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The Clinical Outcomes of Varicocelectomy and Assisted Reproductive Technology to Treat Men Infertility: A Meta-Analysis

Hongfang Yuan[1#], Martin Kuete[1,2#], Fan Yang[1], Yao Chen[1], Zhiyong Hu[1], Bozhen Tian[1], Kai Zhao[1] and Huiping Zhang[1*]

[1]*Family Planning Research Institute, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei-430030, China*

[2]*Faculty of Medicine and Biomedical Science, University of Yaounde, Yaounde, Messa-Yaounde, Cameroon*

[#]*Equally contribute to this work.*

[*]**Corresponding author:** Huiping Zhang, Family Planning Research Institute, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei-430030, China, Tel: 0086-27-83692651; Fax: 0086-27-83692651; E-mail: familyplanning2013@163.com

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Abstract

The current study aimed to evaluate the effects of varicocelectomy on semen quality and Assisted Reproductive Technology (ART) clinical outcomes. This meta-analysis was performed using Ovid (Medline, Adis, LWW, Embase; 1974 to 2014 November 10) and the PubMed (until 2014 November 10) databases. Male infertility, varicocelectomy and assisted reproductive technology were required as keywords. Data were analysed with STATA 11.0. Odds Ratio (OR) and 95% Confidence Interval (CI) were used to assess the effects of varicocelectomy on the ART clinical outcomes and funnel plots help to detect publication bias. 538 of 1068 participants issue from 7 original sources from diverse area in the world underwent varicocelectomy followed by ART between 2001 and 2011. Globally, defected semen parameters were improved after varicocelectomy among treated groups in all these studies. Significant improvement in clinical pregnancy (OR=1.76; 95% CI: 1.35-2.29, *P*<0.0001) and decrease of miscarriage rate (OR=0.65; 95% CI: 0.42-0.99, P=0.042) after ART use-among treated group; and finally, undergo ART specifically Intracytoplasmic Sperm Injection (ICSI) after varicocelectomy may increase live birth among treated group; Although 4 of these studies showed statistical differences, overall, there is no difference to achieve pregnancy among couples who underwent varicocelectomy and followed ART (OR=1.58; 95% CI: 0.82-3.03; *P*=0.172). Overall, the findings of the study suggested that varicocelectomy improves semen quality and therefore may reduce miscarriages, increase clinical pregnancy and live birth rates of couples who undergo ART specifically ICSI.

Keywords: Varicocelectomy; Male infertility; ART; Pregnancy outcomes

Introduction

Infertility affects 10-15% of couples who are trying to conceive and male factors account for 40-50% [1,2]. Varicocele is responsible for one-third of cases and stand as the most frequent cause for male infertility [3]; 21-41 % of men with primary and up to 81% with secondary infertility are due to varicoceles [4,5]. Even though, varicocele pathophysiology remains unclear, Sofikitis et al. [4] recently demonstrated the whole defect mechanism on testicular spermatogenetic activity and epididymal spermatozoa maturation process. The development of varicocele affecting leydig cell secretory function results in bilateral intratescular testosterone content although, impact the sertoli cell secretory function. The most important outcomes of varicocele repair in male infertility should be the pregnancy and live birth for the couple. Unfortunately, the management of male infertility associated with varicocele has always remained one of the most difficult and constant critical issue for human reproduction. Hence, despite the great spectacular progress of assisted reproductive technologies (In Vitro Fertilization/ Intracytoplasmic Sperm Injection IVF/ICSI, Intrauterine Insemiation/ IUI); very few Randomized, Controlled Trials (RCT) set real evident benefit of varicocelectomy on men fertility. Thus, patients with varicocele are generally recommended to undergo varicocelectomy to reverse its impairments and mostly in some cases, surgical varicocele repair are followed by Assisted Reproductive Technology (ART) [5-11]. Since decades, varicocelectomy benefits remain very controversial. Some studies suggested that varicocelectomy may improve clinical pregnancy and live birth rates by ICSI of infertile couples in which the male partner has clinical varicocele [6,12-15] In contrast, several others have shown that varicocelectomy does not impact pregnancy outcomes [7,16-18], even following ICSI procedures and surgical repair itself is a trauma to testis and spermatogenesis. However, according to the 2004 and 2006 Recommendation of the male infertility by the American Urological Association (AUA) and American Society for Reproductive Medicine (ASRM), [2,19,20] and the European Association of Urology (EAU) 2012 guidelines [3,21], varicocele repair should be considered in cases of a clinical varicocele, semen abnormal parameters with more or 2 years of infertility and otherwise unexplained infertility.

To date, varicocele repair of infertile couple following by assisted reproductive technology remains controversial. Several relevant studies did not draw a definitive conclusion whether varicocelectomy is effective and beneficial to treat men infertility. However, constant and further questions are still without answers on it real necessity compared with ART. In addition, there is a huge dispute about the effects of varicocelectomy on ART. Does varicocelectomy increase assisted reproductive technology clinical outcomes? Therefore, we performed this meta-analysis to assess the effects of varicocelectomy on semen quality and ART clinical outcomes.

Materials and Methods

Selection of studies

We identified comprehensive literature from Ovid (Medline, Adis, LWW, Embase; 1974 to 2014, November 10) and the PubMed (until 2014, November 10) databases. We used: male infertility, varicocelectomy and assisted reproductive technology as searching keywords. All articles performed were in english and limited to human. Reference lists of the selected studies. In addition, relevant update reports were checked.

Assessment of studies and inclusion criteria

Two investigators independently performed and assessed the quality of each article using the Newcastle-Ottawa Scale [22]. Study inclusion criteria based on discrepancies and recommendations from previous relevant articles and scientific societies (*American Society of Andrology, American Urological Association, American Society for Reproductive Medicine, European Association of Urology, European Academy of Andrology* and WHO [23]) for the management of male infertility due to varicoceles. The eligible studies met: 1) Study design included comparison of outcomes of varicocelectomy; 2) Participants with varicocele underwent ART; 3) No difference in the demographic characteristics of subjects; and 4) Outcomes included clinical pregnancy, miscarriages and live births.

Statistical analysis

The raw data extracted from eligible studies were assessed for completeness observations to guarantee the accuracy and integrity during the transfer process. Data were entered into STATA11.0 and the OR and its 95% CI to analyze the effects of varicocelectomy on the ART clinical outcomes. Heterogeneity was evaluated using the Chi-squared and $P<0.05$ was considered statistically significant, the random effects model was used; otherwise, the fixed effects model was adopted. We used funnel plots to assess publication bias.

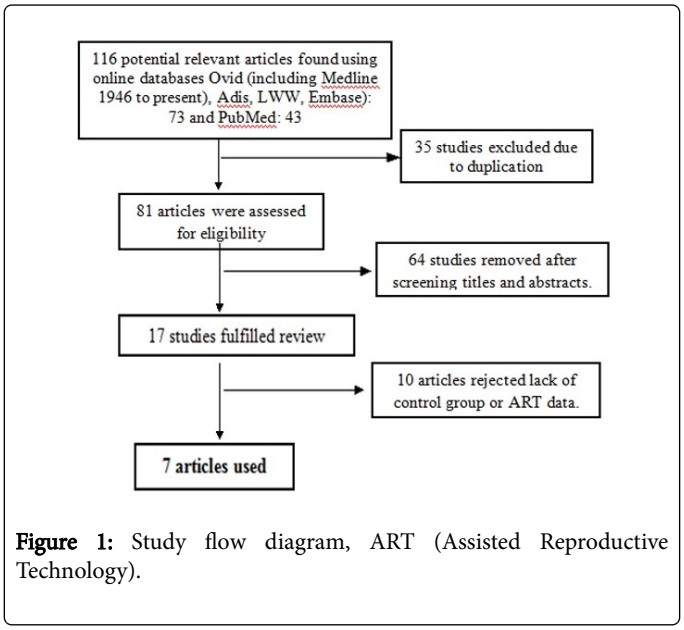


Figure 1: Study flow diagram, ART (Assisted Reproductive Technology).

Study	Study design	Nation	Duration of data collection	Sample size (n)		Mean of age (Yr)	
				Treated (VC)	Control	Treated (VC)	Control
Daitch et al. [11]	Retrospective	USA	--	34	24	--	--
Inci et al. [10]	Retrospective	Turkey	2001.1-2008.5	35	9	34.8	32.3
Haydardedeoglu et al. [8]	Retrospective	Turkey	2003.11-2008.4	31	65	28.74 ± 5.19	29.43 ± 3.90
Esteves et al. [9]	Retrospective	Brazil	2002.1-2008.7	80	162	35.80 ± 5.4	35.40 ± 6.30
Pasqualotto et al. [7]	Retrospective	Japan	2007-2011	169	79	--	--
Shiraishi et al. [5]	Retrospective	Brazil	2000-2008	21	53	37.80 ± 0.47	36.1 ± 0.55
Gokce et al. [6]	Retrospective	Turkey	2006.1-2010.7	169	138	34.80 ± 4.30	34.40 ± 4.10
VC: Varicocele							

Table 1: Characteristics of studies and varicocele status.

Results

Characteristics of studies and participants

Of 116 potentially relevant articles, six pertinent studies and one review included original data were finally used for this meta-analysis (Figure 1). Seven retrospectives studies were analyzed from America (USA, Brazil) and Asia (Turkey, Japan); data of six studies were collected during the period of 2001-2013. Total of 1068 participants included in this research; 538 men from couples having history of successful varicocelectomy before ARTs and 530 participants as control (Table 1). Four of five studies mentioned the mean age showing that treated group are about 34 years; however, mean age was globally similar among treated and untreated groups. The effect of varicocelectomy on semen quality and ART clinical outcomes (Pregnancy, miscarriages and live birth).

Study	Status of semen	Techniques for varicocele repair	The effect of varicocelectomy on semen quality in treated and untreated participants	ARTs
Daitch et al. [11]	Asthenospermia	Inguinal Ivanissevich or subinguinal microsurgical	Varicocelectomy did not improve semen parameters in treated vs untreated.	IUI
Inci et al. [10]	Azoospermia	Inguinal or subinguinal microsurgical	Varicocelectomy increased the sperm retrieval rate via microTESE in treated group (30% vs 53% , OR=2.63, 95% CI: 1.05–6.60, P=0.036).	ICSI
Haydardedeoglu et al. [8]	Azoospermia	Inguinal or subinguinal microsurgical	Varicocele repair can significantly improve the sperm retrieval rate of treated group via TESE (60.81% and 38.46% respectively, P =0.01)	ICSI
Esteves et al. [9]	Azoospermia	Macrosurgical	Varicocele repair improved sperm count (P=0.02), number of motile sperm (P<0.001) and total sperm count (P<0.001); no difference in progressive motility, percentage strict morphology and decreased the sperm defect score (P=0.01) among treated and untreated groups.	ICSI
Pasqualotto et al. [7]	Oligoasthenozo-ospermia	Not stated	Not stated	ICSI
Shiraishi et al. [5]	Azoospermia excluded	Subinguinal microsurgical	Varicocele repair improved just semen volume (P=0.0043), however no difference in sperm concentration, sperm motility and morphology among treated and untreated groups.	ICSI
Gokce et al. [6]	Azoospermia	Subinguinal microsurgical	Semen parameters were improved after varicocelectomy but no statistical difference on progressive motility and percentage strict morphology of pre and postoperative compared to control groups.	ICSI

ARTs: Assisted Reproductive Technologies; OR: Odds Ratio;

IUI: Intrauterine Insemination;

TESE: Testicular Sperm Extraction; vs: versus;

CI: Confidence Internal; ICSI: Intracytoplasmic Sperm Injection

Table 2: The effect of varicocelectomy on semen quality.

All participants presented fertility problems with abnormal semen quality. The severe abnormality of sperm found in four studies was azoospermia, two other studies noted each oligoasthenozoospermia, asthenospermia and another excluded azoopermia and leukocytospermia for semen abnormalities. All treated patients underwent surgical repair for varicocele followed ART. According to varicocele correction, inguinal or subinguinal microsurgical techniques were frequently used in 5/7 of studies.

Globally, most defected semen parameters were improved after varicocelectomy among treated groups in all these studies ($P<0.05$). However, no statistical difference showed mainly on progressive motility and percentage strict morphology. Application of ART especially ICSI was widely provided to 1010 participants in 6 of these studies (Table 2).

Pregnancy outcomes reported show significant statistical clinical pregnancy rate on varicocele followed ART among treated group compared to untreated in four studies favouring varicocelectomy. Overall, the result showed significant difference of studies (OR=1.76; 95% CI: 1.35-2.29, P=0.000) (Table 3) and funnel plot (Figure 2) suggested publication bias found among these studies. In two of studies, no differences were reported about the miscarriages in treated and control groups. Although, in general significant statistical difference was reported (OR=0.65; 95% CI: 0.42-0.99, P=0.042) (Table 4); thus, varicocelectomy may help to reduce miscarriages among couples who undergo ART.

Publication bias of studies showed in Figure 3. We detected that heterogeneity was statistical significant (Chi-squared test, $P=0.000$) that led to the use of random effects model to analyse live birth outcomes. The achievement of pregnancy illustrated by the live birth examined in these studies was controversial.

Three studies reported no difference of live birth increasing among treated compared to untreated group. Even if 4 of these studies showed statistical differences, overall, there is no difference to achieve pregnancy among couples who underwent varicocelectomy and followed ART (OR=1.58; 95% CI: 0.82-3.034; P=0.172) (Table 5). Regarding the funnel plot, the publication bias existed in these studies (Figure 4).

Discussion

Data analyzed in the current study revealed that 538 participants from diverse area in the world, issue from 7 original sources underwent varicocelectomy following by ARTs during the period of 2001-2011; this may be sufficient to assess male infertility due to varicoceles regarding the existing controversies [4,7,14,16,24,25] and based on updated recommendations and guidelines for good practices [3,4,19-21,23].

Study	Treated(n)		Control (n)		OR	95% CI	Weight	Odds Ratio
	A	B	C	D				M-H, Fixed, 95% CI
Daitch et al. [11]	11	23	4	20	2.391	[0.657, 8.703]	3.78%	
Inci et al. [10]	11	24	2	7	1.604	[0.286, 9.12]	2.60%	
Haydardedeoglu et al. [8]	23	8	34	31	2.621	[1.024, 6.712]	6.75%	
Esteves et al. [9]	48	32	73	89	1.829	[1.062, 3.151]	23.00%	
Pasqualotto et al. [7]	13	8	15	38	4.117	[1.420, 11.934]	3.86%	
Shiraishi et al. [5]	52	117	25	54	0.96	[0.540, 1.707]	28.11%	
Gokce et al. [6]	105		65	73	1.872	[1.185, 2.958]	31.89%	
Total (95%CI)					**1.756**	[1.347, 2.288]	100.00%	
Total (N)	263	275	218	312				
Heterogeneity Chi Square=7.71 (d.f.=6), P^a=0.260 ; I^2 (Variation in OR attributable to heterogeneity)=22.2% Test of overall effect OR=1; Z=4.17 *P*=0.000								
A: number of clinical pregnancies in treated group; B: number failed to conceive in treated group; C: number of clinical pregnancy in control group; D: number failed to conceive in control group; OR: odds ratio; d.f.: degree of freedom; CI: confidence interval; P^a : value of Q-test for heterogeneity test								

Table 3: Clinical pregnancy outcome in treated (varicocelectomy) vs control group after ART.

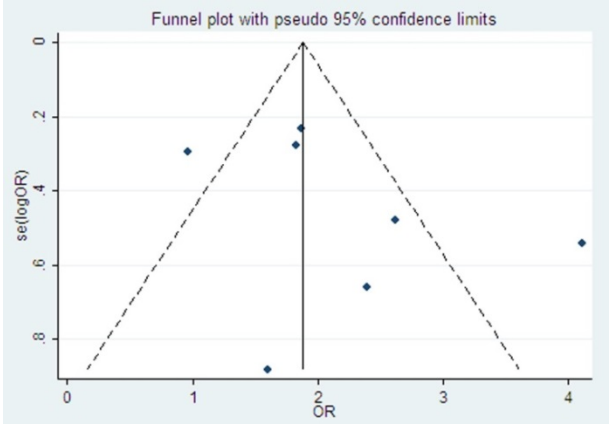


Figure 2: Publication bias for clinical pregnancies.

The mean age of 4 studies showed mid advanced age (34 years old) for men to conceive; most studies suggested the average interval of about 6 months from varicocelectomy to ART [1,24,26,27]. Regarding the present observation, discrepancies and limited outcomes of varicoclectomy following ART among couples with middle advanced age, female age and couple's time desire to conceive in practice must be accounted. Although, longer interval between varicocelectomy and ART seems to be more productive [6,11,28,29]. The effect of varicocele repair using microsurgical techniques among men with azoospermia was predominant in this study largely promoted semen quality and clinical outcomes of couples who underwent ARTs. This result was previously demonstrated in some studies [23,25,30-32].

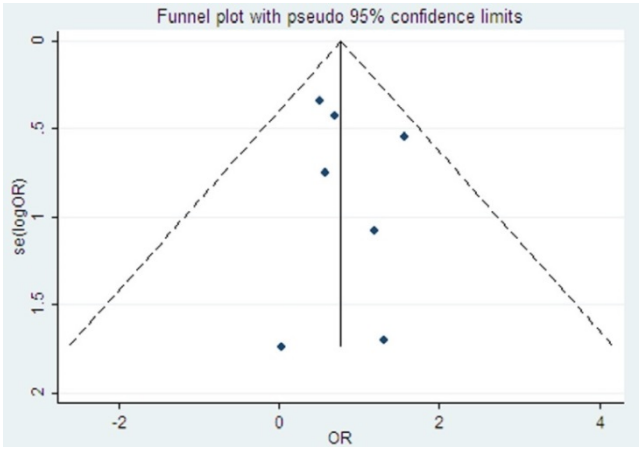


Figure 3: Publication bias for miscarriages.

Moreover, several studies reported the effectiveness of IUI or ICSI to increase clinical outcomes [30,33], however Baker et al. [12] found that high DNA fragmentation index (>30) help to achieve spontaneous pregnancy. Thoroughly, spontaneous pregnancy should remain the ultimate standard for evaluating the succeed management of male

infertility due to varicocele treatment. Despite the conclusion issued from Evers et al. [17] in 2003 and the recent study from Pasqualotto et al. [7] demonstrated that surgical procedure did not have any impact on pregnancy or miscarriage rates following ICSI of couples with exiting varicocele repaired, however several other studies argue that varicocelectomy has beneficial effects on ART outcomes [27,29,34].

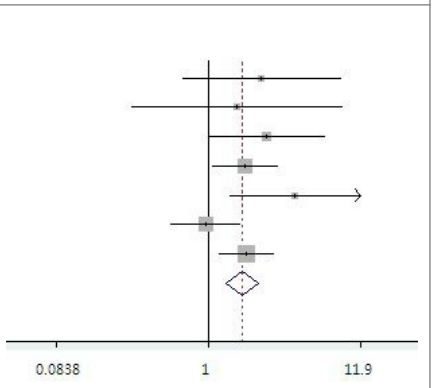
Study, year	Treated(n)		Control(n)		OR	95% CI	Weight	Odds Ratio
	A	B	C	D				M-H, Fixed, 95% CI
Daitch et al.[11]	0	11	3	1	0.019	[0.001, 0.568]	8.75%	
Inci et al.[10]	2	9	0	2	1.316	[0.047, 37.157]	1.17%	
Haydardedeoglu et al.[8]	3	20	7	27	0.579	[0.133, 2.519]	9.07%	
Esteves et al.[9]	11	37	22	51	0.689	[0.298, 1.594]	24.85%	
Pasqualotto et al.[7]	2	11	2	13	1.182	[0.142, 9.827]	2.90%	
Shiraishi et al. [5]	40	12	17	8	1.569	[0.544, 4.525]	9.79%	
Gokce et al. [6]	25	80	25	40	0.500	[0.255, 0.979]	43.47%	
Total (95%CI)					**0.646**	[0.424, 0.985]	100.00%	
Total (N)	82	180	76	142				
Heterogeneity Chi squrare = 7.92 (d.f.= 6), Pa=0.244; I2 (Variation in OR attributable to heterogeneity)=24.2% Test of overall effect OR=1; Z=2.03 P=0.042								
A: number of miscarriages in treated group; B: number of clinical pregnancies until delivery in treated group; C: number of miscarriages in control group; D: number of clinical pregnancy until delivery in control group; OR: odds ratio; d.f.: degree of freedom; CI: confidence interval; P: value of Q-test for heterogeneity test; P^a: value of Q-test for heterogeneity test								

Table 4: Miscarriage outcome in treated (varicocelectomy) vs control group after ART.

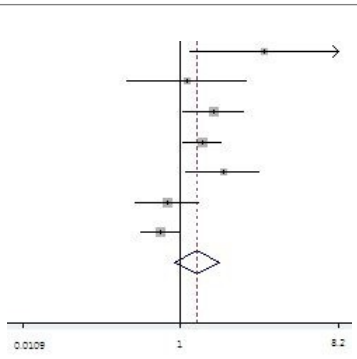
Study	Treated(n)		Control(n)		OR	95% CI	Weight	Odds Ratio
	A	B	C	D				M-H, Fixed, 95% CI
Daitch et al. [11]	11	23	1	23	11.00	[1.311, 92.299]	6.66%	
Inci et al. [10]	9	26	2	7	1.212	[0.212, 6.935]	%8.67	
Haydardedeoglu et al. [8]	20	11	27	38	2.559	[1.055, 6.205]	18.05%	
Esteves et al. [9]	37	43	51	111	1.873	[1.080, 3.248]	19.61%	
Pasqualotto et al. [7]	11	10	13	40	3.385	[1.172, 9.775]	14.23%	
Shiraishi et al. [5]	12	157	8	71	0.678	[0.266, 1.732]	15.50%	
Gokce et al. [6]	80	88	40	25	0.568	[0.317, 1.019]	19.27%	
Total (95%CI)					1.576	[0.820, 3.026]	100.00%	
Total (N)	191	356	142	215				
Heterogeneity Chi square=20.51 (d.f.=6), P^a=0.002 ; I^2 (Variation in OR attributable to heterogeneity)=70.7% Estimate of between-study variance Tau^2=0.4865; Test of overall effect OR=1; Z=1.37 P=0.172								
A: number of live births in treated group; B: number of miscarriages and failed to clinical pregnancy in treated group; C: number of life births in control group; D: number of miscarriages and failed to clinical pregnancy in control group; OR: odds ratio; d.f.: degree of freedom; CI: confidence interval; P^a : value of Q-test for heterogeneity test;								

Table 5: Live birth outcome in treated (varicocelectomy) vs control group after ART.

In this study, even though, clinical pregnancy, miscarriages and live birth rates were independently inconsistent; however, global findings showed that varicocelectomy improves semen quality and therefore reduced miscarriages (OR=0.65; 95% CI: 0.42-0.99, P=0.042), increased pregnancy (OR=1.76; 95% CI: 1.35-2.29, P=0.000) and live birth rates (OR=1.58; 95% CI: 0.82-3.034; P=0.172) of couples who underwent ART especially ICSI. Overall, the use of ART specifically ICSI after varicocelectomy found in 6 studies of the current investigation revealed the increase of clinical outcomes. Performing ART after varicocele repaired among men with infertility is a long time procedure and requires couples' adherence as well as costs and unknown long-term effects of ART. All studies included were retrospective design and even whether random effect model was used to analyze live birth outcomes, the non- randomization of participants in each study for varicocelectomy followed by ART may affect original data. Giving the existing controversies and different updated recommendations for male infertility due to varicoceles, further studies with randomized, control trials are valuable.

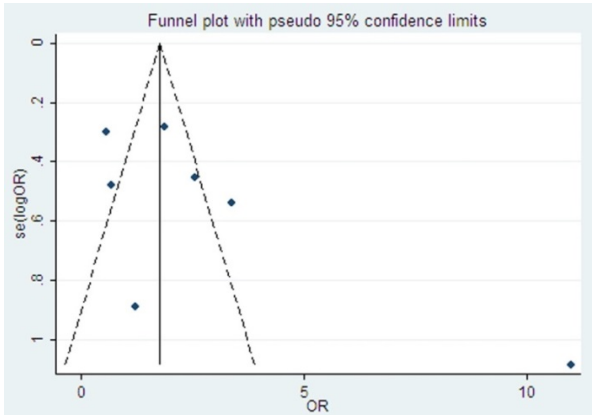


Figure 4: Publication bias for live births.

Conclusion

Varicocelectomy improved semen quality; furthermore, it may reduce miscarriages, increased clinical pregnancy and live birth rates of couples who underwent ART specifically ICSI. In spite of the long-term procedure, high associated costs and medical risks of ART, the current meta-analysis suggested that varicoceletomy is beneficial for infertile men prior to ART.

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Declarations

All authors declare no competing financial interests.

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