Varicocele treatment in non-obstructive azoospermia: a systematic review

Stephanie Jensen and Edmund Y. Ko

Department of Urology, Loma Linda University Health, Loma Linda, CA, USA

ABSTRACT

Objective: To review the available literature and identify factors associated with successful outcomes after varicocele repair (VR) in the setting of non-obstructive azoospermia (NOA).

Methods: The PubMed and EMBASE databases were searched for relevant articles. Primary outcomes were return of spontaneous spermatogenesis, sperm retrieval rates (SRRs), and unassisted and assisted pregnancy rates. Histopathological subtypes, when available, were used for subgroup analysis.

Results: A total of 16 articles were finally included. The average sample size was 43 and average duration of follow-up was 10.5 months. The average rate of primary spermatogenesis after VR was 27.3%. The average SRR, across five studies in men with NOA undergoing microscopic testicular sperm extraction status after varicocelectomy, was 48.9% vs 32.1% for the untreated cohort groups, and the average spontaneous pregnancy rate was 5.24%. Histopathology subtype was a significant contributing factor when analysed.

Conclusion: Varicocele repair should be considered in men with NOA, as it may allow some patients to avoid assisted reproductive technologies and improves success rates when utilised.

Introduction

Male factor infertility affects up to half of all couples struggling to conceive, and 10–20% of men evaluated for infertility are found to be azoospermic [1,2]. Azoospermia is defined as the complete absence of sperm from the ejaculate and the diagnosis requires examination of the pellet of a centrifuged semen sample on at least two occasions [3]. Non-obstructive azoospermia (NOA) is most often a result of primary testicular dysfunction, although endocrine abnormalities are a factor in some cases. Varicoceles are found in 20% of the general male population, in up to 40% of men with infertility, and specifically 4.3–13.3% of men with NOA [4,5]. The role of varicoceles in NOA has not been fully elucidated. The current best practice statement on the evaluation of azoospermic males from the AUA acknowledges that impaired spermatogenesis associated with varicoceles may be reversible but does not give a clear recommendation for management [3]. The treatment of varicoceles in the setting of infertility has been postulated to allow for the induction of spermatogenesis, improvement in spontaneous pregnancy rates, and increased sperm retrieval rates (SRRs) using assisted reproductive technology (ART). This systematic review was performed with the objective of evaluating the utility of varicocele repair (VR) in the setting of NOA and to identify factors that consistently contribute to successful outcomes.

Methods

Search strategy

An electronic search for relevant articles was performed using PubMed and EMBASE databases. There were no restrictions placed on the date of publication, and all literature published up until September 2020 was included. Any articles not published in English were excluded. Search terms included non-obstructive azoospermia, varicocele, varicocelectomy and infertility. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol was used to report our findings [6].

Eligibility criteria

Studies evaluating the benefit of treating varicoceles in the management of NOA were included in this review. This included prospective and retrospective cohort studies, as well as randomised controlled trials. Systematic reviews, meta-analyses, and studies including patients with obstructive azoospermia or cryptorchidism were excluded. The diagnosis of NOA was based on history and physical examination, hormone levels, and karyotype analysis, as well as two separate pelleted semen samples. For any studies that included ‘virtual’ azoospermia or oligospermia, only the data for the patients with NOA were included. If the data were not reported separately for patients with NOA in the
In the preoperative period, varicoceles were categorised as either spontaneous or assisted, indicating use of ART.

**Conclusion**

Results were reviewed to assess the efficacy of these procedures. The mean (range) follow-up period was 10.5 (6–22) months. The studies included in this review were of good quality. Future studies should aim to include larger sample sizes and randomise participants to ensure the accuracy of the results.

Data on spermatogenesis, SRRs, pregnancy rates, relapse rates and histopathology were collected and pooled to calculate average values.

**Risk of bias assessment**

None of the reviewed studies were randomised controlled trials.

---

**Figure 1. Article selection process.**
Table 1. Summary of data from included articles.

| Study (first author, year) | Study type   | N   | Varicocele grade, % | Postoperative spermatogenesis, % | SRR, % | Pregnancy rate, % | Relapse rate, % | Histopathology, % | Conclusions |
|---------------------------|--------------|-----|---------------------|----------------------------------|--------|-------------------|-----------------|------------------|-------------|
| Abdel-Meguid, 2012 [9]    | Prospective cohort | 31  | Grade I – 40        | 32.3                             | –      | –                 | 6.5             | HS – 41.9         | Testicular histopathology was the sole parameter associated with recovery of motile sperm |
|                           |              |     | Grade II – 34       |                                  |        |                   |                 | LMA – 19.4       |             |
|                           |              |     | Grade III – 26      |                                  |        |                   |                 | EMA – 6.5        |             |
|                           |              |     |                     |                                  |        |                   |                 | SCO – 32.3       |             |
| Aboutaleb, 2014 [18]      | Prospective cohort | 20  | –                   | 30                               | –      | –                 | –               | HS – 35           | HS patients have a better chance of SA improvement after VR than MA or SCO patients |
|                           |              |     |                     |                                  |        |                   |                 | LMA – 0          |             |
|                           |              |     |                     |                                  |        |                   |                 | EMA – 15         |             |
|                           |              |     |                     |                                  |        |                   |                 | SCO – 50         |             |
| Elbardisi, 2019 [12]      | Retrospective cohort | 42  | Grade I – 4.8       | 26.2                             | –      | –                 | 0               | HS – 19.1         | VR in NOA can result in spermatogenesis with highest success expected in HS |
|                           |              |     | Grade II – 47.6     |                                  |        |                   |                 | LMA – 0          |             |
|                           |              |     | Grade III – 31      |                                  |        |                   |                 | EMA – 21.4       |             |
|                           |              |     |                     |                                  |        |                   |                 | SCO – 59.5       |             |
| Haydardedeoglu, 2009 [21] | Retrospective cohort | 96  | Grade I – 0         | –                                | 60.8   | 74.2              | –               | –                | VR should be considered for all NOA with palpable varicocele |
|                           |              |     | Grade II – 0        |                                  |        |                   |                 | –                |             |
|                           |              |     | Grade III – 100     |                                  |        |                   |                 | –                |             |
| Inci, 2009 [22]           | Retrospective cohort | 96  | Grade I – 24        | –                                | 53     | 31.4              | –               | –                | VR in NOA increases SRR in micro-TESE |
|                           |              |     | Grade II – 24       |                                  |        |                   |                 | –                |             |
|                           |              |     | Grade III – 35.4    |                                  |        |                   |                 | –                |             |
| Kirac, 2012 [17]          | Prospective cohort | 23  | Grade I – 13        | 30.4                             | –      | 13                | –               | –                | VR in men with NOA can result in SA improvement, but will likely still require ART |
|                           |              |     | Grade II – 13       |                                  |        |                   |                 | –                |             |
|                           |              |     | Grade III – 39.1    |                                  |        |                   |                 | –                |             |
|                           |              |     | Grade IV – 47.9     |                                  |        |                   |                 | –                |             |
| Lee, 2006 [14]**          | Prospective cohort | 19  | Grade I – 10.5      | 36.8                             | –      | 5.3               | –               | HS – 15.8         | VR should be considered for all NOA patients with palpable varicocele, although benefit in patients with SCO is uncertain |
|                           |              |     | Grade II – 42.1     |                                  |        |                   |                 | MA – 31.6        |             |
|                           |              |     | Grade III – 47.4    |                                  |        |                   |                 | SCO – 52.6       |             |
| Matthews, 1998 [11]       | Prospective cohort | 22  | Grade I – 12        | 55                               | –      | 14                | –               | –                | VR resulted in induction or enhancement of spermatogenesis in most men |
|                           |              |     | Grade II – 37       |                                  |        |                   |                 | –                |             |
|                           |              |     | Grade III – 51      |                                  |        |                   |                 | –                |             |
| Ozman, 2018 [20]**        | Prospective cohort | 32  | Grade I – 31.3      | 15.6                             | –      | –                 | –               | HS – 34.4         | VR can result in improvement of SA, testicular volume was found to be predictive |
|                           |              |     | Grade II – 59.4     |                                  |        |                   |                 | MA – 31.2        |             |
|                           |              |     | Grade III – 9.3     |                                  |        |                   |                 | SCO – 34.4       |             |
| Pasqualatto, 2006 [19]    | Prospective cohort | 27  | –                   | 33.3                             | –      | 3.7               | 56              | HS – 33.3         | All NOA should be considered for VR, cryopreservation should be discussed due to possibility of relapse |
|                           |              |     |                     |                                  |        |                   |                 | LMA – 0          |             |
|                           |              |     |                     |                                  |        |                   |                 | EMA – 29.6       |             |
|                           |              |     |                     |                                  |        |                   |                 | SCO – 37         |             |
| Sajadi, 2018 [16]         | Retrospective cohort | 57  | Grade I – 21.1      | 14                               | 36.8   | 92                | –               | –                | VR may have positive effect on postoperative spermatogenesis, but effect appears to be more significant on microdissection TESE results |
|                           |              |     | Grade II – 42.1     |                                  |        |                   |                 | –                |             |
|                           |              |     | Grade III – 36.8    |                                  |        |                   |                 | –                |             |
| Schlegel, 2003 [15]       | Retrospective cohort | 31  | –                   | 22                               | –      | –                 | –               | HS – 40           | VR will rarely change need for TESE in NOA and should probably be limited to younger men with larger varicoceles |
|                           |              |     |                     |                                  |        |                   |                 | MA – 24          |             |
|                           |              |     |                     |                                  |        |                   |                 | SCO – 36         |             |
| Shiraishi, 2017 [8]       | Prospective cohort | 83  | Grade I – 0         | 24                               | 36     | 6                 | –               | HS – 16           | Cell cycle assessment can predict sperm recovery after VR |
|                           |              |     | Grade II – 62.7     |                                  |        |                   |                 | LMA – 20         |             |
|                           |              |     | Grade III – 37.3    |                                  |        |                   |                 | EMA – 12         |             |
|                           |              |     |                     |                                  |        |                   |                 | SCO – 52         |             |

(Continued)
Table 1. (Continued).

| Study (first author, year) | Study type | N | Varicocele grade, % | Postoperative spermatogenesis, % | SRR, % | Pregnancy rate, % | Relapse rate, % | Histopathology, % | Conclusions |
|---------------------------|------------|---|---------------------|---------------------------------|--------|------------------|----------------|------------------|-------------|
| Ustuner, 2015 [23]***     | Prospective cohort | 19 | Grade I – 21.1, Grade II – 52.6, Grade III – 26.3 | – | – | – | HS – 10.5, LMA – 0, EMA – 5.3, SCO – 73.7 | VR can result in significant improvement in testicular histology |
| Youssef, 2009 [13]*      | Prospective cohort | 54 | Grade I – 34.2, Grade II – 53.2, Grade III – 46.8 | 3.9 | – | – | Normal – 1.5, HS – 42.6, LMA – 29.6, EMA – 18.5, SCO – 40.7 | NOA patients most likely to benefit from varicocele repair are those with HS and LMA |
| Zampieri, 2013 [10]       | Prospective cohort | 36 | Grade I – 11, Grade II – 0, Grade III – 100 | 57.8 | 63.2 | – | – | – | VR in NOA significantly increases SRR |

SA: semen analysis.
*Varicocele grade data did not differentiate between complete and virtual azoospermia.
**Histopathology categorised as MA without specifying early vs late.
***Subset of patients with histopathology identified as SCO with focal spermatogenesis excluded.

Sperm retrieval rates

Four of the five studies that evaluated SRRs had a cohort of patients with NOA that had not undergone VR [10,16,21,22]. The average SRR across the five studies for men with NOA undergoing microscopic testicular sperm extraction (micro-TESE) status after varicocelectomy was 48.9% vs 32.1% for the untreated cohort groups [8,10,16,21,22].

Pregnancy rates

Pregnancy rates were evaluated in nine of the reviewed studies [10,11,13,14,16,17,19,21,22]. The average spontaneous pregnancy rate was 5.24% [11,13,14,17,19]. Of the patients who underwent intracytoplasmic sperm injection (ICSI) after VR, the average pregnancy rate was 65.2%, in comparison to the pregnancy rate for untreated cohort groups following ICSI, which averaged 39.5% [10,16,21,22].

Azoospermia relapse

Azoospermia relapse rates were examined in three studies with a range of 0% to 56%, with an average rate of 20.8% [9,12,19].

Histopathology

Testicular histopathology was reviewed in eight of the included papers [8,11–15,18,20,23]. The biopsy samples were obtained either prior to or at the time of varicocelectomy, and specimens were categorized based on histopathological criteria into the following groups: SCO, EMA, LMA, HS and normal spermatogenesis. The only study that found any biopsies consistent with normal spermatogenesis included patients with virtual azoospermia and did not specify how many of the patients with virtual azoospermia fell into each category. Several studies combined EMA and LMA into a general maturation arrest (MA) category. To allow for comparison, the EMA and LMA data, when reported separately, were combined. On average, 49.4% of patients evaluated in these studies were categorised as SCO, 27.6% as MA, and 26.9% as HS. Seven of the eight papers assessed post-varicocelectomy spermatogenesis for each group [9,12–15,18,20,23]. On average, 62.9% of patients with HS were found to have presence of sperm in postoperative semen analysis, as compared to 26.3% of patients with MA and 7.3% of patients with SCO. One study repeated testicular biopsies between 8 and 20 months after varicocelectomy and found that fewer biopsies were consistent with SCO (47.4% from 73.7%) with proportional increases in MA (10.5% from 5.3%) and SCO with focal spermatogenesis (26.3% from 10.5%) categories [23].

Gene expression

Shiraishi et al. [8] analysed genome-wide mRNA expression levels using transcriptome analysis. Over 23,000 genes were screened, and several of the genes found to be upregulated were noted to be cell cycle related. The level of expression of one of these genes, proliferating cell nuclear antigen (PCNA), was evaluated, and the mean number of PCNA-positive cells was found to be the only parameter that was significantly associated with sperm recovery. This was in comparison to patient characteristics, laboratory values, and histology results.
Discussion

Varicocele is one of the most common correctable causes of male infertility. However, infertility associated with NOA and varicocele can be challenging to manage. Even in the absence of karyotype abnormalities and Y chromosome microdeletions, varicocelectomy repair has resulted in variable improvements in spermatogenesis, SRRs, and pregnancy rates [24]. For this reason, there continues to be investigation into factors that may help predict success after varicocelectomy in men with NOA. Interpretation of the data on this topic is difficult as most of the available studies have small sample sizes, are retrospective in nature, and lack a control group. A systematic review of the papers that fit the specified search criteria was performed in order to identify trends in data, as well as areas that warrant further investigation.

Spermatogenesis, SRRs and pregnancy rates after VR were evaluated in most of the included studies. Some of these studies included patients with chromosomal abnormalities. However, when analysed as a subgroup, the data did not differ significantly from the remainder of the cohort [22]. Approximately one-third of patients were found to have sperm present in their postoperative ejaculate, although with a wide range of motility rates. On average, sperm could be retrieved in almost half of the patients after VR in comparison to approximately one-third of the patients in the control groups. This is consistent with the higher pregnancy rates found in those using ART vs control groups. These findings are supportive of the current recommendations to consider treatment of clinically palpable varicoceles when present in patients with NOA. However, there remains a significant portion of patients who fail to benefit from the procedure.

Testicular histology may provide further guidance in determining which patients are most likely to benefit from VR. Patients with histology categorised as HS consistently have higher rates of postoperative spermatogenesis, in comparison with the very low rates seen in the SCO groups. In addition, several authors argue that the patients with SCO with sperm in the postoperative ejaculate were likely incorrectly categorised due to sampling error. As SCO was found in nearly half of the biopsied patients, it is important to discuss the potentially low rate of success when reviewing the risks and benefits of VR. However, Ustuner et al. [23] did note improvement in the histology findings of some patients postoperatively. In patients with a high level of concern or at a high risk of postoperative complications, it may be advisable to obtain a testicular biopsy prior to VR. Also of consideration is the potential for azoospermia relapse, which has been documented, but not frequently investigated.

In regard to future directions, further investigation into the implications of gene expression may help clarify which patients have the best prognosis after VR. However, as varicocelectomy is a very low-risk surgical procedure, it could be argued that the potential benefits of proceeding with VR may outweigh those derived from further evaluations to allow for more accurate preoperative counselling.

Conclusions

Varicocele repair is the only surgical treatment that has demonstrated the return of sperm to the ejaculate in this patient population, and the results of the present review indicate that it can potentially result in significant improvements in several other fertility parameters including SRRs and pregnancy rates. Although not directly evaluated in every study, the improvement in spermatogenesis rates indicates that varicocelectomy could allow a proportion of patients to avoid the time and cost associated with ART. Additional prospective cohort or randomised controlled trials are needed to further study this specific population.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Stephanie Jensen http://orcid.org/0000-0002-4384-4444
Edmund Y. Ko http://orcid.org/0000-0002-7465-3616

References

[1] Esteves SC, Miyaoaka R, Roque M, et al. Outcome of varicocele repair in men with nonobstructive azoospermia: systematic review and meta-analysis. Asian J Androl. 2016 Mar-Apr;18(2):246–253. . PMID: 26680033; PMCID: PMC4770494.
[2] Gudeman SR, Townsend B, Fischer K, et al. Etiology of azoospermia in a military population. J Urol. 2015 Apr;193(4):1318–1321. Epub 2014 Oct 16. PMID: 25444960.
[3] Jarow J, Sigman M, Kolettis P, et al. The evaluation of the azoospermic male: AJU best practice statement. American Urological Association; 2011 [cited 2021 Oct 1]. Available from: https://www.auanet.org/guidelines/azoospermic-male-best-practice-statement.
[4] Pryor JL, Howards SS. Varicocele. Urol Clin North Am. 1987 Aug;14(3):499–513. PMID: 3303595.
[5] Fretz PC, Sandlow JI. Varicocele: current concepts in pathophysiology, diagnosis, and treatment. Urol Clin North Am. 2002 Nov;29(4):921–937. PMID: 12516762.
[6] Moher D, Shamseer L, Clarke M, et al.; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015 Jan 1;4(1):1. PMID: 25554246; PMCID: PMC4320440.
[7] Dubin, L., Amelar RD. Varicocele size and results of varicocelectomy in selected subfertile men with varicocele. Fertil Steril. 1970 Aug 21(8):606–609. PMID: 5433164.

[8] Shiraishi K, Oka S, Matsuyama H. Predictive Factors for Sperm Recovery after Varicocelectomy in Men with Nonobstructive Azoospermia. J Urol. 2017 Feb;197(2):485–490. Epub 2016 Aug 18. PMID: 27545577.

[9] Abdel-Meguid TA. Predictors of sperm recovery and azoospermia relapse in men with nonobstructive azoospermia after varicocelectomy. J Urol. 2012 Jan;187(1):222–226. Epub 2011 Nov 17. PMID: 22100001.

[10] Zampieri N, Bosaro L, Costantini C, et al. Relationship Between Testicular Sperm Extraction and Varicocelectomy in Patients With Varicocele and Nonobstructive Azoospermia. Urology. 2013 Jul;82(1):74–77. Epub 2013 May 13. PMID: 23680120.

[11] Matthews GJ, Matthews ED, Goldstein M. Induction of spermatogenesis and achievement of pregnancy after microsurgical varicocelectomy in men with azoospermia and severe oligoasthenospermia. Fertil Steril. 1998 Jul;70(1):71–75. PMID: 9660424.

[12] Elbardisi H, El Ansari W, Majzoub A, et al. Does varicocelectomy improve semen in men with azoospermia and clinically palpable varicocele? Andrologia. 2020 Mar;52(2):e13486. Epub 2019 Dec 11. PMID: 31825116.

[13] Youssef T, Abd-Elaal E, Gaballah G, et al. Varicocelectomy in men with nonobstructive azoospermia: is it beneficial? Int J Surg. 2009 Aug 7;7(4):356–360. Epub 2009 May 29. PMID: 19482096.

[14] Lee JS, Park HJ, Seo JT. What is the indication of varicocelectomy in men with nonobstructive azoospermia? Urology. 2007 Feb;69(2):352–355. PMID: 17320677.

[15] Schlegel PN, Kaufmann J. Role of varicocelectomy in men with nonobstructive azoospermia. Fertil Steril. 2004 Jun;81(6):1585–1588. PMID: 15193481.

[16] Sajadi H, Hosseini J, Farrahi F, et al. Varicocelectomy may improve results for sperm retrieval and pregnancy rate in non-obstructive azoospermic men. Int J Fertil Steril. 2019 Jan;12(4):303–305. Epub 2018 Oct 2. PMID: 30291690; PMCID: PMC6186284.

[17] Kiraç M, Deniz N, Birı H. The effect of microsurgical varicocelectomy on semen parameters in men with non-obstructive azoospermia. Curr Urol. 2013 Jan 6;6(3):136–140. Epub 2012 Dec 21. PMID: 24917731; PMCID: PMC3783270.

[18] Aboutaleb HA, Elsherif EA, Omar MK, et al. Testicular biopsy histopathology as an indicator of successful restoration of spermatogenesis after varicocelectomy in non-obstructive azoospermia. World J Mens Health. 2014 Apr;32(1):43–49. Epub 2014 Apr 25. PMID: 24872951; PMCID: PMC4026233.

[19] Pasqualotto FF, Sobreiro BP, Hallak J, et al. Induction of spermatogenesis in azoospermic men after varicocelectomy repair: an update. Fertil Steril. 2006 Mar;85(3):635–639. PMID: 16500331.

[20] Özman O, Çıtgez S, Şimşekoğlu F, et al. Effect of varicocelectomy on restoration of spermatogenesis in patients with non-obstructive azoospermia. J Urol Surg. 2019;6:130–134.

[21] Haydardedeoglu B, Turunc T, Kılıçdag EB, et al. The effect of prior varicocelectomy in patients with nonobstructive azoospermia on intracytoplasmic sperm injection outcomes: a retrospective pilot study. Urology. 2010 Jan;75(1):83–86. Epub 2009 Nov 13. PMID: 19913887.

[22] İnci K, Hasçicek M, Kara O, et al. Sperm retrieval and intracytoplasmic sperm injection in men with nonobstructive azoospermia, and treated and untreated varicocele. J Urol. 2009 Oct;182(4):1500–1505. Epub 2009 Aug 15. PMID: 19683732.

[23] Ustuner M, Yılmaz H, Yavuz U, et al. Varicocelectomy repair improves testicular histology in men with nonobstructive azoospermia. Biomed Res Int. 2015;2015:709452. Epub 2015 Oct 27. PMID: 26601110; PMCID: PMC4639637.

[24] Weedin JW, Khera M, Lipshultz LI. Varicocelectomy repair in patients with nonobstructive azoospermia: a meta-analysis. J Urol. 2010 Jun;183(6):2309–2315. Epub 2010 Apr 18. PMID: 20400156.