Comparison of sperm parameters and fertility rate in subclinical varicocele patients treated with varicocelectomy versus no varicocelectomy: a systematic review

ABSTRACT

Introduction: Subclinical varicocele is defined as non-palpable varicocele which diagnosed solely through imaging examination, namely ultrasonography. Despite the current high prevalence of subclinical varicocele as one of the most common causes of men infertility, there is still lack of evidence regarding the need to perform varicocelectomy among these patients. This systematic review aims to evaluate and compare the sperm parameters and fertility rate of subclinical varicocele patients treated with varicocelectomy versus no treatment.

Methods: A systematic literature search was conducted on the international databases PubMed, Scopus, Cochrane, EMBASE, EBSCOHost, and Google Scholar published in the last ten years up to August 21st, 2022. Risk of bias assessment was performed using the Newcastle-Ottawa Scale tools for cohort study and converted regarding the AHRQ standards.

Results: Three cohort studies were conducted in three different countries with 363 patients. The risk of bias assessment revealed that all of the three studies included in this review have good quality and low risk of bias. Varicocelectomy significantly improves sperm parameters in terms of sperm concentration (p<0.05) and sperm motility (p<0.05) while its effects on sperm morphology are not significant (p>0.05). The effects of varicocelectomy on fertility rate are reported by one study by Cantoro et al. as significant (p=0.011).

Conclusion: Varicocelectomy correction has been proved to significantly improve sperm parameters in terms of sperm concentration and motility, while its effect on fertility rate remains unclear and no conclusion can be drawn yet. Therefore, this study recommends further randomized controlled studies with larger sample size in the future to prove the effectiveness of varicocelectomy in subclinical varicocele patients before its implementation in clinical settings.

Keywords: Subclinical varicocele, varicocelectomy, sperm parameter, fertility, systematic review.


INTRODUCTION

Varicocele remains as one of the most common causes of men infertility, affecting up to 35% of men with infertility problems around the world. However, it is also found in 15% of healthy men without clinical symptoms of infertility. By definition, varicocele is the condition when the veins within the scrotum enlarge due to defective valves in the veins. While the exact pathogenesis of how varicocele impacts one's fertility is not fully understood until today, some researchers believe that varicocele causes disruption of the testicular drainage, thus, causing increased testicular temperature and dysfunction of sperm production.

Recently, the oxidative stress theory has emerged as an important contributory factor due to an association between elevated reactive oxygen species and impaired sperm function in men with varicocele. Additionally, reduction of oxidative stress markers has been noted after varicocele repair.

Varicoceles can be classified according to its severity based on the Dubin and Amelar system, which consists of grade 1, grade 2, and grade 3. Varicoceles are visible through the scrotum and can be palpated while standing, which is classified as grade 3. If the varicoceles are not visible but still can be palpated while standing without Valsalva maneuver, they are regarded as grade 2. Meanwhile, grade 1 varicoceles refer to non-palpable varicoceles in normal conditions and only palpable during Valsalva maneuver while standing. Furthermore, an enlargement of the venous plexus which is not palpable even with Valsalva maneuver, but is diagnosed through ultrasound imaging is regarded as a subclinical varicocele (SCV). The prevalence of subclinical varicocele among infertile men is estimated around 55-70% according to study by Yarborough et al.

However, to this day, the treatment guideline for subclinical varicocele, as proposed by the American Urological Association (AUA) and the American Society for Reproductive Medicine (ASRM) remains unclear regarding the need of surgical correction. These guidelines, on the contrary, recommend...
surgical correction strictly for patients with clinical varicocele when the sperm parameters are abnormal. Therefore, patients with subclinical varicocele which still have normal sperm parameters, should not be treated with varicocelectomy. On the other hand, several recently conducted cohort studies revealed that surgical correction might improve sperm parameters in patients with subclinical varicocele. In addition, these studies have also found that surgical varicocelectomy may enhance the fertility rate among couples with the men having subclinical varicocele.5,10

Therefore, this study aims to systematically analyze and compare the sperm parameters and fertility rate between subclinical varicocele patients treated with varicocelectomy versus no varicocelectomy. The author hopes this study may provide clear understanding of current evidence regarding the need for surgical correction in the form of varicocelectomy among patients with subclinical varicocele.

MATERIALS AND METHODS

This study was conducted according to the Cochrane Handbook 6.2 and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).11

Information sources and search strategy

The author performed a systematic literature search in databases including PubMed, Scopus, Cochrane, EMBASE, EBSCOhost, and Google Scholar, searching for studies implementing varicocelectomy procedures to improve infertility problems among patients with subclinical varicocelectomy up to August 21st 2022 with the following keywords: (varicocelectomy OR subclinical varicocelectomy) AND (subclinical varicocele) AND (sperm analysis OR spermiogram OR sperm OR fertility OR paternity). The detailed keywords for each database can be seen in Table 1.

Study eligibility criteria

The authors predetermined the following inclusion criteria: (1) type of study, clinical trials; (2) study population, patients with subclinical varicocele as diagnosed by physician; (3) intervention, varicocelectomy surgical procedure with control group consists of no treatment or no surgical procedure; (4) outcomes, sperm parameters (i.e., sperm motility and morphology), and fertility or paternity rate. Meanwhile, the exclusion criteria are set to: (1) unsuitable study design; (2) incomplete outcome data; (3) irretrievable full-text articles; (5) no control group; and (6) languages other than English.

Data extraction

The following data were extracted: (1) author and year of publication; (2) study characteristics, including study design and location of study; (3) study population, including sample size and mean age; (4) intervention, characteristics of each intervention and control group; and (5) study outcomes, including the assessed parameters, values with and without intervention, as well as significance (p-values) whenever applicable.

Quality assessment

The quality of each study was assessed using the Newcastle-Ottawa Scale for Cohort Studies (NOS-Ottawa). The overall quality of study is then converted based on the Agency for Healthcare Research and Quality (AHRQ) standards into good, fair, or poor quality, as shown in Table 4. Independent author performed this assessment and any disagreements were resolved based on consensus.

RESULTS

Search results and study selection

The results from our initial search from PubMed, Scopus, Cochrane, EMBASE, EBSCOhost, and Google Scholar using previously mentioned strategy resulted in a total of 1,465 studies (Figure 1). Before the screening process, we excluded 451 studies either deduplicated or 852 studies

<table>
<thead>
<tr>
<th>Database</th>
<th>Search strategy</th>
<th>Findings</th>
<th>Included Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopus</td>
<td>TITLE-ABS-KEY ((varicocelectomy OR subclinical varicocelectomy) AND (subclinical varicocele) AND (sperm analysis OR spermiogram OR sperm OR fertility OR paternity))</td>
<td>55</td>
<td>1</td>
</tr>
<tr>
<td>EBSCOhost</td>
<td>(varicocelectomy OR subclinical varicocelectomy) AND (subclinical varicocele) AND (sperm analysis OR spermiogram OR sperm OR fertility OR paternity)</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>EMBASE</td>
<td>(varicocelectomy OR subclinical varicocelectomy) AND (subclinical varicocele) AND (sperm analysis OR spermiogram OR sperm OR fertility OR paternity)</td>
<td>83</td>
<td>0</td>
</tr>
<tr>
<td>Google Scholar</td>
<td>(varicocelectomy OR subclinical varicocelectomy) AND (subclinical varicocele) AND (sperm analysis OR spermiogram OR sperm OR fertility OR paternity)</td>
<td>1,250</td>
<td>3</td>
</tr>
</tbody>
</table>
for other reasons. Furthermore, 81 and 57 studies were excluded after title and abstract screening, respectively. Studies that are not related to our main topics are excluded in this phase. In addition, 21 studies were further excluded since 8 studies only measured qualitative outcomes, 6 studies used other language than English, and 7 studies were not available in full-text versions. The final search yielded in a total of 3 studies, consisting of mostly prospective cohort studies to be included in further analysis.

**Study characteristics**

All three studies included are cohort studies conducted in three different countries with different socioeconomic backgrounds, namely Spain, Italy, and Iraq. These studies were conducted in a range of years between 2012-2022. Among the included studies, participants were adult patients with subclinical varicocele as diagnosed by their physicians. Subclinical varicocele was defined as a finding from ultrasonography (USG). Patients included in these studies are not related to other infertility problems. Moreover, the patients’ partners were normal without infertility problems as clinically checked by gynecologists. On the other hand, the control group is patients not given any surgical intervention. Outcomes measured via sperm parameters (including sperm concentration, sperm motility, and sperm morphology) and fertility or paternity rates. The detailed characteristics of included studies are shown in Table 2, while the detailed study outcomes are presented in Table 3.

**Risk of bias assessment**

The results from bias assessment were shown in Table 4 with the details shown in Appendix 1. In summary, we found that all studies included in this review have good quality in terms of AHRQ standards. Therefore, we found that all studies included in this review were of low risk of bias.

**Improvement of sperm parameters after varicocelectomy**

**Sperm concentration**

Studies by Cantoro et al. and Hammadi et al. reported the effect of varicocelectomy in terms of sperm parameters. The first indicator of sperm is concentration. These two studies consistently reported similar findings: the statistically significant differences of improvement regarding sperm concentration of individuals treated with varicocelectomy compared to no treatment (p<0.05).

**Sperm motility**

Second observed sperm parameter is sperm motility. The study by Cantoro et al. and Hammadi et al. reported similar superiority of the group of patients treated with varicocelectomy versus no treatment. These studies have shown that the percentage of motile sperms increases significantly after varicocelectomy procedure (p<0.05).

**Sperm morphology**

For the third parameter, namely sperm morphology, study by Cantoro et al. and Hammadi et al. again reported similar superiority of intervention group when compared to control group. In this case, these studies examined the percentage sperm with normal morphology compared to the total sperm. However, the differences are not statistically significant (p>0.05)

**Sperm DNA fragmentation**

Study by Garcia-Peiro et al. examined the sperm samples using DNA fragmentation technique. This examination technique results in several indicators, such as the terminal transferase dUTP nick-end labeling (TUNEL), sperm chromatin structure assay (SCSA), sperm chromatin...
Mechanisms of varicocelectomy

Theoretically, varicocelectomy is defined as a surgical procedure to remove the swollen veins in the scrotal area or also called varicose veins. In the current treatment guidelines, varicocelectomy is not recommended for patients with non-palpable varicoceles, where the sperm parameters are actually normal. Therefore, the current AUA/ASRM guidelines recommend that clinicians should not perform varicocelectomy in patients with non-palpable varicoceles.

Table 2. Study characteristics.

<table>
<thead>
<tr>
<th>Author; year of publication</th>
<th>Study design</th>
<th>Location</th>
<th>Subject characteristics</th>
<th>Sample characteristics</th>
<th>Follow-up duration</th>
<th>Intervention group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garcia-Peiro et al. (2014)</td>
<td>Cohort study</td>
<td>Bellaterra, Spain</td>
<td>Infertile male patients with subclinical varicocele diagnosed by scrotal Doppler ultrasonography (ScV). Patients were surgically treated with varicocelectomy. Patients with genitourinary inflammation, leukocytospermia, or altered hormonal profiles were excluded from the study.</td>
<td>Intervention: 10 patients; 25-35 y Control: 16 patients; 25-35 y</td>
<td>6-12 months</td>
<td>Surgical varicocelectomy procedure was performed by patient's consent (n=10)</td>
<td>Patients received no treatment</td>
</tr>
<tr>
<td>Cantoro et al. (2015)</td>
<td>Cohort study</td>
<td>Ancona, Italy</td>
<td>Patients diagnosed with subclinical left-sided varicocele, primary infertility persisting &gt;1 year despite regular unprotected intercourse, one or more abnormal semen parameters, and without other male infertility factor. The partners of these patients were normal without infertility problems as evaluated by gynecologist.</td>
<td>Intervention: 218 patients; 29.4 ± 5.1 y Control: 119 patients; 31.3 ± 4.2 y</td>
<td>39.4 ± 6.5 months</td>
<td>Varicocele treatment in the form of embolization</td>
<td>Patients were only observed without any intervention</td>
</tr>
<tr>
<td>Hammadi et al. (2015)</td>
<td>Cohort study</td>
<td>Baghdad, Iraq</td>
<td>Patients with subclinical varicocele diagnosed by Doppler ultrasound studies presented to Al-Yarmouk teaching Hospitals seeking advice for infertility treatments. Exclusion criteria include recurrent varicocele, azoospermic (zero sperm in ejaculate) or have cause of infertility other than varicocele.</td>
<td>Intervention: N/A Control: N/A</td>
<td>3-6 months</td>
<td>Varicocelectomy was done using inguinal approach</td>
<td>Patients received no treatment</td>
</tr>
</tbody>
</table>

DISCUSSION

Current guidelines on subclinical varicocele treatment

Varicocelectomy is a surgical procedure to remove the swollen veins in the scrotal area or also called varicose veins. Theoretically, varicocelectomy is defined as a surgical procedure to remove the swollen veins in the scrotal area or also called varicose veins. In the current treatment guidelines, varicocelectomy is not recommended for patients with non-palpable varicoceles, where the sperm parameters are actually normal. Therefore, the current AUA/ASRM guidelines recommend that clinicians should not perform varicocelectomy in patients with non-palpable varicoceles.

Another parameter which needs to be assessed when determining the benefits of varicocelectomy is pregnancy rates. Study by Cantoro et al. reported the pregnancy rate of the patient's partners after approximately 39 months following the procedure. This resulted in a statistically significant difference between the intervention group and control group, 46.3% and 11.8% respectively (p=0.011). Furthermore, annual pregnancy rate in the group of patients treated with varicocelectomy equals to 11%, compared to 4% in those without treatment.
varicoceles. Varicocelectomy mainly consists of two different techniques, namely microscopic varicocelectomy and laparoscopic varicocelectomy.\textsuperscript{18} Both techniques are performed under general anesthesia and usually do not need any inpatient care.\textsuperscript{17} Firstly, microscopic varicocelectomy is the procedure performed through a small incision in the subinguinal or inguinal region. This procedure uses a powerful microscope to help the surgeon identify small veins that need to be ligated. Microscopic varicocelectomy usually lasted for only 2-3 hours and recommended as the gold-standard approach, however this applies for clinical varicocele patients only. The superiority of microscopic varicocelectomy was based on its high success rates without significant complications.\textsuperscript{18}

On the other hand, other technique is also available, called laparoscopic varicocelectomy. In this technique, the surgeon will perform varicocelectomy using a video camera and surgical equipment, passing through an incision in the lower abdomen area. The downside of this technique is that there will be fewer veins to ligate because of the characteristic of vein networks in that area. However, this procedure is relatively fast compared to microscopic varicocelectomy, usually only last 30-40 minutes.\textsuperscript{17,19}

**Efficacy of varicocelectomy on subclinical varicocele**

In this study, the author examines the efficacy of the varicocelectomy procedure on subclinical varicocele cases by determining sperm parameters and fertility rate. Sperm parameters assessed include sperm concentration, sperm motility, and sperm morphology. Sperm concentration was defined as the sperm count per milliliter (mL). The normal range of sperm concentration in adult men is 15-200 million per mL. Meanwhile, sperm motility is defined as sperm with progressive forward motions of at least 25 micrometers every second. The normal range of sperm motility is 32-75 percent. Lastly, sperm morphology, while consisting of various types, is indicated abnormal if the morphology of the sperm unable it to have progressive motility. The normal range of sperm morphology is

<table>
<thead>
<tr>
<th>Author; Year of publication</th>
<th>Study outcomes</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Significance (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garcia-Peiro et al. (2014)</td>
<td>TUNEL (%)</td>
<td>31.38 (17.99–74.10)</td>
<td>31.38 (17.99–74.10)</td>
<td>p &gt;0.05</td>
</tr>
<tr>
<td></td>
<td>SCSA (%)</td>
<td>26.18 (8.99–68.77)</td>
<td>21.30 (12.94–74.48)</td>
<td>p &gt;0.05</td>
</tr>
<tr>
<td></td>
<td>SCD (%)</td>
<td>29.00 (24.00–70.00)</td>
<td>37.75 (19.50–78.00)</td>
<td>p &gt;0.05</td>
</tr>
<tr>
<td></td>
<td>DDS (by SCD) (%)</td>
<td>17.25 (10.00–30.00)</td>
<td>19.50 (11.50–37.00)</td>
<td>p &gt;0.05</td>
</tr>
<tr>
<td>Cantoro et al. (2015)</td>
<td>Sperm concentration (million/mL)</td>
<td>Baseline: 16 ± 5.6</td>
<td>Baseline: 18 ± 4.1</td>
<td>p &gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Sperm total motility (%)</td>
<td>Postintervention: 7 ± 5.6</td>
<td>Postintervention: 17 ± 5.6</td>
<td>p &lt;0.05*</td>
</tr>
<tr>
<td></td>
<td>Sperm normal morphology (%)</td>
<td>Baseline: 61.85 ± 21.07</td>
<td>Baseline: 64.75 ± 23.85</td>
<td>NS</td>
</tr>
<tr>
<td>Hammadi et al. (2015)</td>
<td>Pregnancy rate (%)</td>
<td>Baseline: 62.7 ± 13.6</td>
<td>Baseline: 61.85 ± 21.07</td>
<td>p &gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Annual pregnancy rate (million/mL)</td>
<td>Baseline: 40.4 ± 14.7</td>
<td>Baseline: 42.6 ± 16.9</td>
<td>p &lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Percentage of motile sperm (%)</td>
<td>Baseline: 27.6 ± 5.2</td>
<td>Baseline: 26.9 ± 4.4</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Percent of sperm with normal morphology (%)</td>
<td>Baseline: 14.8</td>
<td>Baseline: 11.8</td>
<td>P = 0.011</td>
</tr>
</tbody>
</table>

*Significant results. Abbreviations: TUNEL: Terminal transferase dUTP nick-end labeling; SCSA: sperm chromatin structure assay; SCD: sperm chromatin dispersion (SCD); DDS: DNA degraded sperm; NS: non-significant.
**Table 4. Quality assessment of selected studies (AHRQ grading calculation).**

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Total quality score</th>
<th>AHRQ Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Representativeness of exposed cohort</td>
<td>Selection of nonexposed cohort</td>
<td>Ascertainment of exposure</td>
<td>Demonstration that outcome of interest was not present at start of study</td>
<td>Design or analysis controlled for confounders</td>
</tr>
<tr>
<td>Garcia-Peiro et al.</td>
<td>a(*)</td>
<td>a(*)</td>
<td>a(*)</td>
<td>a(*)</td>
<td>b(*)</td>
</tr>
<tr>
<td>13(2014)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cantoro et al. 13</td>
<td>a(*)</td>
<td>a(*)</td>
<td>a(*)</td>
<td>a(*)</td>
<td>b(*)</td>
</tr>
<tr>
<td>(2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hammadi et al. 14</td>
<td>a(*)</td>
<td>a(*)</td>
<td>a(*)</td>
<td>a(*)</td>
<td>b(*)</td>
</tr>
<tr>
<td>(2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

The study is considered:
- Good: 3 or 4 stars in selection domain AND 1 star in comparability domain AND 2 or 3 stars in outcome domain.
- Fair: 2 stars in selection domain AND 1 star in comparability domain AND 2 or 3 stars in outcome domain.
- Poor: 0 or 1 stars in selection domain AND 0 star in comparability domain AND 0 or 1 stars in outcome domain.

(*) Stars are given for each of the study aspects.
limitations in this study. First, the included studies have relatively high heterogeneity in terms of included subjects, with no clear inclusion and exclusion criteria, so we do not know whether the included patients have previously normal or abnormal sperm parameters before the treatment. This is highly important as previous study shows that varicocelectomy is actually beneficial if the patient has abnormal sperm parameters before the treatment. The second limitation of this review study is that the author could not perform meta-analysis due to limited amount of data from recent studies. Therefore, as a recommendation for the future, the author recommends further studies in the form of a randomized controlled trials (RCT) with bigger sample size to conclude a solid recommendation for clinical settings.

CONCLUSION
In conclusion, varicocelectomy correction in subclinical varicocele patients has been clinically significant in improving sperm parameters, namely sperm concentration and sperm motility rate. However, it is still unclear whether varicocelectomy in subclinical varicocele patients can improve the fertility rates among couples. Due to limited number of data and no available data from randomized controlled trials from recent studies, this study recommends the need to perform randomized studies in the future regarding this issue to conclude a solid recommendation for clinical settings finally.

CONFICT OF INTEREST
Author declares there is no conflict of interest regarding publication of this study.

ETHICAL CONSIDERATION
Ethical clearance in systematic review is not mandatory.

FUNDING
None.

REFERENCES