

Conference Paper

The Role of Varicocele Repair in Non-Obstructive Azoospermic Men: A systematic Review

Donny Eka Putra,¹ Ponco Birowo,¹ Indah Suci Widyahening,² Nur Rasyid,¹ and Akmal Taher¹

¹Department of Surgery, Division of Urology, Faculty of Medicine, Universitas Indonesia/Department of Urology, Cipto Mangunkusumo Hospital, Jalan Diponegoro no. 71, Jakarta 10430, Indonesia

²Department of Community medicine, Faculty of Medicine, Universitas Indonesia, Jalan Pegangsaan Timur 16/Centre for Clinical Epidemiology & Evidence-based Medicine, Cipto Mangunkusumo Hospital-Faculty of Medicine Universitas Indonesia, Jalan Diponegoro no. 71, Jakarta 10430, Indonesia

Abstract

The outcomes of varicocele repair in non-obstructive azoospermic men remain the subject of controversy. Until now, small studies with small number of patients performed make it difficult to assess the efficacy of varicocele surgery in men with non-obstructive azoospermia. This review is performed to evaluate quality of the sperm among non-obstructive azoospermic men after varicocele repair.

Keywords: varicocele repair, azoospermia, non-obstructive, systematic review

Corresponding Author: Ponco Birowo; email: ponco.birowo@gmail.com

Received: 24 August 2016

Accepted: 25 September 2016

Published: 4 October 2016

Publishing services provided by Knowledge E

© Donny Eka Putra et al. This article is distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use and redistribution provided that the original author and source are credited.

Selection and Peer-review under the responsibility of the ASPIRE Conference Committee.

1. Introduction

Varicocele is one of the most frequent disorders detected in infertile men, resulting in approximately 35-40% with primary infertility and 80% with secondary infertility [1]. Varicocele often results in sperm production disorders marked by the abnormal quality of semen, ranging from oligospermia to azoospermia [2]. Non-obstructive azoospermia was reported at 4.3 to 13.3% in infertile men with clinical varicocele [3].

Nowadays, even though pregnancy can be achieved through a single sperm using intracytoplasmic sperm injection (ICSI), the success rate of ICSI using the motile sperm in ejaculate is higher than that of sperm using testicular sperm extraction (TESE) [2]. Thus, a specific therapy based on the etiopathology has been voted to be the best form of therapy, including varicocele surgery. In addition, varicocele repair is more cost-effective than ICSI [4]. The major benefit of varicocele surgery in azoospermic men with failure of spermatogenesis is the production of motile sperm in the ejaculate. Induction of spermatogenesis in men with azoospermia following varicocele surgery has a significant impact on alternative therapies of couple fertility, enabling the couple to achieve spontaneous pregnancy or even test tube babies and obviate the need for sperm retrieval techniques [4,5].

OPEN ACCESS

However, varicocele surgery in men with azoospermia remains a controversial matter and the benefit of this surgery still need to be clarified [1,6]. It has been reported in a number of articles that the success rate of varicocele surgery in elderly patients with NOA with improvement of semen parameter varies between 0 to 57% [3].

Since the report of varicocele surgery to improve sperm parameters in men with azoospermia was seen in few studies with small number of patients, this review was performed to improve the quality of evidence regarding benefit of varicocele surgery in men with NOA.

2. Experimental Details

2.1. Search Methods for Study Identification

The electronic database from PUBMED, EMBASE and the Cochrane library was investigated for studies published to date, using the combination of key words: varicocelectomy, varicocele repair and azoospermia. The most recent electronic database search was performed in July 2015. The searches were conducted by two researchers (PB and DEP). Additional studies identified through individual searches during the past ten years were based on textbook references and all primary articles, including the abstract of the proceeding book.

2.2. Study Selection Criteria

The studies selected in the analysis were those studies that examined sperm analysis following varicocele repair in non-obstructive azoospermic men. Studies with prospective or retrospective design published in English were also included. We excluded patients with obstructive azoospermia, severe oligozoospermia and cryptozoospermia for quantitative analysis.

2.3. Data Collection and Analysis

All studies were screened based on the titles and abstracts derived from electronic database searches, and complete manuscripts of all citations that corresponded to the inclusion criteria. The selected studies were assessed for eligibility for systematic review and meta-analysis using modified Newcastle-Ottawa Quality Assessment Scale for Observational Studies (Wells, 2000; Table 1). Three categories were assessed including selection of cohorts, comparability of cohorts, outcome and follow-up. We used qualitative assessment of selection cohorts and outcome categories for each study. Three reviewers (PB, DEP, and ISW) completed the quality assessment and any disagreements regarding inclusion criteria were resolved by discussion and consensus.

	Schlegel	Kim	Matthews	Pasqualotto	Kadioglu	Cakan	Esteves	Lee	Ishikawa	Meguid	Kirac	Aboutaleb
Selection												
Representativeness of exposed cohort	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ascertainment of exposure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome of interest was not present at start of study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome												
Assessment of outcome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Follow up long enough for outcomes to occur	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Adequacy of follow up of cohort	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

TABLE 1: The Modified Newcastle – Ottawa Quality Assessment Scales for Observational Studies. The qualitative measurement (yes or no) is used to assess quality of evidence on selected studies.

2.4. Statistical Analysis

Statistical analysis using SPSS software included 2-tailed Monte Carlo Fisher’s exact test to analyze variables with $p < 0.05$ considered statistically significant.

3. Results and Discussion

Three hundred and sixty citations were identified by means of electronic database and manual searches. Among those studies, 146 studies were excluded due to irrelevance to the objective of this review or failure to comply with the inclusion criteria. One hundred and ninety-seven studies were eliminated due to duplication and 3 studies because the author was unable to assess fully the complete manuscripts. One study was excluded due to duplication of data in a later paper [7,8]. Another study was excluded because final analysis of outcome detected a subject diagnosed with cryptozoospermia [2]. Altogether 12 studies were included in the review. Study searches and selection flowchart (PRISMA) are presented in Figure 1.

Twelve studies involving 261 men were included in the qualitative review [1,3,5,6,8–15]. Among those studies, 6 studies were retrospective studies, 5 studies were prospective studies and one study was undefined. Nine studies only involved males with non-obstructive azoospermia and varicocele. Two studies also involved males with oligoasthenozoospermia and varicocele [1,13]. One study involved males with cryptozoospermia or virtual azoospermia [10]. These three studies did not include a final analysis of outcome with subjects diagnosed with oligoasthenozoospermia and cryptozoospermia [1,10,13].

All studies were published between 1998 and 2014. The spectrum of studies varied from 6 males to 31 males [3,13]. The majority of males had undergone varicocele repair and testicular biopsy/TESE at the time of varicocele repair, however, 20 males only had

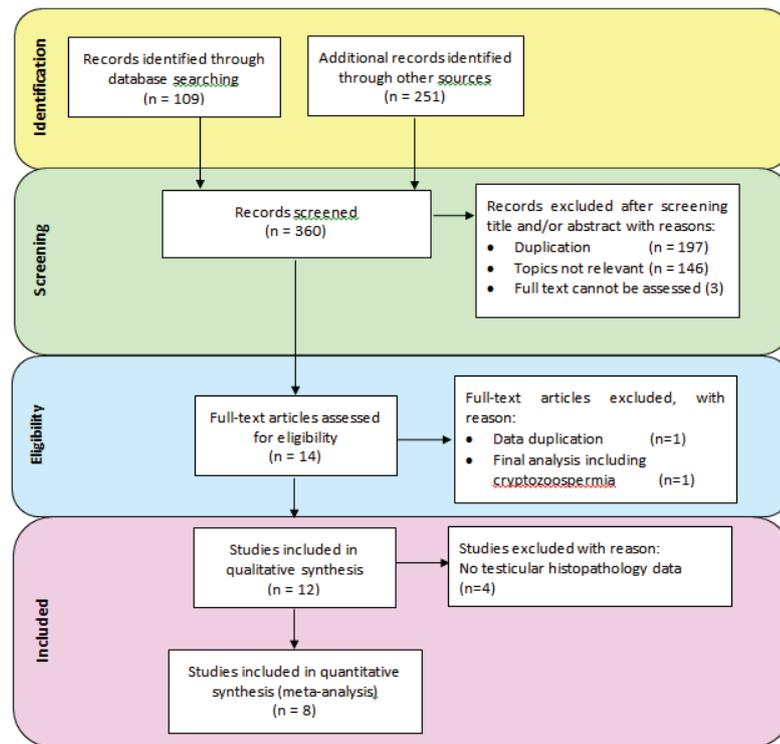


Figure 1: Flowchart of study searches and selection flowchart (PRISMA).

References	Year	Follow up (months)	Study design	Intervention	No. Pts	Bilateral repair (%)	No postop sperm improvement	Mean postop sperm density	Success rate (%)
Schlegel PN et al.	2004	14.7	Retrospective	Subinguinal	31	94	7	Unclear	22
Kim ED et al.	1999	15	Undefined	Inguinal	28	71	12	1.2 x 10 ⁶	43
Matthews GJ et al.	1998	10.3	Prospective	Subinguinal	22	77	12	2.2 x 10 ⁶	55
Pasqualotto FF et al.	2006	Undefined	Prospective	Subinguinal	27	56	9	1.6 x 10 ⁶	33
Kadioglu A et al.	2001	13.4	Retrospective	Inguinal	24	71	5	0.04 x 10 ⁶	21
Cakan M et al.	2004	Undefined	Retrospective	Inguinal	13	15	3	0.7 x 10 ⁶	23
Esteves SC et al.	2005	18.9	Retrospective	Subinguinal	17	65	8	0.8 x 10 ⁶	47
Lee et al.	2007	7.4	Retrospective	Inguinal	19	21	7	0.36 x 10 ⁶	36
Ishikawa T et al.	2007	Undefined	Retrospective	Subinguinal	6	17	2	0.2 x 10 ⁶	33
Abdelmeguid TA	2012	19.3	Prospective	Subinguinal	31	61	10	2.3 x 10 ⁶	32
Kirac M et al.	2012	11.4	Prospective	Subinguinal	23	65	7	1.3 x 10 ⁶	30
Aboutaleb HA et al.	2014	17.3	Prospective	Subinguinal	20	100	6	2 x 10 ⁶	30

TABLE 2: Characteristics of selected studies of varicocele repair in men with NOA.

varicocele repair [14]. All the studies determined the quality of sperm count following varicocele repair as an outcome measure. The quality of studies was assessed using the Newcastle-Ottawa Quality Assessment Scale. The characteristics of studies are presented in Table 2.

The sperm count proved successful following varicocele repair in 88 men (33.7%). There was variability in the reported sperm count improvement following varicocele

References	Timing of biopsy relative to varicocele repair	Testicular biopsy	Testicular histopathology	No. varicocele repair	No postop sperm improvement	Success rate (%)	P value
Pasqualotto FF et al.	Time of repair	Bilateral	SCO MA HS	10 8 9	4 3 2	40 38 22	0.852
Abdel-meguid TA	Time of repair	Undefined	SCO MA HS	10 2 13	0 0 7	0 0 54	0.008
Aboutaleb HA et al.	Time of repair	Bilateral	SCO MA HS	10 3 7	0 0 6	0 0 86	0.000
Total			SCO MA HS	30 13 29	4 3 15	13 23 52	0.000

TABLE 3: Summary of prospective studies about outcome of varicocele repair in men with NOA based on testicular histopathology. SCO = sertoli-cell only, MA = maturation arrest, HS = hypospermatogenesis.

References	Timing of biopsy relative to varicocele repair	Testicular biopsy	Testicular histopathology	No. varicocele repair	No postop sperm improvement	Success rate (%)	P value
Kadioglu A et al.	Time of repair	Unilateral	SCO MA HS	5 6 3	0 0 1	0 0 33	0.214
Cakan M and Altug	Time of repair	Bilateral	SCO MA HS	5 1 5	0 0 2	0 0 40	0.543
Esteves SC et al.	Time of repair	Bilateral	SCO MA HS	6 5 6	0 3 5	0 60 83	0.012
Lee et al.	Time of repair	Unilateral	SCO MA HS	10 6 3	1 4 2	10 67 67	0.031
Total			SCO MA HS	26 18 17	1 7 10	4 39 59	0.000

TABLE 4: Summary of retrospective studies about outcome of varicocele repair in men with NOA based on testicular histopathology. SCO = sertoli-cell only, MA = maturation arrest, HS = hypospermatogenesis.

repair. The postoperative mean sperm count in 7 studies ranged from $0.04 \pm 0.03 \times 10^6/\text{ml}$ to $2.3 \pm 1.7 \times 10^6/\text{ml}$ [1,3,9,10,13–15]. In 4 studies, a mean sperm recovery was reported based on testicular histology [5,8,11,12]. Postoperatively, the mean sperm count of hypospermatogenesis pattern ranged from $0.5 \pm 0.62 \times 10^6/\text{ml}$ to $1.2 \times 10^6/\text{ml}$, early maturation arrest from $0.17 \pm 0.27 \times 10^6/\text{ml}$ to $1.6 \pm 3.1 \times 10^6/\text{ml}$, and SCO pattern from 0 to $1.6 \pm 2.59 \times 10^6/\text{ml}$. The mean sperm count for non-obstructive azoospermia was found to be unclear in one study [6].

The meta-analysis included eight studies that compared the quality of sperm count following varicocele surgery based on testicular histology [3,5,8–12,15]. These studies comprised of 179 men. Two studies did not perform testicular biopsy [1,14]. One study evaluated association between testicular biopsy and sperm retrieval rate on TESE [6]. One study failed to report the total results of testicular biopsy [13].

Meta-analysis showed significant difference in sperm improvement between SCO, early maturation arrest, and hypospermatogenesis pattern ($p = 0.000$, 95%CI = 0.000; 0.063). The SCO and early maturation arrest had a lower sperm improvement rate than the hypospermatogenesis pattern. The outcome of varicocele repair on men with NOA based on prospective studies can be seen in Table 3.

A similar result was also found on the outcome of varicocele repair on men with NOA based on retrospective studies. There was significant difference in sperm improvement between SCO, early maturation arrest, and hypospermatogenesis pattern ($p = 0.000$, 95% CI = 0.000;0.073). The SCO and early maturation arrest had a lower sperm improvement rate than the hypospermatogenesis pattern. The outcome of varicocele repair on men with NOA based on retrospective studies can be seen in Table 4.

Our meta-analysis has demonstrated that a number of non-obstructive azoospermic men may well benefit from varicocele repair, resulting in motile sperm in the ejaculate. There is a significant relationship between the testicular histopathology pattern and improvement of sperm quality following varicocele repair. Eight studies showed that the hypospermatogenesis pattern had a higher success rate in sperm improvement

than the SCO and early maturation arrest pattern. A total of 88 men (33.7%) demonstrated improvement of sperm following varicocele repair.

The studies featured the diagnosis of azoospermia based on at least 2 semen analyses after 2-5 days of abstinence. The samples were centrifuged and no sperm was detected in the pellet to confirm complete azoospermia. This definition corresponds to the standard examination and processing of human semen according to WHO. All studies also used primary infertility as inclusion criteria. However, there was not any information about laboratory for sperm analysis.

Microsurgical inguinal or subinguinal varicocelectomy was the technique used to repair varicocele in all studies. Only one study performed open varicocelectomy without the use of microscope. The microsurgical technique, either inguinal or subinguinal, demonstrated fewer recurrences and complications and resulted in a higher spontaneous pregnancy rate compared to other techniques [16]. Today, it has become the best treatment modality of varicocele for infertile men. The studies therefore showed significant differences in the technique used for varicocele repair.

Based on preoperative data, variations have been found in the performance of genetic testing between the studies. Seven studies carried out genetic testing to review karyotype abnormality or Y-chromosomal microdeletion. Two studies did not report genetic testing [1,8]. Two further studies performed genetic testing in some of the patients [8,11]. Two other studies performed only karyotyping testing without Y-chromosomal microdeletion [10,13]. Genetic abnormalities could be the cause of azoospermia in these patients which may suggest differing opinions.

Some studies performed varicocele repair only for clinical varicocele [3,9,11,15]. The remaining studies performed varicocele repair for subclinical and clinical varicocele. Therefore, this review is unable to provide a full assessment regarding the effect of varicocele repair in subclinical varicocele or clinical varicocele.

Open testicular biopsy was performed in all studies that reported association between testicular biopsy and the outcome of varicocele repair. The biopsies were classified as SCO, early maturation arrest, late maturation arrest and hypospermatogenesis. Diagnosis of sertoli-cell-only pattern was based on the absence of germinal cells, early maturation arrest when spermatogenesis halted at primary spermatocytes and late maturation arrest when spermatogenesis halted at the level of spermatid. Hypospermatogenesis pattern, defined as mature spermatozoa, was present in decreased numbers.

The authors did not analyse the outcome of varicocele repair in late maturation arrest pattern. Open testicular biopsy was carried out on healthier testis based on size or consistency before or at the same time of varicocele repair. However, only two studies mentioned that varicocele repair and open testicular biopsy were performed by one surgeon only or together with a team [6,15]. This may result in differing opinions regarding the performance. The association of testicular histopathology with sperm improvement following varicocele repair is in agreement with the meta-analysis determined by Weedin et al. (2010) [17]. However, our systematic review included three further studies, and analysis was limited to the motile sperm in ejaculate to determine successful outcome of varicocele repair. These three studies showed that varicocele

repair improved sperm count in non-obstructive azoospermic men [3,14,15]. Hypospermatogenesis and late maturation arrest pattern were associated with an optimal outcome of varicocele repair. These results suggest that non-obstructive azoospermic men with later stage spermatogenesis may well benefit from varicocele repair.

Our meta-analysis included only studies that used open or microsurgical varicocele repair technique. However, meta-analysis by Weedin et al. included a number of studies that reported internal spermatic vein embolization in men with clinical varicocele [17].

A meta-analysis by Elzanaty S showed that varicocele repair in men with non-obstructive azoospermia showed a higher success rate in hypospermatogenesis and late maturation arrest pattern than the SCO pattern [18]. The analysis included 5 studies that reported the outcome of varicocele repair in men with non-obstructive azoospermia and clinical varicocele. This result is in accordance with our result. The authors included a subclinical varicocele group in meta-analysis. However, our meta-analysis did not analyse the outcome of varicocele repair in the late maturation arrest pattern.

The differences in study design demonstrated the weakness of this meta-analysis. Both prospective and retrospective studies were included in this review and analyzed separately. The studies included are observational with no control group and comprise a small number of patients only. However, it may prove difficult to perform prospective and randomized controlled trials because those men with varicocele and non-obstructive azoospermia represent a small group only of infertile men. In addition, a control group of patients will remain azoospermic.

Other limitations of this review include genetic testing and the participation of one surgeon only or a team is not always clearly stated. This will lead to bias.

4. Conclusion

Varicocele repair may be benefit on non-obstructive azoospermic men who had later stage spermatogenesis. However, there are some limitations on available studies which served to influence the quality of evidence.

References

- [1] G. J. Matthews, E. D. Matthews, and M. Goldstein, Induction of spermatogenesis and achievement of pregnancy after microsurgical varicocelectomy in men with azoospermia and severe oligoasthenospermia, *Fertility and Sterility*, **70**, no. 1, 71–75, (1998).
- [2] T. Youssef, E. Abd-Elal, G. Gaballah, S. Elhanbly, and E. Eldosoky, Varicocelectomy in men with nonobstructive azoospermia: Is it beneficial? *International Journal of Surgery*, **7**, no. 4, 356–360, (2009).
- [3] T. A. Abdel-Meguid, Predictors of sperm recovery and azoospermia relapse in men with nonobstructive azoospermia after varicocele repair, *Journal of Urology*, **187**, no. 1, 222–226, (2012).

- [4] R. Miyaoka and S. C. Esteves, A critical appraisal on the role of varicocele in male infertility, *Advances in Urology*, Article ID 597495, (2012).
- [5] M. Çakan and U. Altuğ, Induction of spermatogenesis by inguinal varicocele repair in azoospermic men, *Systems Biology in Reproductive Medicine*, **50**, no. 3, 145–150, (2004).
- [6] P. N. Schlegel and J. Kaufmann, Role of varicolectomy in men with nonobstructive azoospermia, *Fertility and Sterility*, **81**, no. 6, 1585–1588, (2004).
- [7] F. F. Pasqualotto, A. M. Lucon, J. Hallak, P. M. Góes, L. B. Saldanha, and S. Arap, Induction of spermatogenesis in azoospermic men after varicocele repair, *Human Reproduction*, **18**, no. 1, 108–112, (2003).
- [8] F. F. Pasqualotto, B. P. Sobreiro, J. Hallak, E. B. Pasqualotto, and A. M. Lucon, Induction of spermatogenesis in azoospermic men after varicolectomy repair: An update, *Fertility and Sterility*, **85**, no. 3, 635–639, (2006).
- [9] E. D. Kim, B. B. Leibman, D. M. Grinblat, and L. I. Lipshultz, Varicocele repair improves semen parameters in azoospermic men with spermatogenic failure, *Journal of Urology*, **162**, no. 3, 737–740, (1999).
- [10] A. Kadioğlu, A. Tefekli, S. Cayan, E. Kandirali, F. Erdemir, and S. Tellaloğlu, Microsurgical inguinal varicocele repair in azoospermic men, *Urology*, **57**, no. 2, 328–333, (2001).
- [11] S. C. Esteves and S. Glina, Recovery of spermatogenesis after microsurgical subinguinal varicocele repair in azoospermic men based on testicular histology, *International Braz J Urol*, **31**, no. 6, 541–548, (2005).
- [12] J. S. Lee, H. J. Park, and J. T. Seo, What Is the Indication of Varicolectomy in Men with Nonobstructive Azoospermia? *Urology*, **69**, no. 2, 352–355, (2007).
- [13] T. Ishikawa, Y. Kondo, K. Yamaguchi, Y. Sakamoto, and M. Fujisawa, Effect of varicolectomy on patients with unobstructive azoospermia and severe oligospermia, *BJU International*, **101**, no. 2, 216–218, (2008).
- [14] M. Kiraç, N. Deniz, and H. Biri, The effect of microsurgical varicolectomy on semen parameters in men with non-obstructive azoospermia, *Current Urology*, **6**, no. 3, 136–140, (2013).
- [15] H. Aboutaleb, E. Elsheri, M. Omar, and T. Abdelbaky, Testicular biopsy histopathology as an indicator of successful restoration of spermatogenesis after varicolectomy in non-obstructive azoospermia, *World J Mens Heal*, 32–43, (2014).
- [16] M. Cocuzza, M. A. Cocuzza, F. M. P. Bragais, and A. Agarwal, The role of varicocele repair in the new era of assisted reproductive technology, *Clinics*, **63**, no. 3, 395–404, (2008).
- [17] J. W. Weedn, M. Khera, and L. I. Lipshultz, Varicocele Repair in Patients With Nonobstructive Azoospermia: A Meta-Analysis, *Journal of Urology*, **183**, no. 6, 2309–2315, (2010).
- [18] S. Elzanaty, Varicocele repair in non-obstructive azoospermic men: Diagnostic value of testicular biopsy-A meta-analysis, *Scandinavian Journal of Urology*, **48**, no. 6, 494–498, (2014).