

## Relation of the varicocele duration and infertility to the outcome of varicocelectomy in terms of changes in sperm motility and pregnancy rates

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### ABSTRACT

**Background:** Clinically varicocele (VCL) is defined as tortious dilation of the pampiniform venous plexus. Anatomically it includes the area between the testis and the final venous drainage which comprises pampiniform plexus, inguinal, and testicular veins. An important complication of advanced VCL is male infertility in 15-20% of cases. VCL is a correctible cause of male infertility. Pathophysiological consequences of VCL on the testes are variable from one person to another in deteriorating quantity, motility, and morphology of sperms.

**Aim:** In this study, VCL complication consequences on sperm motility had been studied and concentrated as one of the most important fertilizing factors, in order to set a correct reversing time for the VCL effects on the testes.

**Material and methods:** This clinical study was carried out in 3 years, from march 2016 to April of 2019, In which (86) male varicocele-related infertility cases were collected in whom (54) primary and (32) secondary infertility cases.

Seminal fluid analyses were performed intervalley every three months pre and postoperatively. Hormonal assays included serum (FSH, LH, Testosterone, Prolactin, and TSH).

The VCL patients were grouped according to VCL dependent infertility duration into three groups:

1st group or early (less than one year). 2nd group or middle stage (less than two but more than one year). 3rd group or late stage (more than two years). All had been managed by operations (laparoscopic or open inguinal) and ± supplementary antioxidant medicines. Follow-up then continued for 18 months after treatment.

**Results:** overall response of conceiving was 39.5%, in Group 1, while 56% of the response was recorded in Group 2, and 31.42% in Group 3.

Subclinical group got 50% of the recovery. In the laparoscopic class, 20% bilateral varicocele was observed during the operation. In 8 (9.4%) patients of G2 and G3, subnormal testosterone levels were observed to reverse after the operation.

**Conclusion:** The presence of varicocele is directly associated with congestion and a back-pressure effect on the testes, and the longer duration of varicocele with the majority of spermatic veins is associated with epididymal destructive changes moreover to testicular tissues. Consequently, more irreversible bad spermatic parameters were observed due to more aggressive testicular and epididymal endothelial damage.

**Keywords:** VCL (Varicoceles), Sperm Motility, Infertility.

## علاقة مدة دوالي الخصية والعقم بنتائج استئصال دوالي الخصية من حيث التغيرات في حركة الحيوانات المنوية ومعدلات الحمل

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## الخلاصة

**الخلفية:** يتم تعريف دوالي الخصية سريريًا على أنها تمدد ملتوي للضفيرة الوريدية الشكل. من الناحية التشريحية، يشمل المنطقة الواقعة بين الخصية والتصريف الوريدي النهائي الذي يشتمل على الضفيرة العضدية والأوردة الإربية والأوردة الخصية. أحد المضاعفات المهمة لمرض دوالي الخصية المتقدم هو العقم عند الذكور في ١٥-٢٠٪ من الحالات. دوالي الخصية هو سبب صحيح للعقم عند الذكور. تختلف العواقب الفيزيولوجية المرضية للدوالي على الخصيتين من شخص لآخر في تدهور كمية الحيوانات المنوية وحركتها وشكلها.

**الهدف:** في هذه الدراسة تمت دراسة آثار مضاعفات دوالي الخصية على حركة الحيوانات المنوية وتركيزها كأحد أهم عوامل التخصب، وذلك من أجل تحديد زمن عكس صحيح لتأثيرات الدوالي على الخصية.

**المواد طرق العمل:** تم إجراء هذه الدراسة السريرية في ٣ سنوات، من مارس ٢٠١٦ إلى أبريل من عام ٢٠١٩، حيث تم جمع (٨٦) حالة عقم مرتبطة بدوالي الخصية من الذكور منهم (٥٤) حالة عقم أولية و (٣٢) حالة عقم ثانوية. تم إجراء تحليلات السائل المنوي كل ثلاثة أشهر قبل وبعد العمل الجراحي. وشملت الاختبارات الهرمونية المصل (هرمون تحفيز الجريبات، التستوستيرون، البرولاكتين، والهرمون المحفز للغدة الدرقية). تم تجميع مرضى دوالي الخصية وفقًا لمدة العقم المعتمدة على الدوالي إلى ثلاث مجموعات:

المجموعة الأولى أو المبكرة (أقل من سنة واحدة). المجموعة الثانية أو المرحلة المتوسطة (أقل من سنتين ولكن أكثر من سنة). المجموعة الثالثة أو المرحلة المتأخرة (أكثر من عامين). تم علاج جميع هذه الحالات عن طريق العمليات الجراحية (بالمناظر أو الأربية المفتوحة) والأدوية المضادة للأكسدة التكميلية. ثم استمرت المتابعة لمدة ١٨ شهرًا بعد العلاج..

**النتائج:** بلغت نسبة الاستجابة الإجمالية للحمل ٣٩.٥٪ في المجموعة الأولى، بينما سجلت ٥٦٪ من الاستجابة في المجموعة الثانية، و ٣١.٤٢٪ في المجموعة الثالثة. حصلت المجموعة تحت السريرية على ٥٠٪ من نسبة الشفاء. في فئة المناظر، لوحظ وجود ٢٠٪ من دوالي الخصية الثنائية أثناء العملية. في ٨ (٩.٤٪) من مرضى المجموعة الثانية والثالثة، لوحظ انعكاس مستويات هرمون التستوستيرون دون الطبيعية بعد العملية.

**الاستنتاج:** وجود دوالي الخصية يرتبط بشكل مباشر بالاحتقان وتأثير الضغط الخلفي على الخصيتين، كما أن المدة الأطول لدوالي الخصية مع غالبية الأوردة المنوية ترتبط بالتغيرات المدمرة للبربخ وأنسجة الخصية. ونتيجة لذلك، لوحظت المزيد من المعلمات المنوية السيئة التي لا رجعة فيها بسبب الضرر الأكثر عدوانية في الخصية والبربخ البطانية.

**الكلمات المفتاحية:** دوالي الخصية، حركة الحيوانات المنوية، العقم.

## INTRODUCTION

Varicocele is one of the predominant causes of infertility as the latest study on the distribution of diagnostic categories in a group of infertile men attending male infertility found that varicocele formed 629 of a total of 2383 cases (26.4%) of male infertility treatment<sup>1,2</sup>.

pathologically, varicocele has been defined as the venous dilatation that causes incompetence and then allows pathological reflux of blood to the internal spermatic vein (testicular vein)<sup>1-3</sup>.

The range of vein pathological changes is variable, but it usually involves dilatation of the internal spermatic veins to the level of the final drainage into the left renal vein or the inferior vena cava. Vascular dilatation may be caused by:

1. Valvular incompetence of the internal spermatic veins<sup>4-6</sup>.
2. Mechanical pressure by superior mesenteric artery syndrome ('nutcracker' phenomenon) on the left renal vein<sup>7</sup>.
3. Although practically in most of the cases left varicocele is predominant but in an autopsy study Absence of valves is detected in 40% of the left and 23 % of right spermatic veins, respectively, which explains the predominance of

left-sided varicoceles<sup>8</sup>. There are other concealed factors that play a role moreover to VCL's negative consequences as there are males with varicoceles that are fertile, but others have sperm that is compromised in function morphology, numbers, or motility<sup>5,6,8</sup>.

4. Elevated hydrostatic pressure in the internal spermatic veins normally or pathologically.
5. Pelvic and muscular defects in the wall of the veins<sup>9-15</sup>.

Varicocelectomy is the ligation of the dilated vein by surgery or microscopic embolization, it's by far the most commonly performed surgery for the treatment of male infertility. The goal of treatment of the varicocele is to ligate the refluxing congesting venous drainage to the testis while maintaining arterial and lymphatic supply to restore normal physiological blood flow to the testes, subsequently at least 50% of patients may return to be fertile<sup>8-11</sup>. Subjective experiences showed a familial inherited genetic pattern. The hot climate and occupational and long-term intense physical activity deteriorated semen quality in men with varicocele<sup>16-19</sup>.

**PATIENTS AND METHOD**

This study was carried from march 2016 up to march 2019, included 86 males of (54) primary and (32) secondary infertile patients diagnosed with varicocele. The main abnormality dealt with was asthenospermia by three intervals of basal seminal fluid analysis (BSA). The ages of the patients were between 27-46 years. Related hormonal assays were routinely performed including serum (FSH, LH, Testosterone, and Prolactin). First, the patients were grouped into mild, medium, and severe grades of varicoceles depending on clinical evidence and the degree of venous dilatation with associated reflux by colored Doppler ultrasonography<sup>2-4,7,8</sup>.

In this study, patients with VCL were grouped according to infertility duration and motility disorder into early (less than one year) patients with asthenospermia above 20% activity but below 35% motility., 2nd group (more than one year but less than three) in this group, the motility arranged between (20-25) %, and the third group (more than three years) motility (20-25%) swinging with treatment up and down. Follow-up then continued for one year after treatment. The recurrent varicoceles are excluded from the study. For statistical analysis, a one-way ANOVA test, or so-called one-way analysis of variance is used between groups and degrees of varicocele with a p-value of < 0.001.

**RESULTS**

The distribution of the cases shown according to the groupings was as in (Table 1). While the distribution of the cases according to the grading was seen in (Table 2). The types of operations applied are shown in (Table 3). While the success rate of getting pregnancy after varicocelectomy between 1-3 years period shown in (Table 4). In Figure 1 the seminal fluid analysis of two brothers with infertility problems, in which the grade of the second sample was more advanced than the first who was in grade 1.

Table 1: Distribution of the cases according to groupings.

Types	Total	Group 1	Group 2	Group 3	subclinical	+ Family history
Primary infertility	54	24	13	14	3	12
Secondary infertility	32	13	10	7	2	5

Table 2: distribution of the cases according to the grading.

Clinical	Total	Grade I	Grade II	Grade III	Subclinical
Primary infertility	54	12	28	11	3
Secondary infertility	32	14	6	10	2
<b>Total</b>	<b>86</b>	<b>26</b>	<b>34</b>	<b>21</b>	<b>5</b>

Table 3: distribution of the cases according to operation types.

Operation type	1ary infertility	2ary infertility	Bilateral varicocele	supportive medicines	No supportive medicines
Inguinal	23	21	4	16	19
Subinguinal	14	6	3	6	18
Laparoscopic	15	3	4	9	6
Mixed	2	2	2	4	0

Primary cases managed both by open and laparoscopy (Figure 2) ± supplementary treatments with nearly equal results, all of the secondary varicocele managed by inguinal approach and supplementary treatment with acceptable results. The supplementary treatment is used in 14 patients, which were Daflon 500 mg (Diosmin plus 50 mg hesperidin) tablets in doses of two tablets daily for 2 months twice daily, ± Tamoxifen 20 mg/day), and in 30 patient various other antioxidants were used for 3-6 months. The positive response of the added supplementary group was observed in 9 (18%) cases of secondary infertility patients 14(43.7%) patients had previous difficult conception histories. All the hormonal assays were within normal ranges except for (16) cases that had hyperprolactinemia (Serum prolactin levels were > 15.3microgram /dL).

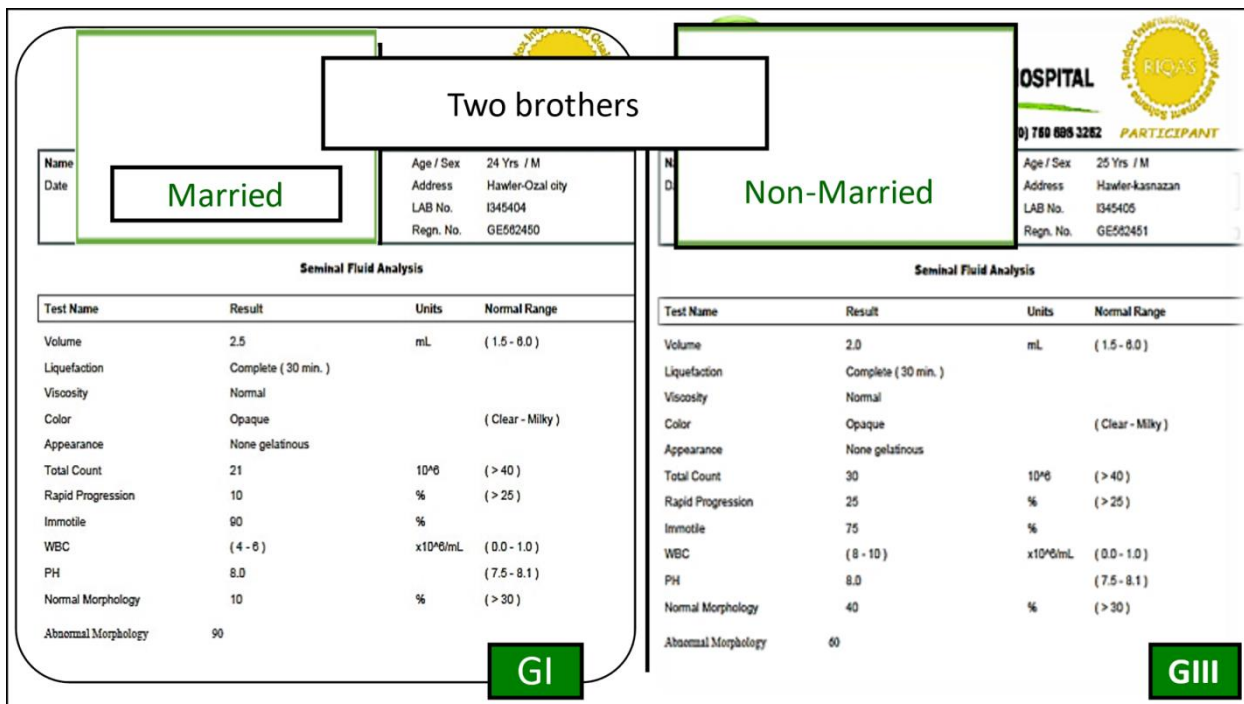


Figure 1: Comparison results of SFA parameters of two brothers with various grades.

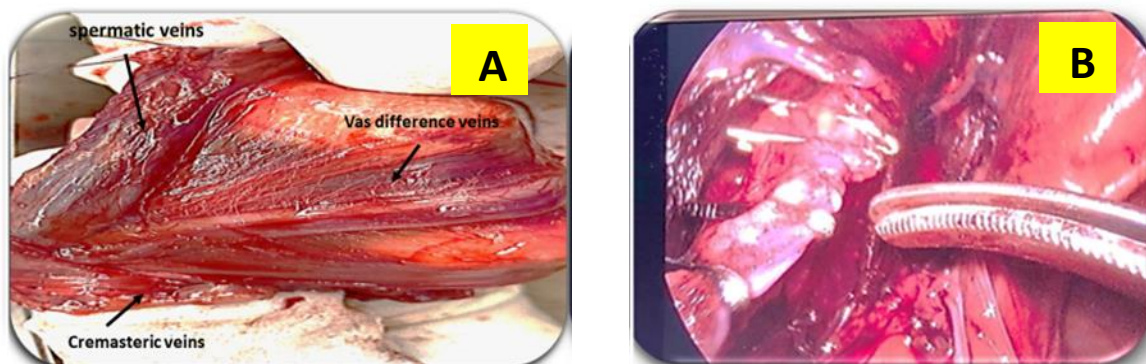


Figure 2: both open and laparoscopic varicocelectomy. A: Subinguinal Varicocelectomy, B: Laparoscopic Varicocelectomy/ Three ports infra umbilical.

Significant changes observed (Table 4) with varicocele were sperm parameters changes and mainly asthenospermia found in whom motility of the sperms was less than 35% (P<0.001).

In a total of (32) cases where laparoscopically managed only (4) 20% of them were observed to have bilateral varicoceles during operation. While by open varicocelectomy (7) cases were bilateral, so total (12.8%).

Table 4: Results of motility changes and fertility achieved after treatments.

Patients Number	GP1	GP2	Gp3	Grading	Motility	Duration months	pregnancy	Percent	P Value
21	18	3	0	G1+2 + 3	> 35%	3	15	71.43	<0.001*
27	10	15	2	G1+2+3	>35%	3-6	16	59.3	
21	2	5	4	G1+2+ 3	>35%	3-12	3	21.4%	
25	1	6	18	G1+2+ 3	< 20%	24	0	0%	
Total	31	29	26	86	< 40	3-12	34	39.5	

\*ANOVA TEST between groups pregnancy rate

## DISCUSSION

### Testicular Histopathological Consequences of VCL:

According to previous studies, all the pathological consequences of VCL on the testicular tissues and cells are described by many studies, including seminiferous tubules, germinal cells, Sertoli cells, Leydig cells, or sustentacular cells, testicular blood barrier, and eventually on the sperm cells which may be interpreted by interferences with the sperm cells mitosis and meiosis. Accordingly, the truth of the productive abilities of the affected testis is greatly reduced which is translated by sperm parameter changes in the basal spermatic fluid analysis. In this study like others VCL was a predominant cause of infertility. Varicoceles formed 35- 45% of the causes of male primary infertility and affect 45 to 81 percent of men with secondary infertility, as the bulk of male factor infertility increased rather than female in the last studies, accordingly, the varicocele percentages increased proportionally to the other causes<sup>1, 2, 4</sup>.

Testicular atrophy and a risk factor for hypogonadism, are the last relevant complications of VCL<sup>5-10</sup>.

These risks will be doubled when there are bilateral VCLs are far more common (80% to 90%) in the left testicle. In this study 12.8% of cases showed bilateral varicoceles, this finding was also mentioned by other studies with variable incidences, with up to 30% to 40% probability of bilateral conditions recorded<sup>3, 4, 8, 11, 12</sup>.

Another cause of subfertility in varicocele patients is excessive ROS (reactive oxygen species) is associated with sperm DNA fragmentation due to Testicular blood barrier damage<sup>11-14, 20-22</sup>, and this explains the severely affected sperm parameters in non-reversible cases of infertility group III. Accordingly, the testicular venous back pressure leads to testicular congestion, moreover to cremasteric veins of the vas and epididymis<sup>10, 12, 16, 28</sup>.

In our study, a number of (6) used to work in crude oil fields and refineries complained of varicoceles, which drives with other studies that assumed the sperm damage to excess heat is caused by increased oxidative stress and toxic materials on the sperm from blood pooling causing reduced oxygenation, direct hydrostatic pressure injury effects on the testis, toxin formation, hypoxia, and autoimmunity<sup>8, 10, 12, 15, 29, 30</sup>.

Toxic metabolites from kidneys and adrenals including cadmium blamed for the exaggeration of the testicular conditions moreover to other toxic materials as this situation observed in (GIII) long-standing VCL even not responded to treatment<sup>28-34</sup>.

Regarding asthenospermia, some of the authors favor the decreased sperm nuclear DNA integrity which has been linked to reduced sperm motility, viability, counts, and abnormal morphology<sup>6, 10, 13-15</sup>.

Another study by (Luna Samanta et al 2018) showed that impaired mitochondrial structure and function in varicocele may lead to oxidative stress, reduced ATP synthesis, and sperm dysfunction<sup>30</sup>. By the discussed points which had been mentioned above all the studies approve that advanced VCLs consequences will be directly translated on the motility of the sperm and accordingly, we depend on this parameter in our study rather than the number and form of sperms.

### Epididymal Changes with Varicocele

It is a well-established previously studied fact that the final stages of sperm maturation and motility are initiated and completed in the various parts of the epididymis (the initial segment, the caput, corpus, and cauda epididymis). Each part has its own specialized functions including toxic fluids elimination, mobilization, nutrition, and maturation. Accordingly, may be some of (GII) and most of (GIII) of this study had one or more constituents of the epididymal pathological changes due to VCLs, the damages occurred in the epididymis are either fairly treatable or even irreversible, and that was the state with most of the GIII cases of our study. In an experimental study on rats, a positive correlation was found between epididymal endothelial damage and the duration of varicocele accordingly, earlier treatment reduces this damage<sup>15, 16</sup>.

In a study by Wei Zhou, et al (2018) the authors concluded that the epididymal environment is crucial for sperm maturation and supporting their storage. Indeed, since sperm are transcriptionally and translationally silent cells, their functional transformation relies entirely on the creation and maintenance of a highly specialized epididymal luminal milieu. This unique epididymal microenvironment is controlled by endothelial lining cells of ducts<sup>15, 17, 27, 28, 32, 33</sup>.

Compositional analysis of the luminal fluids collected from the epididymis of a variety of species has revealed the complexity of this milieu, with a diversity of inorganic ions, proteins, and small non-coding RNA transcripts having been identified to date<sup>15, 27</sup>. Moreover, with longer-lasting varicoceles, the testicular immune response, including the production of anti-sperm antibodies and inflammatory factors, activation of inflammatory pathways, and destruction of the testicular blood barrier may be involved in the pathogenesis of varicocele mediated by epididymis<sup>17, 25-27, 31, 34</sup>.

In another study testicular blood barrier damage and anti-sperm antibody formation are claimed to be the epididymal pathological response to the abnormal quality of sperms delivered to it from the testes<sup>13,18,19</sup>. Our study with corrugation with other studies proved that early varicocele repair is the only way to reverse all early pathological consequences of VCLs and to stop further advanced VCL-related consequences on the fertility of men<sup>22-24</sup>.

## CONCLUSION

The results of this study support and recommend early correction of varicocele by any method has better curative results for infertility due to less irreversible testicular and epididymal damage, accordingly the longer duration of epididymal damage will lead to irreversible stages. From the results recorded above, we assume that longstanding VCLs-related severe asthenospermia, in spite of its degree, less will be responded to operations for the provocation of sperm and fertility.

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