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Effect of redo varicocelectomy on semen parameters and pregnancy outcome: An original report and meta-analysis

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Abstract

Recurrence following varicocelectomy is an important cause of treatment failure and persistence of subnormal semen parameters. This original study was combined with a systemic review and meta-analysis aiming to evaluate the efficacy of redo varicocelectomy on male fertility potential and pregnancy outcome. The retrospective study included 32 patients who underwent microsurgical subinguinal varicocelectomy for patients with recurrent varicocele. Changes in semen parameters and hormone profiles before and after surgery were compared. The literature review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and included seven articles in addition to our original report. Results of the original study revealed statistically significant improvements in sperm concentration, progressive motility, total motile sperm count and normal morphology following redo varicocelectomy. The meta-analysis results echoed those reported in our original study and depicted significant improvements in sperm concentration (mean difference [MD] = +20.281 million/ml, $p < 0.001$), total motility (MD = +9.659%, $p = 0.001$), total motile sperm count (MD = +23.258 million sperm, $p < 0.001$) and normal morphology (MD = +4.460%, $p < 0.001$). Overall pregnancy outcome was reported in seven studies with a rate of 34.6%. No significant changes were noted in any of the collected hormone results both in this original report and in the meta-analysis. In conclusion, redo varicocelectomy has a beneficial role on male fertility potential and can be offered for men with recurrent varicocele as directed by their individual clinical condition.

KEYWORDS
male infertility, pregnancy, recurrent varicocele, redo varicocelectomy, semen parameters

1 | INTRODUCTION

Varicocele is the abnormal dilatation of the pampiniform venous plexus draining the testis. It is prevalent in 15% of the general male population and in 35% and up to 80% of males with primary and secondary infertility respectively (Clarke, 1966). There are many postulated pathophysiological mechanisms behind varicocele-induced infertility, and the current evidence suggests a beneficial effect for

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varicocele repair on male fertility potential and pregnancy outcome (Jensen et al., 2017; Kohn et al., 2017; Kroese et al., 2012).

Many operative methods have been used in the primary repair of varicocele, including open, laparoscopic and microsurgical ligation and radiographic embolisation. Though a clinical benefit is expected to occur with any approach, microsurgical varicocelectomy is believed to be associated with the lowest postoperative complications including varicocele recurrence and hydrocele formation (Cayan et al., 2009; Diegidio et al., 2011).

Recurrent varicocele is the most common complication of varicocelectomy, ranging from 0% to 35% depending on the surgical technique employed (Rotker & Sigman, 2016). Its occurrence may impede the surgical outcome resulting in failure of conception. The main cause of varicocele recurrence and persistence is the lack of ligation of all the veins that possess the ability to develop varicocele (Coolsaet, 1980; Franco et al., 1999).

Since redo-varicocelectomy may carry higher risks for complications, recurrent varicocele has been treated less frequently and with radiographic embolisation rather than surgery. Nonetheless, several reports recently have shown a benefit for the surgical methods, specifically, the microsurgical technique (Çayan et al., 2019).

Very few studies assessed the role of redo-varicocelectomy on semen parameters and pregnancy rates and therefore not enough evidence is available to reach a solid consensus. This study aimed at assessing the outcome of redo-varicocelectomy on male fertility potential. The study objectives were to: (1) evaluate changes in semen parameters and hormone profile following redo microsurgical subinguinal varicocelectomy on patients with recurrent varicocele; (2) perform a systemic review and meta-analysis of our results and others published in literature to reach a solid verdict.

2 | MATERIALS AND METHODS

2.1 | Retrospective study

2.1.1 | Study design and population

A retrospective chart review was performed on patients who underwent microsurgical varicocelectomy at Hamad Medical Corporation, Doha, Qatar between 1 January 2011 and 1 January 2018 to identity those who underwent redo surgery for recurrent varicocele. The retrospective study design was verified by the centre's ethical committee and was approved by the IRB (MRC-1252/11). A waiver of informed consent was provided by the investigators.

Patients who had abnormal genetics (abnormal karyotype or chromosome Y microdeletion), history of post pubertal mumps orchitis, history of chemo and/or radiotherapy or history of medical treatment before the procedure were excluded.

2.1.2 | Data collection

Collected data from patients' records included patient demographics, the time interval from the previous varicocelectomy and the indication for the redo procedure. Additionally, patient's semen parameters and hormonal profile results [follicle stimulating hormone (FSH), luteinising hormone (LH), Testosterone, prolactin (PRL), and estradiol (E2)] were retrieved, including both the initial and the follow up results 6 months after the surgery.

2.1.3 | Study procedures

The semen tests were done on samples obtained via masturbation following 2–7 days of abstinence and were analysed according to the WHO criteria 10th edition (Cooper et al., 2010). Third-generation chemiluminescence immune assay had been used for the hormonal tests.

The analysis was performed in the same laboratory with blood samples collected between 7 and 10 AM. [FSH (n = 1–19 IU/L), LH (n = 1–9 IU/L), prolactin (n = 73–407 mIU/L), total testosterone (n = 10.4–35 nmol/L), and estradiol (n = 73–275 pmol/L)].

Varicocelectomy was performed using the microsurgical subinguinal approach. All cases were done by the same urology team implementing a standardised approach. After obtaining the necessary surgical consent forms, surgeries were done under general anaesthesia, using 2–3 cm subinguinal incision. Following delivery of spermatic cord, the cord was inspected for the presence of dilated external spermatic veins which were ligated. Following dissection of the external spermatic fascia, a surgical microscope (Pentero 900, Carl Zeiss Meditec, Jena, Germany) was used under ×18 magnification to explore the cord and identify, separate, ligate (using titanium clips) and divide the internal spermatic veins. A micro doppler probe was also utilised to identify and preserve the testicular artery. Lymphatic vessels and the vas deferens were also preserved.

2.2 | Systemic review and meta-analysis

2.2.1 | Search strategy

The review was performed according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines. An electronic search was performed using Pubmed, Science Direct, Cochrane Network, Scopus and Google Scholar databases and utilising the keywords: 'Recurrent Varicocele', 'Male Infertility', and 'Redo Varicocelectomy'. 'angioembolization' and 'sclerotherapy'. The search was filtered for articles published in English without time limits for the year of publication.

2.2.2 | Eligibility and inclusion criteria

Studies reporting at least one postoperative outcome including changes in semen parameters, serum hormone levels or pregnancy rates following recurrent varicocele repair were included in the analysis.

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2.2.3 | Screening and data collection

Two independent authors reviewed and assessed the retrieved abstracts and applied the inclusion criteria. A third author was available to solve any discrepancies.

This was followed by summarising and analysing the data that included year of publication, number of patients, mean and standard deviation of the age, previous varicocele (unilateral, bilateral), duration since previous varicocelectomy (years), type and laterality of varicocelectomy, pregnancy outcomes, as well as the pre-operative and post-operative measures of the testicular size, semen volume, sperm concentration, motility, progressive motility, normal morphology, testosterone, FSH, LH, and total motile sperm count (TMSC) in addition to post-operative complications.

2.2.4 | Quality assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for non-randomised studies (Stang, 2010). This 'star system' scale was developed to assess the quality of case–control and cohort studies. The system evaluates and allocates stars for studies on three broad perspectives: selection of study groups (0–3 stars), comparability of the groups (0–2 stars) and ascertainment of exposure or outcome (0–3 stars). A maximum of 9 stars can be given for each study and studies with ≥7 stars are considered of good quality while those with 4–6 or <4 stars have fair or poor quality respectively. Discrepancies in quality assessment were discussed and resolved by two authors (AM and MA).

2.3 | Statistical analysis

The Shapiro–Wilk test for normality was performed to identify the distribution of the study variables. Frequencies (%) were used to report categorical data, while the mean ± *SD* (*SE*) was used to present continuous values. Wilcoxon Signed-Rank test was used to compare semen and hormone results before and after varicocelectomy. A *p*-value below 0.05 was considered statistically significant. Statistical analysis of collected data was performed using SPSS version 20 (IBM, Armonk, NY, USA). The meta-analysis was performed using the comprehensive meta-analysis software. Statistical significance was set at alpha = 0.05. The *Q* statistic was used to test between study homogeneity and it was rejected when the *Q* statistic *p*-value <0.10. The I^2 statistic was also measured which describes the percentage of variation across studies that is due to heterogeneity rather than chance (I^2 = 100% x [*Q*-*df*]/*Q*, where *df* is the degree of freedom). Mild heterogeneity may be considered with an I^2 result of <25%, while moderate and marked heterogeneity can be expected with an I^2 result of 25–75% and >75% respectively (Higgins et al., 2003). Because semen data can vary in sequential analyses or between one measurement and the other, the random-effects model was used to adjust for heterogeneity and possible bias among studies.

3 | RESULTS

3.1 | Retrospective study

A total of 962 patients were screened to identify those who underwent the varicocelectomy as a redo procedure for recurrent varicocele. Of these, 32 patients met the eligibility criteria and had a mean age and mean BMI of 39.94 ± 9.56 years and 30.4 ± 3.56 Kg/m^2 respectively. Twenty-three patients (71.88%) had primary infertility, and nine patients (28.12%) had secondary infertility. Twenty-eight patients had recurrent varicocele on the left side whereas the remaining four had bilateral recurrent varicocele. Furthermore, on examination, 5.3% had left grade I recurrence, 57.9% had grade II, and 10.5% had grade III. For the right recurrent varicocele, all cases had grade II.

A statistically significant increase in sperm concentration, progressive motility, TMSC, and normal morphology were observed post-operatively (Table 1). Semen volume and total motility showed no significant change after surgery. All hormones, including FSH, LH, estradiol, prolactin, and testosterone did not show any statistically significant improvement postoperatively. There were no reported post-operative complications in any of the included patients.

3.2 | Meta-analysis

During the electronic search and literature review, 81 articles were identified (Figure 1). After screening the title and abstracts, 18 unrelated articles were excluded. From the 63 articles remaining, 46 articles were screened out as they did not report the fertility outcome or the effect of redo varicocelectomy on semen. Another ten studies were removed as they were review articles. The remaining seven articles were included in the meta-analysis in addition to our current study (Cayan & Akbay, 2018; Chen, 2014; Grober et al., 2004; Madjar et al., 1998; Punekar et al., 1996; Sze et al., 2008; Yan et al., 2017; Table 2).

Of the seven articles, four evaluated the outcome of micro surgical technique (Cayan & Akbay, 2018; Chen, 2014; Grober et al., 2004; Madjar et al., 1998), two the radiological approach (Punekar et al., 1996; Sze et al., 2008) and one looked for both open retroperitoneal and laparoscopic surgery (Yan et al., 2017).

Quality assessment revealed that two studies were of good quality (9 stars) (Cayan & Akbay, 2018; Chen, 2014), while the remaining studies were of fair quality (5–6 stars).

The results of the meta-analysis revealed a significant improvement in sperm concentration postoperatively, which was observed in five studies (including our study) with a mean difference (MD) of +20.281 million/ml [9.81–30.75] (p < 0.001). Moderate heterogeneity was noted for the changes in sperm concentration (*Q* statistic 6.17, p = 0.187, I^2 = 35.4%) (Figure 2). Total motility was also reported by five articles and showed a significant improvement with a mean increase of +9.659% [3.7–15.6] (p = 0.001) again with a moderate level of heterogeneity (*Q* statistic 5.81, p = 0.214,

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Parameter	Preoperative (mean ± *SD*)	Postoperative (mean ± *SD*)	*p* Value
Volume (ml)	2.7 ± 1.45 (0.34)	2.67 ± 2.09 (0.49)	0.71
Concentration (10^6/ml)	26.43 ± 25.76 (6.07)	43.99 ± 48.39 (11.41)	0.031*
Total Motility (%)	35.44 ± 24.88 (5.87)	40.06 ± 23.03 (5.43)	0.5
Progressive Motility (%)	12.33 ± 13.47 (3.18)	18.67 ± 18.2 (4.29)	0.038*
TMSC (10^6)	25.35 ± 28.15 (4.98)	51.7 ± 65.87 (15.53)	0.05*
Normal Morphology (%)	9.03 ± 3.27 (3.31)	5.17 ± 0.59 (3.13)	0.033*
Estradiol (pmol/L)	79.14 ± 38.12 (14.41)	98.14 ± 36.71 (13.87)	0.16
FSH (mIU/ml)	7.14 ± 3.39 (1.13)	6.31 ± 2.74 (0.91)	0.89
LH (mIU/ml)	4.29 ± 1.74 (0.58)	3.71 ± 1.36 (0.45)	0.44
Prolactin (nmol/dl)	235.93 ± 26.15 (26.15)	271 ± 43.79 (43.79)	0.51
Testosterone (ng/dl)	14.51 ± 10.47 (3.49)	16.17 ± 7.29 (2.43)	0.21

TABLE 1 Changes in semen parameters and hormone results following microsurgical subinguinal varicocelectomy

Note: $p < 0.05$ is considered statistically significant.
Abbreviations: FSH, follicle stimulating hormone; LH, luteinizing hormone; Wilcoxon Signed-rank test; TMSC, total motility sperm count.

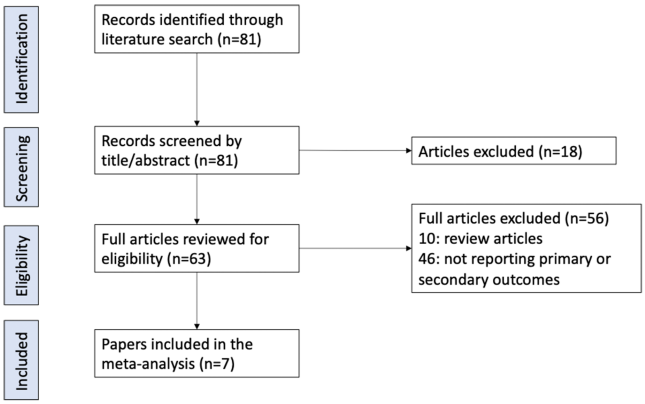

FIGURE 1 Preferred reporting items for systematic reviews and meta-analysis flow diagram

$I^2 = 31.1\%$) (Figure 3). Progressive motility was only reported by the current study. It showed a significant mean increase postoperatively by +6.34%. Morphology was reported by three articles and showed a significant postoperative improvement with a MD of+4.460% [2.32–6.61] ($p < 0.001$) and a low level of heterogeneity (Q statistic 0.91, $p = 0.636$, $I^2 = 0.0\%$) (Figure 4). Similarly, TMSC was reported by three studies and also displayed a significant improvement with a MD+ 23.258 million sperm [15.62–33.17] ($p < 0.001$) and a low level of heterogeneity (Q statistic 0.05, $p = 0.977$, $I^2 = 0.0\%$) (Figure 5). Overall pregnancy outcome was reported in seven studies with a rate of 34.6%. Three studies evaluating redo microsurgical varicocelectomy reported a pregnancy rate of 13%, 23% and 39.7% (Cayan & Akbay, 2018; Chen, 2014; Grober et al., 2004). One study evaluating radiological embolisation showed a pregnancy rate of 17% (Punekar et al., 1996), and one study evaluated open retroperitoneal and laparoscopic approaches reporting a pregnancy rate of 53.3% and 58.8% respectively (Yan et al., 2017). No significant changes were noted in any of the collected hormone results both in this original report and in the meta-analysis (Figure 6).

3.3 | Complication rate

In the four articles utilising micro surgical approach, the postoperative complication rate was low and acceptable. Hydrocele formation was noted in one study with a rate of 4.3% (Madjar et al., 1998). In another article, postoperative edema formation was present in 4.8% of patients (Chen, 2014). Hematomas were also noticed in 1.66% of patients (Cayan & Akbay, 2018). None of the articles reported testicular atrophy.

The complication rate was higher in the laparoscopic and open retroperitoneal studies (11.8% and 33.3% respectively; Yan et al., 2017). Hydrocele formation, testicular artery injury, vascular and abdominal organ injury, and infection were reported in the retroperitoneal series with an incidence of 10%, 3%, 10%, and 6% respectively (Yan et al., 2017). Whereas in the laparoscopic technique the risks of Hydrocele formation, testicular artery injury, vascular and abdominal organ injury, and infection was 3% for all (Yan et al., 2017).

4 | DISCUSSION

This retrospective chart review and meta-analysis evaluated the role of redo varicocelectomy on male fertility potential of patients with recurrent varicocele. Microsurgical subinguinal varicocelectomy was the most common procedure utilised by five studies including our study. Two studies utilised radiographic embolisation while laparoscopic and open retroperitoneal varicocelectomy were used in the remaining study.

The results of this retrospective study and the meta-analysis reveal that a significant improvement in various sperm parameters can be achieved following redo varicocelectomy. This finding further underscores the detrimental effect of varicocele on male fertility potential and identifies the importance of successful treatment to achieve a significant improvement in semen quality. Varicocele is the most common correctable cause of male infertility (Agarwal &

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TABLE 2 Characteristics of the studies included in the meta-analysis

Authors	Study design	Sample size	Operative procedure	Newcastle Ottawa Scale result			
				Selection	Comparability	Outcome	Total
Chen, 2014	Retrospective study	38	Microsurgical subinguinal	****	**	***	9
Grober et al., 2004	Retrospective chart review	54	Microsurgical subinguinal	***	_	***	6
Madjar et al., 1998	Retrospective study	23	Microsurgical subinguinal	***	_	***	6
Cayan & Akbay, 2018	Retrospective study	120	Microsurgical subinguinal	****	**	***	9
Punekar et al., 1996	Prospective study	28	Radiological embolization	***	_	***	6
Sze et al., 2008	Prospective study	5	Radiological embolization	***	-	**	5
Yan et al., 2017	Prospective trial	64	Open retroperitoneal and laparoscopic	**	_	***	5
Current Study	Retrospective study	32	Microsurgical subinguinal	***	-	***	6

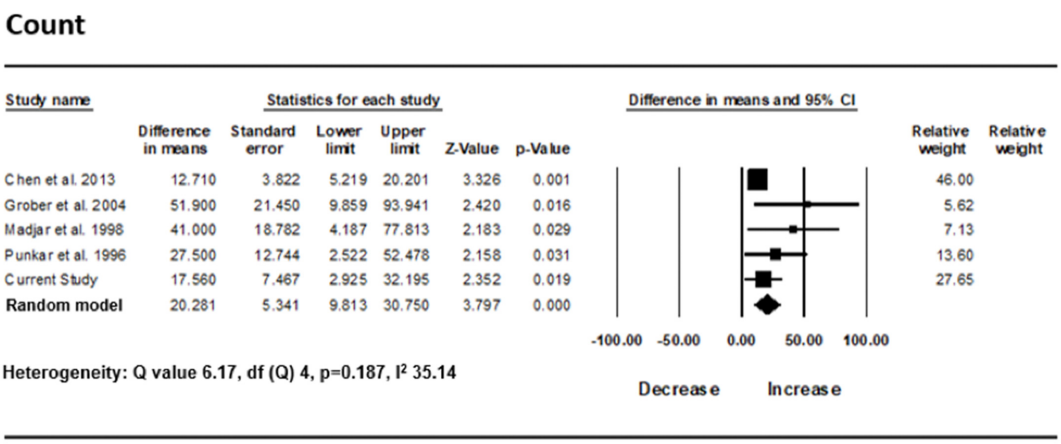

FIGURE 2 Forest plot reporting changes in sperm concentration following redo varicocelectomy

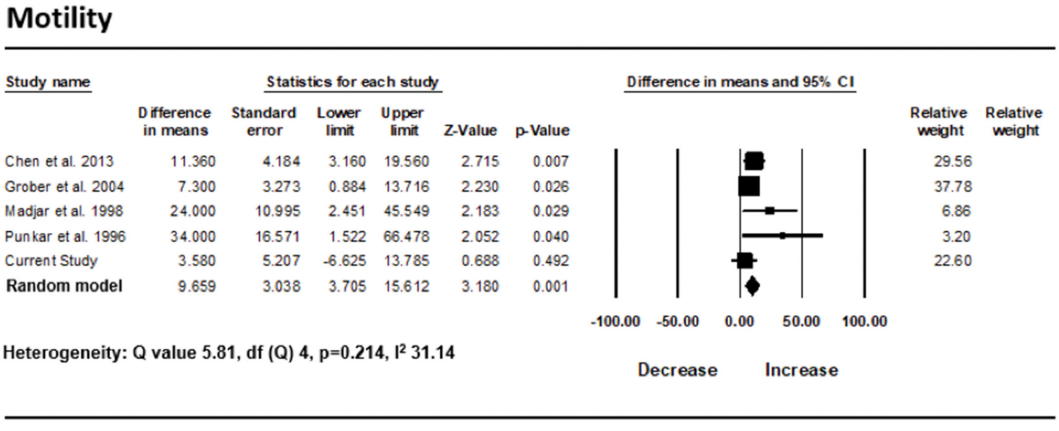

FIGURE 3 Forest plot reporting changes in total motility following redo varicocelectomy

Esteves, 2016). Various mechanisms have been hypothesised to explain the pathophysiology of varicocele induced testicular dysfunction. Testicular hyperthermia, tissue ischemia and oxidative stress are perhaps the most important consequences of venous reflux that can impair sperm quantity and quality (Majzoub et al., 2016). It is therefore imperative to obviate venous reflux with any varicocele treatment and failure to do so would result in suboptimal restoration of male fertility potential. Patients with persistent or recurrent venous

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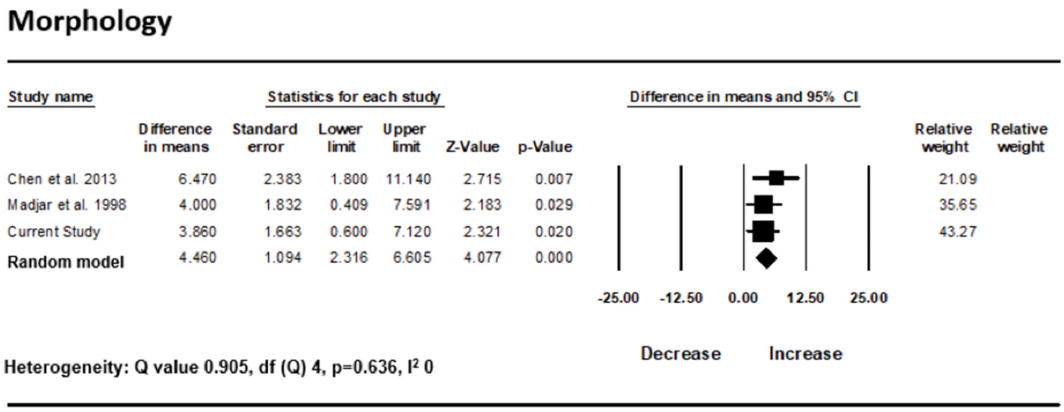

FIGURE 4 Forest plot reporting changes in normal morphology following redo varicocelectomy

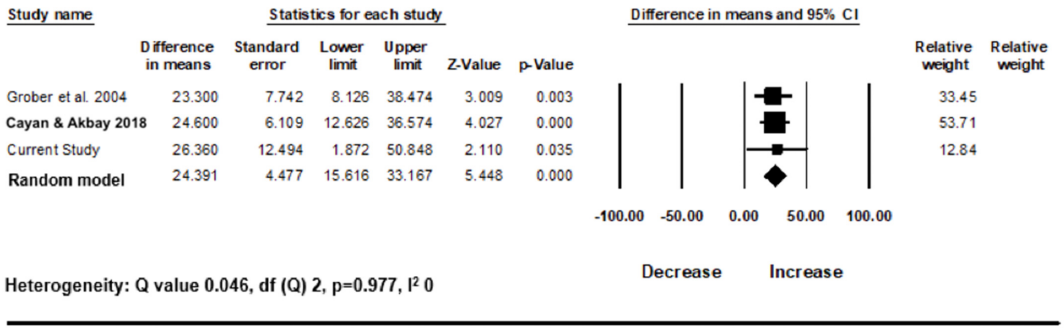

FIGURE 5 Forest plot reporting changes in total motility sperm count following redo varicocelectomy

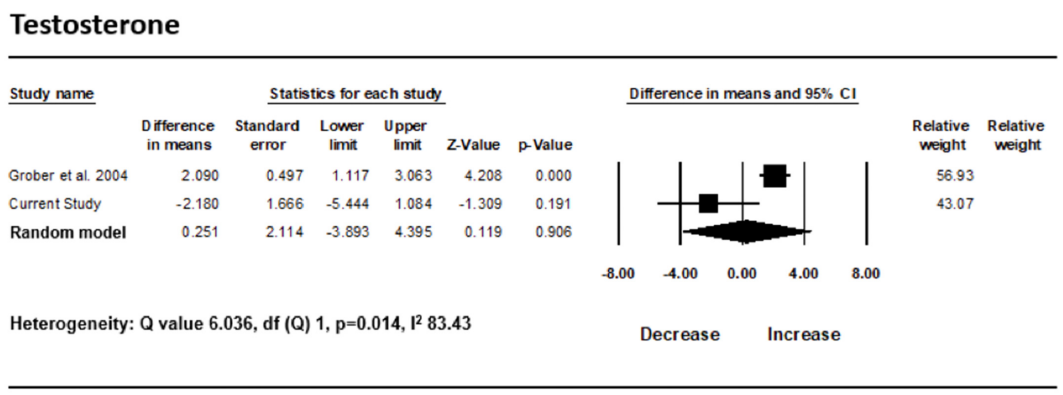

FIGURE 6 Forest plot reporting changes in testosterone following redo varicocelectomy

reflux following varicocele ligation would benefit from a redo-operation to ensure that the testicular parenchyma is safeguarded from the effects of varicocele

Pregnancy is undoubtedly the most important outcome to look for following varicocele ligation. This outcome was reported by seven of the included studies and an overall pregnancy rate of 34.6% was achieved following redo varicocelectomy. An improvement in spontaneous pregnancy rate following varicocele ligation has been established by three meta-analyses reporting odds ratios of 1.82 (95% confidence interval [CI]: 1.37–2.41; $p < 0.0001$; Birowo et al., 2020), 2.39 (95% CI 1.56–3.66, $p < 0.001$; Kroese et al., 2012) and 4.15 (95% CI 2.31–745, $p < 0.001$; Kim et al., 2013). Nonetheless, the pregnancy outcome after a redo varicocelectomy is unknown. This meta-analysis reveals that a similar spontaneous pregnancy rate can be expected in men undergoing redo varicocelectomy compared with those undergoing treatment

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for the first time who have a reported pregnancy rate between 33% and 42% (Watanabe et al., 2005).

Redo varicocelectomy may be technically challenging and fear from higher postoperative complications could be a reason for avoiding such procedures in patients with evidence of recurrent disease. Nonetheless, an acceptable complication rate can be expected following redo varicocelectomy as revealed in the included results of this review. Injury to the testicular artery occurred in 3% of the cases (Yan et al., 2017), while postoperative hydrocele was reported at a range of 3%–10% (Cayan & Akbay, 2018; Madjar et al., 1998; Yan et al., 2017). Despite that, these results cannot be generalised due to the small sample size of their respective studies.

4.1 | Strengths and limitations

The retrospective nature and small sample size of our original study can be considered as limitations; however, these results were combined with those from the published literature and data from 364 redo varicocelectomy were analysed. While the original study did not report the spontaneous pregnancy rate, this outcome was collectively reported by seven of the included studies in the meta-analysis. We were also not able to perform subgroup analysis or comparisons between the outcomes of different varicocele ligation methods due to either small studies' sample size or unavailability of necessary data.

5 | CONCLUSION

Redo varicocelectomy is a safe and effective treatment option for men with varicocele recurrence. Significant improvements in sperm concentration, total and progressive motility and normal morphology can be achieved postoperatively. Furthermore, the reported spontaneous pregnancy rates following redo varicocelectomy are similar to those reported after an initial varicocele treatment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data is available upon request.

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