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REVIEW ARTICLE

Male infertility and varicocele: myths and reality

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Abstract

Varicocele is among the most common causes of male infertility. It is also one of the most controversial issues in the field of Andrology, especially regarding why, when and to whom varicocelectomy should be applied. Many experts believe that the surgical repair of varicocele should be applied only in a meticulously selected group of infertile men, although there are no generally accepted criteria. Up to now, the only confirmed prognostic factor for achievement of pregnancy after varicocelectomy is the age of the female partner. Given the wide application of intra - cytoplasmic sperm injection (ICSI) during the last few years, the modern research approaches should compare the benefits of varicocelectomy and ICSI, taking under consideration both the efficacy and the cost-effectiveness of the methods. *Hippokratia 2007; 11 (3): 99-104*

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Infertility is considered one of the main public health issues, as it affects about 15% of the couples of reproductive age[1]. The male factor is involved in 40% - 50% of infertility cases[2]. The most common type of male infertility is idiopathic infertility, which is characterized by the presence of one or more abnormal semen parameters with no identifiable cause[3]. Another common cause of male infertility is varicocele, which in a European study was found to affect 16.6% of 7.802 men referred for infertility[4]. Our research group, has estimated that the percentage of infertile men with varicocele in the Greek population is 21%[5].

Reports regarding the presence of varicocele in the testis are dated back to the 1st century A.C., when the Greek physician Celsus noted that: "The veins are swollen and twisted over the testicle, which becomes smaller than its fellow, in as much as its nutrition has become defective."[6]. The first notice that varicocele might be related to infertility was made between the end of the 19th and the beginning of the 20th century when surgical repair of varicocele was shown to improve the quality of sperm. Tulloch in 1952 first reported that bilateral surgical repair of varicocele in a man with azoospermia resulted in an increase in sperm concentration (27 x 10^6 / ml) and a spontaneous pregnancy[7]. Since then, many studies have been focused on the diagnostic and therapeutic approach of varicocele for fertility purposes, but none of them has provided a clear answer concerning the relationship between varicocele and infertility. The fact that varicocele is a common problem among infertile men does not indicate that it is the main cause of infertility, since the co-existence of congenital or acquired idiopathic testicular dysfunction with varicocele is a frequent finding[8].

It is important to note that in 78% - 93% of cases varicocele is located on the left side[9]. The increased frequency of bilateral localization documented in more recent studies can be due to the use of modern diagnostic means, such as conventional or Doppler ultrasound of the scrotum[10-12].

Varicocele can be categorized as: *First grade:* enlargement of the venous plexus of spermatic tone is evident only by palpation during the Valsalva manoeuvre. *Second grade:* enlargement of the venous plexus of spermatic tone is evident only by palpation at upright position. *Third grade:* enlargement of the venous plexus of spermatic tone is visually evident[13].

The non-palpable enlargement of the venous plexus of the spermatic tone, which is diagnosed only by ultrasound, angiography or any other imaging method, is defined as subclinical varicocele[14].

Etiology

The etiology of varicocele is not fully elucidated. According to one theory, varicocele is the result of anatomical differences between the right and left spermatic vein. In fact, the right internal spermatic vein inserts directly into the inferior vena cava at an acute angle, while the left internal spermatic vein inserts into the left renal vein at a right angle. It is believed that this disparity leads to an increase in the hydrostatic pressure of the left spermatic vein, which is subsequently transferred to the venous plexus of the spermatic tone causing its dilation [15]. A second theory is based on the observation that internal spermatic veins lack functional valves, which can lead to regression of blood. Finally, a third theory suggests that

there is a partial obstruction of the left spermatic vein due to the compression of the left renal vein between the aorta and the upper mesenteric artery ("the nutcracker phenomenon")[15].

Pathophysiology

The adverse effect of varicocele on spermatogenesis can be attributed to many factors such as an increased testicular temperature, increased intratesticular pressure, hypoxia due to attenuation of blood flow, reflux of toxic metabolites from the adrenal glands and hormonal profile abnormalities[16-19].

Varicocele is characterized by increased temperature of the scrotum possibly due to reflux of warm blood from the abdominal cavity. This is caused primarily by insufficiency of the internal spermatic vein valves[20] and secondarily by malfunction of the valves of the external spermatic and cremasteric veins[21]. Surgical repair of varicocele has been shown to restore the temperature in both animals and humans. The mechanism by which temperature influences spermatogenesis is not clearly understood. According to one theory, it is caused by thermal damage of the DNA and proteins in the nucleus of spermatic tubules' cells and / or Leydig cells[15, 16].

The increased vein pressure can influence testicular blood flow via compensational reduction of the arterial flow required to preserve the homeostasis of the intratesticular pressure[18]. A study showed that in men with varicocele, the mean increase in the pressure of the venous plexus of the spermatic tone was 19.7 mm Hg, compared to the control group[22].

Increased concentration of regressed toxic metabolites in the testes (e.g. catecholamines from the adrenal glands) can cause chronic vasoconstriction and subsequent dysfunction of the spermatic epithelium[15].

A multicentre study of the World Health Organization (WHO) showed that men with varicocele over 30 years of age had significantly lower levels of testosterone compared to younger men with varicocele, while the same results were not confirmed in men without varicocele[13]. It is speculated that the low levels of testosterone observed in those men are caused by reduction of its production due to dysfunction of Leydig cells. However, this study failed to explain whether the reduced levels of testosterone are due to varicocele or due to coexistence of primary testicular failure. On the other hand, it has been demonstrated that testosterone levels in men with varicocele and no other testicular pathology are within the normal range[23]. It has to be noted that varicocele can not result in clinical hypogonadism.

The exact mechanism by which the above factors contribute to the adverse effect of varicocele on spermatogenesis has not been fully clarified. It is speculated that the main mechanism is DNA damage in sperm heads due to oxidative stress. The later is caused either by the presence of high levels of reactive oxygen species or by reduced antioxidant capacity. It is interesting to note that these results were confirmed in fertile as well as in infertile men with varicocele[24]. Thus, it becomes obvious that oxidative stress is directly related to varicocele, independent of the fertility status. Nevertheless, oxidative stress is known to have adverse effects on sperm structure and function, such as membrane lipid alterations, disruption of sperm metabolism, reduction of its motility[25], DNA fragmentation[26] and reduced overall sperm quality[27].

It has been observed that in men with varicocele germ cell apoptosis is a very common phenomenon[28]. Indeed, germ cell apoptosis and subsequent oligozoospermia can be attributed to increased scrotal temperature, increased intratesticular cadmium concentration and reduced levels of androgens[29].

Having in mind that both the pathophysiology of varicocele and its relationship with infertility remain unclear, it could be speculated that possibly varicocele represents a defense mechanism in an attempt to repair a possible testicular dysfunction, rather than being the cause of it[30]. This is further supported by the fact that about 2/3 of men with varicocele retain their fertility[6, 31] and that fertility potential is not always improved after surgical repair of varicocele[30, 32]. On the other hand, the speculation that varicocele is a cause of male infertility is based mainly on the increased incidence of this condition among infertile men, on the correlation of varicocele with reduced semen parameters and reduced testicular size and finally on the improvement of semen parameters and pregnancy rates after surgical repair of varicocele.

Relationship between varicocele and male infertility

A possible reason for linking varicocele with infertility is the fact that it appears 2 – 3 times more frequently in men that attend infertility clinics, than in men of the general population or of proven fertility[4,6,32,33]. However, the results from different studies are highly controversial. The prevalence of varicocele in the general population varies from 4% to 30%[6, 32]. The prevalence among infertile men also varies between different studies from 17% to 41%[4, 33]. This variation indicates either that the prevalence of varicocele is very different among the different populations or that the diagnosis for this condition is very subjective and thus varies among researchers. Interestingly, a multicentre study from the WHO published in 1992 showed that the frequency of varicocele in infertile couples among different geographical regions varied from 6% to 47%[13].

The issue of subjectivity in the diagnosis of varicocele has long been a subject of debate. In a study by Hargreave and Liakatas[34], the two researchers examined separetly the same patients (n = 138) and found the prevalence of varicocele to be 31% and 19%, respectively. Moreover, 18 men were diagnosed having a large varicocele according to one or the other researcher, but agreement in the diagnosis achieved only for 10 (56%) of them. Thus, it becomes obvious that the estimated high prevalence of varicocele in infertile men can be due to

examiner's bias. One should not forget that the men that attend infertility clinics usually undergo extensive examination. Therefore, even small grade varicocele will not be missed, in contrast to the general population, which usually acts as the control group. In addition, men might have one or two abnormal semen analyses with no other obvious clinical cause. Thus, the physician in an attempt to find a cause for the infertility might subconsciously exaggerate on the varicocele diagnosis[32].

Varicocele and semen parameters

There is still an ongoing debate among researchers as to if and to what extend varicocele affects semen parameters, which usually vary from normal to mild or moderate asthenospermia, teratospermia or asthenoteratospermia. Initially, sperm concentration is not seriously affected, though later all three sperm parameters can gradually deteriorate, resulting in azoospermia in very few cases[23]. A recent study reported significantly lower semen parameters in infertile men with varicocele, compared to the fertile control group but there was no association with the size of the varicocele[35]. However, the sample number in this study was small (40 men in each group), which might have affected the validity of the results. The low sperm concentration is attributed by some researchers to the high germ cell apoptosis usually observed in those men, while the low motility is attributed either to the increased concentration of reactive oxygen species or to the presence of antisperm antibodies[36].

It has been demonstrated that infertile men with varicocele usually have slightly elevated levels of serum FSH[23,37]. However, semen does not seem to be affected, as further studies revealed that infertile men and men of the general population with or without varicocele do not present any significant difference regarding the semen parameters[32]. On the other hand, a large scale study by the WHO showed significantly lower sperm concentration in infertile men with varicocele, compared to men with idiopathic infertility, but did not give any evidence regarding motility and morphology of the sperm[13].

The hypothesis that varicocele can cause testicular damage was primarily confirmed on pubertal boys, in which it was shown that the slight reduction in the size of the ipsilateral testis was restored by surgical repair of varicocele[38]. However, this reduction in the testicular size is quite different from the bilateral small testicular size (< 10 cm^3) seen in adults with concomitant increased FSH.

It seems that fertile and infertile men with varicocele have similar semen parameters with those without the condition. Thus, it is speculated that varicocele affects fertility and sperm quality in some, but not in all men. Another assumption is that sperm quality is not affected by varicocele as such, but simply coexists in some men with idiopathic infertility and abnormal semen parameters.

Varicocele and progressive reduction of fertility

The hypothesis that varicocele progressively affects testicular function in adult men is based on the observation that the condition is more frequent in infertile men, especially in those with secondary infertility[39,40]. It is speculated that secondary infertility is due to the chronic and progressively increased influence of varicocele[39]. Based on these assumptions, some studies suggest the surgical repair of varicocele, in order to avoid any negative effects on testicular function. Nevertheless, those studies have several drawbacks as they fail to mention any possible reduction in semen parameters and choose to concentrate on the increased prevalence of varicocele in older couples. As an exception, progressively decreased sperm concentration was mentioned only in one study[41]. In addition, one should not forget the negative effect of the female age on couple's fertility, independently of the male fertility potential. On the other hand, there are some studies that do not confirm the increased prevalence of varicocele in men with secondary infertility[42], thus the progressive detrimental effect of varicocele on the testes should be considered with caution.

The effects of varicocelectomy on male infertility

For many years varicocele was considered an important cause of male infertility as numerous studies showed improvement (30% to 60%) in semen parameters after varicocelectomy[33,43]. However, these findings were not fully accepted due to serious methodological disadvantages, such as that the main outcome was improvement in semen parameters and not pregnancy rate. The main disadvantage in these studies was the lack of a control group.

It is true that infertile couples with sperm counts less that 5 x 10^6/ml and established infertility for at least one year are capable of achieving natural conception (36%) without any therapy[44]. This observation reveals the significant role of the control group in such studies, suggesting that if someone had his varicocele repaired, any pregnancy after surgery could be attributed erroneously to varicocelectomy. Besides, it is known since 1951 that both motility and sperm count in men with oligo-asthenospermia have a tendency to increase after repeated measurements[45]. Baker et al were the first to explain this phenomenon mathematically, which is called "regression towards the mean" and it is related to all clinical studies[46]. When a patient is under observation before an intervention, and there is high parameter variabilitw in the measurements, it is possible to observe a significant improvement in these parameters, even if the intervention is not effective. Despite the surgical repair of varicocele, a previously low sperm concentration can increase and a previously high sperm concentration can decrease. Thus, it is obvious that studies on the effectiveness of varicocelectomy, which showed improvement in sperm count and motility but had no control group, must not be taken under much consideration[46].

There are only a few prospective controlled studies

available in the literature with pregnancy rate as the main outcome[30, 47–54]. The most well designed study is probably that of Nieschlag et al[30]. In this study 62 infertile couples were randomized to varicocele repair (30 with surgical ligation of the spermatic vein and 32 with angiographic embolization) in contrast to 63 infertile couples that underwent counseling only. No statistically significant difference was found in pregnancy rates between the two groups, during a period of twelve months. In an attempt to find other prognostic factors, pregnancy rates were not related to semen parameters, hormonal levels, varicocele grade or men's age, but only to female age. As far as sperm quality is concerned, the total number of spermatozoa was generally increased in both groups, but the difference became significant only in the group that underwent varicocele repair. No significant difference was found between the two groups in any other semen parameters or hormonal levels (FSH, LH and Testosterone).

An important step in the investigation of the role of varicocele in male infertility was a systematic review written by Evers et al[31]. The aim of this review was to investigate if the surgical repair of varicocele improved pregnancy rates in couples with male factor or unexplained infertility. The authors reviewed nine studies with considerable differences in the inclusion criteria (men with clinical varicocele and normal sperm[47, 48], men with subclinical varicocele[51-53], surgical ligation[47, 49, 51–53], embolization[30, 48, 50, 54] and counseling[30, 50]). The relative benefit in the group of therapeutic intervention was 1.10 (95% CI 0.73 - 1.68), revealing that there is no significant benefit from the varicocele repair in infertile couples in whom varicocele is the only abnormal finding. In addition, during analysis of the subgroups, it became obvious that surgical repair of varicocele is not effective in men with clinical or subclinical condition and to those with normal semen parameters. Only one study by Madgar et al[49] showed statistically significant higher pregnancy rates after surgical repair of varicocele by high ligation of the left spermatic vein. However, when Madgar's results were combined to Nieschlag's[30], which were the two studies including only men with clinical varicoceles and abnormal semen parameters, it became evident that pregnancy rates do not increase significantly after surgical repair of varicocele, compared to the control group.

Another controversial issue is the relationship between varicocele and azoospermia. The main question is whether azoospermia is due to varicocele or to co-existent primary testicular failure. As a consequence, there is no consensus on whether to operate varicocele in azoospermic men with maturation arrest or Sertoli Cell-Only Syndrome (SCOS). Furthermore, the question still remains as to whether surgical repair of varicocele on the above conditions should be recommended, in order to avoid obtaining sperm by TEsticular Sperm Extraction (TESE) for fertilization with Intra-Cytoplasmic Sperm Injection (ICSI). The use of motile sperm from the ejaculate gives better fertilization, cleavage and pregnancy rates than those from TESE in ICSI[55, 56]. It is generally accepted that sperm production after varicocele repair recovers in a small degree, but remains suboptimal. Onset of spermatogenesis and presence of sperm in the ejaculate was evident in one clinical study in 33% of azoospermic men who underwent varicocelectomy[57]. However, this study had no control group and it showed that 55% of men progressively became azoospermic within one year after surgery. These results led to the conclusion that azoospermia probably was cryptozoospermia[57]. Another retrospective study showed that 22% of men with non – obstructive azoospermia had some motile and immotile spermatozoa in the ejaculate within a period of 14.7 months after varicocele repair, but only 9.6% had enough motile spermatozoa that could be used for ICSI[58]. In addition, the percentage of sperm that could be isolated with TESE did not increase after surgery. These results are not a surprise: a study performed in our unit showed that varicocele was the only cause of azoospermia in only 1.6% of the 187 azoospermic men examined[59]. *In conclusion, men with clinical varicocele and non-obstructive azoospermia are not expected to retain satisfactory sperm quality after varicocelectomy, so to be able to achieve pregnancy either with intercourse or with Intra-Uterine Insemination (IUI) or ICSI without the use of TESE.*

At this point it is worthwhile to comment on the relationship between varicocele and impaired histological diagnosis of the testis. It is very likely that varicocele and primary testicular failure such as idiopathic non-obstructive azoospermia can coexist. The only way to investigate this relationship is to repeat the testicular biopsy after the surgical repair of varicocele. The persistence of SCOS after surgery denotes that varicocele co-existed with primary testicular failure, which of course was not affected by the surgery. Thus, if there is a need to decide whether to surgically repair the varicocele or not, especially in men with non-obstructive azoospermia, the physician must first answer the question if it is the varicocele that causes the testicular damage or the two conditions simply coexist. The answer to this question could possibly explain the differences observed in the improvement of semen parameters and pregnancy rates after varicocele repair[30, 49].

Subclinical varicocele

Nowadays, it is widely accepted that the optimum diagnostic method for varicocele is the palpation of the scrotum at the upright position during a Valsalva manoeuver[13]. The non-palpable enlargement of the venous plexus of the spermatic tone, which can be diagnosed only by imaging techniques, is defined as subclinical varicocele[14]. The accuracy of the imaging techniques, such as Doppler ultrasonography and angiography, is low: one study has shown that the accuracy of colored Doppler is approximately 60% compared to angiography, which is considered as the gold standard[60]. In any case, most researchers agree that the detection of a sub-

clinical varicocele is not an indication for surgical repair, mainly because the prospective controlled studies which have included men with subclinical varicocele failed to report an increase in the pregnancy rate postoperatively[51-53]. Thus, the main method for the diagnosis of a varicocele is the physical examination by palpation, whereas Doppler ultrasonography should be used to confirm the clinical findings.

Varicocele and ICSI

The development of ICSI as the method of choice in cases of severe male factor infertility triggered scientists to modify their diagnostic and therapeutic approach[61]. Thus, a frequent question regarding the therapeutic approach of infertile couples with varicocele is whether to treat this condition first or apply directly TESE / ICSI. The advantage of treating varicocele first is that, if it is successful, it provides a good opportunity for natural conception[62]. In addition, it is more cost-effective, especially if future pregnancies are planned[63].

In order to repair a varicocele the following criteria should be fulfilled[62]:

1. Involuntary infertility of at least one year.

2. Presence of a palpable varicocele at the upright position and during a Valsalva manoeuver.

3. No detectable or at least no irreversible cause of female infertility.

4. Normal testicular size (> 15 cm^3) or small reduction of the ipsilateral testis[5].

5. Evaluation of at least two semen analyses at three months interval. The presence of normal semen analyses excludes varicocele as the cause of infertility. The usual effects of varicocele on sperm parameters include mild and moderate asthenospermia, teratospermia or astheno-teratospermia. Initially, sperm concentration is not seriously affected, though later all three semen parameters can gradually deteriorate, resulting in azoospermia in very few cases[23].

6. Normal values or slight increase (less than the double of the upper normal range) of serum FSH levels, as very high levels of serum FSH denote primary testicular failure.

Additional factors that must be considered before deciding the therapeutic approach of varicocele in an infertile couple include[62]:

1. The advanced age of the wife (older than 35 years) and high serum FSH levels should drive the decision towards the ICSI solution rather than repair of varicocele[30].

2. In case of chronic presence of varicocele and advanced male age, surgery should be avoided.

3. Surgical repair of varicocele is recommended in case of secondary male infertility[39, 40]. On the other hand, if the patient has primary infertility, azoospermia, small testicular size and high serum FSH levels, the presence of varicocele should be ignored and surgery should be avoided, as the diagnosis in this case pleads towards primary testicular failure.

4. The diagnosis of SCOS or maturation arrest in FNA or open testicular biopsy denotes primary testicular failure. Thus, the presence of varicocele should be ignored. On the contrary, the presence of mild or moderate hypospermatogenesis can be attributed to varicocele in which case surgery can be a reasonable therapeutic approach.

Conclusion

Varicocele is one of the most debatable issues in the field of male infertility mainly with regard to surgical intervention. Many scientists believe that the surgical repair of varicocele should include a very narrow group of infertile men. Nevertheless, there are no widely accepted criteria regarding the selection of this group of men. With the development of the ICSI technique during the last few years, research should focus mainly on the effectiveness of surgical repair of varicocele taking under consideration the pregnancy rates of the methods, their cost-effectiveness as well as the couple's preferences.

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