Evaluation of the Association of the Presence of Subclinical Varicocele with Subfertility in Men

Original Article

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ABSTRACT

Background: The negative impact of clinical varicocele on fertility has been thoroughly investigated. On the other hand, subclinical varicocele is a well-defined ultrasonographic finding and is more common than clinical varicoceles. It remains to be resolved wheather or not subclinical varicocele is a contributor to subfertility in men.
Purpose: To investigate a possible association between subfertility and subclinical varicocele in men.
Patients and Methods: After exclusion of cases with clinical varicocele; a total of 40 subfertile men were compared to 40 fertile men regarding standard semen parameters and scrotal ultra-sonography findings.
A scrotal ultrasonography was performed to measure testicular veins diameters at, erect position. Also, to detect the presence/absence of reversal of blood flow (regurge) > 1 second in testicular veins during Valsalva maneuver. Subclinical varicocele was diagnosed when testicular vein diameter was ≥ 2.5 mm with positive regurge. Cases with subclinical varicocele had the testicular veins' diameters correlated to the standard semen analysis parameters.
Results: There was significantly higher left and bilateral testicular vein(s) regurge and left sided subclinical varicocele in the subfertile group. Testicular veins diameters were not correlated to the standard semen parameters.
Conclusion: Subclinical varicocele should be considered as a possible etiological factor for subfertility in men.

Key Words: Male subfertility, male infertility semen, sperm, subclinical, varicocele.

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INTRODUCTION

Infertility affects about 7% of men. Despite the great progress in the diagnostic procedures, especially in the field of genetics, the etiology of infertility is still obscure in 50% of infertile men. So, diagnostic tools are crucial to identify the cause of infertility[1,2].

A major cause of male subfertitity is varicocele that is clinically diagnosed by physical examination. The relationship of clinical varicocele to subfertility in men has been thoroughly investigated[3-6]. Some researchers are still against the relationship of varicocele to subfertility3,however, significant studies clarified the negative impact of varicocele on standard semen parameters. Moreover, recent works shed light on the detrimental effects of varicocele on the molecular and ultrastructural features of sperm and the testicular microenvironment. Furthermore the positive impact of varicocele treatment on fertility has been evaluated in many studies [4-6].

The non-palpable enlargement of the venous plexus of the spermatic vein(s), only diagnosed by imaging techniques, is defined as subclinical varicocele, which are more common than clinical varicoceles. Noteworthy, subclinical varicocele is present in 44% and 60% of fertile and infertile men, respectively[7-9].

The relation of subclinical varicocele to subfertility in men is more controversial than that of varicocele. A debate is still going on regarding surgical treatment of the right sided subclinical varicocele accompanied left-sided clinical varicocele. Beneficial effects of treatment of subclinical varicocele, on semen parameters and fertility potentials, were revealed in several studies. Subsequently, many investigators are inclined to operate on the accompanying right sided subclinical varicocele, for that

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proven beneficial effects of the treatment[10- 13]. Although the subclinical varicocele is well-defined sonographically, in clinical practice, infertile men without palpable varicoceles are not referred for sonography. Besides, those with a subclinical varicocele are not routinely treated, despite having the scrotal US the very sensitive, non-invasive and inexpensive diagnostic technique.

This study aimed to investigate the association between the presence of subclinical varicocele and the subfertility in men.

PATIENTS AND METHODS

This cross sectional study was conducted in the period from April 2015 till June 2016. This research was designed to evaluate the presence of subclinical varicocele in subfertile men compared to fertile controls. Group 1 was designed to include 40 sub-fertile men, who had one or more abnormal standard semen parameter(s). Group 2 was designed to include 40 fertile men; each having fathered a child within the preceding year and had normal standard semen parameters.

After approval by the Andrology Board and the ethics committee, Faculty of Medicine, Cairo University, Egypt, informed consents were taken from eligible participants.

Sub-fertile and fertile men were subjected to history taking, general and genital examinations, including examination for the presence of clinical varicocele, provided two semen analyses, evaluated according to the World Health Organization guidelines 2010[14], and had ultrasonographic examination of the scrotal compartment.

Exclusion criteria were; history of exposure to gonadotoxins as chemotherapy, radiotherapy and/or pesticides, alcohol and/or illicit drug(s) intake, history of testicular torsion and/or testicular trauma, history of orchitis, prior or current surgical treatment for subfertility, female factor infertility and older female age (> 35). We also excluded cases with genetic disorders as Klinefelter's syndrome, presence of clinical varicocele, difficulty in the diagnosis of a clinical varicocele (e.g. presence of hydrocele, testis lies high up in the scrotum) and/ or leucocytospermia. Furthermore, fertile men with any abnormality in standard semen parameters, infertile men with normal standard semen parameters and/or men who had heterogonous testis on scrotal ultrasonography were excluded from the study.

Patients were advised to stand up for 5- 10 minutes to allow the varicocele to fill up prior to scrotal ultrasonography. A color Doppler ultrasound machine with a 10 MHz linear array transducer with a color flow mapping was used. A blind operator, to either group, screened participants, by scrotal ultrasonography, to measure testicular volume and testicular veins diameters, (erect position), and to detect the presence/absence of reversal of blood flow (regurge), of more than one second, in testicular veins, during Valsalva maneuver. Color Doppler ultrasound (CDU) defined the presence of subclinical varicocele in case that the testicular vein diameter was ≥ 2.5 mm with presence of regurged blood of more than one second [15,16].

Statistical analysis:

Data management and analyses were performed using Statistical Package for Social Sciences, version 21 (SPSS Inc., Chicago, IL, USA). Numerical data were summarized using range, means and standard deviations. Categorical data were summarized as numbers and percentages. Numerical data were explored for normality using Kolmogrov-Smirnov test and Shapiro-Wilk test. Comparisons between the two groups were done using the Student's t-test and Mann-Whitney test for normally and non-normally distributed numeric variables, respectively. Comparisons between groups, with respect to categorical data, used Chi Square test. Spearman's correlation coefficients were calculated to measure the strength of associations. All p-values were two-sided. P-values < 0.05 were set as significant.

RESULTS

The present study included eighty men with none palpable varicocele, 40 subfertile (group 1) and 40 fertile (group 2). Group 1 included 31 (77.5%) men with primary infertility and 9 (22.5%) men with secondary infertility.

The age ranged from 23 to 52 (mean 32.7 ± 7) years in group1 versus 23 to 53 (mean: 34.7 ± 7.4) years for group 2, with no significant statistical difference. The number of smokers was 16 (40%) and 18 (45%) in groups 1 and 2, respectively with no significant difference.

The left testicular size, sperm concentration and motility were significantly lower ($P< 0.001$) in group one. –Non-significant differences ($P> 0.05$) were found between groups regarding the right and left testicular vein diameters. The standard semen parameters, right and left testicular sizes and testicular veins diameters in groups 1 and 2 are shown in Table 1.

In group1; there were significantly higher left testicular vein regurge ($P= 0.025$), bilateral regurge ($P= 0.025$) and left sided subclinical varicocele (0.03). Table 2 presents the right and left testicular veins regurge and presence of varicocele in groups 1 and 2.

Testicular veins diameters were insignificantly correlated ($P> 0.05$) to the standard semen parameters. The correlations between right/ left testicular veins diameters and the standard semen analysis parameters in sub-fertile and fertile cases proven to have right/left subclinical varicocele(s) are shown in Table 3.

Table 1: Testicular sizes, semen parameters and diameters of the right and left testicular veins for sub-fertile/fertile groups

	Sub-fertile group		Fertile group		P value
	Mean	SD	Mean	SD	
Right testis size (mL)	15.1	2.2	16.1	1.9	0.047
Left testis size (mL)	13.8	2.6	16.1	3.1	<0.001
Semen volume (mL)	3.31	1.00	2.49	0.66	< 0.001
Sperm motility (%)	31.9	26.4	60.4	12.6	< 0.001
Sperm concentration million/mL	35.6	35.5	63.3	23.8	< 0.001
Abnormal forms (%)	36.1	29.2	17.8	7.0	0.006
Right testicular vein diameter (mm)	2.09	0.51	2.20	0.35	0.25
Left testicular vein diameter (mm)	2.43	0.65	2.34	0.75	0.14

Table 2: Right/left testicular vein(s) regurge(s) and presence of varicocele in sub-fertile/fertile groups (number= %)

	Sub-fertile group		Fertile group		P-value
	N	%	N	%	
Right testicular vein regurge	14	35.0%	12	30.0%	0.633
Left testicular vein regurge	23	57.5%	13	32.5%	0.025
Bilateral regurge	14	35.0%	7	17.5%	0.025
Right sided subclinical varicocele	6	15.0%	5	12.5%	0.745
Left sided subclinical varicocele	17	42.5%	8	20.0%	0.03
Bilateral subclinical varicocele	6	15.0%	3	7.5%	0.33

Table 3: Correlations of right/ left testicular veins diameters to the standard semen analysis parameters in sub-fertile cases/ sub-fertile and fertile cases proved to have right/ left subclinical varicocele(s)

	Sperm concentration		Sperm motility		Abnormal forms	
	R	P-value	R	P-value	R	P-value
Right testicular vein diameter (subfertile)	0.30	0.24	0.30	0.25	0.34	0.19
Left testicular vein diameter (subfertile)	0.34	0.19	0.38	0.14	0.46	0.07
Right testicular vein diameter (subfertile and fertile	0.19	0.34	0.22	0.26	0.29	0.27
Left testicular vein diameter (subfertile and fertile)	0.02	0.92	0.02	0.89	0.28	0.18

DISCUSSION

Subfertile men with clinical varicocele had a significant decrease in testicular size compared with fertile men[17]. In the current study, the subfertile group had a significantly smaller (P<0.001) left testicular size compared with the fertile group despite absence of clinical varicocele. The significant decrease of left testicular size was accompanied by a significantly higher (P= 0.025) left testicular vein regurge and significantly higher (P= 0.03) left sided subclinical varicocele. This may point to a possible local effect of the subclinical varicocele on testicular size supported by a previous study by Zini *et al* who, tried to determine the impact of left sided clinical and subclinical varicoceles on the loss of testicular volume [18]. Their study compared the right testicular volume to that on the left side among infertile men diagnosed with left sided clinical or left sided subclinical varicocele. Interestingly, they found that not only the clinical varicocele but also the subclinical varicocele was associated with left testicular volume loss[18].

Clinical varicocele is thought to increase testicular temperature and is commonly associated with male subfertility[17]. Rao *et al*[19]demonstrated deleterious effects of transient scrotal hyperthermia on spermatogenesis. Such negative effects were serious, but reversible, possibly mediated through an oxidative stress.

In this study, the presence of left sided and bilateral testicular vein(s) regurge(s) were significantly higher in the subfertile group. Testicular veins regurged blood had a higher temperature than the intra-scrotal temperature.

Whether the regurged-blood may be a cause of intermittent testicular hyperthermia enough to herald the fertility potential in men with left sided subclinical varicocele, is an issue worth study.

In the present work, although subfertility in men was associated with subclinical varicocele, the testicular veins' diameters were not significantly correlated (P > 0.05) to the standard semen parameters. This can be explained on the basis of recent studies that shed light on the varicocele detrimental effects on the molecular and ultra-structural features of sperm and the testicular microenvironment[4]. Agarwal *et al*[20], for the first time, identified differentially expressed proteins (DEP) with distinct reproductive functions extracted from spermatozoa4 of men. The DEP were altered in infertile men with bilateral varicocele, and

so bilateral varicocele-associated infertility in men can be due to changes of DEP. Moreover, a human morphologically normal spermatozoon may have non-condensed chromatin[21]. Accordingly, we recommend further research to investigate whether subclinical varicoceles have roles in unexplained subfertility.

Does subclinical varicocele contribute to subfertility? The answer to this question may help to discover/find an obscure etiology of subfertility in men. Moreover, it can improve the fertility potential with repair of the subclinical varicoceles. On the other hand, unnecessary interventions to the subclinical varicocele should be obviated in case it is not contributing to subfertility.

CONCLUSION

Subfertility in men may be associated with the presence of left sided subclinical varicocele recommending the consideration of subclinical varicocele as a possible etiology for subfertility in men.

CONFLICT OF INTEREST

There are no conflicts of interest.

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