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INVITED REVIEW

Male Fertility

# Outcome of varicocele repair in men with nonobstructive azoospermia: systematic review and meta-analysis

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The objective of this systemic review was to evaluate the benefit of repairing clinical varicocele in infertile men with nonobstructive azoospermia (NOA). The surgically obtained sperm retrieval rate (SRR) and pregnancy rates following assisted reproductive technology (ART) with the use of retrieved testicular sperm were the primary outcomes. The secondary outcomes included the presence of viable sperm in postoperative ejaculate to avoid the testicular sperm retrieval and pregnancy rates (both assisted and unassisted) using postoperative ejaculated sperm. An electronic search to collect the data was performed using the MEDLINE and EMBASE databases until April 2015. Eighteen studies were included in this systematic review and accounted for 468 patients who were diagnosed with NOA and varicocele. These patients were subjected to either surgical varicocele repair or percutaneous embolization. Three controlled studies evaluating sperm retrieval outcomes indicated that in patients who underwent varicocelectomy, SRR increased compared to those without varicocele repair (OR: 2.65; 95% CI: 1.69–4.14;  $P < 0.001$ ). Although pregnancy rates with the use of testicular sperm favored the varicocelectomy group, results were not statistically significant (clinical pregnancy rate OR: 2.07; 95% CI: 0.92–4.65;  $P = 0.08$ ; live birth rate OR: 2.19; 95% CI: 0.99–4.83;  $P = 0.05$ ). The remaining fifteen studies reported postoperative semen analysis results. In 43.9% of the patients (range: 20.8%–55.0%), sperm were found in postoperative ejaculates. Pregnancy rates for unassisted and assisted (after IVF/ICSI) were 13.6% and 18.9% in the group of men with sperm in postoperative ejaculates, respectively. Our findings indicate that varicocelectomy in patients with NOA and clinical varicocele is associated with improved SRR. In addition, approximately 44% of the treated men will have enough sperm in the ejaculate to avoid sperm retrieval. Limited data on pregnancy outcomes with both postoperative ejaculated sperm and harvested testicular sperm preclude any firm conclusion with regard to the possible increased fertility potential in treated individuals. In conclusion, the results of our study indicate that infertile men with NOA and clinical varicocele benefit from varicocelectomy. Given the low/moderate quality of evidence available, it is advisable that doctors discuss with their patients with NOA the risks and benefits of varicocele repair.

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## INTRODUCTION

Infertility has become a world's public health challenge affecting 1 in every 6 couples trying to conceive, roughly with the same incidence of prostate cancer in men at screening age according to the American Cancer Society.<sup>1,2</sup> Half of these cases are due to a male-related problem, which may or may not be treatable or reversible.<sup>3</sup>

Nonobstructive azoospermia (NOA) is the most severe condition in male infertility and affects 10% of the infertile men.<sup>4</sup> Before the availability of assisted reproductive technology (ART), only donor sperm provided a real chance of conception in couples affected by this condition. Advances in ART, especially intracytoplasmic sperm injection (ICSI) and microsurgical methods of testicular sperm retrieval made biological fatherhood possible for approximately 20%–40% of the men with NOA.<sup>5</sup>

Varicocele is found in approximately 5% of the men with NOA, but its role in the pathophysiology of azoospermia is not fully established.<sup>6</sup> While it is still debatable whether varicocele is coincidental or contributory to spermatogenesis disruption in these men, its surgical treatment has been aiming at improving sperm production. Even a modest induction in spermatogenesis leading to the presence of motile sperm in the postoperative ejaculate could help these previously azoospermic men to establish a pregnancy either assisted or unassisted, thus expanding the couple's reproductive options.<sup>6</sup> Treatment goals are, therefore, allowing the appearance of small quantities of sperm in the ejaculate, consequently obviating the need for sperm retrieval (SR), or increasing the likelihood of SR success.

The objective of this study was to collect and summarize the evidence that evaluated the benefit of repairing clinical varicoceles in azoospermic men with NOA.

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## MATERIALS AND METHODS

### Search strategy

An exhaustive electronic search was performed using the MEDLINE and EMBASE databases until July 2015. We also searched for the references of the identified articles. There were no limits placed on the year of publication, but we restricted the search to articles published in English. The search combined terms and descriptors related to varicolectomy, varicocele repair, azoospermia, nonobstructive azoospermia, sperm retrieval, sperm retrieval techniques, ART, and ICSI. The study was exempted from Institutional Review Board approval given that it did not involve any human intervention. We utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement to report results.<sup>7</sup>

### Eligibility criteria and data extraction

This review included studies evaluating the benefit of repairing clinical varicocele in men with NOA. Clinical varicoceles were considered those diagnosed based on the finding of varicose veins in the spermatic cord, either by visual inspection or by palpation with or without the aid of the Valsalva maneuver during a clinical examination with the patient in a standing position. Azoospermia was diagnosed in at least two separate semen analyses after careful examination of the pelleted semen. Only studies involving men with absolute azoospermia were included. In the series that included patients with so-called “virtual” azoospermia in which few sperm have been found in semen analysis either before or after centrifugation, only data related to absolute azoospermia (if available) were included. The diagnosis of NOA was based on history, clinical examination, hormone (FSH, LH, and testosterone) levels, and confirmed in a histopathology specimen taken before or during the varicocele repair. Series in which histopathology results revealed the presence of normal spermatogenesis were excluded. Only studies reporting pregnancy with the use of sperm obtained postoperatively were included. ART was defined according to the International Committee for Monitoring Assisted Reproductive Technology (ICMART) as all treatments or procedures that include the *in vitro* handling of both human oocytes and sperm or of embryos for the purpose of establishing a pregnancy. This included *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) and embryo transfer.<sup>8</sup> As such, ART did not include assisted insemination (artificial insemination) using sperm from either a woman's partner or a sperm donor for the purpose of this review.

The selection criteria are described in **Table 1**. Two independent authors (RM and SCE) assessed all abstracts retrieved from the search and obtained full manuscripts of the citations that met the inclusion criteria. These authors evaluated the study's eligibility and subsequently extracted the data. Any discrepancies were solved by agreement and if needed, they reached consensus with a third author (AA). A fourth author (MR) summarized the data and performed meta-analysis when appropriate. All authors critically analyzed the summarized results.

### Outcome measures

The SRR and pregnancy rates following ART with the use of retrieved testicular sperm were the primary outcomes. The secondary outcomes were the presence of enough viable sperm in postoperative ejaculate to avoid the testicular sperm retrieval, and pregnancy rates (both assisted and unassisted) using postoperative ejaculated sperm. A subgroup analysis was conducted to determine the role of testicular histopathology and varicocele grade on primary and secondary outcomes. Histological patterns of Sertoli cell-only (SCO), maturation arrest (MA), and hypospermatogenesis (HS) were included. Based

upon clinical examination, varicocele was graded into (1) grade 1: palpable only during Valsalva maneuver, (2) grade 2: palpable at rest, but not visible, and (3) grade 3: visible and palpable at rest.<sup>1</sup>

Successful retrievals were defined as the presence of sperm in testicular biopsy specimens. The SRR was the number of successful retrievals divided by the number of retrievals. Clinical pregnancy was defined as a pregnancy observed sonographically by the visualization of a fetal heartbeat by 7 weeks of gestation. The clinical pregnancy rate was the number of clinical pregnancies expressed per 100 embryo transfers. The live birth rate was defined as the ratio between the number of deliveries resulting in at least one live birth and the number of embryo transfers. Natural pregnancy was defined as a pregnancy resulting in at least one live birth obtained without medical assistance.

### Risk of bias assessment

We followed the Cochrane Collaboration guidelines to assess the risk of bias in studies that included a control group of untreated men with clinical varicocele.<sup>9</sup> We evaluated sequence generation, allocation concealment, blinding, and incomplete outcome data. A low risk of bias was considered when a judgment of “yes” for all domains was obtained, whereas a high risk of bias was considered when a judgment of “no” for one or more domains was obtained. An unclear risk of bias was defined when an “unclear” judgment in any domain was considered. The quality assessment of the included trials is shown in **Supplementary Table 1**.

### Analysis

Data on the dichotomous outcomes in the studies that included a control group of untreated men with clinical varicocele were pooled to obtain the odds ratio (OR) and its corresponding 95% confidence interval (CI) for the occurrence of an outcome event. Statistical significance was set at  $P < 0.05$ . We pooled the outcome data from studies as presented in **Supplementary Table 1** using a Mantel-Haenszel model and applied the fixed-effects model.<sup>10</sup> To quantify the statistical heterogeneity, we used  $I^2$  statistic to describe the variations across trials that were due to heterogeneity and not to sampling error. We used the Review Manager 5 software to conduct the meta-analysis (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

**Table 1: Selection criteria of included studies (PICOS)**

	Included	Excluded
Population	Infertile men with clinical varicocele and NOA	Virtual azoospermia Testicular histopathology showing normal spermatogenesis Use of donor sperm for assisted conception
Intervention	Varicolectomy (surgical ligation or percutaneous embolization)	
Comparison	Nonintervention/observation	
Outcomes		
Primary outcomes	Sperm retrieval rate Pregnancy rates in ART using retrieved testicular sperm	
Secondary outcomes	Presence of enough viable sperm in postoperative ejaculate to avoid testicular sperm retrieval Pregnancy rates (both unassisted and assisted) using postoperative ejaculated sperm	
Study type	Any type	

ART: assisted reproductive technology; NOA: nonobstructive azoospermia



## RESULTS

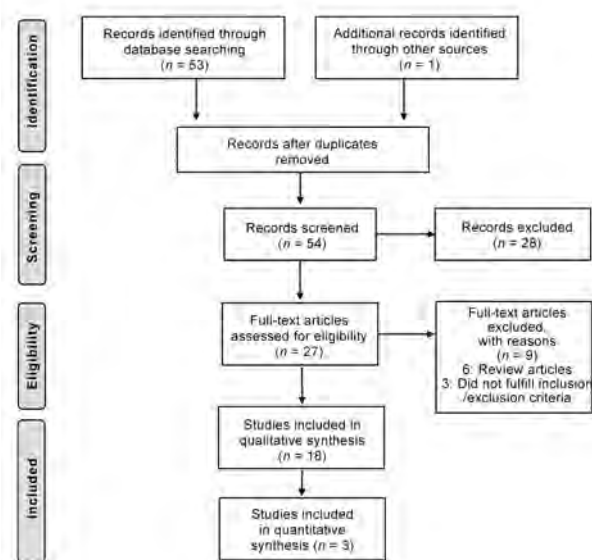
Our electronic search retrieved 54 articles. After screening the titles and abstracts, we determined that 27 articles were deemed eligible for inclusion. Among these, nine articles were excluded. Of these, six were review articles and three did not fulfill the inclusion criteria.<sup>11–13</sup> The study of Schlegel and Kaufmann included men with clinical and subclinical varicoceles, and the authors did not perform a separate analysis of each varicocele subtype.<sup>11</sup> The series reported by Shefi *et al.* described sperm mapping using fine needle aspiration (FNA) technique and included patients with virtual azoospermia.<sup>12</sup> The series reported by Youssef *et al.* also included men with virtual azoospermia as well as patients with histopathology results showing normal spermatogenesis, which does not fit in the diagnosis of NOA.<sup>13</sup> The complete selection process is depicted in **Figure 1**.

### Description of the included studies

Eleven retrospective and seven prospective studies were included in this systematic review and accounted for 468 treated patients who had complete azoospermia and were subjected to either surgical varicocele repair or percutaneous embolization.<sup>6,14–30</sup> In 13 of the included studies, patients were subjected to varicocele repair using either inguinal or subinguinal microsurgical methods.<sup>6,14–17,19,22–27,30</sup> In one<sup>29</sup> and three studies,<sup>18,20,28</sup> respectively, inguinal macroscopic varicocelectomy and anterograde or retrograde percutaneous embolization were the treatment methods. Among the studies, the vast majority ( $n = 14$ ) evaluated solely NOA men with treated varicoceles; these studies were, therefore, included in the qualitative analysis (**Figure 1**).

A control group of NOA men with untreated varicocele was included for comparison in three series, all of which were included in the quantitative analysis (**Figure 1**).<sup>26,29,30</sup> These aforementioned series evaluated SRR by microdissection testicular sperm extraction (micro-TESE) and accounted for 159 treated and 241 untreated patients. Two of these series also evaluated pregnancy outcomes after sperm injections with retrieved testicular sperm and accounted for 100 treated and 40 untreated men.<sup>29,30</sup>

The characteristics of all studies included in this systematic review are presented in **Supplementary Table 2**.



**Figure 1:** Flowchart for the trial identification and selection process.

## Outcomes

### Sperm retrieval rates in treated and untreated men

Four studies reported data on sperm retrieval,<sup>6,26,29,30</sup> three of which included a control group of men with NOA and untreated varicocele for comparison.<sup>26,29,30</sup> The data of these three studies were included in a meta-analysis. A significant benefit on sperm retrieval rates was found for NOA patients with clinical varicocele that were subjected to varicocelectomy before sperm retrieval (OR: 2.65; 95% CI: 1.69–4.14;  $P < 0.0001$ ;  $I^2 = 0$ , **Figure 2**). The mean  $\pm$  s.d. time interval between varicocele repair and sperm retrieval was  $10.86 \pm 11.12$  months (range: 3–23.6 months). Inci *et al.* reported SRR of 53% in treated compared with 30% in untreated patients (OR: 2.63; 95% CI: 1.05–6.60;  $P = 0.036$ ).<sup>30</sup> The series by Haydardedeoglu *et al.* included the largest cohort published so far.<sup>29</sup> Sperm retrieval rates were significantly higher in varicocele-treated patients (60.8% vs 38.46%,  $P = 0.01$ ). Zampieri *et al.* also reported significantly higher SRR in the group of treated men (57.8 vs 27%,  $P < 0.05$ ).<sup>26</sup> Paternal age in treated and untreated groups was not different in these aforementioned studies.

### Pregnancy rates in ART cycles using retrieved testicular sperm in treated and untreated men

Two studies reported data on pregnancy by ICSI using retrieved testicular sperm,<sup>29,30</sup> both of which included a control group of men with NOA and untreated varicocele for comparison.<sup>26,29,30</sup> These studies were summarized and included in a meta-analysis to evaluate both clinical pregnancy rates (CPR) and live birth rates (LBR). Inci *et al.* reported that CPR (31.4% vs 22.4%) and LBR (25.7% vs 22.2%) were not statistically different in treated and untreated patients, respectively.<sup>30</sup> In contrast, both CPR (74.4% vs 52.3%;  $P = 0.03$ ) and LBR (64.5% vs 41.5%;  $P = 0.02$ ) were significantly higher in the varicocele-treated group in the series by Haydardedeoglu *et al.*<sup>29</sup> In this aforementioned series, implantation rates (IRs) were also significantly higher in the group subjected to varicocelectomy compared to the group subjected to ICSI with untreated varicocele (40.6% and 26.0%, respectively;  $P = 0.03$ ). The clinical characteristics of female partners, embryonic parameters, and number of transferred embryos did not differ in the treated and untreated groups in these two aforementioned studies. The summarized evidence indicated that the odds for achieving clinical pregnancy (OR: 2.19; 95% CI: 0.99–4.83;  $P = 0.05$ ;  $I^2 = 0$ , **Figure 3**) and live birth (OR: 2.07; 95% CI: 0.92–4.65;  $P = 0.08$ ;  $I^2 = 0$ , **Figure 4**) using testicular sperm retrieved by micro-TESE and used for sperm injections were not statistically different between treated and untreated men.

### Sperm retrieval rates according to testicular histopathology and varicocele grade

Only one study provided data on SRR after varicocelectomy according to histopathology results.<sup>6</sup> This study included 17 patients, of which nine remained azoospermic after microsurgical varicocele repair and were subjected to micro-TESE. Overall, SRR was 44.4%. According to histopathology results, SRR was 100% in HS (2 patients) and MA (2 patients) and 16.6% (1 of 6 patients) in SCO.

As far as varicocele grade is concerned, only patients with grade 3 varicocele had been operated in the studies of Zampieri *et al.* and Haydardedeoglu *et al.*<sup>26,29</sup> Men with grade 3 varicocele also made up the control group in the former while varicocele grade in controls was not reported in the latter. Inci *et al.* reported that SRR was not statistically different among patients with grade 1 (33.3%), grade 2 (40.0%), and grade 3 (27.3%) varicocele.<sup>30</sup>

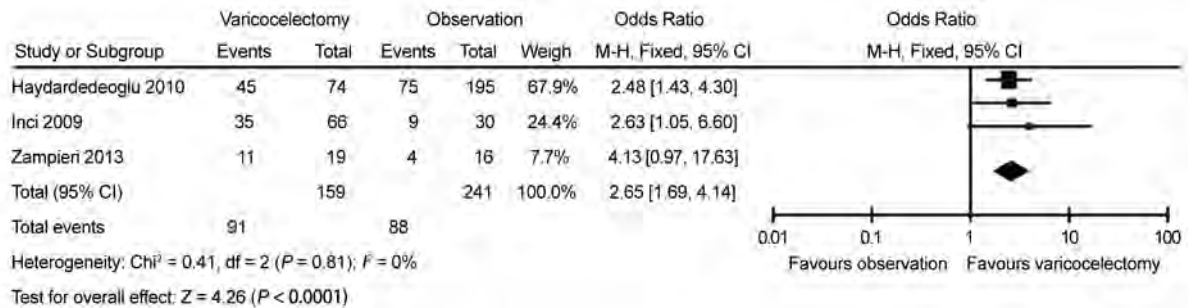


Figure 2: Forest plot of comparison: sperm retrieval rate in patients with NOA and previous varicocele repair versus no varicocele repair.

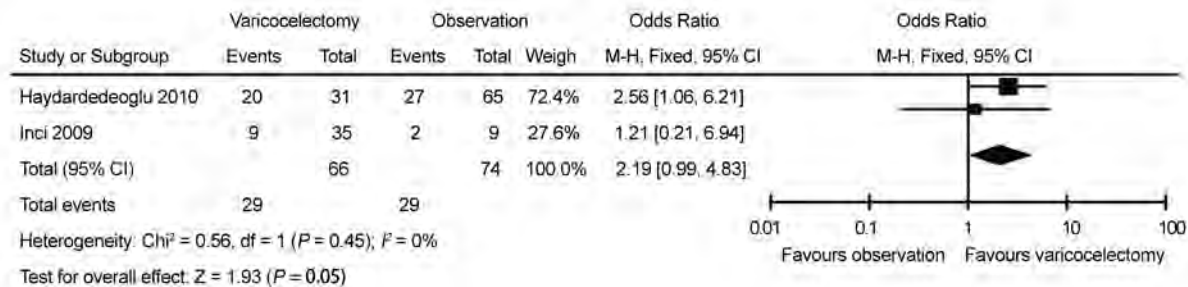


Figure 3: Forest plot of comparison: live birth rate after ICSI in patients with NOA and previous varicocele repair versus no varicocele repair.

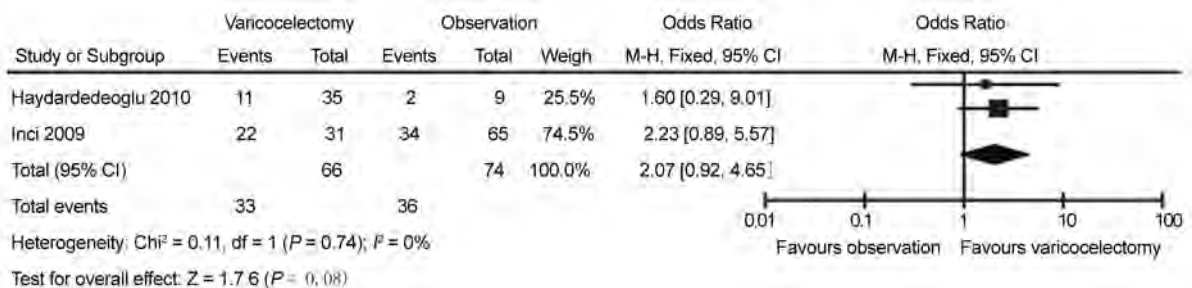


Figure 4: Forest plot of comparison: clinical pregnancy rate after ICSI in patients with NOA and previous varicocele repair versus no varicocele repair.

### Presence of sperm in postoperative ejaculate

Sixteen of the included studies accounting for a total cohort of 344 men reported data related to the presence of sperm in the postoperative ejaculate (Table 2). The mean  $\pm$  s.d. age and follow-up of this cohort were  $32.5 \pm 2.36$  years and  $12.36 \pm 5.49$  months, respectively.

In 43.9% (151/344) of the patients (range: 20.8%–55.0%), sperm was found in postoperative ejaculates. The mean  $\pm$  s.d. sperm count and motility were  $1.82 \times 10^6 \pm 1.58 \times 10^6$   $\text{ml}^{-1}$  (95% CI:  $0.98 \times 10^6$ – $2.77 \times 10^6$   $\text{ml}^{-1}$ ) and  $22.9\% \pm 15.5\%$  (95% CI: 12.5%–33.2%), respectively. The interval between varicocele repair and appearance of sperm in postoperative ejaculate varied from 4.5 to 11 months in the few studies which included this information. For all other studies, time points when postoperative ejaculate was assessed were described, but mean time to sperm appearance was not specified. None of the studies provided a control group of untreated men with clinical varicocele for comparison. It was not possible to perform a meta-analysis for the presence of sperm in postoperative ejaculate due to the lack of a comparison group.

### Presence of sperm in postoperative ejaculate after varicocele repair according to testicular histopathology and varicocele grade

Eight of the included studies reported data concerning the presence of sperm in postoperative ejaculate according to testicular histopathology results (Table 3). A total of 161 men with a mean  $\pm$  s.d. age of  $31 \pm 2.0$  years and follow-up period of  $13.28 \pm 4.73$  months were included; all of them were subjected to microsurgical varicocele repair. Testicular biopsies were performed either before or during the varicocele repair. Histopathology revealed SCO, MA, and HS in 62, 51, and 48 patients, respectively. Sperm was found in postoperative ejaculates in 9.7% (6/62) of the patients with SCO, 35.3% (18/51) with MA, and 56.2% (27/48) of those with HS. Overall, there was a significant increase in the chance of finding sperm in the postoperative ejaculate in patients with HS compared to MA (OR: 2.35; 95% CI: 1.04–5.29;  $P = 0.04$ ) and SCO (OR: 12.0; 95% CI: 4.34–33.17;  $P < 0.001$ ). Patients with MA had a higher chance of the sperm presence in postoperative ejaculates compared to those with SCO (OR: 5.09; 95% CI: 1.83–14.10;  $P = 0.001$ ).

**Table 2: Characteristics of included studies evaluating postoperative semen analysis of men with NOA subjected to varicocelectomy and pregnancy rates with the use of postoperative ejaculated sperm**

First author, year, and reference number	Mean age (years)	Mean follow-up (months)	Presence of sperm in postoperative ejaculate, n (%)	Mean postoperative sperm count ( $\times 10^6 \text{ ml}^{-1}$ )	Mean Interval between varicocele repair and sperm in ejaculate (months)	Mean postoperative sperm motility (%)	Natural pregnancy (n)	Pregnancy rates by ART (n)
Matthews, 1998 <sup>14</sup>	NR	10.3	12/22 (55.0)	2.20	NR	NR	2/12	1/10
Kim, 1999 <sup>15</sup>	35	15	14/28 (50.0)	1.18	8	44.0	0/14	2/14
Kadioglu, 2001 <sup>16</sup>	30.1	13.4	5/24 (20.8)	0.04*	NR	NR	0/5	NR
Çakan, 2004	29	9	3/13 (23.1)	0.73	4.5	26.0	0/3	0/1
Esteves, 2005 <sup>6</sup>	32	18.9	6/17 (35.3)	0.8*	5	NR	1/6	NR
Gat, 2005 <sup>18</sup>	34.1	12	18/32 (52.6)	3.81	NR	1.2	4/18	5/14
Pasqualotto, 2006 <sup>19</sup>	NR	12	9/27 (33.3)	4.06	NR	37.6	1/9	NR
Poulakis, 2006 <sup>20</sup>	33.8	24.8	7/14 (50.0)	3.10	NR	2.2	2/7	1/5
Ishikawa, 2008 <sup>21</sup>	33.3	>6	2/6 (33.3)	0.07	NR	NR	NR	NR
Cocuzza, 2009 <sup>23</sup>	29.4	9	3/10 (30.0)	5.50	NR	36.6	NR	NR
Lee, 2007 <sup>22</sup>	32	7.4	7/19 (36.8)	0.24	NR	30.2	1/7	NR
Abdel-Meguid, 2012 <sup>24</sup>	34.9	19.3	10/31 (32.3)	2.30	NR	15.3	NR	NR
Kıraç, 2013 <sup>25</sup>	31.7	11.4	7/23 (30.4)	1.34	NR	37.5	1/7	2/6
Zampieri, 2013 <sup>26</sup>	33	6	17/35 (48.6)	0.6	6	11.0	NR	0/4
Aboutaleb, 2014 <sup>27</sup>	29.9	17.3	6/20 (30.0)	2.00	NR	NR	NR	NR
D'Andrea, 2015 <sup>28</sup>	37	6	11/23 (47.8)	1.30	6	10.0	NR	NR

\*Mean total motile sperm count. ART: assisted reproductive technology; NR: not reported; SD: standard deviation; CI: confidence interval; NOA: nonobstructive azoospermia

**Table 3: Presence of sperm in postoperative ejaculate in men with NOA subjected to varicocelectomy according to testicular histopathology results**

First author, year, and reference number	Histopathology category and number of patients	Presence of sperm according to histopathology results		
		SCO (%)	MA (%)	HS (%)
Kadioglu, 2001 <sup>16</sup>	SCO: 7; MA: 14; HS: 3	1/7 (14.3)	3/14 (21.4)	1/3 (33.3)
Çakan, 2004 <sup>17</sup>	SCO: 5; MA: 3; HS: 5	0/5 (0)	1/3 (33.3)	2/5 (40.0)
Esteves, 2005 <sup>6</sup>	SCO: 6; MA: 5; HS: 6	0/6 (0)	3/5 (60.0)	5/6 (83.0)
Pasqualotto, 2006 <sup>19</sup>	SCO: 10; MA: 8; HS: 9	4/10 (40.0)	3/8 (37.5)	2/9 (22.2)
Cocuzza, 2009 <sup>23</sup>	SCO: 4; MA: 4; HS: 2	0/4 (0)	1/4 (25.0)	2/2 (100.0)
Lee, 2007 <sup>22</sup>	SCO: 10; MA: 6; HS: 3	1/10 (10.0)	4/6 (66.7)	2/3 (66.7)
Abdel-Meguid, 2012 <sup>24</sup>	SCO: 10; MA: 8; HS: 13	0/10 (0)	3/8 (37.5)	7/13 (53.8)
Aboutaleb, 2014 <sup>27</sup>	SCO: 10; MA: 3; HS: 7	0/10 (0)	0/3 (0)	6/7 (85.7)

SCO: Sertoli-cell only; MA: maturation arrest; HS: hypospermatogenesis; NOA: nonobstructive azoospermia

Five of the included studies analyzed the association between varicocele grade and the presence of sperm in the postoperative ejaculate (Table 4). A total of 76 patients were evaluated, all of whom had been subjected to microsurgical varicocele repair. Sperm was found in postoperative ejaculates in 7.7% (1/13) of the patients with grade 1 varicocele, 25.8% (8/31) of grade 2, and 34.3% (11/32) of those with grade 3 varicocele. Based on this small cohort, treatment of grades 2 and 3 varicoceles were not associated with higher chance of finding sperm in postoperative ejaculates compared to grade 1 varicocele (OR: 0.19; 95% CI: 0.02–1.59;  $P = 0.09$ ).

#### ***Unassisted and assisted pregnancy rates using postoperative ejaculated sperm***

Pregnancy outcomes with postoperative ejaculated sperm were assessed in eleven of the included studies (Table 2). While clinical pregnancy was reported across these studies, live birth data were presented in only three studies.<sup>15,20,25</sup> The summarized evidence on natural pregnancy accounted for 88 patients who had sperm in postoperative ejaculates, with a mean follow-up of 12.7 months (range: 6–25 months). The pregnancy rate (PR) in this cohort was 13.6% (12/88). In contrast, only seven studies reported ART data in which 11 pregnancies were obtained by ICSI from a treated cohort of 58 couples (PR: 18.9%).

A total of 23 pregnancies (naturally and by ART) were reported using postoperative ejaculated sperm in a cohort of 88 patients with NOA and treated varicocele (PR: 26.1%). It was not possible to perform a meta-analysis of pregnancy rates with postoperative ejaculated sperm due to the lack of a comparison group.

#### **DISCUSSION**

To our knowledge, this is the first study consisting of a pooled analysis addressing the potential benefits of varicocelectomy in NOA men with clinical varicocele, including sperm retrieval rates, the presence of postoperative sperm in the ejaculate, and pregnancy rates. Our results indicate that performing varicocelectomy in patients with NOA and clinical varicocele is associated with improved sperm retrieval rates. In addition, sperm in postoperative ejaculates should be expected in nearly half of the treated men, and testicular histopathology results (if available) indicating hypospermatogenesis or maturation arrest confer a more favorable prognosis to this outcome. An association between varicocele grade and SRR or presence of sperm in postoperative ejaculate remains equivocal.

Varicocele is known to have a detrimental effect on human spermatogenesis, and it is associated with male infertility.<sup>31</sup> Although its pathophysiology has not been fully elucidated, several mechanisms have

**Table 4: Association between varicocele grade and return of sperm to ejaculate after varicocele repair**

First author and reference	Number of patients with sperm in postoperative ejaculate according to varicocele grade (%)	Mean postoperative sperm count
Matthews <sup>14</sup>	NR	
Kim <sup>15</sup>	NR	
Kadioglu <sup>16</sup>	Grade 1: 0/9 (0) Grade 2: 2/11 (18.2) Grade 3: 3/4 (75)	Not reported
Çakan <sup>17</sup>	Grade 1: 0/1 (0) Grade 2: 1/4 (25) Grade 3: 2/8 (25)	Grade 1: NA Grade 2: $0.7 \times 10^6$ ml <sup>-1</sup> Grade 3: $1.2 \times 10^6$ ml <sup>-1</sup> and $0.3 \times 10^6$ ml <sup>-1</sup>
Esteves <sup>6</sup>	NR	
Gat <sup>18</sup>	NR	
Pasqualotto <sup>19</sup>	NR	
Poulakis <sup>20</sup>	NR	
Ishikawa <sup>21</sup>	Grade 1: no patients in this group Grade 2: 2/3 (66.6) Grade 3: 0/3 (0)	Grade 1: NA Grade 2: $0.2 \times 10^6$ ml <sup>-1</sup> Grade 3: NA
Lee <sup>22</sup>	NR	
Cocuzza <sup>23</sup>	Grade 1: no patients in this group Grade 2: 1/4 (25) Grade 3: 2/6 (33.3)	Grade 2: $0.6 \times 10^6$ ml <sup>-1</sup> Grade 3: $12.2 \times 10^6$ ml <sup>-1</sup> and $3.9 \times 10^6$ ml <sup>-1</sup>
Abdel-Meguid <sup>24</sup>	NR	
Kıraç <sup>25</sup>	Grade 1: 1/3 (33.3) Grade 2: 2/9 (22.2) Grade 3: 4/11 (36.3)	Grade 1: $0.001 \times 10^6$ ml <sup>-1</sup> Grade 2: $1.3 \times 10^6$ ml <sup>-1</sup> Grade 3: $2.9 \times 10^6$ ml <sup>-1</sup>
Zampieri <sup>26</sup>	NR	
Aboutaleb <sup>27</sup>	NR	
D'Andrea <sup>28</sup>	NR	

NR: not reported; NA: not available

been proposed to explain its negative impact and include testicular blood stasis, testicular venous hypertension, elevated testicular temperature, increase in spermatic vein catecholamine levels, testicular underperfusion, and elevated oxidative stress.<sup>32</sup> Germ cell apoptosis and subsequent oligozoospermia and azoospermia can be a consequence of increased scrotal temperature, increased intratesticular cadmium concentration, and reduced levels of androgens.<sup>33,34</sup> The mechanism by which temperature affects spermatogenesis is not clearly understood, but the most commonly accepted theory is thermal damage to the DNA and proteins in the nucleus of spermatic and tubule cells and/or Leydig cells.<sup>35,36</sup> Varicocele may thus cause alterations in semen quality to the point of severe oligozoospermia or even azoospermia via progressive testicular damage.<sup>37</sup>

Azoospermia and severe oligozoospermia were reported to range from 4.3% to 13.3% in men with varicocele.<sup>38</sup> Existing data suggest that patients with nonobstructive azoospermia and clinical varicocele may improve seminal parameters following surgical varicocele repair, and the chance of an improvement relates to histopathological testicular diagnosis.<sup>6,39</sup> Notwithstanding, most of the studies evaluating the results of varicocele repair in this category of patients did not include a control group, hence limiting conclusions on the benefits of performing varicolectomy in patients with clinical varicocele and NOA. In fact, only three cohort studies included a control group of untreated patients with NOA and clinical varicocele, all of which assessed sperm retrieval rates as the primary outcome measurement.<sup>26,29,30</sup> We summarized the data of these aforementioned

studies and performed a meta-analysis. Our results indicate that SRRs are significantly higher in patients with NOA and clinical varicocele subjected to microsurgical varicolectomy before sperm retrieval compared to those with no varicocele repair (OR: 2.65; 95% CI: 1.69–4.14;  $P < 0.0001$ ).

In contrast, pregnancy outcomes after sperm injections using testicular sperm retrieved from NOA men with treated varicoceles are less reassuring. Although the odds for both clinical pregnancy and live birth favored couples in which varicocele had been treated, the summarized results did not reach statistical significance. Of note, only two cohort studies compared pregnancy outcome with the use of retrieved testicular sperm for ICSI between men with treated and untreated varicoceles. Both series included relatively few patients and yielded conflicting results. Hence, further research is warranted to evaluate the benefit of varicolectomy before ICSI with regards to pregnancy rates in this subset of men.

The return of viable sperm to the ejaculates of NOA men following varicocele repair is an important achievement for ART purposes. It not only allows patients to attempt biological parenthood but also avoids the need for an invasive procedure for harvesting testicular sperm. Our data indicate that approximately 44% of the treated patients will have enough sperm in postoperative ejaculate to allow ICSI to be performed without the need for sperm retrieval. It has been suggested that fresh ejaculated sperm may yield superior ICSI success rates compared to sperm harvested by TESE.<sup>40</sup> In addition, it is easier for the laboratory to handle such specimens.<sup>41</sup> Hence, whenever possible, it is preferable to use viable sperm from a fresh ejaculate than testicular sperm extraction in preparation for ICSI. Moreover, when TESE is required, the success of SR will be improved by having had the varicocele treated as indicated in this study.

Among the patients who had sperm in postoperative ejaculates, 14% achieved natural pregnancy. Pregnancy rate after ICSI using ejaculated sperm was 18.9%. Considering the presence of sperm in a postoperative ejaculate, the cumulative pregnancy rate (natural plus ART) was 26.1%. Since information regarding the follow-up period was not consistent across studies and not all couples were subjected to ICSI after failure to achieve natural pregnancy, these data should be interpreted with caution.

The only prognostic factor that seems to consistently predict the chances of finding sperm in the ejaculates of NOA men after varicocele repair is testicular histopathology. SCO is associated with the worst outcomes in NOA men with repaired clinical varicoceles. Only 9.6% of these patients will have enough viable sperm in postoperative ejaculate to avoid testicular sperm retrieval compared to 35.3% of men with MA and 56.2% of those with HS. Notwithstanding, the clinical utility of a single biopsy specimen to estimate whether islets of sperm production exist within the testicle is hampered by the heterogeneous distribution of spermatogenesis.<sup>44,42</sup> In addition, variation in interpretation of histologic patterns with inconsistencies among independent pathologists was reported to occur in up to 27% of the testis biopsy results.<sup>43</sup> This may impose a risk of underestimating the reproductive potential of men who may yield a biopsy proven SCO, for example, while harboring islets of sperm production elsewhere in the testicular parenchyma.<sup>44,45</sup> Refining testicular biopsy assessments would help differentiate cases of pure SCO from those of focal spermatogenesis.<sup>42</sup> At present, some authors disregard the need for testicle biopsy preceding varicocele repair in NOA as these men may succeed to ejaculate sperm even in the case of SCO diagnosis.<sup>19</sup> Others deselect men with SCO and Y chromosome microdeletions from treatment based on the argument that it is unlikely that varicolectomy will confer any additional beneficial effect.<sup>6,46,47</sup>

The optimal interval between varicocele repair and sperm extraction in men who remain azoospermic after varicolectomy is still to be defined. Intervals varying from 2 months to 187 months have been reported.<sup>11,29,30</sup> In one series, a shorter interval ( $42.2 \pm 8.9$  months vs  $80.0 \pm 12.3$  months) was associated with better pregnancy outcomes.<sup>29</sup> Given such limited evidence, it seems reasonable to counsel doctors to defer SR for at least 3 months postoperatively based on the duration of the spermatogenic cycle ( $64 \pm 8$  days).<sup>48</sup> If spermatozoa do show up in the postoperative semen analysis, cryopreservation is recommended as relapse into azoospermia has been reported.<sup>19</sup>

Finally, despite the potential benefits of varicocele repair in NOA patients, it has been argued that varicolectomy may not be as cost-effective as straightforward micro-TESE with ICSI.<sup>49</sup> Using a simulated decision analytic model with costing data from the United States for the year 2005, Lee *et al.* suggested that micro-TESE (69 731 USD) was more cost-effective than varicolectomy (79 576 USD) when direct and indirect costs per live delivery were calculated. The authors added that varicolectomy becomes more cost-effective than TESE when: (1) the rate of natural pregnancy after varicolectomy exceeds 40%, or (2) the rate of successful delivery after IVF/ICSI decreases to <10%.<sup>49</sup> Although such decision models can provide a structured cost-effectiveness analysis, they cannot be generalized as costs vary substantially between institutions and countries. Factors such as insurance coverage and success rates of both varicolectomy and TESE-ICSI should be taken into account to allow more individualized results.

## CONCLUSION

The results of our study indicate that infertile men with NOA and clinical varicocele may benefit from varicolectomy. SSR is increased by 2.6-fold in treated patients compared to untreated patients. Moreover, approximately 44% of the treated men will have enough viable sperm in postoperative ejaculate to avoid testicular sperm retrieval. Favorable prognostic factors for the appearance of sperm in postoperative ejaculates were the presence of hypospermatogenesis or maturation arrest in testicular histopathology specimens. Limited data on pregnancy outcomes with both postoperative ejaculated sperm and retrieved testicular sperm preclude any firm conclusion with regard to an arguable increased fertility potential of gametes from treated individuals. Lastly, due to the retrospective nature of the studies included in this systematic review, further research is needed to evaluate conclusively the role of varicocele treatment in infertile men with NOA and clinical varicocele.

## AUTHOR CONTRIBUTIONS

SCE designed the study, participated in the acquisition of data, and helped draft the manuscript. RM participated in the acquisition of data, summarized the collected evidence, and helped draft the manuscript. MR performed the meta-analysis and helped draft the manuscript. AA revised the manuscript and helped coordination. All authors read and approved the final manuscript.

## COMPETING INTERESTS

The authors declared no competing interests.

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