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Impact of Varicocele Repair on Semen Parameters in Infertile Men: A Systematic Review and Meta-Analysis

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Purpose: Despite the significant role of varicocele in the pathogenesis of male infertility, the impact of varicocele repair (VR) on conventional semen parameters remains controversial. Only a few systematic reviews and meta-analyses (SRMAs) have evaluated the impact of VR on sperm concentration, total motility, and progressive motility, mostly using a before-after analytic approach. No SRMA to date has evaluated the change in conventional semen parameters after VR compared to untreated controls. This study aimed to evaluate the effect of VR on conventional semen parameters in infertile patients with clinical varicocele compared to untreated controls.

Materials and Methods: A literature search was performed using Scopus, PubMed, Embase, and Cochrane databases following the Population Intervention Comparison Outcome (PICOS) model (Population: infertile patients with clinical varicocele; Intervention: VR [any technique]; Comparison: infertile patients with clinical varicocele that were untreated; Outcome: sperm concentration, sperm total count, progressive sperm motility, total sperm motility, sperm morphology, and semen volume; Study type: randomized controlled trials and observational studies).

Results: A total of 1,632 abstracts were initially assessed for eligibility. Sixteen studies were finally included with a total of 2,420 infertile men with clinical varicocele (1,424 patients treated with VR vs. 996 untreated controls). The analysis showed significantly improved post-operative semen parameters in patients compared to controls with regards to sperm concentration (standardized mean difference [SMD] 1.739; 95% CI 1.129 to 2.349; $p < 0.001$; $I^2 = 97.6\%$), total sperm count (SMD 1.894; 95% CI 0.566 to 3.222; $p < 0.05$; $I^2 = 97.8\%$), progressive sperm motility (SMD 3.301; 95% CI 2.164 to 4.437; $p < 0.01$; $I^2 = 98.5\%$), total sperm motility (SMD 0.887; 95% CI 0.036 to 1.738; $p = 0.04$; $I^2 = 97.3\%$) and normal sperm morphology (SMD 1.673; 95% CI 0.876 to 2.470; $p < 0.05$; $I^2 = 98.5\%$). All the outcomes showed a high inter-study heterogeneity, but the sensitivity analysis showed that no study was sensitive enough to change these results. Publication bias was present only in the analysis of the sperm concentration and progressive motility. No significant difference was found for the semen volume (SMD 0.313; 95% CI -0.242 to 0.868; $I^2 = 89.7\%$).

Conclusions: This study provides a high level of evidence in favor of a positive effect of VR to improve conventional semen parameters in infertile men with clinical varicocele. To the best of our knowledge, this is the first SRMA to compare changes in conventional semen parameters after VR with changes in parameters of a control group over the same period. This is in contrast to other SRMAs which have compared semen parameters before and after VR, without reference to a control group. Our findings strengthen the available evidence and have a potential to upgrade professional societies' practice recommendations favoring VR to improve conventional semen parameters in infertile men.

Keywords: Male infertility; Semen; Varicocele

INTRODUCTION

Infertility is estimated to impact 15% of couples attempting to conceive worldwide [1]. The male partner is solely responsible in 17.1% of cases [2]. Varicoceles have been identified as the most common surgically correctable cause of male infertility [3]. They are common in the general male population being present in 15% of healthy men [4]. Additionally, 35% to 44% of men with primary infertility and 45% to 81% of men with secondary infertility have a varicocele [5,6]. In a study conducted by the World Health Organization (WHO), it was shown that men with varicocele had lower sperm concentration and motility than men without varicocele [7]. Another study carried out in healthy men in Europe identified deterioration in sperm quality even in men with a grade 1 varicocele [4].

The American Urological Association (AUA) and the American Society for Reproductive Medicine (ASRM) recommend surgical varicocele repair (VR) of clinical varicoceles in non-azoospermic infertile men with abnormal semen parameters (moderate recommendation; moderate evidence level) [8]. Unfortunately, the term “abnormal semen parameters” is not defined. These recommendations are based primarily on the study by Wang et al [9], in which the effect of different VR techniques on sperm concentration and sperm motility were meta-analyzed. In the latter study, surgical techniques with an inguinal and subinguinal approach had the greatest improvement in sperm concentration and sperm motility parameters (compared with the retroperitoneal technique) [8]. The European Association of Urology (EAU) also recommends VR in infertile men with a clinical varicocele, abnormal semen parameters, and without other male causes of infertility (strong recommendation; high evidence level) [10]. Again, the term “abnormal semen parameters” is not defined. These recommendations are essentially based on two meta-analyses (MAs) that reported an improvement of sperm concentration (mean difference [MD] 9.71 and $12.32 \times 10^6/\text{mL}$) [11,12], total sperm motility (MD 9.92% and 10.86%), progressive sperm motility (MD 9.69%), and sperm morphology (MD 3.16%) after microsurgical VR or surgical VR [11,12]. The European Academy of Andrology (EAA) asked the question differently, assessing the management of oligo-astheno-teratozoospermia (OAT) [13]. Based on the WHO study, which found a varicocele in a quarter of the 9,304 men with

OAT [7], the EAA advises discussing VR in infertile couples whose male partner has a palpable varicocele associated with OAT, highlighting the improvement of semen parameters [11,12] and/or fertility rates after VR [14,15].

Hence, although surgical VR is recommended in infertile men with a clinical varicocele and abnormal semen parameters, the sperm parameter(s) used to determine the indication for VR and to assess its efficacy are not detailed. According to a recent worldwide survey, it is also unclear whether VR is indicated or not in cases of isolated oligozoospermia, isolated asthenozoospermia, or isolated teratozoospermia [16].

Despite the well-established role of varicocele in the pathogenesis of male infertility, current literature does not provide enough data to draw firm conclusions as to the impact of VR on semen quality and male fertility potential. Several MAs have shown that it has a positive effect of VR on semen parameters [11,12,17,18]. However, the studies published to date addressing the effect of VR on semen characteristics have been criticized for many reasons such as the inclusion of men with subclinical varicoceles or normal semen parameters, poor study designs, significant drop-outs after randomization, selective reporting or inadequate sample size. Therefore, the aim of this systematic review and meta-analysis (SRMA) was to investigate the impact of VR on conventional semen parameters (semen volume and sperm concentration, total sperm count, total motility, progressive motility, and morphology) in infertile men with clinical varicocele when compared to a control group of infertile men with clinical varicocele that did not undergo VR (*i.e.*, no treatment). The results of the current report will provide an update of the impact of VR on semen parameters in infertile men by adding newer studies and analysing outcomes in comparison to a control group.

MATERIALS AND METHODS

1. Search strategy

A systematic search was conducted from May 2021 to August 2021 using Scopus, PubMed, Embase, and Cochrane databases. In the initial query string on Scopus, the entry term “varicoc*” was searched in combination (AND) with the terms “management” OR “embolization” OR “microsurg*” OR “micro-surg*” OR “repair” OR “correction” OR “treatment” OR “ligation”

OR “surg*” OR “operation” OR “radiolog*”. Alternative entry term was “varicocele”. To identify studies evaluating the effect of VR on semen parameters and natural pregnancy, additional keywords, were “sperm*” OR “semen” OR “ejaculate” OR “azoosperm*” OR “oligozoosperm*” OR “asthenozoosperm*” OR “teratozoosperm*” OR “necrozoosperm*” OR “fragmentation” OR “dna” OR “chromatin” OR “sdf” OR “azoo*” or “oxida*” OR “ros” OR “orp” OR “seminal” OR “astheno*” OR “terato*” OR “oligo*” OR “oxygen” OR “pregnan*” OR “conception” OR “child” OR “conceive*” OR “scsa” OR “tunel” OR “apoptosis” OR “time (AND) to (AND) pregnanc*” OR “fertil*” OR “offspring*”. The query “LIMIT TO (DOCTYPE , “ar”)” was used to limit retrieve only original studies. The same combination of terms was used for PubMed, Embase, and Cochrane databases.

The search strategy was performed in compliance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [19] and the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [20]. Abstracts of the retrieved articles were independently screened by researchers in duplicate and assessed to confirm their eligibility by 48 researchers, who worked in pairs. Disagreements were resolved by a third person.

The protocol of this SRMA has been registered in the PROSPERO database (ID 329842).

2. Selection criteria

This SRMA included all published studies on infertile men with clinical varicocele that measured conventional semen parameters in varicocele-treated patients *vs.* untreated controls. There was no language restriction as translation to English was performed by native language researchers. All eligible studies were selected following the PICOS (Population, Intervention, Comparison, Outcome, Study type) model (Supplement Table 1) [21]. Studies on azoospermia, subclinical varicocele, animal studies, *in vitro* studies, case reports, and case series were excluded.

3. Data extraction

Data extraction was performed by 37 well-trained researchers (24 active researchers and 13 assistant team leaders) divided in four teams, under the supervision of twelve team leaders and co-team leaders. The following data were collected: study design, characteristics of varicocele (laterality, grade, classification used for

grading) and VR (method, laterality), time from VR to last follow-up evaluation, number of patients and controls, semen analysis data - semen volume (mL), sperm concentration ($\times 10^6/\text{mL}$), total sperm count ($\times 10^6$), sperm vitality (%), total sperm motility (%), progressive motility (%), normal morphology (%), in the infertile men that underwent VR *versus* a control group that received no treatment. Data were extracted by one researcher and verified by a second researcher. Any disagreements were resolved by a third senior researcher.

4. Quality assessment

The quality of evidence of the included studies was assessed using the following checklists: the Cambridge Quality Checklist [22], which was applied to observational studies (case-control and cohort), the Cochrane Risk of Bias [23], the Jadad score [24], and the CONSORT (consolidated standards of reporting trials) guidelines [25] which were applied to randomized controlled trials (RCTs). Each study was independently evaluated by two researchers, and disagreements were resolved by a third researcher.

5. Statistical analysis

1) Quantitative data analysis

We used Comprehensive Meta-Analysis Software (Version 2; Biostat Inc., Englewood, NJ, USA) for performing MA on quantitative data. We chose the standardized mean difference (SMD) as the effect size for statistical comparison between cases and controls, which allows the comparison even between those studies which did not measure the outcome using the same instruments. Cochran's Q test and heterogeneity index (I^2) were used to assess heterogeneity across pooled studies, with $p < 0.10$ considered as statistically significant [26]. I^2 is an indicator of heterogeneity and lies between 0% and 100%, where $< 25\%$ suggests low heterogeneity, 50% suggests moderate heterogeneity, and 75% suggests high heterogeneity [27]. The pooled effect size was calculated using either the fixed effect or random effects models, depending upon the level of heterogeneity. In case of low heterogeneity, the fixed effect model was adopted while in case of significant heterogeneity, random effects model was adopted. High resolution forest plots were generated for the SMD and confidence interval (CI) for all studies and the pooled data [28].

2) Cumulative analysis

Cumulative analysis was performed to assess the chronological trend of statistical significance over a period of time. For this, the effect size and the corresponding CI were calculated after the addition of each new study in a temporal manner. The trend of p-value and statistical inference was used to draw inferences regarding the strength of the association, its vulnerability to variations and the history of variations.

3) Sensitivity analysis

The pooled effect size and the corresponding CI were calculated after exclusion of one study at a time. A study resulting in the change of inference upon its exclusion was labelled as a 'sensitive study'.

4) Publication bias analysis

Publication bias was qualitatively analysed by the asymmetry of the funnel plot, which suggested some missing studies on one side of the graph. For quantita-

tive analysis of publication bias, we employed Egger's intercept test, which evaluated statistical significance of publication bias. In case of the presence of publication bias, unbiased estimates were calculated using the 'trim and fill' method [29].

The results were independently verified by four experienced biostatisticians (Rajender Singh, Ahmed Harraz, Ralf Henkel, Nicolas Garrido), and their independent analysis showed full agreement. The results reported in this article were analyzed by Rajender Singh.

RESULTS

Using the above-mentioned search strategy, 1,632 abstracts were extracted. After the removal of 661 duplicates, 971 abstracts were assessed. Of these, 100 articles were identified by title and abstract as review articles, case reports, book chapters, papers on different topics or duplicates and were judged ineligible. Of the

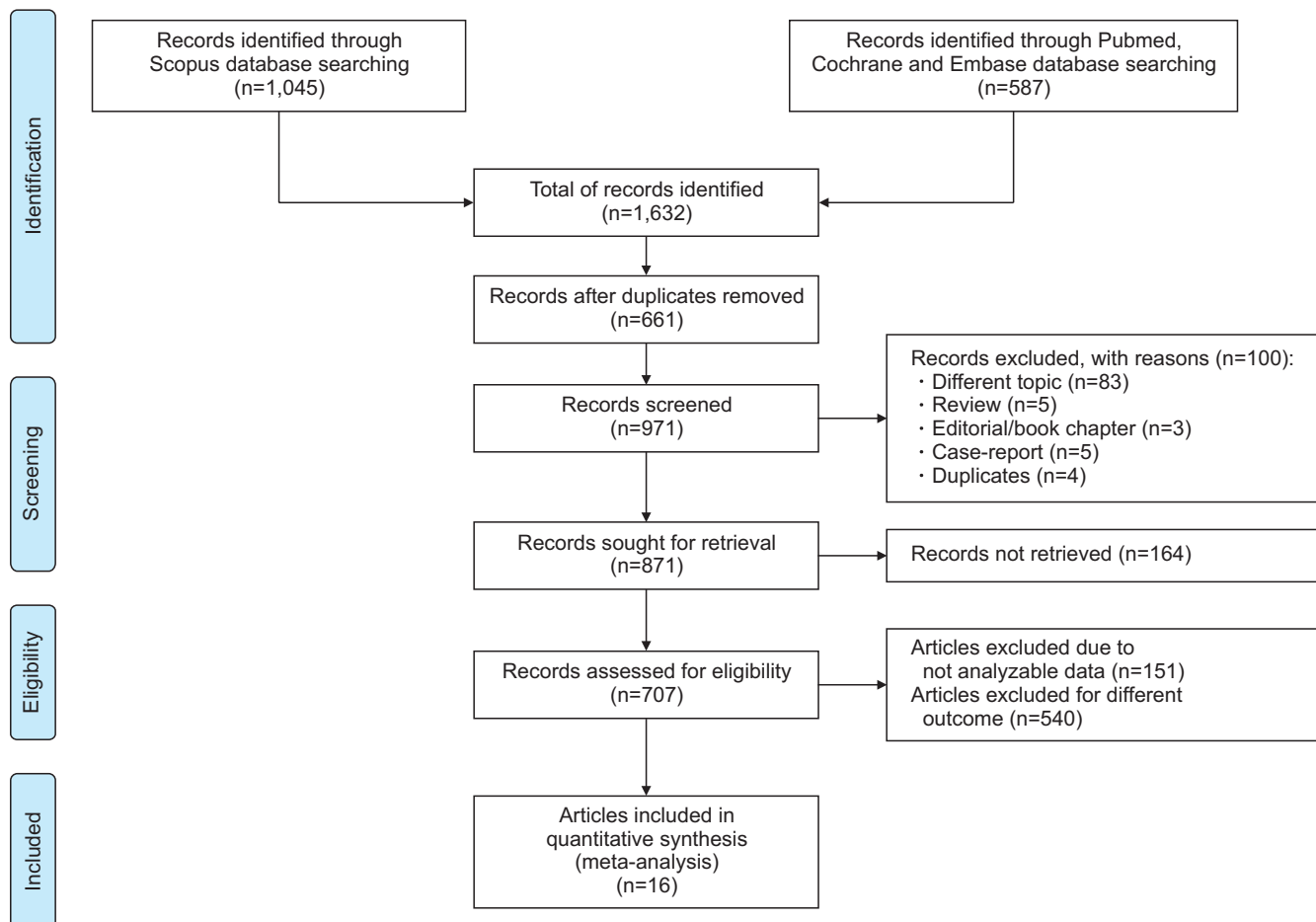


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart.

remaining 871 articles, 164 full-texts were not found, whereas 151 were definitively excluded after reading the full-text because they did not contain analyzable

data. Finally, 537 articles included data of VR in the context of male infertility treatment. Of these, 19 studies assessing the impact of VR *versus* no treatment on

Table 1. Main characteristics of the included studies

First author	Year	Study design	Patients (n)	Controls (n)	Type of VR	Timing of the evaluation (mo)	Outcome					
							SV	SC	TSC	TM	PM	SM
Turgut [35]	2020	Observational	52	36	Microsurgical	3		x		x		x
Gomaa [30]	2018	Observational	45	45	Microsurgical	6	x	x	x	x	x	x
Ketabchi [45]	2018	RCT	24	28	Microsurgical	6			x			
McGarry [31]	2015	Observational	290	155	Microsurgical	6	x	x		x		
Gokce [36]	2013	Observational	168	138	Microsurgical	3		x	x	x	x	x
Mansour Ghanaie [37]	2012	RCT	68	68	NMI	12		x	x		x	x
Ghanem [38]	2011	Observational	64	27	Embolization	12		x			x	x
Abdel-Meguid [39]	2011	RCT	73	72	Microsurgical			x			x	x
Sathya Srini [40]	2011	Observational	100	100	Microsurgical	12		x				
Seo [32]	2010	Observational	25	25	Microsurgical	6	x			x		x
Çakan [33]	2008	Observational	28	23	Unspecified	12	x			x		x
Di Bisceglie [41]	2007	Observational	38	40	Embolization	6		x			x	x
Di Bisceglie [42]	2003	Observational	223	77	Embolization	6		x			x	x
Grasso [43]	2000	RCT	34	34	Microsurgical	12		x			x	x
Okuyama [44]	1988	Observational	141	83	HR	84		x			x	
Nilsson [34]	1979	RCT	51	45	NMI	74	x	x	x	x		

HR: high retroperitoneal, NMI: non-microsurgical, PM: progressive motility, RCT: randomized controlled trial, SC: sperm concentration, SM: sperm morphology, SV: semen volume, TM: total motility, TSC: total sperm count, VR: varicocele repair.

Table 2. Quality of evidence assessment (results of the Cambridge Quality Checklist [22], Cochrane Risk of Bias for Randomized controlled trials [23], CONSORT guidelines [25] and Jadad score [24])

First author	Year	Cambridge Quality Checklist				Cochrane risk of bias for RCTs	CONSORT guidelines (0–25)	Jadad (1–5)
		Checklist for correlates (0–5)	Checklist for risk factors (1–3)	Checklist for causal risk factor (1–7)	Total score (2–15)			
Turgut [35]	2020	1	2	4	7			
Gomaa [30]	2018	2	3	6	11			
Ketabchi [45]	2018					High	15	1
McGarry [31]	2015	3	2	4	9			
Gokce [36]	2013	1	2	6	9			
Mansour Ghanaie [37]	2012					High	14	1
Ghanem [38]	2011	2	3	6	11			
Abdel-Meguid [39]	2011					High	23	5
Sathya Srini [40]	2011	1	3	6	10			
Seo [32]	2010	0	2	6	8			
Çakan [33]	2008	3	2	6	11			
Di Bisceglie [41]	2007	1	3	6	10			
Di Bisceglie [42]	2003	3	2	4	9			
Grasso [43]	2000					High	16	2
Okuyama [44]	1988	1	3	6	10			
Nilsson [34]	1979					Low	10	2

CONSORT: consolidated standards of reporting trials, High: high quality evidence, Low: low quality evidence, RCT: randomized controlled trial.

basic semen parameters were included in the present analysis (Fig. 1). A full list of excluded studies, with reason, is provided in Supplement Table 2.

Among the 19 included studies, 5 reported data on semen volume [30-34], 13 reported sperm concentration [30,31,34-44], 5 reported total sperm count [30,34,36,37,45], 7 reported total sperm motility [30-36], 9 reported progressive sperm motility [30,36-39,41-44], and 11 reported

data on sperm morphology [30,32,33,35-39,41-43]. The main characteristics of the included studies are shown in Table 1.

1. Quality of evidence of included studies

Among the 19 included studies, 11 had an observational design and were evaluated using the Cambridge quality checklist; 5 were RCTs and were evaluated us-

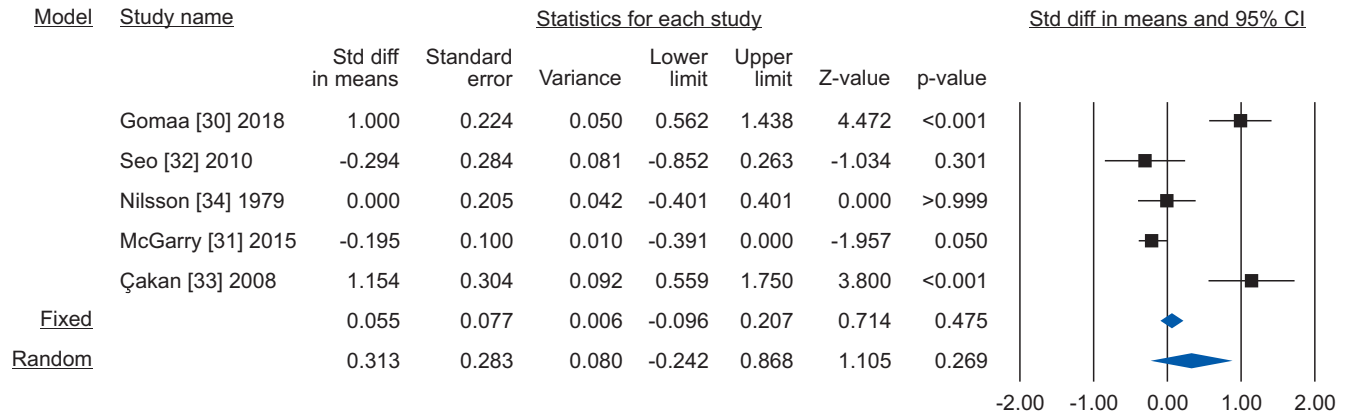


Fig. 2. Forest plot of the semen volume in infertile men with varicocele repair compared to no treatment.

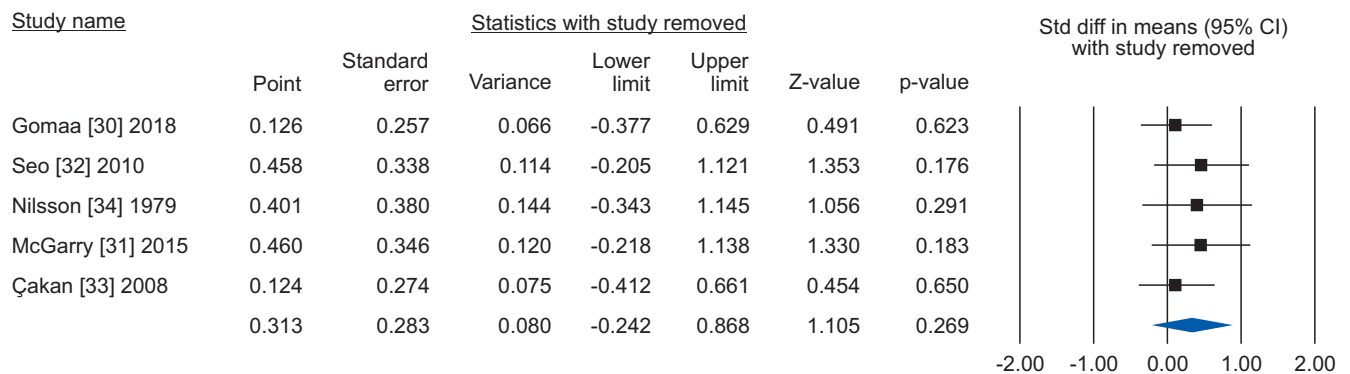


Fig. 3. Forest plot of the semen volume in infertile men with varicocele repair compared to no treatment: sensitivity analysis.

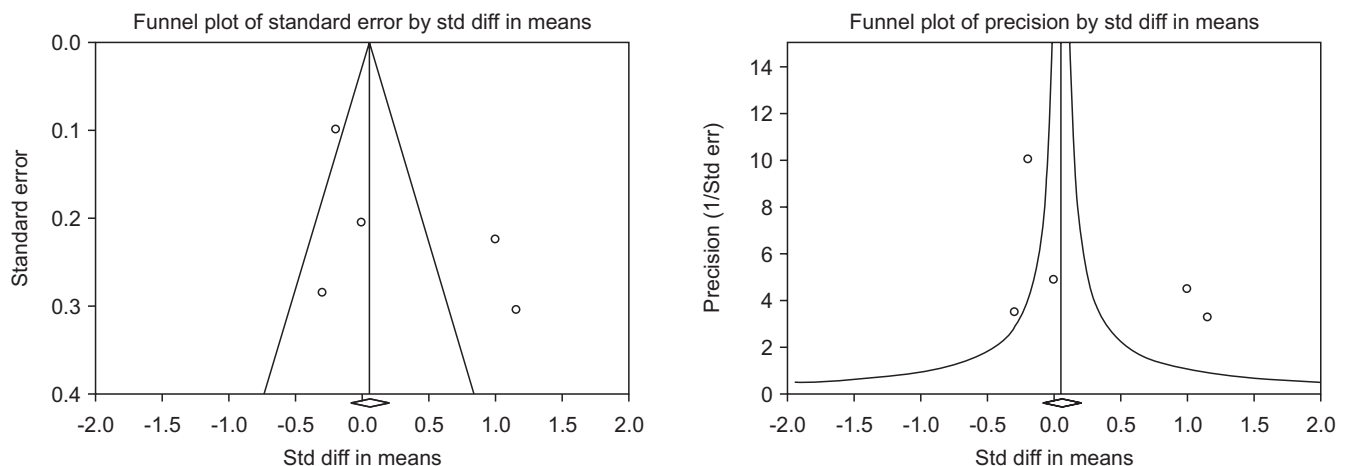


Fig. 4. Funnel plot of the semen volume in infertile men with varicocele repair compared to no treatment.

ing the Cochrane risk bias for RCTs, the CONSORT, and the Jadad's tools (Table 2).

Although the Cambridge scale does not establish a precise threshold to differentiate between high quality and low quality studies, out of a total score of 15, 6 studies scored ≥ 10 [30,33,38,40,41,44], while 5 studies scored 7 to 9 [31,32,35,36,42].

Among the RCTs, the quality of 4 out of 5 studies was ranked as high using the Cochrane's tool [37,39,43,45]. The CONSORT and the JADAD's scales both identified the best quality study among the 4 [39]. Only one RCT's

was judged as of low quality [34].

2. Semen volume

Five [30-34] including 732 patients, 439 cases and 293 controls, reported changes of semen volume. At random effect, SMD was 0.313 (95% CI -0.242 to 0.868; $I^2=89.7\%$; $p>0.05$). Hence, VR non-significantly increased the semen volume (Fig. 2). At the sensitivity analysis no study was sensitive enough to change this conclusion (Fig. 3). Also, Egger's regression model and funnel plots reported no risk of bias (intercept=4.23; 95% CI -4.94 to

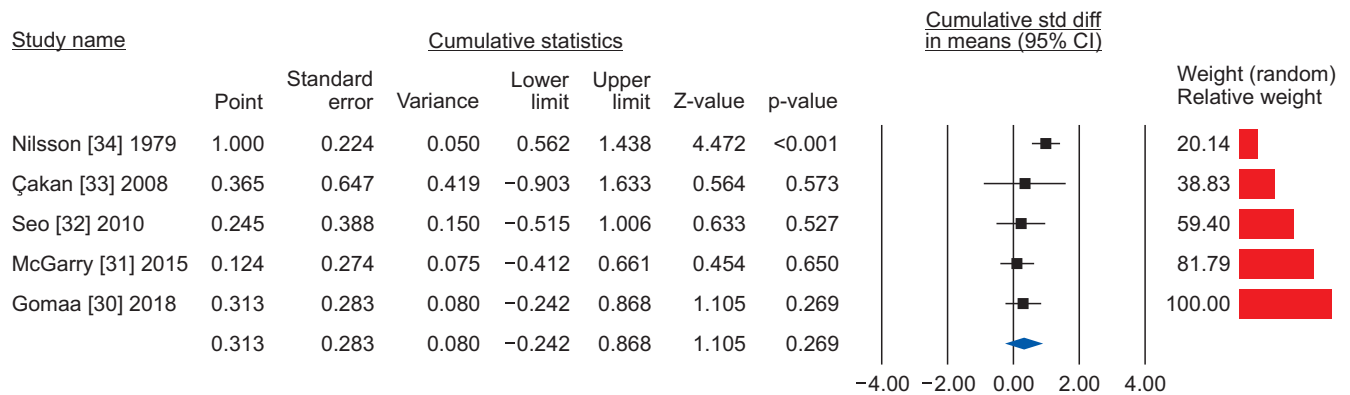


Fig. 5. Forest plot of the semen volume in infertile men with varicocele repair compared to no treatment: cumulative analysis.

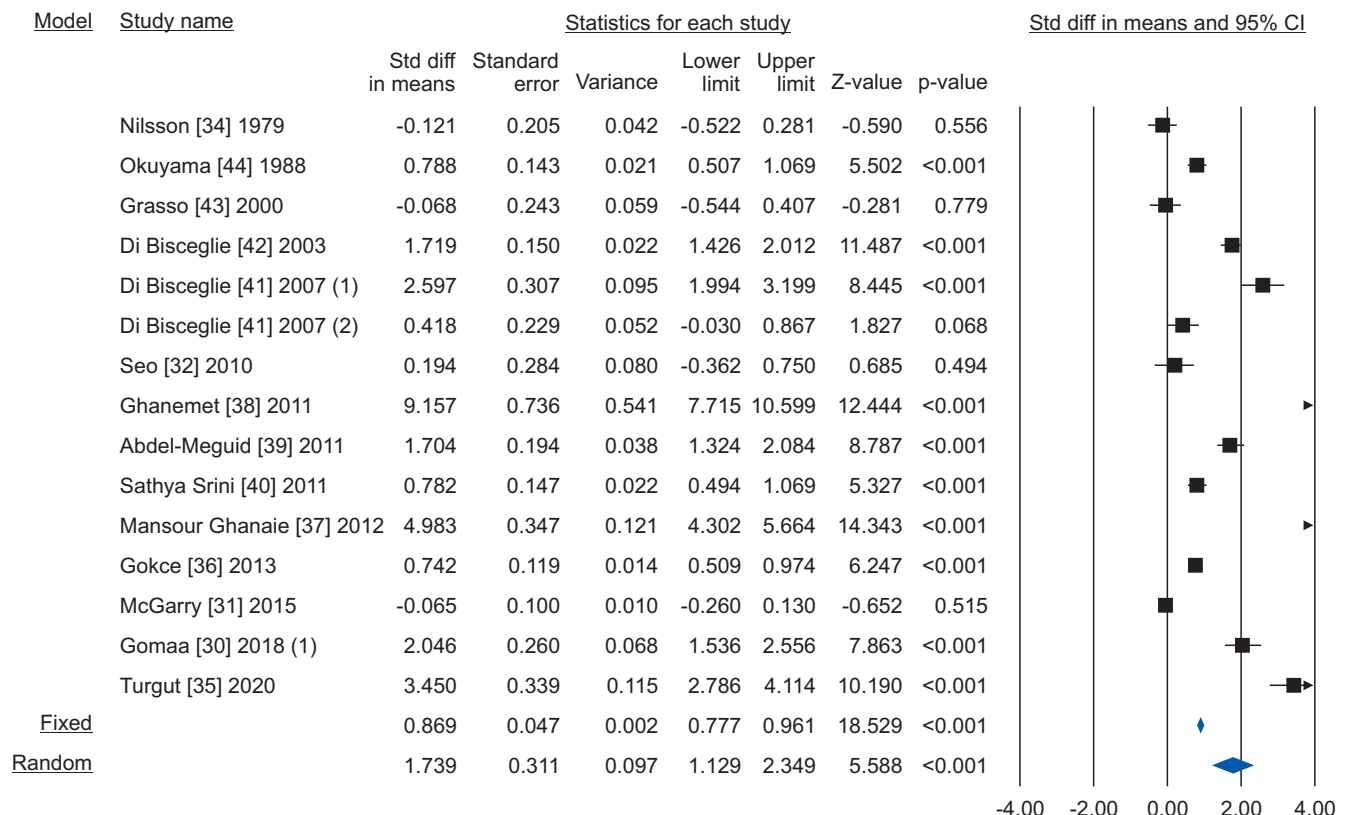


Fig. 6. Forest plot of the sperm concentration in infertile men with varicocele repair compared to no treatment.

13.40; $p=0.23$) (Fig. 4). Cumulative analysis showed consistent non-significant change in semen volume, except the first study [34] (Fig. 5).

3. Sperm concentration

Fourteen studies including 2,267 subjects (1,347 cases vs. 920 controls) evaluated the sperm concentration parameter [30-32,34-44]. Due to the presence of significant heterogeneity, as demonstrated by the Q-test (Q-

value=579.085; $p<0.001$) and the $I^2=97.6\%$, the random effect model was used. There was a significant increase in sperm concentration in favour of VR (SMD 1.739; 95% CI 1.129 to 2.349; $p<0.001$) (Fig. 6). No study was significantly sensitive enough to alter the above results (Fig. 7). There was a significant publication bias as demonstrated by the Egger's test ($p<0.001$) and the asymmetrical funnel plots (Fig. 8). Cumulative analysis showed that sperm concentration achieved significant

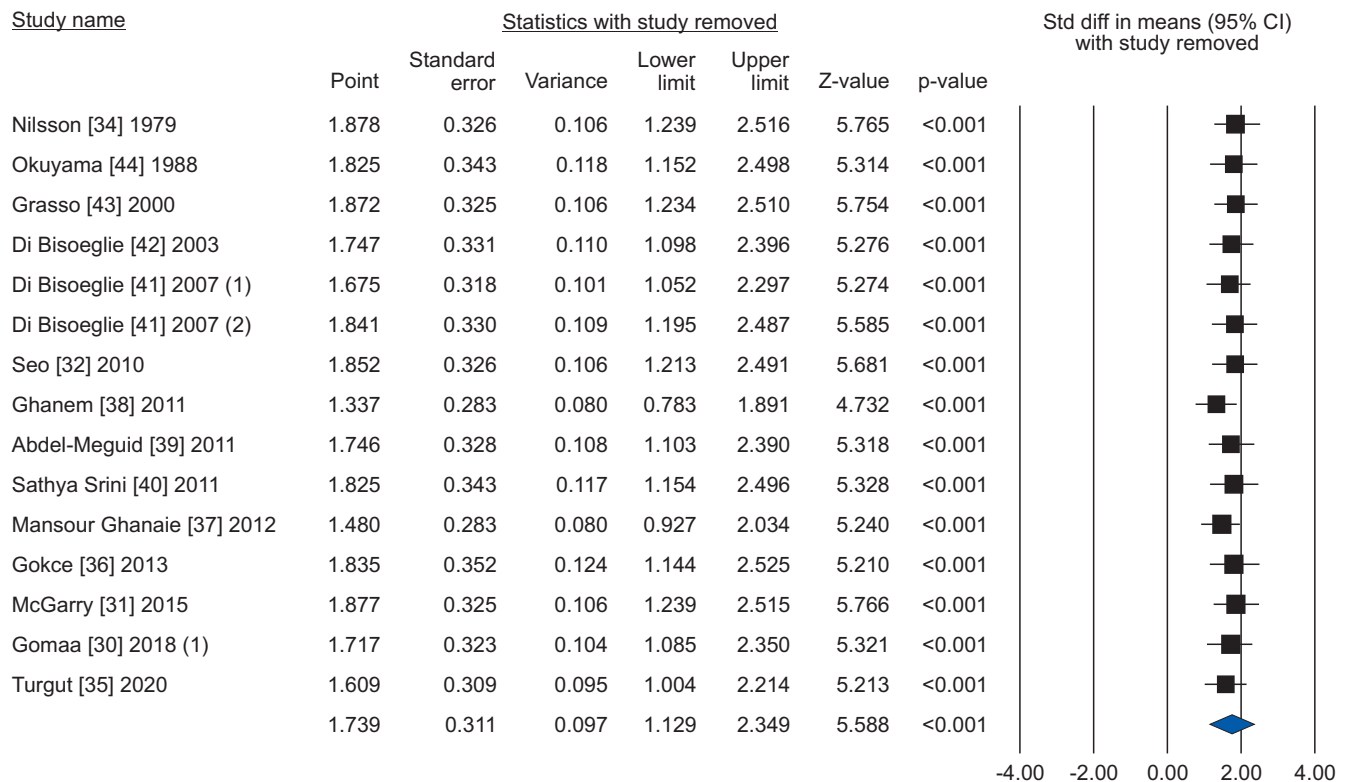


Fig. 7. Forest plot of the sperm concentration in infertile men with varicocele repair compared to no treatment: sensitivity analysis.

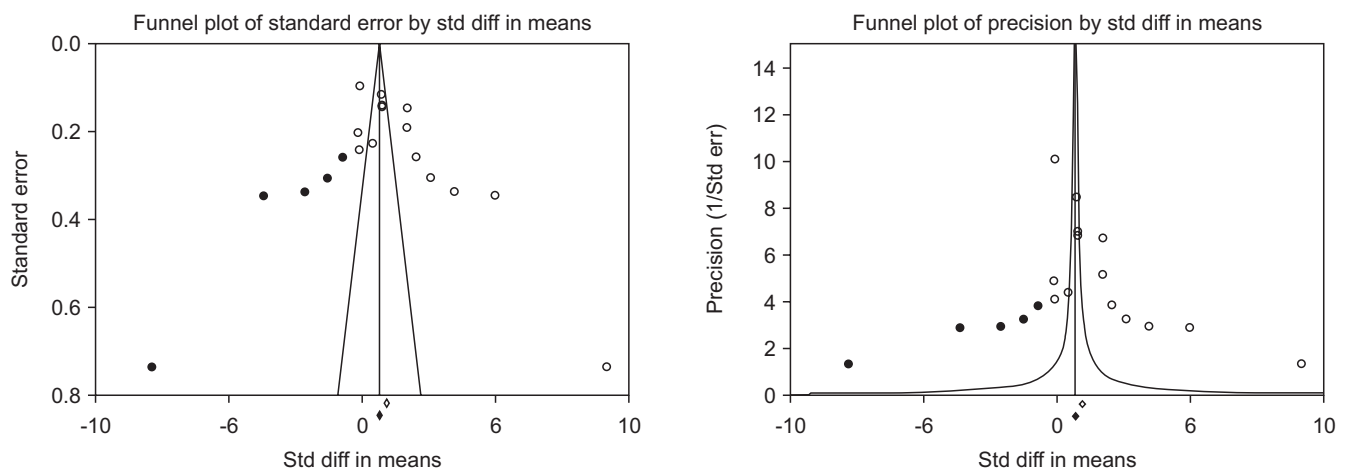


Fig. 8. Funnel plot of the sperm concentration in infertile men with varicocele repair compared to no treatment.

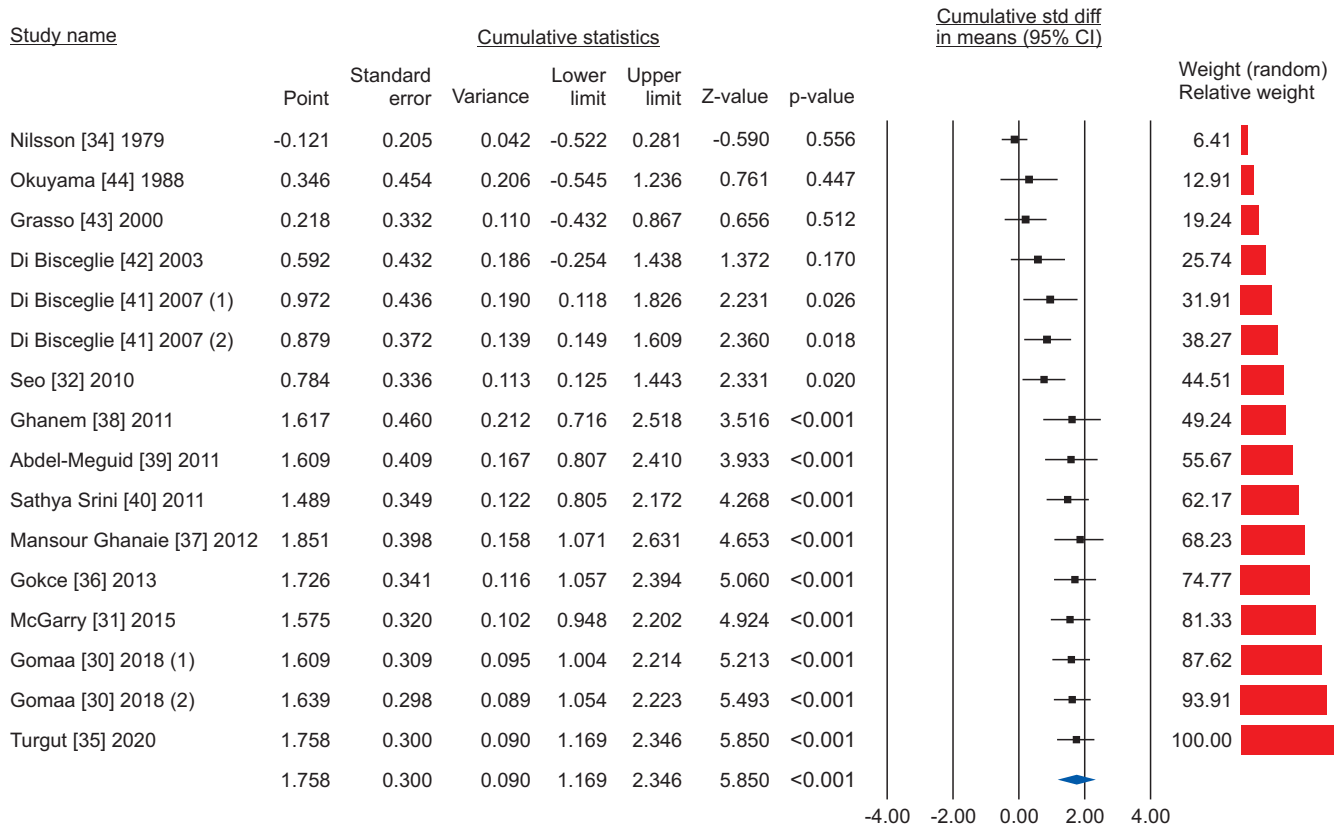


Fig. 9. Forest plot of the sperm concentration in infertile men with varicocele repair compared to no treatment: cumulative analysis.

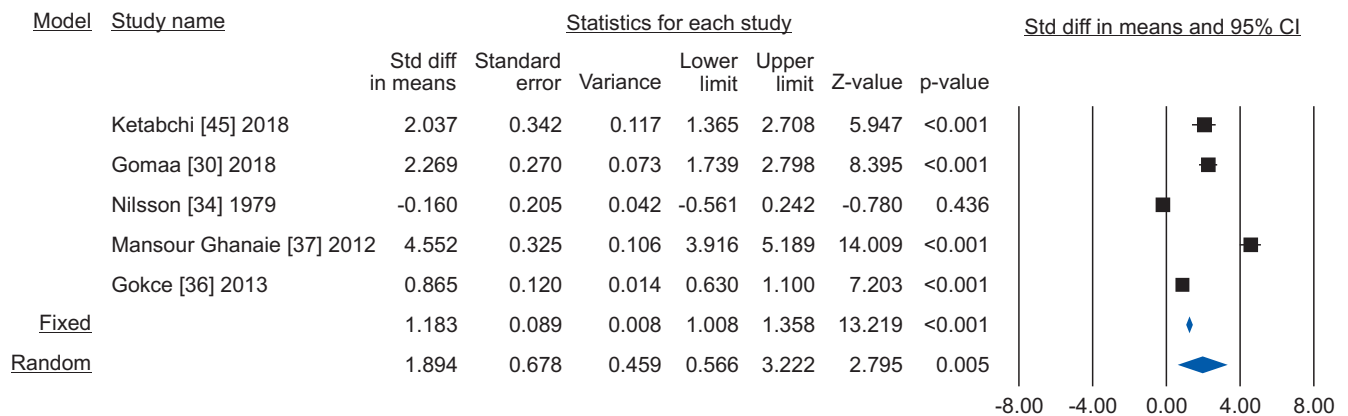


Fig. 10. Forest plot of the total sperm count in infertile men with varicocele repair compared to no treatment.

association with the addition of Di Bisceglie et al [41] in the pool and has stayed significant after that (Fig. 9).

4. Total sperm count

Five studies reported the total sperm count in patients treated with VR against no treatment, for a total of 1,073 patients, including 622 cases and 451 controls [30,34,36,37,45]. The analysis showed a significant improvement in the total sperm count (SMD 1.894; 95% CI

0.566 to 3.222; $p < 0.05$; $I^2 = 97.8\%$) (Fig. 10), and no study was sensitive enough to change this conclusion (Fig. 11). There wasn't significant publication bias as demonstrated by the Egger's test ($p > 0.05$) and the symmetrical funnel plots (Fig. 12). Cumulative analysis showed that total sperm count achieved significance with the addition of Ketabchi et al [45] and stayed significant after that (Fig. 13).

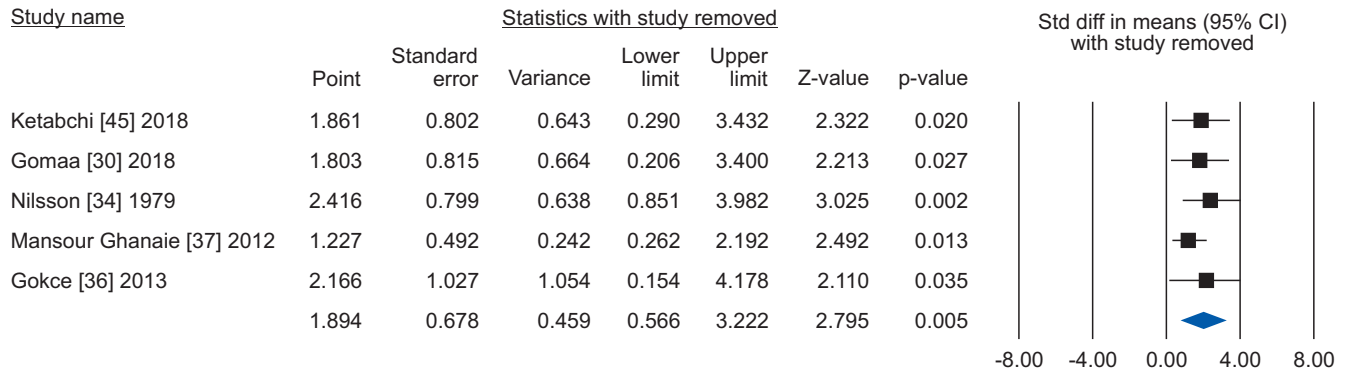


Fig. 11. Forest plot of the total sperm count in infertile men with varicocele repair compared to no treatment: sensitivity analysis.

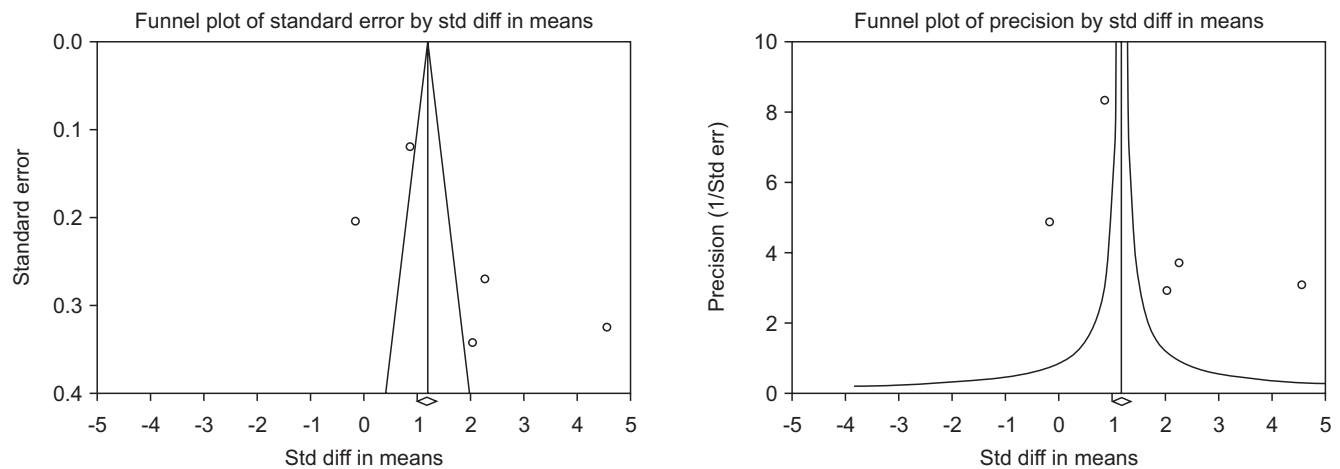


Fig. 12. Funnel plot of the total sperm count in infertile men with varicocele repair compared to no treatment.

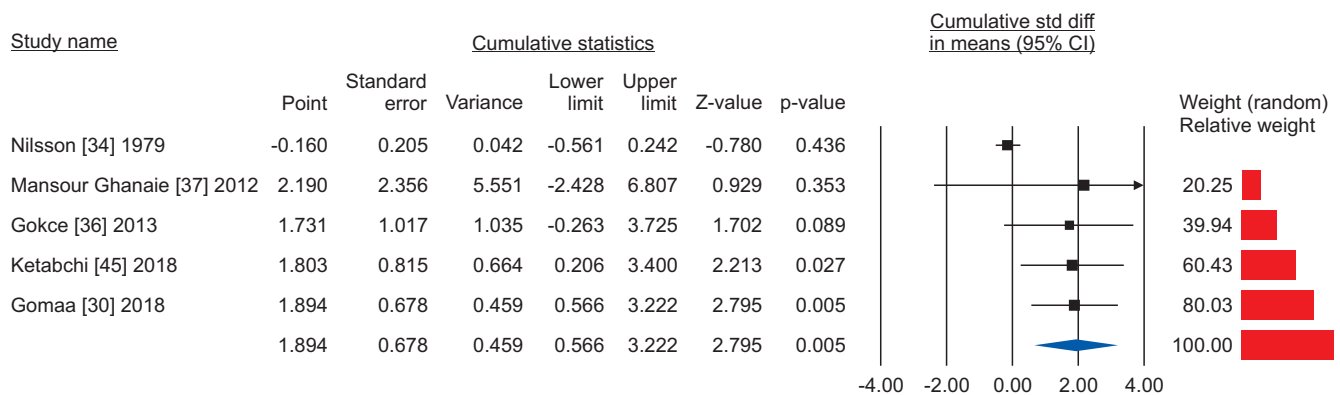


Fig. 13. Forest plot of the total sperm count in infertile men with varicocele repair compared to no treatment: cumulative analysis.

5. Progressive sperm motility

Nine studies assessing the effect of VR on sperm progressive motility were eligible for the analysis [30,36-39,41-44]. The statistical analysis of 1,438 cases (854 cases *vs.* 584 controls) on progressive sperm motility indicated considerable heterogeneity ($I^2=98.5\%$); however, VR demonstrated improvement in all nine studies. The

effect of VR were more distinct in the series of Mansour Ghanaie et al [37] and Di Bisceglie et al [42]. The pooled analysis indicates that VR enhanced progressive sperm motility significantly (SMD 3.301; 95% CI 2.164 to 4.437; $p<0.01$) (Fig. 14). At the sensitivity analysis, no study was sensitive enough to change this conclusion (Fig. 15). Furthermore, publication bias was present,

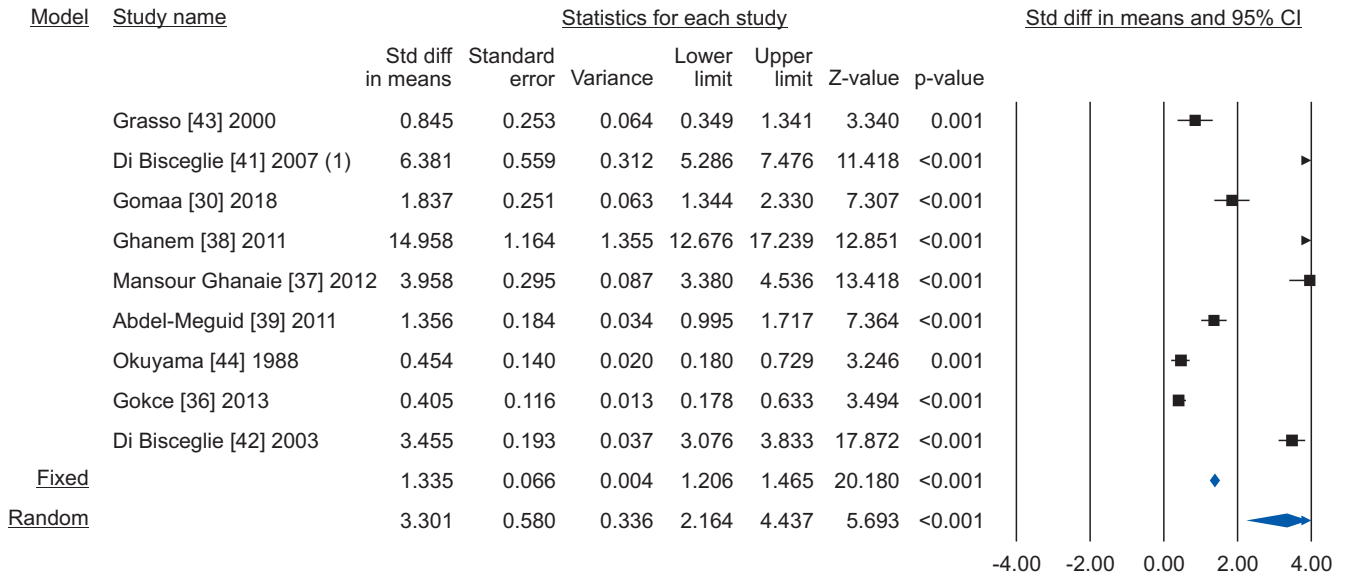


Fig. 14. Forest plot of the progressive sperm motility in infertile men with varicocele repair compared to no treatment.

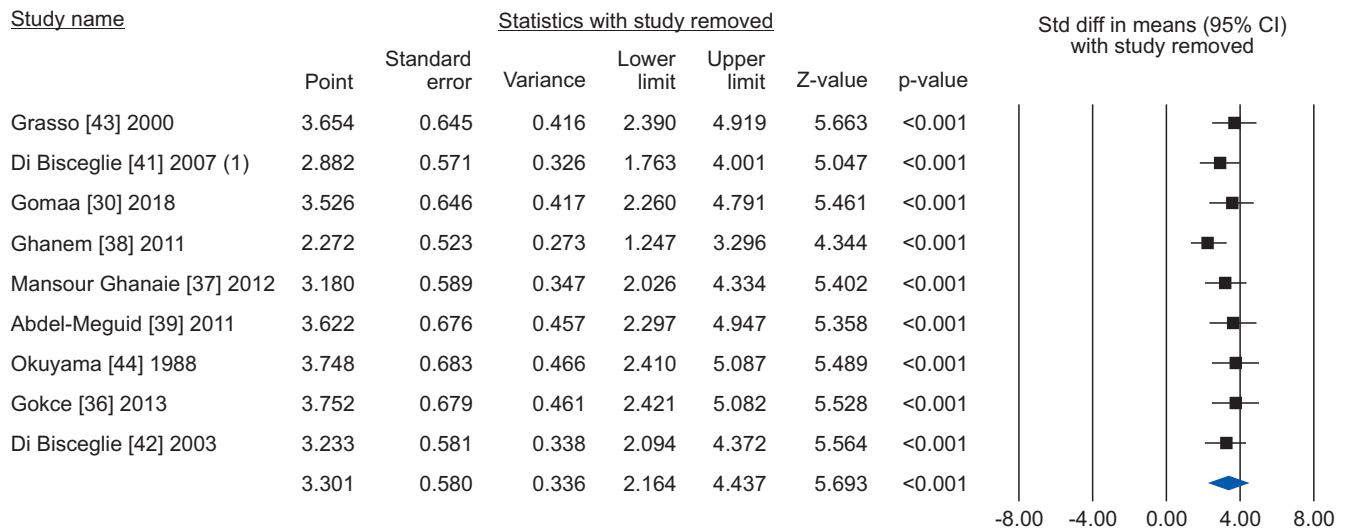


Fig. 15. Forest plot of the progressive sperm motility in infertile men with varicocele repair compared to no treatment: sensitivity analysis.

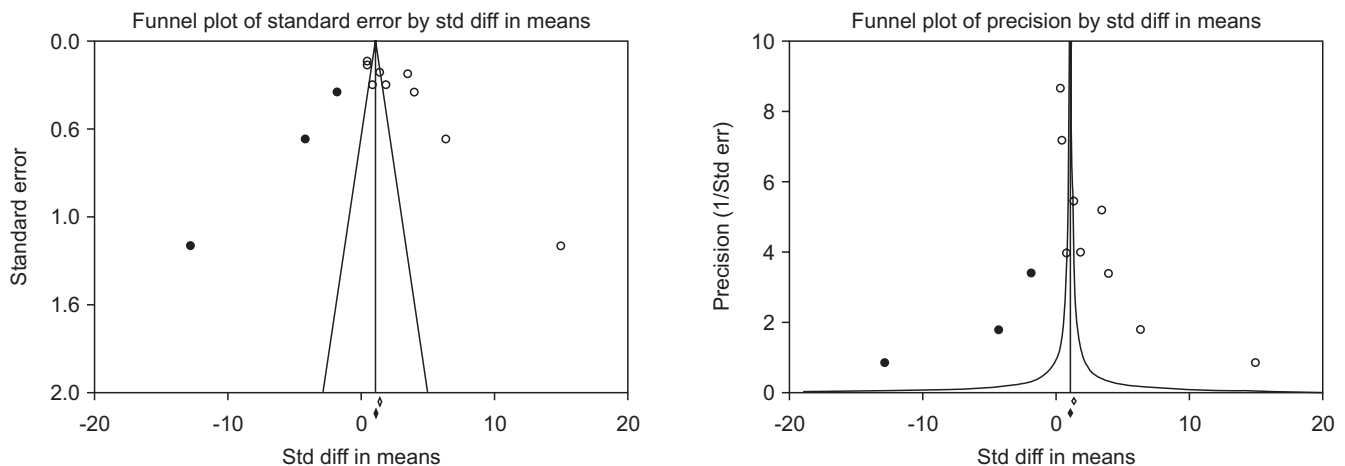


Fig. 16. Funnel plot of the progressive sperm motility in infertile men with varicocele repair compared to no treatment.

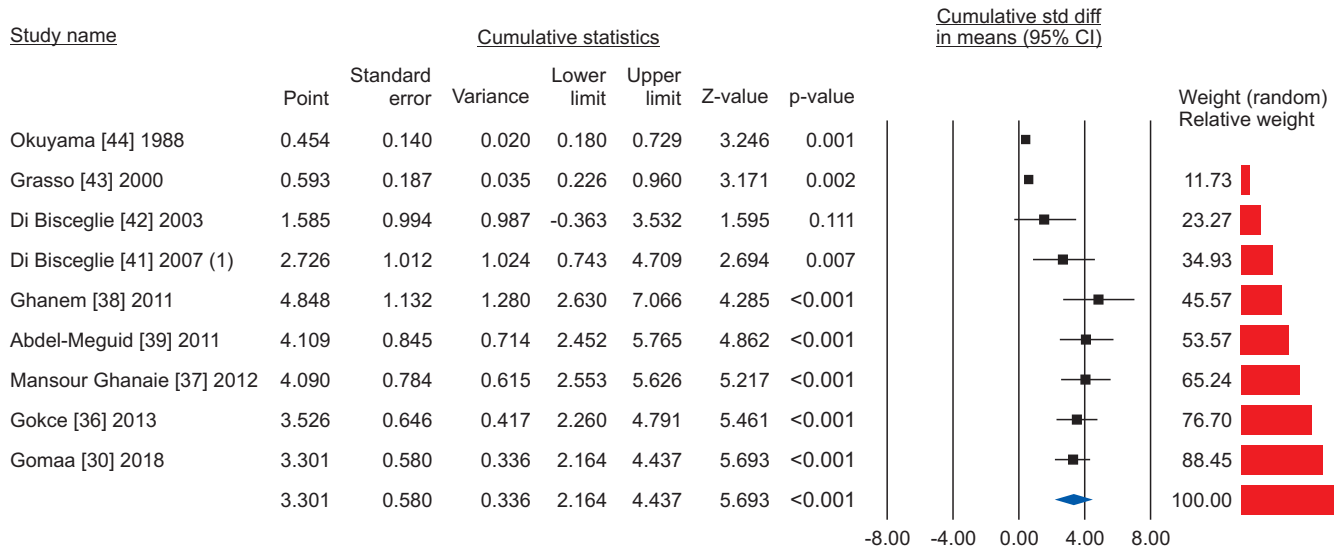


Fig. 17. Forest plot of the progressive sperm motility in infertile men with varicocele repair compared to no treatment: cumulative analysis.

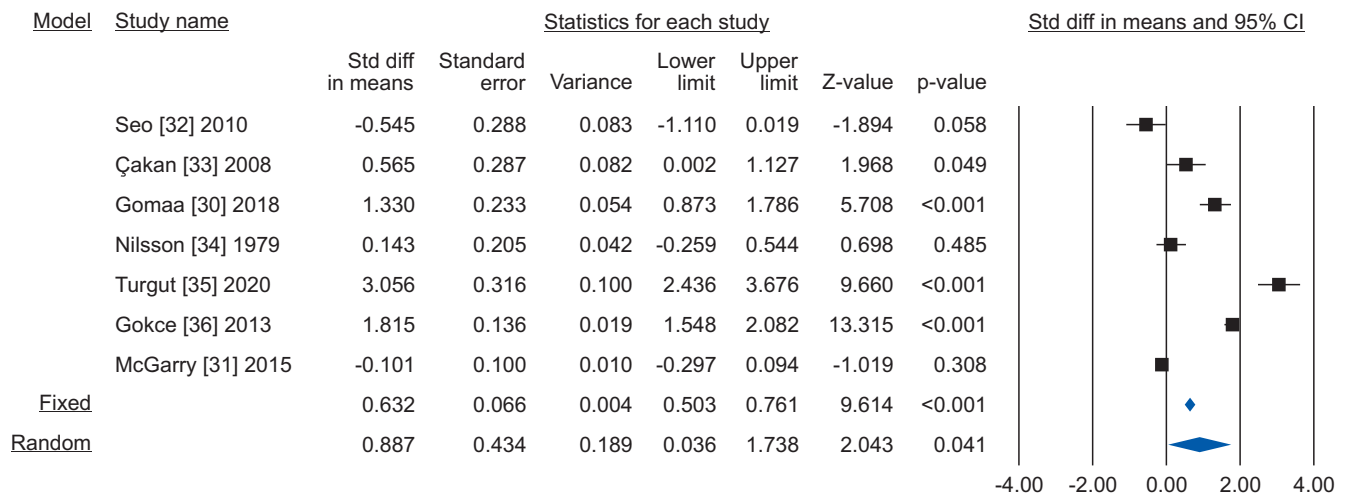


Fig. 18. Forest plot of the total sperm motility in infertile men with varicocele repair compared to no treatment.

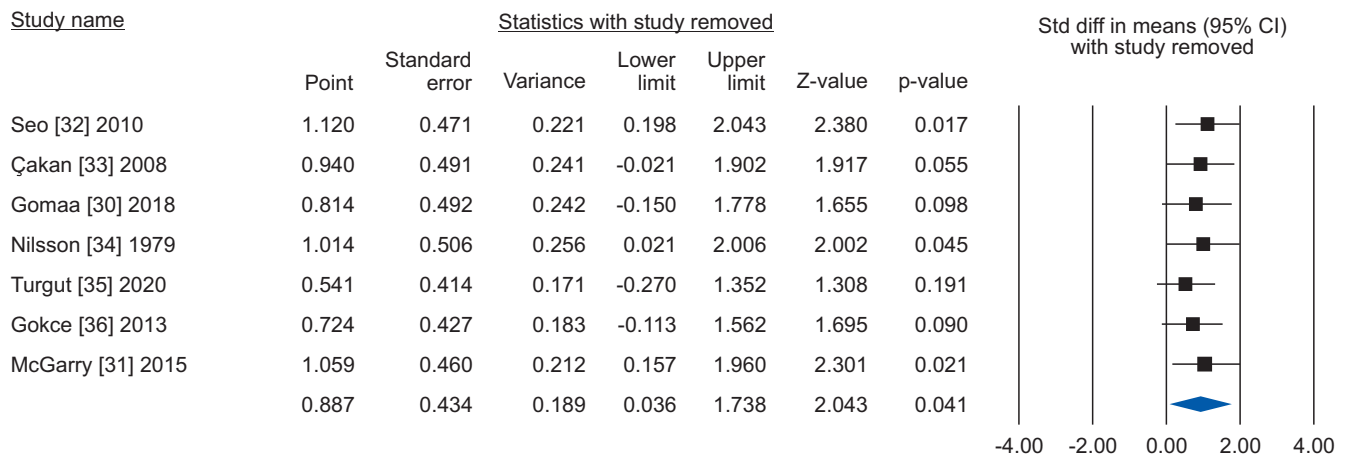


Fig. 19. Forest plot of the total sperm motility in infertile men with varicocele repair compared to no treatment: sensitivity analysis.

as demonstrated by the Egger's test ($p < 0.001$) and the asymmetrical funnel plots (Fig. 16). The adjusted values were SMD 3.239 (95% CI 0.030 to 2.448). Cumulative analysis showed that progressive sperm motility became significant after the addition of Di Bisceglie et al [41] and has stayed significant after that (Fig. 17).

6. Total sperm motility

The random-effects model of 7 studies involving 1,126 participants, 659 who underwent VR and 467 controls [30-36] showed that there was a significant improvement in total sperm motility in the VR group (SMD 0.887; 95% CI 0.036 to 1.738; $p = 0.041$) (Fig. 18). The inter-study heterogeneity was high ($I^2 = 97.3%$). No study was sensitive enough to change the conclusion that VR improves total sperm motility (Fig. 19). No publication bias was found, as demonstrated by the Egger test re-

sults ($p > 0.05$) and the symmetry of the funnel plots (Fig. 20). Cumulative analysis showed that total sperm motility is slightly significant and is highly vulnerable to changes with the addition of further studies (Fig. 21).

7. Sperm morphology

A total of 11 studies included normal sperm morphology in their outcome, overall including 818 cases and 585 controls [30,32,33,35-39,41-43]. There was a significant improvement in normal sperm morphology (SMD 1.673; 95% CI 0.876 to 2.470; $p < 0.05$) (Fig. 22). Furthermore, significant inter-study heterogeneity was found ($I^2 = 98.5%$). Also, sensitivity analysis was performed and no study was sensitive enough to change this conclusion (Fig. 23). Furthermore, publication bias was not present, as demonstrated by the Egger's test ($p > 0.05$) and the symmetrical funnel plots (Fig. 24). Cumula-

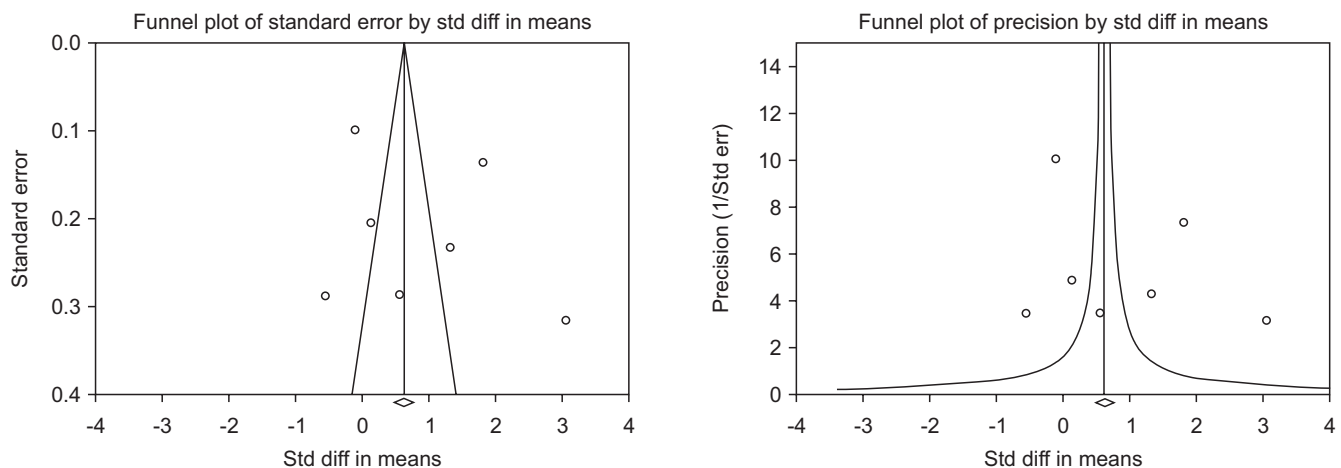


Fig. 20. Funnel plot of the total sperm motility in infertile men with varicocele repair compared to no treatment.

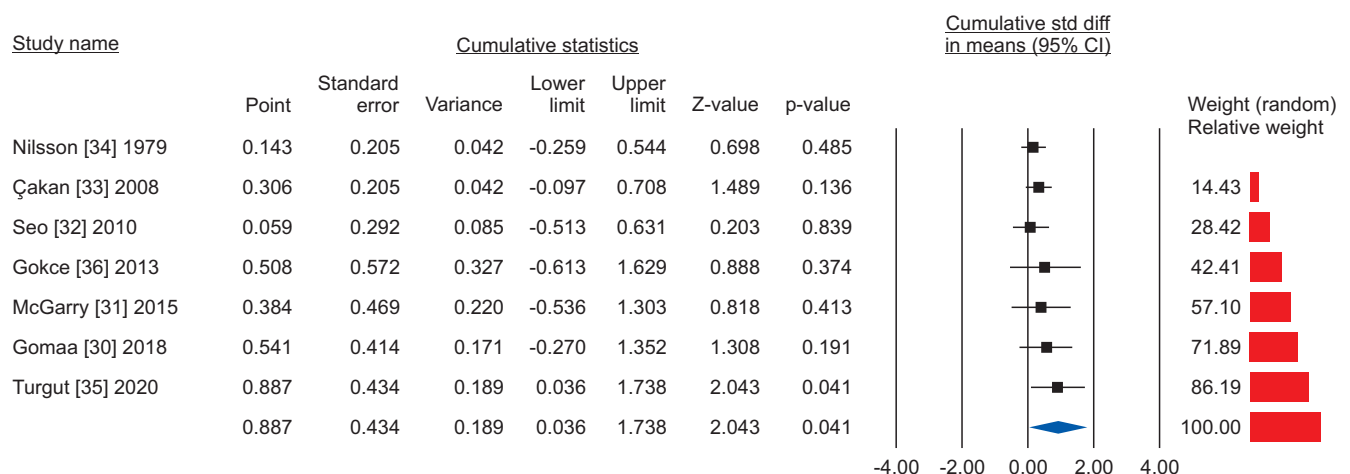


Fig. 21. Forest plot of the total sperm motility in infertile men with varicocele repair compared to no treatment: cumulative analysis.



Fig. 22. Forest plot of the sperm morphology in infertile men with varicocele repair compared to no treatment.

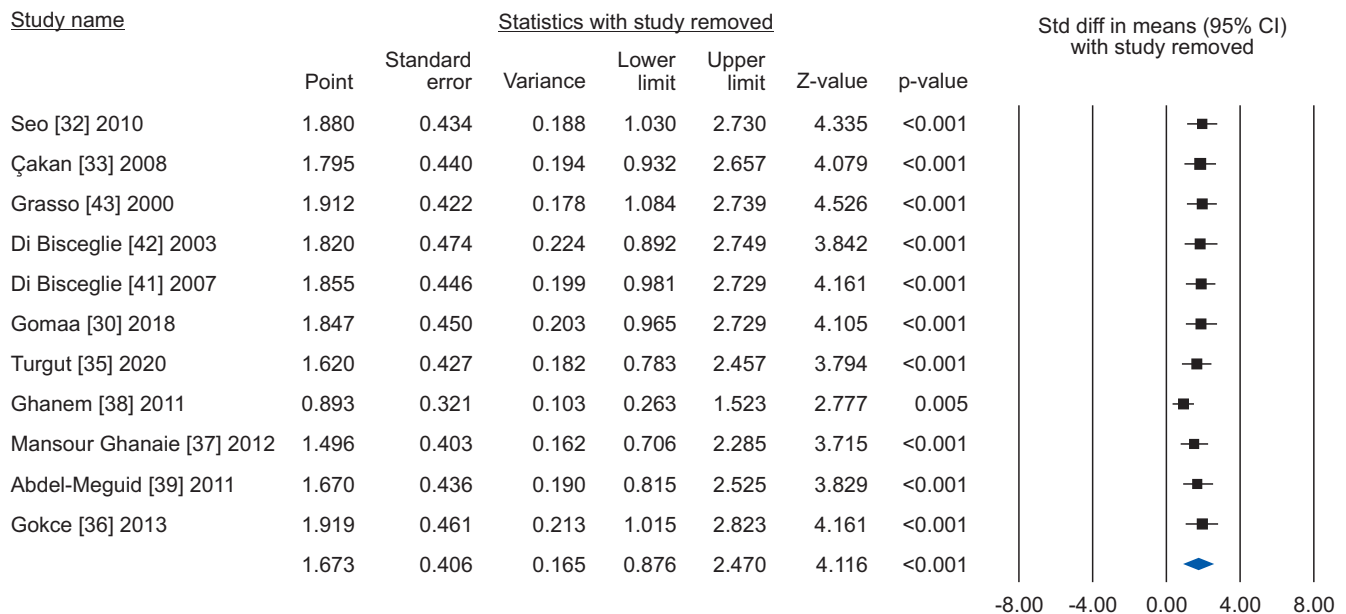


Fig. 23. Forest plot of the sperm morphology in infertile men with varicocele repair compared to no treatment: sensitivity analysis.

tive analysis showed that sperm morphology achieved significance with the addition of Ghanem et al [38] and has stayed significant after that (Fig. 25).

DISCUSSION

Varicocele remains one of the most controversial topics in male infertility. Although most international fertility societies agree on the indication for VR in cases

of male infertility with clinically palpable varicocele and abnormal semen parameters [13,14,46], there are still some clinicians who doubt the beneficial effect of VR on semen parameters and fertility status [47-49].

Results of the current MA indicate significant improvements in sperm concentration (SMD 1.864; $p < 0.001$), total sperm count (SMD 1.894; $p < 0.05$), total sperm motility (SMD 0.887; $p = 0.04$), progressive sperm motility (SMD 3.301; $p < 0.01$), and normal sperm mor-

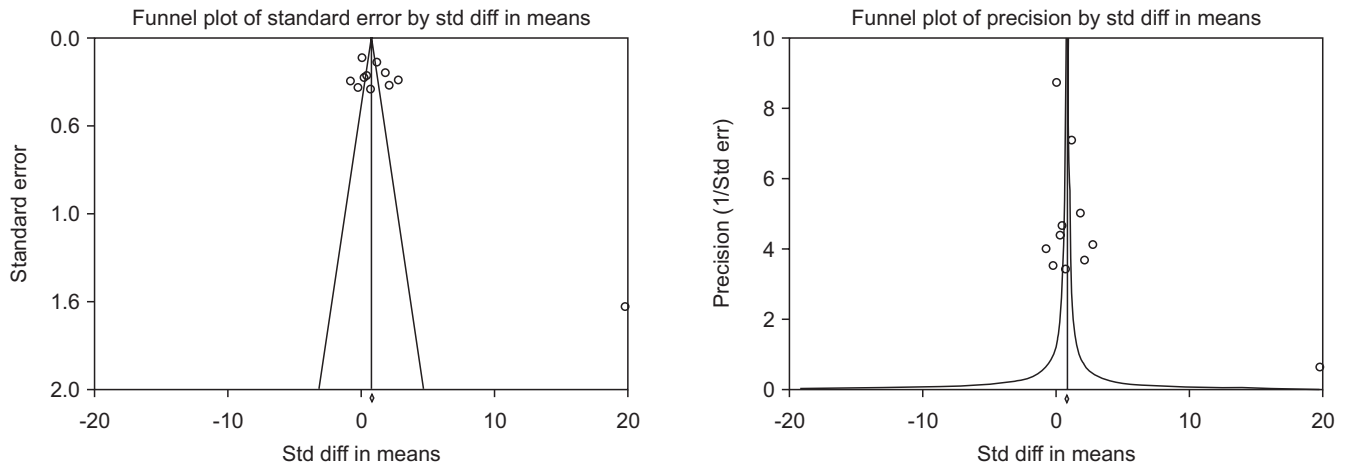


Fig. 24. Funnel plot of the sperm morphology in infertile men with varicocele repair compared to no treatment.

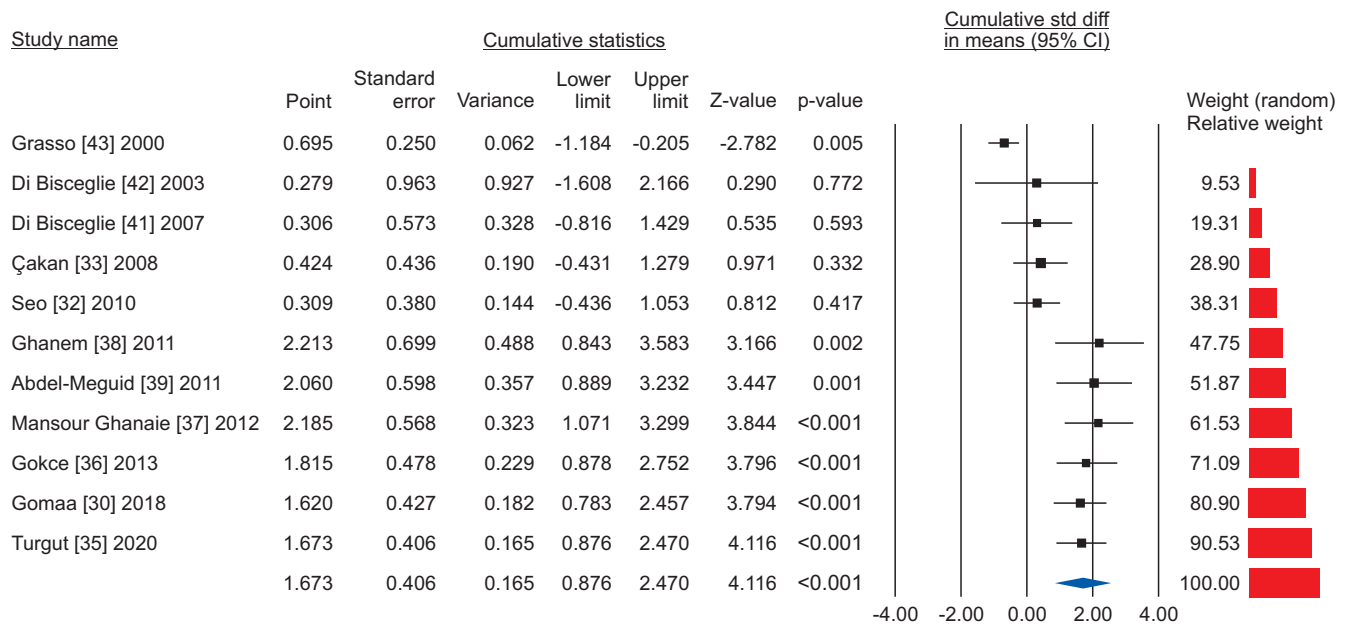


Fig. 25. Forest plot of the sperm morphology in infertile men with varicocele repair compared to no treatment: cumulative analysis.

phology (SMD 1.673; $p < 0.05$) in infertile men with clinically palpable varicocele that underwent VR when compared to men who did not undergo VR. VR was also associated with an increase in semen volume but this was not statistically significant. No publication bias could be found in the analyzed studies semen volume, total sperm count, total sperm motility, and normal morphology. For sperm concentration and progressive motility, no study was sensitive enough to change the conclusion of our findings. However, the results of the current MA are limited by the high heterogeneity noted among the included studies.

Over the last 30 years, nearly 2,000 original articles

have been published on varicocele and about half of them have evaluated the impact of varicocele and VR on semen parameters [50]. Agarwal et al [12] described the positive effect of VR on semen parameters in a MA of 17 studies. The authors evaluated infertile men with bilateral or unilateral clinically palpable varicoceles and at least one abnormality in semen parameters. The study results reported that sperm concentration, morphology, and sperm motility were significantly increased after microsurgical or high-ligation VR. Baazeem et al [11] performed a similar MA evaluating 17 RCTs before and after varicocelectomy. The results of the latter MA demonstrated that VR resulted in a

significant increase in total and progressive sperm motility as well as in sperm concentration. Schauer et al [17] examined the effects of three surgical approaches of VR: subinguinal, inguinal, and high ligation. VR resulted in significant improvement in sperm count and motility independently of the surgical approach. Asafu-Adjei et al [18] performed a MA evaluating the outcome of VR classified by varicocele grade. They concluded that VR showed improvement in sperm concentration and motility across all varicocele grades, but the greatest improvement was observed with higher grade varicoceles. Results emerging from these MAs have led to guidelines from international societies [8,10,13] regarding the indications for VR in the management of clinical varicocele.

Previous MAs explored the effect of VR on semen parameters [11,12,17,51]. All these studies adopted a statistical approach that compared preoperative and postoperative semen analyses. They found statistically significant improvement of different semen parameters post-operatively (Table 3). The authors of these studies suggested that the post-operative improvement of semen parameters is not a mere finding due to repetition of testing but is a result of VR. However, the lack of proper control group in these studies left room for doubt on the efficacy of VR.

For researchers opposing VR as a treatment for male infertility, the main concern is that spontane-

ous improvement of semen parameters can occur even without intervention and this was not accounted for in various studies due to defective analysis resulting from lack of a proper control group [48,52]. During the last decade, several MA studies, including Cochrane Database of systematic reviews [13,53,54], have primarily focused on the differences in pregnancy and/or life birth rates reported with “treated *versus* non-treated” varicoceles. Surprisingly, no previously published MA has addressed the comparison of the “after treatment *versus* after no treatment” variations in conventional semen parameters among patients with varicocele.

In the current MA, we have sought to avoid the shortcomings of previous studies (which compared pre- and post-operative data), and provide more reliable conclusions by only including studies that compared post-operative semen parameters of the treatment group (infertile men where varicocele is repaired) *versus* the parameters after a similar period of time in the control group (infertile patients with varicocele that were not treated). A proper control group is the key to establish a cause-and-effect relationship of a certain variable [55].

To the best of our knowledge, the present study is the first MA primarily assessing the impact of VR on conventional semen parameters in a population of infertile men with clinical varicocele, as compared to no treatment (Table 4). The findings of our MA are in favour of a positive effect of VR on conventional se-

Table 3. Evidence coming from previous meta-analyses on varicocele repair by comparing preoperative and postoperative semen analyses

Study	Number of articles	Number of cases	Findings
Agarwal et al, 2007 [12]	17	1,231 for count 1,015 for motility 528 for morphology	Significant increase of sperm concentration by 9.71 millions/mL (95% CI, 7.34–12.08; p=0.00001). Significant increase of average sperm motility by 9.92% (95% CI, 4.90–14.95; p=0.0001). Significant improvement of sperm morphology with an estimated change of 3.16% (95% CI, 0.72–5.60; p=0.01).
Baazeem et al, 2011 [11]	22 for concentration 17 for motility 5 for progressive motility		Significant improvement of sperm concentration after varicocelectomy (ranging from 4.0 to 60.0 million sperm) (95% CI, 9.45–15.19; p<0.0001). Significant improvement of total sperm motility after varicocelectomy (ranging from 2.7% to 21.4%) (95% CI, 7.07–14.65; p<0.0001). Significant improvement of progressive sperm motility after varicocelectomy (ranging from 5.0% to 15.7%) (95% CI, 4.86–14.52; p=0.003).
Birowo et al, 2020 [51]	7	289	Significant increase of sperm concentration by 9.59 million per mL (mean difference: 9.59; 95% CI, 7.80–11.38; p<0.00001). Significant increase of progressive sperm motility by 8.66% after varicocelectomy (mean difference: 8.66; 95% CI, 6.96–10.36; p<0.00001). Significant increase of normal sperm morphology by 2.73% (mean difference: 2.73; 95% CI, 0.65–4.80; p=0.01).

CI: confidence interval.

Table 4. Summary of the findings of the present study

Outcome	(No. of studies) No. of participants	Results	Heterogeneity	Sensitivity analysis	Risk of bias	Conclusion
SV	(5) 732 total participants 439 treated 293 controls	SMD 0.313; 95% CI -0.242 to 0.868; p>0.05	Significant heterogeneity, I ² =89.7%	No study was sensitive enough to alter the results.	No significant publication bias, Egger's test (p=0.23) and symmetrical funnel plots.	Non-significant increase in SV.
SC	(13) 2,267 total participants 1,347 treated 920 controls	SMD 1.864; 95% CI 1.249 to 2.479; p<0.001	Significant heterogeneity, I ² =97.6%	No study was sensitive enough to alter the results.	Significant publication bias, Egger's test (p<0.001) and asymmetrical funnel plots.	Significant increase in SC, favoring treatment.
TSC	(5) 1,073 total participants 622 treated 451 controls	SMD 1.894; 95% CI 0.566 to 3.222; p<0.05	Significant heterogeneity, I ² =97.8%	No study was sensitive enough to alter the results.	No significant publication bias, Egger's test (p>0.05) and symmetrical funnel plots.	Significant increase in TSC, favoring treatment.
SPM	(9) 1,438 total participants 854 treated 584 controls	SMD 3.301; 95% CI 2.164 to 4.437; p<0.01	Significant heterogeneity, I ² =98.5%	No study was sensitive enough to alter the results.	Significant publication bias, Egger's test (p<0.001) and asymmetrical funnel plots.	Significant increase in SPM, favoring treatment.
TM	(7) 1,126 total participants 659 treated 467 controls	SMD 0.887; 95% CI 0.036 to 1.738; p=0.041	Significant heterogeneity, I ² =97.3%	No study was sensitive enough to alter the results.	No significant publication bias, Egger's test (p>0.05) and symmetrical funnel plots.	Significant increase in TM, favoring treatment.
SM	(11) 1,403 total participants 818 treated 585 controls	SMD 1.673; 95% CI 0.876 to 2.470; p<0.05	Significant heterogeneity, I ² =98.5%	No study was sensitive enough to alter the results.	No significant publication bias, Egger's test (p>0.05) and symmetrical funnel plots.	Significant increase in SM, favoring treatment.

CI: confidence interval, SC: sperm concentration, SM: sperm morphology, SMD: standardized mean difference, SPM: sperm progressive motility, SV: semen volume, TM: total motility, TSC: total sperm count.

men parameters among infertile patients with clinical varicoceles. Our “after treatment *versus* after no treatment” study comparison should provide a more robust, and higher level of evidence than the other previously published MAs that used the usual “before and after treatment” approach.

The primary outcome of the present MA is semen parameters. These represent additional important end point to pregnancy or live birth which are emphasized by other MA on VR [53]. In a recently published global survey, with 574 respondents, exploring the general attitude of clinicians toward the management of varicocele, an increase in the pregnancy rate or in the live birth rate was considered as the primary outcome measure of the success of VR by only 16.3% and the 9.8% of respondents, respectively. Importantly, the 58.7% agreed that a significant improvement in semen parameters could be considered a successful outcome of VR, even if normal values are not reached [16]. This may reflect the understanding that pregnancy and live

birth depend upon both male and female factors. VR could improve semen conventional parameters, but the improvement itself alone may not lead to a proportionate increase in pregnancy rates since it depends on several factors in both the male and the female. Therefore, conventional semen parameters represent a valid outcome measure of VR.

Despite the interesting findings of the current MA, there are a few limitations. First, only a few RCTs fulfilled the criteria for inclusion in the analysis. Second, significant heterogeneity was found for all tested outcomes. Third, risk of publication bias was remarkable for studies addressing the impact of VR on sperm concentration and progressive sperm motility. Fourth, there is a concern regarding the quality of the included studies (Table 4).

1. SWOT analysis

The highlights of our MA are summarized in a SWOT analysis (SWOT stands for strengths [S], weak-



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Fig. 26. Strengths, Weaknesses, Opportunities, and Threats (SWOT) analysis. RCT: randomized controlled trial, VR: varicocele repair.

nesses [W], opportunities [O], and threats [T]) (Fig. 26). The “strengths” (S) and “weaknesses” (W) are related to the internal environment while the “opportunities” (O), and “threats” (T) are all external factors that can either enhance or hinder the development of a subject, respectively [56]. Using the SWOT method, we summarize the main advantages and limitations of our MA on the topic of VR in infertile men with clinical varicocele. We also summarize the factors that could limit the use of the results of this MA and address the opportunities that could ensure the wide diffusion of this MA in the medical and scientific community.

CONCLUSIONS

This SRMA of controlled studies, provides further evidence that VR significantly improves conventional semen parameters. To the best of our knowledge, this is the first SRMA to compare changes in conventional semen parameters after VR with changes in parameters of a control group over the same period. This is in contrast to other SRMAs which have compared semen parameters before and after VR, without reference to a control group. Our findings strengthen the available evidence and have a potential to upgrade professional societies' practice recommendations favoring VR to improve conventional semen parameters in infertile men.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: RC, AA, Rupin S. Data curation: AH. Formal analysis: Rajender S. Investigation: FB, Ramadan S. Methodology: TAAAMH. Project administration: AA, Rupin S. Software: Rajender S. Visualization: all authors. Writing – original draft: all authors. Writing – review & editing: all authors.

Supplementary Materials

Supplementary materials can be found *via* <https://doi.org/10.5534/wjmh.220142>.

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