Subclinical Varicocele: Evaluation and management in infertility. 
A review of the literature.

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Abstract

The subclinical varicocele is defined as an abnormal dilatation of the pampiniform plexus, absent of physical examination and detected only by ultrasound or other imaging modalities. In clinical practice, huge discrepancies exist regarding the optimal management of the condition, mainly due to the fact that a cumulative benefit of interventional treatment has not been provided yet. However, a significant amount of patients seems to be affected and a possible intervention might act beneficially upon infertility. In this review, an effort is made in order the possible role of the condition in infertility to be enlightened, whereas the possible management is also discussed.

A. INTRODUCTION

The varicocele is defined as the abnormal dilatation of the veins in the pampiniform plexus of the scrotum and is regarded as one of the major causes of male infertility [1]. The classification system proposed by Dubin and Amelar is the most widely used and divides the condition in 3 forms according to findings of physical examination, as a combination of inspection and palpation; grade I, as the condition palpable only during Valsava, grade II visible only during Valsava and grade III visible without Valsava [2]. However, an amount of men carry the subclinical form of the disease, i.e. a non-palpable lesion which is diagnosed by ultrasound, venography or other modalities [3]. In case of clinical varicocele, the role of intervention is unquestionable as far as the correction has been proven effective, improving significantly semen parameters and increasing pregnancy rates [4]. On the other hand, the surgical management of the subclinical varicocele

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offers some improvement in semen quality, but no overall benefit on pregnancy rates can be seen \[^5\]. Under these findings and according to current consensus, the surgical correction of varicocele is indicated in patients suffering from infertility who bear the clinical form of the disease, but the data to recommend correction in subclinical forms is still weak \[^6\]. In this paper, we review the literature concerning the subclinical varicocele, regarding the investigation, the clinical significance and available data about the optimal management of the condition.

B. DIAGNOSTIC CRITERIA

According to classical knowledge, the diagnosis of a subclinical varicocele dictates a negative physical examination and the detection of the dilation of the venous plexus by other modalities. Venography has been used for the documentation of the condition and the characteristic reflux of contrast material down to the level of the inguinal canal is considered indicative, whereas the thermal asymmetry between hemiscrotums greater than 0.3 °C is also considered diagnostic of varicocele by other authors \[^7\]. In modern era, ultrasound is regarded as the most applicable tool for the diagnosis of a subclinical varicocele; the measurement of vein diameter is the simplest method used, although an optimal cutoff varies among studies, ranging from 2 mm to 3 mm or more \[^8\]-\[^9\]. Similarly, the upper limit is also questionable, but tortuous veins with diameter larger than 3.5 mm are considered unlikely to be impalpable \[^10\]. However, the measurement of venous size to distinguish between clinical or subclinical varicocele is rather unreliable \[^11\]; despite a significant correlation of venous size by ultrasound with clinical grading \[^12\], some authors observed that an overlapping in vein diameter measurement can be seen between subclinical varicocele and low clinical grades \[^13\], whereas other authors also observed that the actual size of subclinical varicoceles measured during operation may be larger than those forms that have been previously defined as low grade varicocele \[^14\]. An appropriate correlation with clinical grade seems to be reachable if venous reflux is used as criterion; according to Patil’s objective stratification system, a subclinical varicocele is defined as an abnormal dilated veins which does not exhibit longer than 1 s reflux in CDU examination \[^15\]. Other classifications systems may be used for the disclosure of a subclinical varicocele and add additional information, like Chiu’s scoring system, which combines measurements of vein diameter, tortuosity and duration of reflux \[^16\]. The classification by Hirsch is based on the presence of reflux for the diagnosis and grading, giving emphasis in spontaneity and the duration of the flow \[^17\], whereas, Sarteschi’s stratification of varicoceles in five grades makes good use of the presence and location of varicosity and the length of reflux, in correlation with stance and Valsava maneuver \[^18\].

C. CLINICAL SIGNIFICANCE

1. A precursor of clinical varicocele?

The consumption that a subclinical varicocele is a dynamic phenomenon has been demonstrated by some studies. Zampieri and Dall’Agnola, following an adequate amount of adolescents, concluded that subclinical varicocele should be considered a dynamic phenomenon, as far as the condition progressed into clinical varicocele in 36% and 25% of athletes and non-athletes, respectively \[^19\]. In another study, Cervelione et al observed that 28% of children with subclinical varicocele developed the clinical form in a follow-up of 4 years; a higher degree of reflux was seen most commonly in this group \[^20\]. From an epidemiologic point of view, the increase in prevalence of varicoceles from 14% in boys aged 15-19 years to more than 43% in men older than 60 year-old may implicate subclinical forms as a transitional condition which progressed during the years due to age-related phenomena, such as gradual incompetence of valves in spermatic veins \[^21\].

2. Effect on Testicular growth.

The matter of testicular size is quite important in pediatric and adolescent patients with varicocele, as far as testicular asymmetry is regarded the most dominant indication for varicocelectomy, considered as an alternative measurement of impaired spermatogenesis \[^22\]. According to Zampieri et al, subclinical varicoceles may result in growth arrest, highlighting the significance of condition in this subgroup of patients \[^23\]. In adults, Zini et al reported that the presence of left subclinical varicocele was accompanied with decreased testicular volume and asymmetry \[^24\]; Chen also mentioned decreased total testicular volume in patients with the condition, placing them in risk of subfertility \[^25\]. On the contrary, Akcar et al observed that the presence of a subclinical form was not associated with testicular hypotrophy in the affected side \[^26\], whereas some other authors also share the same conclusion \[^27\]. Finally, in another study, subclinical vari-
Varicocele, neither left nor right was crucial in determining differences in size between the testicles [27].

3. Oxidative stress and subclinical varicocele.

The theory of oxidative stress seems to be the most insightful hypothesis regarding the role of varicocele in impaired spermatogenesis; the presence of varicocele render men prone to DNA damage [28], whereas it is associated with elevated levels of oxidative stress in sperm; the surgical correction acts not only therapeutically, improving DNA quality by decreasing DNA fragmentation, but also as a preventive measure against the progressive character of the disease [29,30]. In case of subclinical varicocele, several studies at molecular and cellular level have noted similar effect on sperm biology. First of all, elevated levels of biomarkers of oxidative stress, such as malondialdehyde (MDA) and 8-hydroxydeoxyguanosine (8-OHdG) in association with a significant increase in the percentage of DNA fragmentation, are noted in patients with subclinical varicocele; in addition, elevated levels of a specific chemokine related to endothelium inflammation and sperm motility, called fractalkine, has been observed in infertile patients with subclinical varicocele [31]. According to the same panel of researchers, a marked decrease of total antioxidant capacity (TAC) accompanied with low level leucospermia, constitutes an impaired background for subfertility [32]. Furthermore, Chen and Chiu, have also observed elevated levels of 8-OHdG in semen of patients with subclinical varicocele, especially in cases that specific polymorphisms coexist in the gene which encodes enzyme 8-oxoguanine DNA N-glycosylase (hOGG1), an enzyme which actively excises 8-OHdG; in this specific subgroup of patients, lower mitochondrial DNA copy numbers in spermatozoa (which is correlated with motility) and lower TAC in seminal plasma seem to contribute to subfertility [32]. In another study, patients with clinical and subclinical varicocele is reported to have similar, poor levels of DNA quality, reflecting a low antioxidant capacity [35]. However, some studies have not justified a connection of subclinical varicocele with oxidative stress; Koksal et al reported that levels of MDA in testicular tissue in infertile patients with subclinical varicocele were similar to those without varicocele, whereas advanced clinical grades, especially grade 3 varicoceles carried the most significant changes [36]. In a similar manner, Yoon et al demonstrated that levels of reactive oxygen species (ROS) in the internal spermatic vein in patients with subclinical varicocele did not differ significantly comparing to patients with no varicocele, whereas clinical grades bore significantly higher levels [37]. Finally, Steger et al demonstrated no differences in DFI and MDA between fertile controls and patients with subclinical varicocele, with no deterioration noted in a follow up of 6 months, questioning the necessity of surgery in this group of patients [38].

D. INTERVENTIONAL MANAGEMENT OF UNILATERAL DISEASE.

1. In Favor of correction.

Several studies have highlighted the efficacy of subclinical varicocelectomy in the improvement of fertility status and the increase in pregnancy rates. Marsman et al, curing surgically infertile men with subclinical varicocele demonstrated equal pregnancy rates to clinical varicocelectomy (39.1% vs 42.5%, respectively), questioning the necessity of distinguishing clinical from subclinical forms [39]. Surgical treatment was also deemed as the best management by Seo et al, achieving much higher pregnancy rates than drug therapy or observation [40], whereas Cantoro et al also succeed quiet satisfactory pregnancy rates after embolization (56.3% vs 11.8% in observation group) [41]. Pierik et al reported a significant improvement in motility in patients who had been undergone subclinical varicocelectomy [42], whereas Dhabu-wala concluded that the beneficial effect on pregnancy rates surpass even the benefit of clinical varicocelectomy; therefore, the authors mentioned the crucial role of ultrasound in diagnosing subclinical forms in infertile men [42]. Finally, more recently, some authors concluded
that the microsurgical correction of subclinical forms may improve significantly the total motile sperm count in infertile patients and enable couples to follow a less complex assisted reproduction method or even achieve natural pregnancy [43].

2. **Against correction.**

On the other hand, Yamamoto et al demonstrated that surgery in the subclinical varicocele did not offer any benefit, as far as pregnancy rate was lower than simple observation (6.7% vs 10%) [44]. Similarly, Jarow et al reported that outcomes regarding semen parameters after subclinical varicocelectomy are disappointing, as far as an equal amount of patients may suffer from deterioration of the fertility status postoperatively [45]. Moreover, Unal et al reported that outcomes from surgery regarding pregnancy rates were low and marginally better comparing to drug therapy and concluded that a more effective modality has to be investigated [46]. Finally, in another study, Donkol et al reported that improvement from varicocelectomy was in favor of clinically palpable veins, which exhibit a shunt grade of reflux and were found bilaterally, comparing to subclinical varicocele (36.6% vs 16%, respectively [47].

E. **INTERVENTIONAL MANAGEMENT OF BILATERAL, LEFT CLINICAL – RIGHT SUBCLINICAL VARICOCELE.**

The hypothesis that varicocele is a bilateral disease has been proposed by several authors; incidence of bilaterality is ranging from 46% to 78%, with the majority of right side to be subclinical, i.e. diagnosed by ultrasound of other modalities [48], whereas the impact on spermatogenesis seems to be valuable [49], [50]. Such a fact may add excess importance since conclusions arisen from experimental studies have shown that even left, unilateral varicocele might undermine function of both testicles [51]. This pattern, left clinical-right subclinical varicocele seems to make up a distinct subgroup and the results of a recent, randomized study are quiet encouraging regarding the improvement of semen parameters (sperm count, motility and morphology) and pregnancy rates; pregnancy rate in the bilateral group surged to 42.5% against only 26% to unilateral group, highlighting the superiority of the bilateral correction [52]. Previous reports have also demonstrated satisfactory outcomes with bilateral varicocelectomy, but no significant superiority of the bilateral procedure compared to left, unilateral varicocelectomy [53]. All in all, a recent meta-analysis of four randomized studies concluded that bilateral varicocelectomy was accompanied with better results regarding progressive motility, morphology and pregnancy rates in comparison to unilateral varicocelectomy alone [54]. The number of clinical trials was small, but this seems to be the most reliable evidence; the right subclinical varicocele should not be left untreated.

F. **ROLE OF PHARMACEUTICAL THERAPY**

Zampieri et al, borrowing the idea by the management of other conditions of chronic venous insufficiency, administered bioflavonoids in pediatric patients with subclinical varicocele, observing that progression to clinical varicocele could be impeded to some degree, whereas some cases could even be regressed; however, bioflavonoids had no protective action against testicular growth arrest, and thus the necessity of surgical correction did not reduced, as far as testicular asymmetry remains the dominant indication of intervention in this subgroup [23]. In a study by Unal et al, the administration of clomiphene citrate in infertile patients with subclinical varicocele did not statistically increase sperm density and motility, whereas the pregnancy rate was low; thus, no recommendation in favor of conservative treatment could be made [46]. Finally, Seo et al observed that the administration of L-carnitine resulted in a statistically higher pregnancy rate versus observation strategy (34.5% vs 28.7%) in infertile patients with subclinical varicocele; however, no significant improvement was noticed in semen parameters, whereas varicocelectomy was found superior in these patients [40].

G. **CONCLUSIONS**

To sum up, the role of subclinical varicocele in male infertility is rather blurred as far as discrepancies exist among researchers. However, some data indicate that the condition carry some significance and should not be overtaken. Firstly, the increased incidence in infertile patients, either unilateral left or accompanying a left clinical form as a right subclinical varicocele is involved in the pathogenetic pathway of oxidative stress, a major phenomenon in infertility, a fact that may broaden a new area of research regarding both pathogenesis and possible treatments. Thirdly, although
cumsitive results of studies do not exhibit no benefit on pregnancy rates yet in case of subclinical varicocelectomy alone, the benefit of subclinical varicocelectomy in case of the pattern left clinical-right subclinical is rather clear. Thus, the evaluation of the male infertility should include subclinical varicocele, as far as a significant amount of men will be benefited from the correction.

References


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