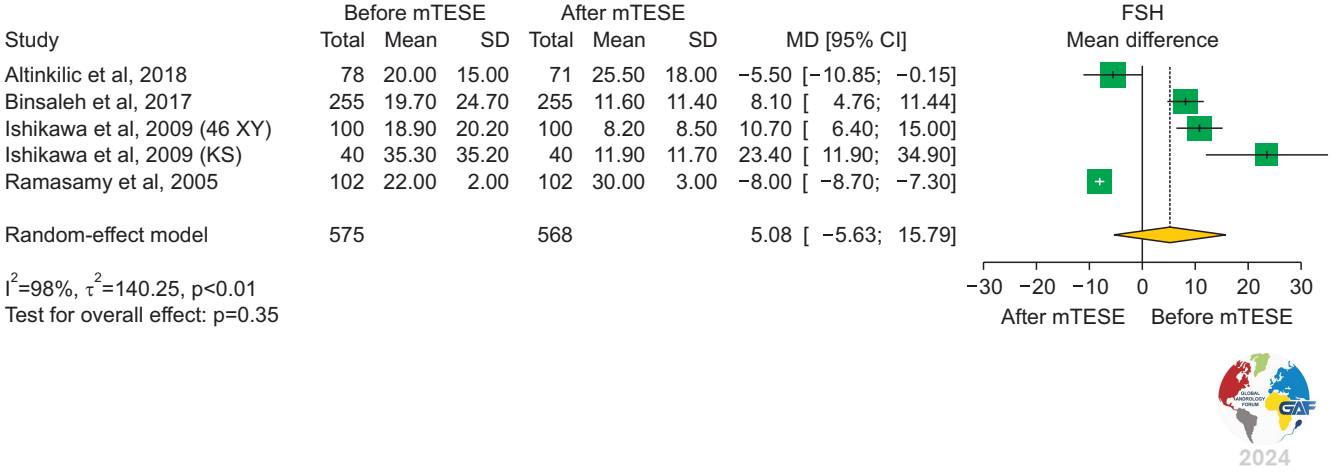

Fig. 5. Forest plot with mean difference (MD) in follicle-stimulating hormone (FSH) level (before and after mTESE). mTESE: microsurgical testicular sperm extraction, SD: standard deviation, CI: confidence interval.

up between 6 to 12 months. The meta-analysis included 744 and 737 patients in the before mTESE and after mTESE groups, respectively. The random effect model was used (I^2=0.96, Q p-value <0.01). The pooled estimate was significantly higher in the before-TESE group (MD 3.81 nmol/L, 95% CI: 0.55:7.06; p=0.02) (Fig. 2). The asymmetry of the funnel plot demonstrates significant publication bias (p=0.01, Egger; Fig. 3). Sensitivity analysis showed one study [36] that changed the pooled estimate when removed (Fig. 4).

2. Change in the FSH levels

Four studies were included [32,33,41,42]. The meta-analysis included 575 patients before mTESE and 568 patients after mTESE, respectively. The random effect model was used (I^2=0.98, Q p-value <0.001). The pooled

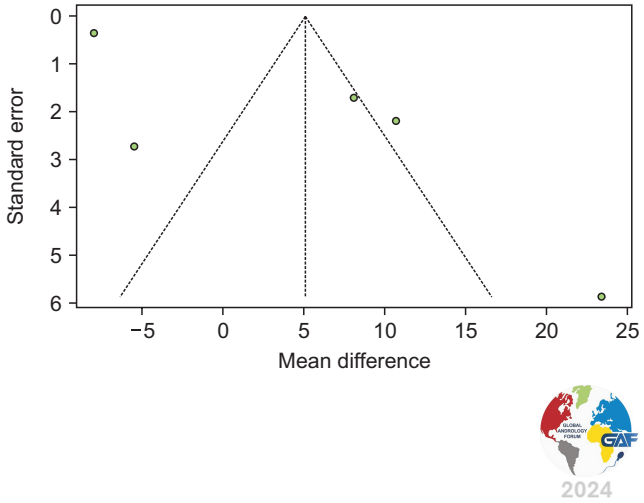

Fig. 6. Funnel plot showing publication bias for the articles on follicle-stimulating hormone.

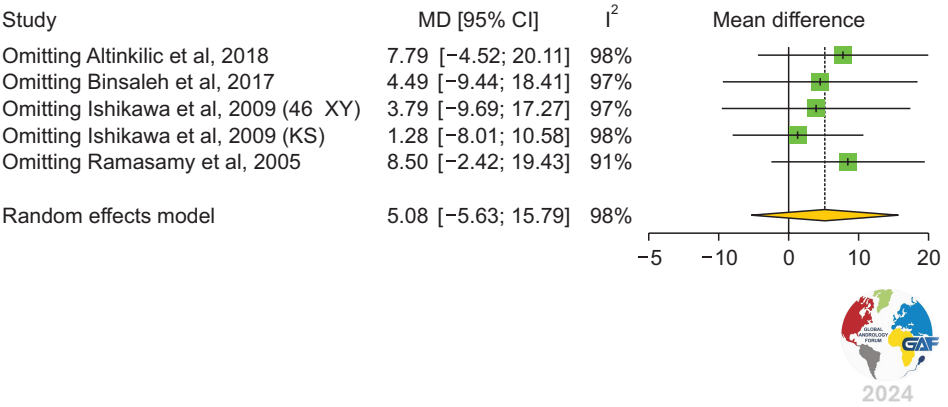

Fig. 7. Sensitivity analysis for follicle-stimulating hormone analysis showing the impact of the removal of individual studies on the pooled estimate. MD: mean difference, CI: confidence interval, KS: Klinefelter syndrome.

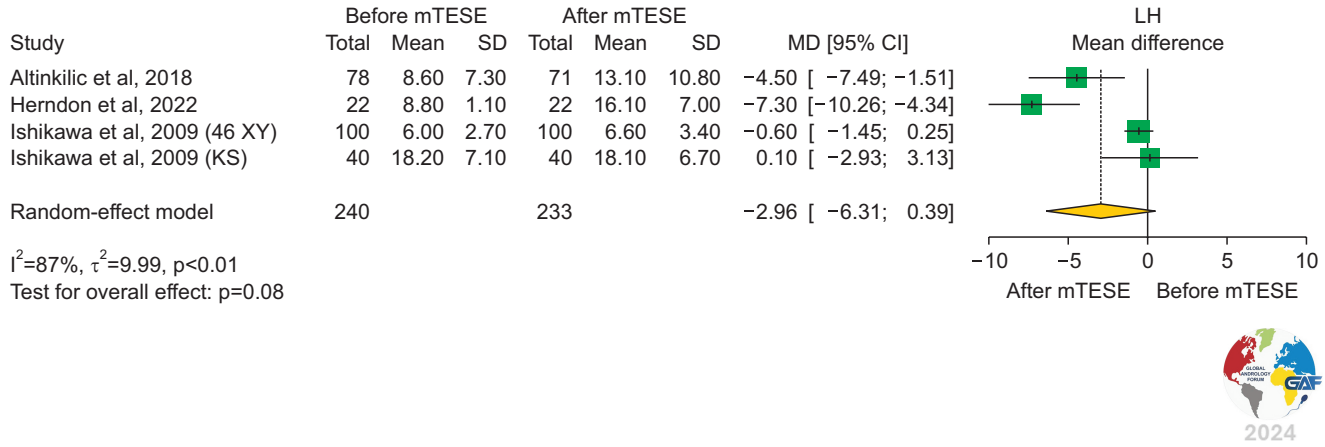

Fig. 8. Forest plot with mean difference (MD) in luteinizing hormone (LH) level (before and after mTESE). mTESE: microsurgical testicular sperm extraction, SD: standard deviation, CI: confidence interval, KS: Klinefelter syndrome.

estimate was not significantly different between the compared groups (MD 5.08 IU/L, 95% CI -5.6:15.8; p=0.35) (Fig. 5). Publication bias is demonstrated in the funnel plot (Fig. 6). Sensitivity analysis showed no studies influenced the pooled estimate when removed (Fig. 7).

3. Change in the LH levels

The number of studies included was three [32,35,41]. The meta-analysis included 240 and 233 patients in the before-TESE and after-TESE groups, respectively. The random effect model was used (I^2=0.87, Q p-value <0.01). The pooled estimate was not significantly different between the compared groups (MD -2.96 IU/L, 95% CI -6.31:0.39; p=0.08) (Fig. 8). Publication bias is demonstrated in the funnel plot (Fig. 9). Sensitivity analysis showed that no studies influenced the pooled estimate when removed (Fig. 10).

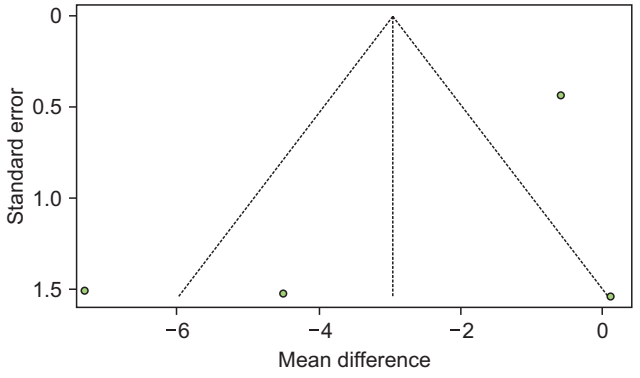

Fig. 9. Funnel plot showing publication bias for the articles on luteinizing hormone (n=4).

4. Change in testicular volume

Three studies were included [32,37,43]. The meta-analysis included 175 and 168 patients in the before-

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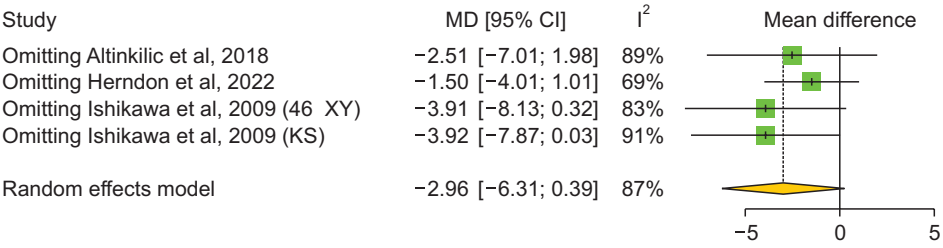

Fig. 10. Sensitivity analysis for luteinizing hormone analysis showing the impact of removal of individual studies on pooled estimate. MD: mean difference, CI: confidence interval.

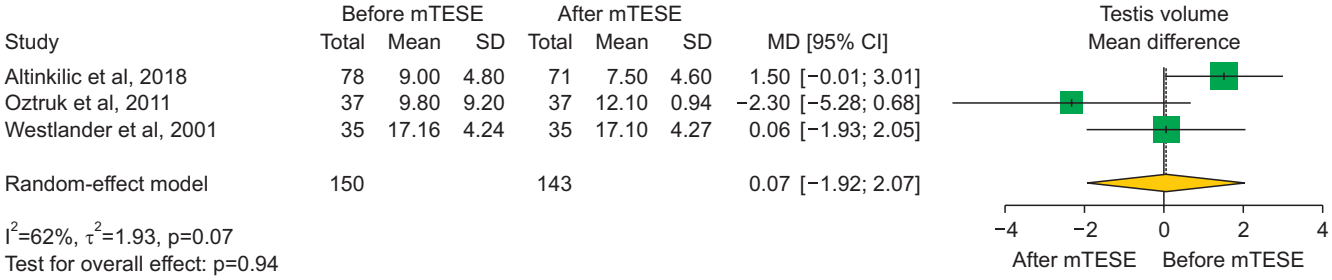

Fig. 11. Forest plot with mean difference (MD) in testicular volume level (before and after mTESE; n=4). mTESE: microsurgical testicular sperm extraction, SD: standard deviation, CI: confidence interval.

TESE and after-TESE groups, respectively. One article was excluded [44] because the testicular volume was not compared to the preoperative values. The meta-analysis included 150 and 143 in the before and after mTESE groups, respectively. The pooled estimate was not significantly different between the compared groups (MD 0.07 mL, 95% CI -1.92:2.07; p=0.94; Fig. 11). Publication bias is demonstrated in the funnel plot (Fig. 12). Sensitivity analysis showed no studies influenced the pooled estimate when removed (Fig. 13).

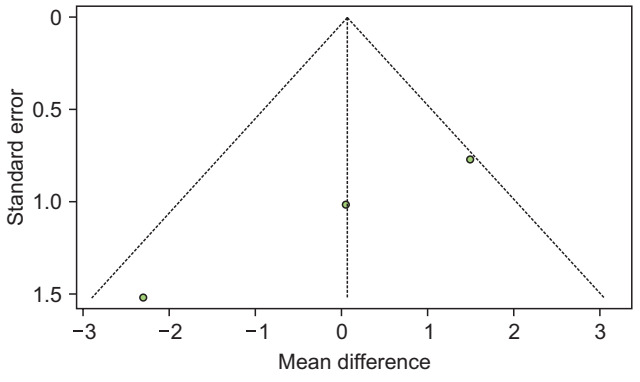

Fig. 12. Funnel plot showing publication bias for the articles on testicular volume (n=3).

5. Change in sexual function

Sexual dysfunction was assessed in two studies [31,34]. Akbal et al [31] evaluated the IIEF-5 in 66 men. The median IIEF-5 scores before mTESE for positive and negative TESE groups were 22 (minimum, 11; maximum, 25) and 23 (minimum, 10; maximum, 25), respectively. After SSR, IIEF-5 scores for positive and negative TESE were 23.5 (minimum, 10; maximum, 25) and 18 (minimum, 15; maximum, 25), respectively. The significant decrease was more evident in men with negative TESE at the end of the follow-up. Eliveld et al [34] reported sexual dysfunctions (hypoactive sexual desire and ED). Lower libido was reported in one patient out of 55 men with OA (1.8%), and 2/177 (1.1%) in

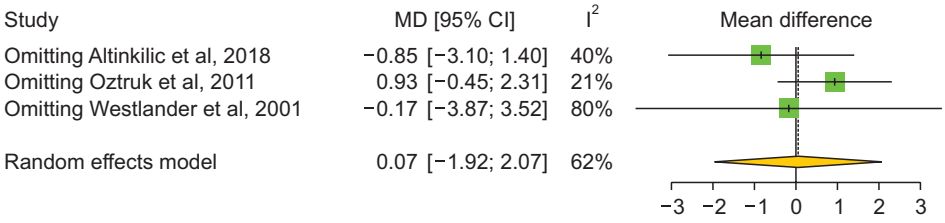

Fig. 13. Sensitivity analysis for testicular volume analysis showing the impact of the removal of individual studies on the pooled estimate. MD: mean difference, CI: confidence interval.

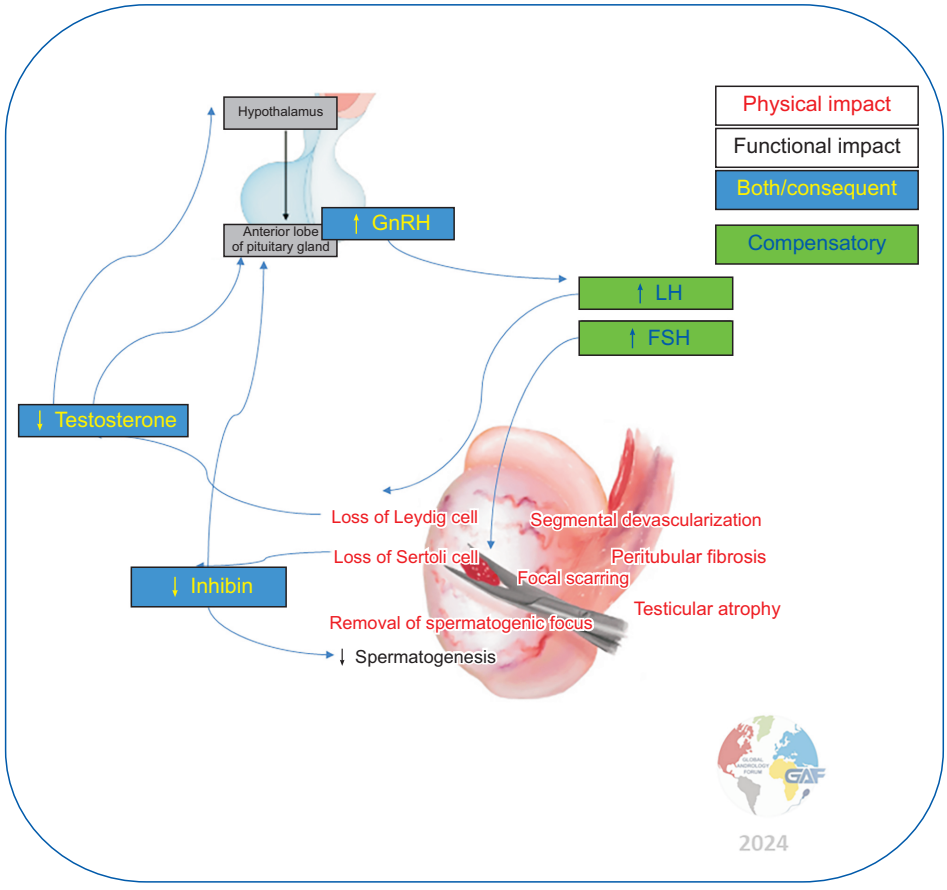

Fig. 14. Impact of testicular sperm extraction on spermatogenesis. FSH: follicle-stimulating hormone, LH: luteinizing hormone, GnRH: gonadotropin-releasing hormone.

NOA. ED was observed in 2/177 men with NOA (1.1%). The article did not assess ejaculatory disorders in their cohort (Table 2).

6. Testicular ultrasound changes

Intraparenchymal hematoma, segmental devascularization, atrophy, and calcifications were documented in two articles [40,44]. Altinkilic et al [32] observed a reversible reduction in the peak systolic velocity, which had been normalized six weeks after SSR. Steele et al [40], however, reported no hematoma on follow-up.

DISCUSSION

In this review, an evaluation was conducted on the gonadal function in men with azoospermia following SSR. The findings of the current SRMA indicate a decline in serum TT levels after mTESE, lasting for at least 14 months. The analysis also showed insignificant changes in serum levels of FSH, LH, and testicular volume. Further, data emerging from this SRMA suggests that some men may experience ED following SSR, along with feelings of depression and anxiety.

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Table 2. Summary of the included articles in our systematic review (n=17)

No.	Study	Design	CQC	No. of patients	Population	Intervention	Follow up	TV	Hormone	Pathology	ULS	HG-S	IIEF
1	Eliveld et al, 2023 [34]	Pro	2,3,2	241	53 OA, 177 NOA, and 11 KS	mTESE	14 mo	NA	↓ in TT in OA, no ≈ in NOA, & no ≈ in KS	SCO (21.5%), mixed pathology (23.7%), MA (9.6%)	NA	OA (3.8%) , NOA (3.3%), KS (36%)	NA
2	Herndon et al, 2022 [35]	Ret	1,2,4	26	NOA with failed extraction	mTESE	6 mo	NA	↓ in TT, significant increase in LH, FSH	NA	NA	8/22 (36%) turned into HG	NA
3	Binsaleh et al, 2017 [33]	Ret	2,2,3	255	NOA	mTESE	12 mo	NA	reversible ↓ in TT, FSH, and LH	Hypospermatogenesis (90%), MA (55.6%), SCO (39%), WTH (0%)	NA	NA	NA
4	Altinkilic et al, 2018 [32]	Pro	1,3,3	78	24 OA, 54 NOA	tri-focal/ mTESE	1.5 mo	↓ in TV	↑ in FSH & LH, ↓ in TT	NA	initial ↓ in PSV & normalized in 6 weeks	NA	NA
5	Ozturk et al, 2011 [37]	Pro	3,2,6	37	NOA	mTESE	12 mo	≈ in TV	≈ in TT & FSH	NA	NA	NA	NA
6	Akbal et al, 2010 [31]	Pro	1,3,6	66	NOA	mTESE	6 mo	NA	↓ TT, ↑ FSH, ≈LH	NA	NA	NA	↓ in negative TESE
7	Ishikawa et al, 2009 [41]	Ret	1,2,3	100 46, XY NOA - 40 with nonmosaic KS	mTESE		NA	↓ in TT in KS ≈NOA - ↑ in NOA, ≈ KS -≈ LH	NA	NA	Not specified	NA	
8	Everaert et al, 2006 [57]	Ret	1,2,3	48	FU available in 31 men with NOA	mTESE		NA	↓ in TT, ≈ in FSH & LH	NA	NA	Not specified	NA
9	Ramasamy et al, 2005 [42]	Ret	3,2,6	543	435 men with NOA underwent 543 TESE attempts	83 (15%) cTESE and 460 (85%) mTESE		NA	↓ 20% in testosterone after 3 and 6 mon, ≈ FSH, LH	213 (61% SCO), 73 (21%) HG, and 62 (18%) MA	NA	NA	NA
10	Komori et al, 2004 [44]	Pro	1,2,2	2 patients (16.7%) KS, 23 patients NOA	cTESE and mTESE			Testosterone ≈	No formation of ASA	NA	NA	NA	NA

Table 2. Continued 1

No.	Study	Design	CQC	No. of patients	Population	Interven-tion	Follow up	TV	Hormone	Pathology	ULS	HG-S	IIEF
11	Okada et al, 2002 [52]	Ret	1,2,2	Comparison of cTESE in 46 Pat. (22 OS and 24 NOA) to 100 mTESE (26 OA and 74 NOA)	cTESE and mTESE		≈in TV	≈ in TT	Maturation arrest and SCO	NA	NA	NA	NA
12	Westlander et al, 2001 [43]	Pro	2,3,2	35	OA (10) NOA (25)	TESA		≈TV	≈TT, ≈ FSH,	NA	FTL: 4/66 6.1%), ITH (one case)	NA	NA
13	Steele et al, 2001 [40]	Pro	2,3,3	16	OA (13), NOA (3)	True cut needle	1 mo	≈TV	≈ FSH, ≈ LH. ≈TT	13 (normal spermatogen-esis), 3 (SCO)	No hematoma	NA	NA
14	Manning et al, 1998 [36]	Pro	1,3,6	15	15 patients with NOA with normal testosterone	mTESE	12 mo	NA	↓ in TT after 6 mo, but improved after 12 mo	NA	NA	NA	NA
15	Schill et al, 2003 [53]	Pro	1,2,4	40	9 (OA) and 31 (NOA) (26 with preoperative recovery)	cTESE		≈ in 4 to 32 mo	↓ in TT	NA	5/26 (19%) pathological conditions	NA	NA
16	Sertkaya et al, 2020 [39]	Pro	1,3,3	60	NOA	mTESE	1 wk	NA	↓ in TT, ↑ LH	NA	NA	NA	NA
17	Takada et al, 2008 [38]	Pro	2,3,3	69	NOA	mTESE	12 mo	NA	↓ in TT (re-covered in hyposper-matogenesis in all patients) and recovered to 50% in KS & to 80% in SCO. ↑ LH in maturation arrest	NA	NA	NA	NA

CQC: Cambridge Quality Checklists: Correlates - Risk factors - Causal risk factors, TV: testicular volume, ULS: ultrasound, HG-S: symptoms of hypogonadism, IIEF: International Index of Erectile Function, Pro: prospective, Ret: retrospective, OA: obstructive azoospermia, NOA: non obstructive azoospermia, KS: Klinefelter syndrome, mTESE: microsurgical testicular sperm extraction, cTESE: conventional testicular sperm extraction, TT: total testosterone, MA: maturation arrest, SCO: sertoli cell only, FTI: focal testicular lesion, ITH: intra-testicular hematoma, FSH: follicle-stimulating hormone, LH: luteinizing hormone, HG: hypogonadal symptoms, PSV: peak systolic velocity, WTH: wide tubular hyalinization.
↓: significant drop, ↑: significant increase, ≈: no change.

The World Journal of MEN's HEALTH

Hypogonadism and temporary reduction in testosterone levels have been documented after SSR [26,34]. Regarding TT reduction, our results agree with Eliveld and her team [26], who demonstrated a trend toward an increased risk for low TT by studying the odds ratios in five articles, including 147 patients before TESE and 134 patients after TESE. The authors also observed a temporary decrease in serum TT levels after TESE (below 12 nmol/L) for at least one year.

Interpreting the consequence of low testosterone levels is inconsistent, given the different cut-off levels suggested by professional societies and expert groups [12,17]. In the current analysis, we considered the last TT measurements in all the included studies, irrespective of the duration. The duration of follow-up ranged between 1 week and 14 months, with most articles evaluating the TT after 12 months. This may reflect the long-term testosterone reduction as opposed to Eliveld and colleagues' conclusions [26], who based their findings on the OR of hypogonadism rather than TT levels.

One of the crucial studies that included 435 participants with NOA who underwent 543 TESE attempts, was excluded because standard deviations were not reported [42]. However, the results of this study align with ours. The authors reported drop in TT to 80% of their pre-TESE levels in men who underwent mTESE and cTESE. The drop was observed 3 to 6 months after SSR. Fortunately, TT recovered to 85% of their baseline levels [42]. The impact of SSR on TT reduction depends on mean preoperative TT levels; based on that, the observed effects may be underestimated in individuals. A decrease in TT levels in individuals could be missed when looking at the mean levels of a cohort. Therefore, normal mean TT levels do not exclude the possibility of finding men with TT levels below 12 nmol/L who are at risk for symptoms of hypogonadism [26].

Another article by Eliveld et al [34] reported a significant drop in TT in OA (n=53). Such observation was not reported in men with NOA (n=177) and those with Klinefelter syndrome (KS) (n=11). In this latter study, the percentage of men indicated for testosterone replacement therapy (TRT) was significantly higher in KS 4/11 (36.4%) as compared with 6/177 (3.4%) and 2/53 (3.8%) in NOA and OA, respectively [34]. The authors did not mention whether TRT was indicated before SSR and whether TRT was deferred to avoid the potential negative impact on SSR success in this category of men.

Testosterone drops due to removal of testicular tissue during TESE, thus reducing the number of Leydig cells. However, with decreased serum TT levels, the remaining Leydig cells will be stimulated by higher LH levels secondary to the hypothalamus-pituitary–gonad axis stimulation thus compensating for the gap [26]. Nevertheless, the significant drop in serum TT levels denotes that the compensatory increase in the LH levels is insufficient to maintain the eugonadal status (Fig. 14). Such a combination of high LH and normal testosterone levels is called compensated hypogonadism, as described by several investigators [41,45]. The factors that lead to uncompensated hypogonadism after SSR need to be investigated.

The inconsistent change in FSH levels in men with NOA may be due to scarring and focal segmental devascularization [5,14] and/or local germ cell loss near the scar postoperatively. It was also suggested that the peritubular scar tissue affects Leydig cells and the germ cell number [43]. The inconsistent changes in FSH and LH after micro-TESE suggest that the testes in patients with NOA who have typical sets of chromosomes (46, XY) are better able to respond than those of patients with 47, XXY. Ishikawa and his team explained this by either a defect in pituitary responsiveness in men with KS or better testicular response in men with idiopathic NOA [41]. It is also suggested that the wide tubular hyalinization of testicular tissue in men with KS provides relative immunity to peritubular scarring postoperatively, consequently, no significant differences are observed in FSH and LH at each postoperative time point [41].

A testosterone drop is directly associated with symptoms of hypogonadism, especially at levels ranging between 8 and 12 nmol/L [12]. Additionally, TT levels may also affect the chances of future TESE success. Cissen et al [46] proposed a prediction model for obtaining spermatozoa by TESE in men with NOA. They reported the following equation: probability=1/[1+exp(-b)], where b=-1.009+(male age×0.058)+(LH* 0.115)+(LH^2* 0.001)+(FSH* -0.019)+(testosterone ×0.034)+(AZFc deletion -1.480)+(idiopathic NOA -0.855) [46]. To determine the overall effect of testosterone in the given equation, the coefficient associated with the testosterone variable is 0.034. This coefficient represents the change in probability for a one-unit change in the testosterone variable, holding all other variables constant. In other

words, for each one-unit increase in testosterone, the likelihood of finding sperm increases and vice versa. Plugging the equation with testosterone reduction (by one unit) will reduce the probability of finding sperm in the next SSR attempt by approximately 0.5%. Since the MD in TT drop is 3.81 (95% CI 0.55–7.06), we can predict a reduction in SSR between 0.3% and 3.2%. However, the drop in TT is usually associated with a compensatory increase in LH and FSH levels, which means a further profound reduction in the probability of successful sperm retrieval.

Corona et al [47] investigated the TESE prediction through meta-regression analysis, which showed that testicular sperm retrieval per cycle was independent of age and hormonal parameters at enrollment. They confirmed the value of testicular volume in prediction and proposed a cut-off level of >12.5 mL for a sperm retrieval rate >60% with an accuracy of 86.2%. However, we selected the prediction model proposed by Cissen et al [46], because of the substantial bias in the meta-analysis by Corona and his team. Esteves et al [48] reported a significantly higher percentage of patients with poor prognosis subjected to mTESE than those submitted to cTESE, besides the lack of documentation of the Sertoli cell only prevalence among the included articles. Moreover, Cissen and his team [46] proposed an equation that helps clinicians predict the TESE probability of any case with NOA as long as the variables are known.

To simplify the underlying pathophysiology, it is known that androgen-binding protein transports androgen to Sertoli cells, which bind to androgen receptors to regulate spermatogenesis [49,50]. At least four steroidogenic enzymes participate in testosterone synthesis: cytochrome P450 cholesterol side chain cleavage enzyme, 3β-hydroxysteroid dehydrogenase, cytochrome P450 17α-hydroxylase/17,20-lyase and 17β-hydroxysteroid dehydrogenase isoform 3. Testosterone metabolic enzyme steroid 5α-reductase 1 and 3α-hydroxysteroid dehydrogenase are expressed in some precursor Leydig cells [49]. Although the mechanism of disruption to spermatogenesis is known; its extent during and after the healing process remains unknown or somewhat unpredictable.

There is growing debate regarding hormonal therapy in eugonadal men with NOA to improve sperm retrieval [51]. Whether hormonal optimization before the second attempt, irrespective of the outcome of the first attempt, would maintain the same chance of sperm retrieval in the second attempt is not clear and warrants further research.

One of the signs associated with hypogonadism is a decrease in testis volume. The study by Okada et al [52] was not included in our analysis because the standard deviations were not shared. However, the authors reported that the frequency of testicular volume reduction after cTESE is ten folds higher than mTESE (10/40 [25.0%] in the cTESE group, compared to 2/80 [2.5%] in the mTESE). On the other hand, Schill et al's article [53] was excluded from the analysis because the authors reported the median values and the standard error of the mean. However, they did not document any reduction in testicular size despite reporting five pathological findings by postoperative ultrasonography.

Eliveld and her team [26] did not conduct a meta-analysis of testicular volume because all studies used different time points and TESE techniques. Nevertheless, we proceeded with the analysis despite the vast time frame ranging from six weeks [32] to 32 months [52]. Testicular size is unlikely to recover over time. Once a significant reduction in volume is observed in 6 weeks, the probability of recovery with further follow-up is remote. On the opposite side, a compensatory increase in LH and, to a lesser extent, FSH may correct TT levels. Therefore, TT follow-up for an extended period is more reasonable. The TESE technique was also not a barrier because of the iterative nature of the SSR process and wide variation in sampling number, size, intraoperative homeostasis, and closure of the tunica albuginea [54].

ED was assessed in 66 patients by Akbal et al [31]. The patients were evaluated with the IIEF-5 [55], and the Hospital Anxiety-Depression Scale [56]. Men who reported new onset ED six months after surgery, had a significant increase of FSH with insignificant elevation in LH levels, while the mean TT levels dropped significantly. Men who reported new-onset ED also reported both depression and anxiety. The authors concluded that failed SSR negatively affects erectile function due to hypogonadism, depression, and anxiety [31]. The higher probability of hypogonadism in men with unsuccessful SSR could be due to more harvested testicular tissue samples. However, the authors did not report the figures. Eliveld et al [34] reported sexual dysfunctions (hypoactive sexual desire and ED) in 4/177 (2.3%) of men with NOA and in one out of eleven men with KS (9.0%). The authors linked the sexual symptoms to

profound hypogonadism in the KS patients 4/11 (36.4%). Whether ED is related to changes in serum testosterone [31-39,57] or anxiety [31] the potential impact needs further investigations.

CONCLUSIONS

This study has some limitations. Heterogeneity in this study stems from differences in testicular histopathology [39,58]. In addition to the variations in the number of samples harvested, other factors such as the hemostasis technique, the closure, the operative time, and the wide range of time between SSR may affect the main outcome measures.

The results of our meta-analysis suggest a significant and possibly permanent reduction of TT levels following SSR. However, due to the varying follow-up periods in this meta-analysis, a long-term follow-up study with a sufficient sample size is needed to validate our findings. We recommend exploring the changes in TT levels after the SSR procedure and linking them to future TESE success when applicable. During patient counseling, it is imperative to consider sexual dysfunction and the possible adverse effects on future TESE.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: WZ, R Saleh, R Shah. Methodology: WZ. Data curation: WZ. Writing – original draft: all authors. Supervision: R Shah, AA. Validation: WZ. Writing – review & editing: WZ, R Saleh, AA.

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