

Varicocelectomy For Infertile Men with Clinical Varicocele and Normal Semen Parameters, In Relation to Pregnancy Rate and Recurrent Spontaneous Miscarriage Incidence: A Systematic Review

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Objectives. Current guidelines suggest performing varicocelectomy only for men with clinical varicocele, infertile, abnormal semen parameters, and impaired testicular development. Varicocelectomy in infertile men with normal semen parameters was deemed to not benefit fertility significantly. The purpose of this systematic review is to discuss articles that studied varicocelectomy in men with clinical varicocele, normal semen analysis, and normal women who experience infertility or spontaneous miscarriage and find out whether there is an improvement in pregnancy and live birth rate.

Methods. The databases used for searching articles in this study are PubMed and Cochrane using the keywords “varicocele”, “normal semen parameters”, “recurrent miscarriage”, “sperm DNA fragmentation”, and “infertility”. The outcome of the articles sought is pregnancy rates and miscarriage rates after varicocelectomy.

Result. After carrying out the article selection process, there are 2 articles used. One study is a randomized control trial and another one is a non-randomized control trial. All enrolled patients had varicocele and normal semen analysis results according to WHO guidelines 2022. The average pregnancy rate after varicocelectomy at a 12-month follow-up interval was 51% in the varicocelectomy group vs 25% in the control group. The average miscarriage rate was 6% in the varicocelectomy group vs 34% in the control group. One study showed a correlation between decreasing Sperm DNA fragmentation and pregnancy rate.

Conclusion. Varicocelectomy may provide benefits in infertile couples and cases of recurrent spontaneous miscarriage with normal female factors and men with varicocele with normal semen parameters.

Keywords: epidermoid cyst, penis

Introduction

Although not a life-threatening condition, infertility is still considered a heavy burden condition because it affects the continuity of one family, and being unable to do so is a great mental burden. Around 8-12% of couples in their reproductive age suffer from infertility [1]. Male factors contribute up to 50% of all infertility cases [2]. Of all of the causes of male infertility, varicocele is the most commonly treated and 40% of infertile men have varicocele [3].

The problem is that not all men with varicocele are infertile and not all have abnormal semen parameters. 15-30% of infertile men have normal semen parameters [4]. This causes a dilemma in the management of varicocele.

Current guidelines by the European Association of Urology suggest weak strength in managing infertile men with normal semen parameters or infertile men with normal semen parameters but increasing sperm DNA fragmentation or recurrent pregnancy loss [5]. The present review summarizes studies that compare the outcome of varicocelectomy and expectant therapy in infertile men with clinical varicocele and normal semen parameters in couple's pregnancy rate, miscarriage rate, and men's semen parameters.

Materials and Methods

The PubMed and Cochrane database was searched from 2012 to 2022. The search was limited to English studies and controlled-trial

studies either randomized or non-randomized. The search terms were “varicocele”, “normal semen parameters”, “recurrent miscarriage”, “sperm DNA fragmentation”, and “infertility”. A combination of two keywords was used using AND to capture all citations that exist (Fig. 1).

The inclusion criteria of the studies are adult, infertile, or recurrent miscarriage couple, normal female factor, clinical varicocele, and normal semen parameters. Studies that include abnormal female factors, subclinical varicocele, and abnormal semen parameters are excluded. The outcome that is desired is pregnancy rate, miscarriage rate, semen parameters, and sperm DNA fragmentation. If there are duplicated studies, the most complete and recent studies are a priority.

Result

The search strategy results in 55 studies from two online databases. The duplicate was removed and after screening the title we ended up with 10 studies. After the full paper was read, eight studies were excluded because they contained samples with abnormal semen parameters, as listed in Figure 1. Eventually, two studies fulfilled the inclusion criteria and were included in the review. Two studies included are by Fathi et al from 2021 and Ghanaie et al from 2012.

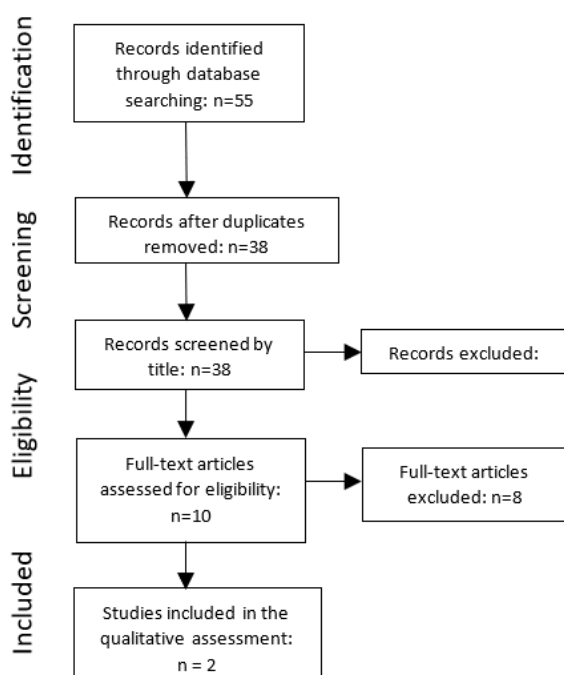


Figure 1. Prisma Flow Chart

Fathi et al. is a non-randomized controlled trial that compares the outcome of pregnancy in infertile couples with men having clinical varicocele but normal semen parameters. This study comprises 95 male samples divided into two groups: varicocelelectomy and expectant therapy group. After 1 year of follow-up, the varicocelelectomy group achieved more pregnancies compared to the other group with a p-value of 0.009. All of the pregnant samples achieved live birth or no incidence of miscarriage. The varicocele repair method that is being used in this study is the microsurgical subinguinal technique [6].

The study by Ghanaie et al. is a randomized controlled trial that compares the outcome of pregnancy and miscarriage between the varicocelelectomy group and the expectant therapy group. All of the females in this group are normal and men present with clinical varicocele and normal semen parameters. This study comprises 136 male samples divided into two groups. After 1 year of following the varicocelelectomy group had a higher pregnancy rate compared to the expectant therapy group with $p < 0.01$. There are incidences of miscarriage in both groups but a much lower percentage in the varicocelelectomy group with a p-value of 0.003. This study uses the inguinal technique for the varicocele repair method [7] (Table 1).

Discussion

The result of our systematic review shows different results from current guidelines that state there are no benefits in varicocelelectomy for infertile men with clinical varicocele and normal semen parameters with the outcome of spontaneous pregnancy compared to expectant therapy [5]. Thus it is still controversial whether we need to do varicocelelectomy for infertile men with clinical varicocele and normal semen parameters or not. Below is a discussion of the result and why varicocelelectomy may benefit spontaneous pregnancy rate in this group. Below is a discussion of the result and why varicocelelectomy may benefit spontaneous pregnancy in this group.

Varicocele and Infertility

The mechanism of varicocele causing infertility is still unclear, but there are a few factors that may act together to be the cause of infertility. The most commonly accepted mechanism is varicocele will cause an increase in hydrostatic pressure and venous reflux. This condition will cause reflux of

Table 1. The outcome of varicocelectomy in infertile men with clinical varicocele and normal semen parameters

Author	Study design	Sample size (n=221)		Method of varicocele repair	Outcome of pregnancy
		Varicocelectomy (n = 113)	Expectant Therapy (n = 108)		
Fathi et al ⁵ , 2021	Non-RCT	45	40	Subinguinal Microsurgical	28 out of 45 (62.2%) in the varicocelectomy group achieved pregnancy compared to 9 out of 40 (30%) in the expectant therapy group. No incidence of miscarriage in this study
Ghanaie et al ⁶ , 2012	RCT	68	68	Inguinal	30 out of 68 (44.1%) in the varicocelectomy group achieved pregnancy compared to 13 out of 68 (19.1%) in the expectant therapy group. The miscarriage rate is much lower in the varicocelectomy group with 4 out of 30 (13.3%) compared to 9 out of 13 (69.2%) in the expectant therapy group

toxic metabolite, hypoxia, and an increase in scrotal temperature, which will inherently cause oxidative stress, increase reactive oxygen species, and decrease total antioxidant capacity. All these factors will result in impaired testicular function. Impaired testicular function not only will decrease the quantity and quality of sperm that is produced, but it will also damage the DNA inside the sperm [6].

A meta-analysis by Zhang et al. shows that men with clinical varicocele have higher sperm DNA fragmentation compared to healthy men [7]. Another study shows that higher sperm DNA fragmentation correlates with lower pregnancy rates and increased miscarriage incidence. Simon et al state that sperm DNA fragmentation was linked to decreased fecundity in men who were planning their first pregnancy and had no prior knowledge of their fertility potential. The interesting part is infertile men with normal semen parameters or idiopathic infertility, can have high sperm DNA fragmentation [8].

Varicocelectomy and Sperm DNA Fragmentation

Whether or not a man has abnormal semen parameters, varicocelectomy will reduce sperm DNA fragmentation in men with clinical varicocele. Therefore, even if the patient has normal semen parameters, the improvement in sperm DNA fragmentation has no link to the pre-operative sperm parameters. The higher the sperm DNA fragmentation

The higher the sperm DNA fragmentation preoperatively, the more improvement in sperm DNA fragmentation will be shown after varicocelectomy [9]. There are mixed findings on whether the improvement of sperm DNA fragmentation after varicocelectomy correlates with classic semen parameters results. Some studies show a correlation between them [10-12] and other studies show no correlation [9][13]. This fluctuation in outcome demonstrates how classic semen parameters are highly biologically variable. The sperm DNA integrity, in contrast, is more biologically stable, and the tests used to assess it have lower levels of interassay variability [10].

Sperm DNA Fragmentation and Pregnancy

The probable reason why infertile men with clinical varicocele and normal semen parameters show improvement in pregnancies and miscarriage incidence are because of the decrease in sperm DNA fragmentation. It has been shown above that classic semen parameters don't correlate with sperm DNA fragmentation and it means that the increase of sperm DNA fragmentation can't be predicted from classic semen parameters.

Only one included study in this review analyzes the correlation between sperm DNA fragmentation and pregnancy outcome. Fathi et al show that men with lower SDF have a higher chance of achieving pregnancy compared to men with higher SDF. Other studies that analyze the correlation between SDF and pregnancy also included samples with

abnormal semen parameters but the result is fairly the same. Smit et al found that men with lower SDF will have a higher chance of achieving pregnancy compared to men with higher ones. Even in the pregnant group, there is a difference between the ones who achieved spontaneous pregnancy and not. The SDF is even lower in the group that achieved spontaneous pregnancy and this shows that the lower the SDF the higher the chance the couple can achieve spontaneous pregnancy [12].

In the setting of assisted reproductive technology (ART), sperm DNA fragmentation also has a role in the success of ART. Men with lower SDF have a higher success rate in ART compared to men with high SDF [12]. This result is also supported by a few other studies with similar results [14-16].

Sperm DNA Fragmentation and Miscarriage Incidence

The malefactor used to be excluded when couples suffered from pregnancy loss because the ability to achieve pregnancy was believed to be a sign that there was no problem with the malefactor and the incidence of pregnancy loss was due to the female's oocyte quality or uterine condition. However recent studies show that man also contributes to the incidence of pregnancy loss through an increase in sperm DNA fragmentation [17].

A study by Haddock et al. found that sperm DNA fragmentation can be used to predict the outcome of live birth. This study shows that couples who achieved live birth have much lower SDF compared to couples suffering from miscarriage [17]. Another study by Busnelli et al also shows similar results where the SDF in men with recurrent pregnancy loss is significantly higher compared to couples that achieve a live birth [18].

Conclusion

Varicolectomy in infertile men with clinical varicocele and normal semen parameters may improve pregnancy rate, miscarriage rate, and semen analysis. Additional randomized controlled trials must be conducted to provide more evidence of the benefits of varicolectomy in infertile men with clinical varicocele and normal semen parameters.

Conflict of interest

The authors declare that they have no conflict of interests.

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