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REVIEW

Male Infertility

Predictors of microsurgical varicocelectomy efficacy in male infertility treatment: critical assessment and systematization

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In this review, we tried to systematize all the evidence (from PubMed [MEDLINE], Scopus, Cochrane Library, EBSCO, Embase, and Google Scholar) from 1993 to 2021 on the predictors of microsurgical varicocelectomy efficacy in male infertility treatment. Regarding the outcomes of varicocele repair, we considered semen improvement and pregnancy and analyzed them separately. Based on the 2011 Oxford CEBM Levels of Evidence, we assigned a score to each trial that studied the role of the predictor. We systematized the studied predictors based on the total points, which were, in turn, calculated based on the number and quality of studies that confirmed or rejected the studied predictor as significant, into three levels of significance: predictors of high, moderate, and low clinical significance. Preoperative total motile sperm count (TMSC) coupled with sperm concentration can be a significant predictor of semen improvement and pregnancy after varicocelectomy. In addition, for semen improvement alone, scrotal Doppler ultrasound (DUS) parameters, sperm DNA fragmentation index (DFI), and bilateral varicocelectomy are reliable predictors of microsurgical varicocelectomy efficacy.

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INTRODUCTION

Varicocele is a common correctable cause of male subfertility.[1,2] Although the mechanisms of the influence of varicocele on male fertility are still being discussed, in general, the results of studies demonstrate that varicocele has a negative impact on spermatogenesis[3,4] and that varicocele correction improves sperm quality and increases real fertility.[5–7] Based on recent data, the European Association of Urology (EAU), the American Urological Association (AUA), and the American Society for Reproductive Medicine (ASRM) recommend surgery for infertile men with clinical varicocele and abnormal semen parameters.[4,8]

Ding *et al.*[9] and Çayan *et al.*[10] in their meta-analyses showed that microsurgical varicocelectomy (with the preservation of the lymphatic and arterial vessels) is the preferred surgical method in the treatment of clinical varicocele in infertile men in comparison with traditional open (without the use of microscopic equipment), laparoscopy, and endovascular vein occlusion. At the same time, varicocelectomy does not always lead to an improvement in sperm quality and fertility recovery: semen improvement after surgery usually occurs in 60%–70% of cases[11,12] and natural pregnancies occur in 25%–40% of couples.[11,13,14]

To date, there have been many studies dedicated to the analysis of factors (predictors) affecting microsurgical varicocelectomy outcomes.[15–17] However, most of these studies are of a retrospective and prospective uncontrolled nature, and the results of most of them are conflicting, which do not allow unequivocal conclusions to be drawn.[18] In this review, we tried to collect and systematize all the evidence on the predictors of microsurgical varicocelectomy efficacy in male infertility treatment.

EVIDENCE ACQUISITION AND ANALYSIS

We found and analyzed publications during the period from 1980 to 2021 from PubMed (MEDLINE), Scopus, Cochrane Library, EBSCO, Embase, and Google Scholar that were dedicated to the study of factors (predictors) that influence varicocele repair (including sclerotherapy) efficacy in subfertile men. We used keywords such as "varicocele," "varicocele repair", "varicocelectomy", "prediction", "fertility", "sperm", "predictors of varicocelectomy", and "prognosis of varicocelectomy" in the search. The search was limited to publications involving human subjects. Studies relating to outcomes other than semen parameters or reproductive outcomes were excluded from the review.

From this period, we identified 104 studies concerning predictors of varicocelectomy in male infertility treatment. Of these, six studies were randomized controlled trials (RCTs), 58 were prospective studies (six of them were controlled), and 40 were retrospective designs. In 57 studies, varicocelectomy was performed by microsurgical techniques. Microsurgery with other techniques (embolization, laparoscopy, open inguinal nonmicroscopic technique, *etc.*) of varicocele repair was

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applied in six studies. Open ligating techniques (nonmicrosurgical retroperitoneal, high/low inguinal, and subinguinal techniques) were performed in 27 studies. Sclerotherapy (antegrade or retrograde) alone was applied in six studies, and laparoscopy was applied in three studies. Different types of surgical techniques were performed in 11 studies. We found no information on the varicocele repair technique used in two studies.

Fifty-seven studies during the period from 1993 to 2021, in which microsurgical varicocelectomy alone was the surgical method of varicocele repair, and four studies, in which microsurgery was the main treatment method for varicocele (and in which other techniques were used in less than 50% of patients), were included in the final analysis. In 34 studies, the authors considered only semen improvement as the outcome measure and dependent (predicted) variable of varicocele repair. Pregnancy alone and pregnancy with semen improvement were considered in 8 and 19 studies, respectively.

The efficacy of microsurgical varicocelectomy was evaluated 3–6 months after surgery by assessing changes in semen parameters and/or rates of natural pregnancies, as well as pregnancies after the use of assisted reproductive technologies (ART) protocols. Our analysis included such clinical parameters as varicocele grade, varicocelectomy side (bilateral or unilateral), testicular volume, body mass index (BMI), male and female (partner) age, infertility duration, sperm concentration, sperm motility, total motile sperm count (TMSC), sperm morphology, sperm DNA fragmentation index (DFI), and scrotal Doppler ultrasound (DUS) parameters (grade/duration of venous reflux, internal spermatic vein [ISV] and external spermatic veins [ESV] diameter, *etc.*), serum follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels, and serum testosterone levels.

We did not include systematic reviews and meta-analyses in our analysis according to the heterogeneity of the included studies. Literature reviews were also not included due to the limited evidence.

GRADATION OF PREDICTORS BY THE LEVEL OF CLINICAL SIGNIFICANCE

Our analysis and "gradation" were based on the amount and quality of the evidence approving or rejecting the given predictor as the significant predictor. We tried to consider the contribution (positive or negative) of each study to the evidence base of the predictor.

For an objective assessment of the clinical significance and the evidence level of the analyzed studies and the studied predictor, we decided to assign an appropriate score for each study based on the 2011 Oxford Centre for Evidence-Based Medicine.[19] We assessed studies according to the design (RCTs; prospective: controlled and uncontrolled; and retrospective) and the power of the study (number of recruited patients), as shown in **Table 1**.

The points scored assessed the clinical significance of each predictor. If the authors approved the factor's predictive role in varicocelectomy efficacy prediction, this work was assigned an appropriate score with a "+" sign; if they did not, with a "–" sign. For example, the final score of the predictor "sperm concentration" was 8: in four studies (2 prospective studies of 4 points, and 2 retrospective studies of 1 point), the prognostic significance of this predictor was confirmed, while in 2 retrospective studies, it was rejected (**Table 2** and **3**). We can perform a simple calculation and obtain a result (total points) as follows: $(2 \times 4 + 2 \times 1) - 2 \times 1 = 8$ points.

The obtained results of the quantitative influence of the factor are presented in **Table 4** and **5**. In accordance with the scores obtained, we divided the predictors into the following groups according to their level of evidence (**Table 3**): I, predictors of high clinical significance (≥10 points); II, predictors of moderate clinical significance (5–9 points); and III, predictors of low clinical significance (<5 points).

Table 1: Types of evidence with appropriate score[a]

Level	*Types of evidence*	*Score*
1	Systematic review of randomized trials	x[b]
2	Randomized trial or observational study with dramatic effect	10
3	Nonrandomized controlled cohort/follow-up study[c]	3–5
	Prospective uncontrolled study with <100 patients	3
	Prospective uncontrolled study with 100–300 patients	4
	Prospective uncontrolled study with more than 300 patients	5
	Prospective controlled study	5
4	Case series, case–control studies, or historically controlled studies[c]	1–3
	Retrospective study with <100 patients	1
	Retrospective study with 100–500 patients	2
	Retrospective study with more than 500 patients	3
	Retrospective study with a control group	3
5	Mechanism-based reasoning	x[b]

[a]Modified from 2011 OCEBM levels of evidence. [b]Systematic reviews and literature reviews were not included in the analysis. [c]Scores of prospective (3–5) and retrospective (1–3) studies were determined by the study power (sample size and existence of the control group). OCEBM: Oxford Centre for Evidence-Based Medicine

COMMENTS TO THE ANALYSIS AND LIMITATIONS

According to the results of our analysis, the baseline semen parameters, *i.e.*, sperm concentration and TMSC, can both be considered reliable predictors of microscopic varicocelectomy effectiveness. In addition, for semen improvement alone, scrotal DUS parameters (high grade and duration of venous reflux, spermatic vein diameter more than 2.5 mm), performance of bilateral varicocelectomy, and initially low sperm DFI can be significant predictors of microsurgical varicocelectomy success. For the rest of the parameters, there are still many unresolved issues. In addition, there are many debates on the preoperative (cutoff) values of these parameters. For example, some authors proposed an initial low TMSC ($<5 \times 10^6$) as a significant predictor of postoperative semen improvement.[13,20] Simultaneously, Cayan *et al.*[21] and Matkov *et al.*[22] suggested that an initial high TMSC ($\geq 5 \times 10^6$) leads to significant semen improvement after varicocele repair. Concerning pregnancies after varicocelectomy, most authors agree that an initial high TMSC leads to a higher chance of conception.[23,24] The same situation holds for sperm concentration. Different authors proposed different initial values of the sperm concentration (from 2×10^6 ml^{-1} to 20×10^6 ml^{-1}) as a marker of varicocelectomy success.[25–27]

We studied several analytical reviews and meta-analyses dedicated to the study of factors affecting varicocelectomy efficacy in male subfertility treatment for comparative objectives. For example, the review by Samplaski and Jarvi[18] concluded that baseline semen parameters, varicocele grade, and male age are significant predictors of varicocelectomy efficacy. This is consistent with the findings of the meta-analysis by Wang *et al.*[28] where the authors showed that in men with a baseline TMSC of more than 20×10^6, the natural pregnancy rate was 55.4%, while in men with an initial TMSC of 1.5×10^6–5×10^6, the rate was only 26.8%. In addition, Shomarufov *et al.*[29] in their critical review concluded that the initial semen parameters, sperm DFI, and scrotal DUS parameters could be considered important prognostic factors of varicocele repair success. The above statements are consistent with our conclusions in terms of TMSC, sperm concentration, sperm DFI, and scrotal DUS parameters as significant predictors of semen improvement after microsurgical varicocele repair.

Until now, there have been debates on the superiority of bilateral varicocelectomy over unilateral repair (in the case of right-sided

Table 2: Predictors of semen improvement after microsurgical varicocelectomy

Predictors	*Studies supporting the predictive role*		*Studies rejecting the predictive role*	
	Study	*Score*[a]	*Study*	*Score*[a]
Clinical and anamnestic parameters				
Varicocele grade	Machen *et al.*[35] 2020	2	Bolat *et al.*[36] 2019	−2
	Palmisano *et al.*[15] 2019	4	Kimura *et al.*[37] 2017	−2
	Shabana *et al.*[25] 2015	4	Wang *et al.*[38] 2015	−3
	Kadioglu *et al.*[39] 2014	1	Enatsu *et al.*[26] 2014	−4
	Samplaski *et al.*[40] 2014	5	Baker *et al.*[41] 2013	−1
	Bozhedomov *et al.*[42] 2014	1	Chen and Chen[43] 2011	−3
	Azab *et al.*[44] 2012	2	Kondo *et al.*[45] 2009	−1
	Choi *et al.*[46] 2009	2	Shindel *et al.*[47] 2007	−3
	Fujisawa *et al.*[48] 2002	3	Ishikawa and Fujisawa[49] 2005	−1
	Steckel *et al.*[50] 1993	3		
Varicocelectomy side (bilateral or unilateral)	Palmisano *et al.*[15] 2019	4	Öğreden *et al.*[51] 2017	−4
	Sun *et al.*[52] 2018[b]	10	Çayan *et al.*[53] 2017	−5
	Bozhedomov *et al.*[42] 2014	1	Baker *et al.*[41] 2013	−1
	Elbendary and Elbadry[54] 2009	4	Kondo *et al.*[45] 2009	−1
	Baazeem *et al.*[55] 2009	2		
	Libman *et al.*[56] 2006	2		
	Pasqualotto *et al.*[57] 2005	3		
	Fujisawa *et al.*[58] 2003	4		
	Matkov *et al.*[22] 2001	1		
	Scherr and Goldstein[59] 1999	3		
Male age	Palmisano *et al.*[15] 2019	4	Madhusoodanan *et al.*[60] 2020	−1
	Kimura *et al.*[37] 2017	2	Bolat *et al.*[36] 2019	−2
	Lee *et al.*[61] 2015	2	Çayan *et al.*[53] 2017	−5
	Samplaski *et al.*[40] 2014	5		
	Choi *et al.*[46] 2009	2		
	Shindel *et al.*[47] 2007	3	Yazdani *et al.*[62] 2015	−3
	Shiraishi *et al.*[63] 2003	3	Enatsu *et al.*[26] 2014	−4
			Baker *et al.*[41] 2013	−1
			Azab *et al.*[44] 2012	−2
			Chen and Chen[43] 2011	−3
			Hsiao *et al.*[64] 2011	−2
			Reşorlu *et al.*[65] 2010	−1
			Kondo *et al.*[45] 2009	−1
			Ishikawa and Fujisawa[49] 2005	−1
			Fujisawa *et al.*[48] 2002	−3
Infertility duration	Zorba *et al.*[66] 2009	3	Madhusoodanan *et al.*[60] 2020	−1
			Fujisawa *et al.*[48] 2002	−3
Testicular volume	Lee *et al.*[61] 2015	2	Enatsu *et al.*[26] 2014	−4
	Chen[67] 2014	3	Baker *et al.*[41] 2013	−1
	Chen and Chen[43] 2011	3	Azab *et al.*[44] 2012	−2
	Choi *et al.*[46] 2009	2	Kondo *et al.*[45] 2009	−1
	Fujisawa *et al.*[48] 2002	3		
BMI	Ates *et al.*[68] 2019	1	Chen[67] 2014	−3
			Baker *et al.*[41] 2013	−1
			Chen and Chen[43] 2011	−3
Semen parameters				
Sperm concentration	Madhusoodanan *et al.*[60] 2020	1	Baker *et al.*[41] 2013	−1
	Masterson *et al.*[13] 2019	1	Kondo *et al.*[45] 2009	−1
	Shabana *et al.*[25] 2015	4		
	Lee *et al.*[61] 2015	2		
	Enatsu *et al.*[26] 2014	4		
	Azab *et al.*[44] 2012	2		
	Choi *et al.*[46] 2009	2		
	Fujisawa *et al.*[48] 2002	3		

Contd...

Table 2: Contd...

Predictors	Studies supporting the predictive role		Studies rejecting the predictive role	
	Study	*Score*[a]	*Study*	*Score*[a]
Sperm motility	Shabana *et al.*[25] 2015	4	Enatsu *et al.*[26] 2014	−4
	Samplaski *et al.*[40] 2014	5	Baker *et al.*[41] 2013	−1
	Azab *et al.*[44] 2012	2		
	Choi *et al.*[46] 2009	2		
TMSC	Samplaski *et al.*[20] 2017	2		
	Samplaski *et al.*[40] 2014	5		
	Cayan *et al.*[21] 2002	5		
	Matkov *et al.*[22] 2001	1		
Sperm morphology	Samplaski *et al.*[40] 2014	5	Baker *et al.*[41] 2013	−1
	Abdelbaki *et al.*[69] 2017	5		
Sperm DFI	Ni *et al.*[70] 2016	5		
	Kadioglu *et al.*[39] 2014	1		
Serum hormones (FSH, LH, and testosterone) level				
Serum FSH and LH levels	Ok *et al.*[17] 2020	2	Kimura *et al.*[37] 2017	−2
	Madhusoodanan *et al.*[60] 2020	1		
	Lee *et al.*[61] 2015	2	Enatsu *et al.*[26] 2014	−4
	Chen[67] 2014	3	Baker *et al.*[41] 2013	−1
	Azab *et al.*[44] 2012	2	Ishikawa and Fujisawa[49] 2005	−1
	Chen and Chen[43] 2011	3		
	Kondo *et al.*[45] 2009	1		
	Fujisawa *et al.*[48] 2002	3		
Serum testosterone level	Ok *et al.*[17] 2020	2	Enatsu *et al.*[26] 2014	−4
	Kondo *et al.*[45] 2009	1	Baker *et al.*[41] 2013	−1
			Chen and Chen[43] 2011	−3
			Fujisawa *et al.*[48] 2002	−3
DUS parameters				
Veins diameter (ISV and ESV)	Chen[67] 2014	3		
	Hafez[71] 2009	3		
	Hussein[72] 2006	4		
	Schiff *et al.*[73] 2006	3		
Degree (grade)/duration of venous reflux	Goren *et al.*[74] 2016	3		
	Chen[67] 2014	3		
	Hafez[71] 2009	3		
	Hussein[72] 2006	4		
	Schiff *et al.*[73] 2006	3		
	Shiraishi *et al.*[63] 2003	3		
Other scrotal DUS parameters	Akand *et al.*[75] 2017	3		
	Ortapamuk *et al.*[76] 2005	3		

[a]Modified from 2011 OCEBM levels of evidence; [b]randomized clinical trial. BMI: body mass index; DUS: scrotal Doppler US; TMSC: total motile sperm count; DFI: DNA fragmentation index; FSH: follicle-stimulating hormone; LH: luteinizing hormone; ISV: internal spermatic vein; ESV: external spermatic vein

Table 3: Predictors of pregnancy after microsurgical varicocelectomy

Predictors	Studies supporting the predictive role		Studies disproving the predictive role	
	Study	*Score*[a]	*Study*	*Score*[a]
Clinical and anamnestic parameters				
Varicocele grade	Harnisch *et al.*[77] 2014	2	Shomarufov *et al.*[23] 2021	−1
	Fujisawa *et al.*[48] 2002	3	Bolat *et al.*[36] 2019	−2
	Steckel *et al.*[50] 1993	3	Zhang *et al.*[24] 2017	−4
			Peng *et al.*[27] 2015	−2
			Enatsu *et al.*[26] 2014	−4
			Baker *et al.*[41] 2013	−1
			Leung *et al.*[78] 2013	−1
			Zini *et al.*[79] 2008	−3
			Ishikawa and Fujisawa[49] 2005	−1

Contd...

Table 3: Contd...

Predictors	*Studies supporting the predictive role*		*Studies disproving the predictive role*	
	Study	*Score*[a]	*Study*	*Score*[a]
Varicocelectomy side (bilateral or unilateral)	Sun *et al.*[52] 2018[b]	10	Shomarufov *et al.*[23] 2021	−1
	Elbendary and Elbadry[54] 2009	4	Almekaty *et al.*[80] 2019[b]	−10
	Baazeem *et al.*[55] 2009	2	Öğreden *et al.*[51] 2017	−4
	Libman *et al.*[56] 2006	2	Çayan *et al.*[53] 2017	−5
	Pasqualotto *et al.*[57] 2005	3	Zhang *et al.*[24] 2017	−4
	Matkov *et al.*[22] 2001	1	Peng *et al.*[27] 2015	−2
	Scherr and Goldstein[59] 1999	3	Baker *et al.*[41] 2013	−1
Male age	Shomarufov *et al.*[23] 2021	1	Almekaty *et al.*[80] 2019[b]	−10
			Bolat *et al.*[36] 2019	−2
			Zhang *et al.*[24] 2017	−4
			Çayan *et al.*[53] 2017	−5
			Yazdani *et al.*[62] 2015	−3
			Peng *et al.*[27] 2015	−2
			Harnisch *et al.*[77] 2014	−2
			Enatsu *et al.*[26] 2014	−4
			Baker *et al.*[41] 2013	−1
			Leung *et al.*[78] 2013	−1
			Zini *et al.*[79] 2008	−3
			Ishikawa and Fujisawa[49] 2005	−1
			Fujisawa *et al.*[48] 2002	−3
Female (partner) age			Zhang *et al.*[24] 2017	−4
			Harnisch *et al.*[77] 2014	−2
			Baker *et al.*[41] 2013	−1
			Leung *et al.*[78] 2013	−1
			Zini *et al.*[79] 2008	−3
			O'Brien *et al.*[81] 2004	−5
Infertility duration	Shomarufov *et al.*[23] 2021	1	Zhang *et al.*[24] 2017	−4
	Zorba *et al.*[66] 2009	3	Peng *et al.*[27] 2015	−2
			Harnisch *et al.*[77] 2014	−2
			Leung *et al.*[78] 2013	−1
			Zini *et al.*[79] 2008	−3
			Fujisawa *et al.*[48] 2002	−3
Testicular volume	Almekaty *et al.*[80] 2019[b]	10	Shomarufov *et al.*[23] 2021	−1
	Fujisawa *et al.*[48] 2002	3	Zhang *et al.*[24] 2017	−4
			Enatsu *et al.*[26] 2014	−4
			Baker *et al.*[41] 2013	−1
			Leung *et al.*[78] 2013	−1
BMI			Shomarufov *et al.*[23] 2021	−1
			Zhang *et al.*[24] 2017	−4
			Baker *et al.*[41] 2013	−1
Semen parameters				
Sperm concentration	Peng *et al.*[27] 2015	2	Shomarufov *et al.*[23] 2021	−1
	Enatsu *et al.*[26] 2014	4	Leung *et al.*[78] 2013	−1
	Fujisawa *et al.*[48] 2002	3		
	Kamal *et al.*[82] 2001	2		
Sperm motility	Shomarufov *et al.*[23] 2021	1	Peng *et al.*[27] 2015	−2
	Zini *et al.*[79] 2008	3	Enatsu *et al.*[26] 2014	−4
			Leung *et al.*[78] 2013	−1
TMSC	Shomarufov *et al.*[23] 2021	1		
	Zhang *et al.*[24] 2017	4		
	Cayan *et al.*[21] 2002	5		
	Matkov *et al.*[22] 2001	1		
Sperm morphology	Zini *et al.*[79] 2008	3		
Sperm DFI	Ni *et al.*[70] 2016	5	Baker *et al.*[41] 2013	−1
Serum hormones (FSH, LH, and testosterone) level				

Contd...

Table 3: Contd...

Predictors	Studies supporting the predictive role		Studies disproving the predictive role	
	Study	Score[a]	Study	Score[a]
Serum FSH and LH levels	Ok *et al.*[17] 2020	2	Peng *et al.*[27] 2015	−2
	Zhang *et al.*[24] 2017	4	Harnisch *et al.*[77] 2014	−2
	Fujisawa *et al.*[48] 2002	3	Enatsu *et al.*[26] 2014	−4
			Baker *et al.*[41] 2013	−1
			Leung *et al.*[78] 2013	−1
Serum testosterone level	Ok *et al.*[17] 2020	2	Zhang *et al.*[24] 2017	−4
			Peng *et al.*[27] 2015	−2
			Enatsu *et al.*[26] 2014	−4
			Baker *et al.*[41] 2013	−1
			Leung *et al.*[78] 2013	−1
			Fujisawa *et al.*[48] 2002	−3

[a]Modified from 2011 OCEBM levels of evidence; [b]randomized clinical trial. BMI: body mass index; TMSC: total motile sperm count; DFI: DNA fragmentation index; FSH: follicle-stimulating hormone; LH: luteinizing hormone

Table 4: Classification of the studied predictors of semen improvement with their scores

Groups	Predictors	Total score
Group I: predictors of the high clinical significance	Varicocelectomy side (bilateral or unilateral)	23
	Degree (grade)/duration of venous reflux	19
	Sperm concentration	17
	TMSC	13
	Veins diameter (ISV)	13
	Sperm DFI	10
Group II: predictors of the moderate clinical significance	Serum FSH or LH levels	9
	Sperm motility	8
	Varicocele grade	7
	Other scrotal DUS parameters	6
	Testicular volume	5
	Sperm morphology	5
Group III: predictors of the low clinical significance	Infertility duration	−1
	BMI	−6
	Serum testosterone level	−8
	Male age	−8

BMI: body mass index; DUS: scrotal Doppler US; TMSC: total motile sperm count; DFI: DNA fragmentation index; FSH: follicle-stimulating hormone; LH: luteinizing hormone; ISV: internal spermatic vein; ESV: external spermatic vein

Table 5: Classification of the studied predictors of pregnancy with their scores

Groups	Predictors	Total score
Group I: predictors of the high clinical significance	TMSC	11
Group II: predictors of the moderate clinical significance	Sperm concentration	9
Group III: predictors of the low clinical significance	Sperm DFI	4
	Sperm morphology	3
	Testicular volume	2
	Serum FSH or LH levels	−1
	Varicocele side (bilateral or unilateral)	−2
	Sperm motility	−2
	BMI	−6
	Infertility duration	−11
	Varicocele grade	−11
	Female (partner) age	−16
	Serum testosterone level	−17
	Male age	−40

BMI: body mass index; TMSC: total motile sperm count; DFI: DNA fragmentation index; FSH: follicle-stimulating hormone; LH: luteinizing hormone

subclinical varicocele). Recent meta-analyses compared unilateral versus bilateral varicocelectomy.[30,31] The authors agreed that performing bilateral varicocelectomy significantly improved sperm quality and the chances of conception in infertile couples.[30,31] In our analysis, bilateral varicocelectomy was the most important factor for semen improvement after surgery.

Our analysis showed that varicocele grade has little impact on varicocelectomy success. This conflicts with the results of the systematic review by Asafu-Adjei *et al.*[32], where they analyzed the literature on the effect of the varicocele grade on varicocelectomy efficacy in subfertile men. The authors concluded that the varicocele grade had a direct impact on varicocelectomy success. However, given that the studies included in the review[32] were heterogeneous, the validity of this conclusion may be debatable.

This review has some critical limitations. For example, the results of three RCTs (where the patients underwent mostly non-microsurgical varicocele repair) showed the significance of the female partner's age as a significant predictor of pregnancy after varicocelectomy. However, according to our results this factor was assigned to the low clinical significance predictors' group.[33,34] Of course, we should consider that the most recent of these RCTs was conducted in 2012.[34] In addition, according to a recent meta-analysis, the varicocele grade affects varicocelectomy efficacy; however, according to our results, this factor was considered not significant.[32] The above disadvantages may be related to the novel approach of the evidence analysis, which was based on an easy-to-use (with consideration of the study's design and power according to the CEBM[19] classification) assessment of the study's quality.

CONCLUSIONS

Preoperative TMSC coupled with sperm concentration can be a significant predictor of semen improvement and pregnancy after varicocele repair. In addition, for semen improvement alone, scrotal DUS parameters, sperm DFI, and bilateral varicocelectomy can be reliable predictors of microsurgical varicocelectomy success. Other parameters had low evidence or clinical significance levels. Interestingly, although microsurgical varicocelectomy is the "gold standard" option for varicocele repair, there is still insufficient high- or moderate-quality evidence on predictors of this technique efficacy, especially in terms of real fertility recovery (pregnancy and live birth).

AUTHOR CONTRIBUTIONS

ABS and VAB worked up conception and design of the study. ABS, AAF, SAA, and IPM searched, assembled, and analyzed the literature data. NIS and AAK drafted and revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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