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INVITED REVIEW

Male Fertility

Critical appraisal of conventional semen analysis in the context of varicocele

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Varicocele is present in approximately 15% of men, and, although it is the most commonly diagnosed cause of male infertility, nearly two-thirds of men with varicoceles remain fertile. It was decided to make use of the current evidence obtained from the previous meta-analyses between 2004 and 2015 as well as available articles covering this field, preferably randomized controlled articles dealing with the topic of semen analysis before and after repair. Two important meta-analyses were discussed as well as other articles dealing with the topic of semen analysis before and after varicocelectomy. The evidence suggests that all semen parameters improve after varicocele repair. Based on the available evidence, it is clear that there is a benefit in treating men with a palpable varicocele. One can expect that all semen parameters will improve within 3 months after repair.
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INTRODUCTION

Male infertility compromises about 40% or more of infertile couples. Often male factor infertility is unexplained. Varicocele is dilated tortuous spermatic veins usually palpable around the left testis.

Varicocele presents in approximately 15% of men, and, although it is the most commonly diagnosed cause of male infertility, nearly two-thirds of men with varicoceles remain fertile.[1] The fact that most of the work on varicocele repair is retrospective of the evidence of surgical repair and its value in the improvement of fertility is still debated. Eighty-five percent of patients will have a left varicocele and the balance palpable on the right side or bilateral. 11.7% of infertile men with normal semen analysis and 25.4% of those with abnormal analysis were found to have a clinical varicocele. The reason for this discrepancy that some are fertile but others are not, remains unknown, although it is postulated that the cause of infertility is due to increased temperature[1] affecting the DNA fragmentation ratio and reactive oxygen species.[2–4]

There are a number of treatments available to handle varicoceles. These treatments can be radiological ablation or surgical of which the microsurgical method gives the best long-term results with less complications. It is the consensus opinion of most that only clinically palpable varicoceles should be operated on. The laparoscopic approach does not seem to be superior to the open microsurgical method and thus lately not the operation of choice.[1]

There are a number of interesting factors to be studied in men with varicocele. The interest of the authors for this article is to evaluate the impact/effect of repair of varicocele on semen parameters. It was decided to make use of the current evidence obtained from the previous meta-analyses between 2004 and 2015 as well as available articles covering this field, preferably randomized controlled articles dealing with the topic of semen analysis before and after repair.

THRESHOLD VALUES FOR SEMEN ANALYSIS

WHO lower reference limits

The WHO has published revised lower reference limits for semen analyses.[5] The following parameters represent the generally accepted 5th percentile (lower reference limits and 95% confidence intervals [CIs] in parentheses), derived from a study of over 1900 men whose partners had a time-to-pregnancy of ≤12 months. The suggested lower thresholds (subfertile values) were as follows: volume: 1.5 ml (95% CI: 1.4–1.7), Sperm concentration: <15 million spermatozoa per milliliter (95% CI: 12–16), Total sperm number: <39 million spermatozoa per ejaculate (95% CI: 33–46), Morphology: ≤4% normal forms (95% CI: 3–4), using the "strict" Tygerberg method,[6] Vitality: 58% live (95% CI 55–63), Progressive motility: <32% (95% CI: 31–34), and Total motility (progressive + nonprogressive motility): <40% (95% CI: 38–42).[5,7,8]

These values will be looked at when analyzing the reports on semen parameters and varicocele. However, since many articles are dating back to periods even before 2000, other thresholds will also be taken into consideration. The percentage increasing or dropping of the parameters will also be taken into account in interpreting the effect of varicocelectomy as well as the concentration per milliliter.

EVIDENCE AVAILABLE ON THE VALUE OF VARICOCELECTOMY ON SEMEN ANALYSIS OR SEMEN PARAMETERS

Meta-analysis

In an attempt to obtain the best evidence, meta-analyses are very helpful to form opinions on a topic and specifically on this topic. Agarwal *et al.*[9] reported an important meta-analysis, and I am quoting them directly:

"To determine the efficacy of varicocelectomy in improving semen parameters. A meta-analysis was performed to evaluate both

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randomized controlled trials and observational studies using a new scoring system. This scoring system was developed to adjust and quantify for various potential sources of bias, including selection bias, follow-up bias, confounding bias, information or detection bias, and other types of bias, such as misclassification. Of 136 studies identified through the electronic and hand search of references, only 17 studies met the inclusion criteria. The study population was infertile men with clinically palpable unilateral or bilateral varicocele and at least one abnormal semen parameter who had undergone surgical varicocelectomy (high ligation or inguinal microsurgery). Only those studies that had at least three semen analyses (i.e., sperm count, motility, and morphology) per patient, before and after surgical varicocelectomy, were included." The following results were reported: "the combined analysis demonstrated that the sperm concentration increased by 9.71×10^6 ml^{-1} (95% CI: 7.34–12.08; $P < 0.00001$) and motility increased by 9.92% (95% CI: 4.90–14.95; $P = 0.0001$) after microsurgical varicocelectomy. Similarly, the sperm concentration increased by 12.03×10^6 ml^{-1} (95% CI: 5.71–18.35; $P = 0.0002$) and motility increased by 11.72% (95% CI: 4.33–19.12; $P = 0.002$) after high ligation varicocelectomy. The improvement in World Health Organization sperm morphology was 3.16% (95% CI: 0.72–5.60; $P = 0.01$) after both microsurgery and high ligation varicocelectomy."

They concluded that surgical varicocelectomy significantly improved semen parameters in infertile men with palpable varicocele and abnormal semen parameters.

In a follow-up meta-analysis in 2011, Baazeem *et al.*[10] reported on the assessment of the effect of varicocelelectomy on male infertility. For the purpose of accuracy, the authors are also quoted verbatim:

"Four randomized controlled trials reporting on pregnancy outcomes after repair of clinical varicoceles in oligozoospermic men were identified. Using the random effect model, the combined odds ratio was 2.23 (95% CI: 0.86–5.78; $P = 0.091$), indicating that varicocelectomy is moderately superior to observation, but the effect is not statistically significant. They identified 22, 17, and 5 prospective studies reporting on sperm concentration, total motility, and progressive motility, respectively, before and after repair of clinical varicocele. The random effect model combined improvement in sperm concentration was 12.32×10^6 ml^{-1} (95% CI: 9.45–15.19; $P < 0.0001$). The random effect model combined improvement in sperm total and progressive motility were 10.86% (95% CI: 7.07–14.65; $P < 0.0001$) and 9.69% (95% CI: 4.86–14.52; $P = 0.003$), respectively. These results indicate that varicocelectomy is associated with a significant increase in sperm concentration as well as total and progressive motility. They stated that prospective studies also show that varicocelectomy reduces seminal oxidative stress and sperm DNA damage as well as improving sperm ultramorphology."

The report by Baazeem *et al.*[10] concluded: "although there is no conclusive evidence that a varicocele repair improves spontaneous pregnancy rates, varicocelectomy improves sperm parameters (count and total and progressive motility), reduces sperm DNA damage and seminal oxidative stress, and improves sperm ultramorphology."

There are few randomized controlled studies dealing with the benefit of varicocelectomy in men with abnormal semen parameters. Abdel-Meguid *et al.*[11] studied men in this fashion with at least one impaired semen parameter (sperm concentration $<20 \times 10^6$ ml^{-1}, progressive motility <50%, or normal morphology <30%). One group received treatment (subinguinal microsurgical varicocelectomy) and the control group was observed.

They reported: "in CA (Control arm) within-arm analysis, none of semen parameters revealed significant changes from baseline (sperm concentration [$P = 0.18$], progressive motility [$P = 0.29$], and normal morphology [$P = 0.05$]). Conversely, in TA (treatment arm) within-arm analysis, the mean of all semen parameters improved significantly in follow-up versus baseline ($P < 0.0001$). In between-arm analysis, all semen parameters improved significantly in the TA versus CA ($P < 0.0001$)."[11]

OTHER ARTICLES DEALING WITH THE IMPACT OF VARICOLOELECTOMY ON SEMEN PARAMETERS

Asthenospermia

According to Will *et al.*[4] 19% of subfertile men would suffer from asthenozoospermia if diagnosed with varicocele.[4,12] There is consensus in the literature that motility will improve in patients where a palpable varicocele was treated.[12–14]

Teratozoospermia

The problem with the literature on sperm morphology is the fact that most articles consist of retrospective data and small studies. Therefore, controlled prospective studies are highly needed in the field.

The following authors observed improvement in sperm morphology after varicocelectomy.[15–17] Interestingly, the study by Cakan *et al.*[17] showed no improvement in morphology and semen parameters in the control group with no pregnancies over a 12-month follow-up period. As mentioned before, the meta-analysis by Agarwal *et al.*[9] also concluded that sperm morphology improved after treatment of the varicocele. In contrast to the above, a number of authors did not see any improvement in sperm morphology after surgical removal.[18,19]

Oligozoospermia

Studies that examined men with low sperm counts in the less severe range showed greater postoperative improvements. Madgar *et al.*[20] restricted their prospective study to men with sperm concentration between 5×10^6 and 20×10^6 ml^{-1} to limit the number of confounding variables; and they were able to demonstrate a significant improvement in sperm concentration, motility, and morphology (by 6 months postoperatively) and higher pregnancy rates than the control group. As mentioned, Baazeem *et al.*[10] noted similar improvements in semen parameters in their recent review of 360 patients with sperm concentrations ranging 1×10^6–20×10^6 ml^{-1}.

Severe oligozoospermia/nonobstructive azoospermia

Studies from a number of authors published evidence to support that men with severe oligozoospermia ($<5 \times 10^6$ ml^{-1}) are less likely to see improvements in semen parameters.[21–23] Kamal *et al.*[21] were also able to display a direct relationship between preoperative sperm count and postoperative pregnancy rates. It was observed that men with severe oligozoospermia had much lower chance of spontaneous pregnancy (8% compared to 61% in those with sperm concentration more than 5×10^6 ml^{-1}).[21]

Matthews *et al.*[24] wrote recently: "early reports of varicocele repair demonstrate the potential, in some, to induce spermatogenesis." Matthews *et al.*[24] as well as Kim *et al.*[25] showed improvement in semen parameters in patients with oligozoospermia and azoospermia. The Matthews group also observed pregnancies after varicoloelectomy in their study.[24]

The question about who are the best candidates for treatment is asked. A number of researchers showed that those with hypospermatogenesis and maturation arrested at later stages are more likely to see return of motile sperm and even pregnancies postoperatively.[25–28]

As a general principle, one must do a semen analysis at regular intervals (every 6 weeks) and it is a good strategy to freeze sperm as soon as motile samples are available.[28,29]

Sperm DNA damage

There is a difference between opinions and conflicting results about DNA damage and varicocele possibly due to the size of varicocele. With the advent of new laboratory assessment tools to aid in selection of higher quality sperm with less DNA fragmentation for use with ICSI,[30–32] it will be interesting to see if varicocelectomy will be required in the future for specifically selected patients prior to ICSI.[4]

TIME TO IMPROVEMENT

In a retrospective study by Al Bakri *et al*.[33] they evaluated the time taken to observe improvement in semen parameters. All men had at least two preoperative semen analyses as well as semen testings at 3 and 6 months postoperatively.

The authors concluded that after 3 months the maximum effect and benefit was observed.[33] There was a significant improvement in concentration and motility in the 100 men that met the inclusion criteria after 3 months, but this did not change at 6 months or longer. There were no statistically significant differences in the improvement of semen volume, motility, count, or total motile count among the results at 3, 6 and more than 9 months postoperatively.

CONCLUSION

Based on the available evidence, it is clear that there is a benefit in treating men with a palpable varicocele. One can expect that all semen parameters will improve within 3 months after repair. It is thus important to examine all men in a fertility clinic, especially those with abnormal semen parameters to be able to make sound clinical decisions and consider a varicocelectomy.

COMPETING INTERESTS

The author declares no competing interests.

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