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Varicocele As A Risk Factor For Male Infertility: A Clinical And Epidemiological Study

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Abstract
Varicocele is one of the most common factors of male infertility, affecting sperm quality and reproductive potential. The purpose of this clinical and epidemiological study is to evaluate the incidence of varicocele among men with infertility, including clinical and subclinical forms, and to identify their effect on spermogram parameters, DNA fragmentation, and hormonal profile. The study involved 200 men with infertility and 100 control participants with normal fertility. The diagnosis of varicocele was carried out using physical examination and ultrasound examination with color Doppler mapping. The results showed that varicocele was detected in 66% of patients with infertility, including 18% with a subclinical form. Varicocele was associated with a significant decrease in sperm concentration, motility, and morphology, as well as an increase in the DNA fragmentation index. Hormonal changes indicated a functional strain on the reproductive system. The data obtained confirm the need for a comprehensive diagnosis of varicocele, including subclinical forms, for effective management of patients with male infertility.
Keywords: *varicocele; male infertility; subclinical varicocele; spermogram; fragmentation of sperm DNA; hormonal profile; ultrasound; dopplerography; reproductive function*

INTRODUCTION

Male infertility is one of the most urgent medical and social problems of modern healthcare. According to estimates by the World Health Organization (WHO), up to 15-20% of couples of reproductive age face difficulties conceiving, while in 40-50% of cases the cause lies in the pathology of the male body. Varicocele, varicose veins of the spermatic cord, is considered one of the most common and potentially treatable factors of male infertility. The prevalence of varicocele among the general male population is about 15%, while in men with fertility disorders this figure reaches 35-40% or more. This indicates a potentially significant role of this condition in the pathogenesis of male infertility. Pathology can occur in both clinical and subclinical forms, the latter often remains undiagnosed in daily urological practice. At the same time, subclinical varicocele can have no less pronounced negative effects on spermatogenesis than the manifest form, especially in patients with concomitant metabolic or hormonal disorders. The lack of pronounced symptoms and low awareness among general practitioners and even urologists leads to late diagnosis and, as a result, loss of time for effective therapy [1].

In addition, the question remains the subject of scientific discussion: is varicocele the cause of infertility or just a concomitant condition? A number of studies confirm the improvement of spermatogenesis and an increase in the probability of conception after surgical correction of varicocele, which strengthens the arguments in favor of its pathogenetic significance. However, other publications indicate a weak correlation between the severity of varicocele and disorders of spermatogenesis, especially in cases of subclinical forms, which requires further epidemiological and clinical analysis.The clinical form of varicocele is diagnosed by physical examination and / or ultrasound with Dopplerography, usually accompanied by palpable or visualized varicose veins of the pelvic plexus. Subclinical varicocele, on the contrary, is not detected by examination, but can be detected by ultrasound in horizontal and vertical positions with a Valsalva sample. Different studies give different estimates of the prevalence of the subclinical form: from 5 to 25% in men with normal sperm parameters and up to 30-40% in men with idiopathic infertility [2].

The relationship of varicocele with other reproductive disorders is also of interest. A number of studies show that men with varicocele have a significantly higher risk of pathozoospermia, oligozoospermia and asthenozoospermia. Increased content of reactive oxygen species (ROS) in semen, decreased antioxidant activity, fragmentation of sperm DNA — all this is typical for men with varicocele and may be a pathophysiological substrate of impaired fertility [3].

Understanding the pathophysiological mechanisms by which varicocele affects male fertility is key to understanding the clinical significance of this pathology. Although the exact pathogenetic pathways are still being studied, several biological processes have been identified that play an important role: testicular thermoregulation disorders, venous stasis and hypoxia, oxidative stress, hormonal disorders, and damage to sperm DNA. These mechanisms, as a rule, act in a complex, potentiating a general negative effect on spermatogenesis. One of the most studied mechanisms of the negative effect of varicocele is an increase in temperature in the scrotum and testicles. Under normal conditions, the temperature of the testicles is maintained 2-4 °C below body temperature, which is critically important for normal spermatogenesis. Varicose veins of the lozoid plexus lead to a decrease in the effectiveness of thermoregulation: a retrograde flow of venous blood warmed in the abdominal cavity occurs in the direction of the testicles. An increase in local temperature by 0.6–1.0 °C, recorded in varicocele, has an inhibitory effect on Sertoli and Leydig cells, reducing the production of sperm and testosterone [4].

Studies based on thermography confirm that the scrotal skin temperature in patients with varicocele is significantly higher than in healthy men. These data are especially significant for subclinical forms of varicocele, in which there are no palpatory signs, but temperature changes are already present, indicating a latent pathogenetic effect [5].

Venous hypertension and venous stasis lead to impaired blood drainage from the testicle, which in turn causes tissue hypoxia. Chronic insufficiency of blood supply disrupts the metabolism of seminal epithelial cells, in particular Sertoli cells, which leads to apoptosis and a decrease in synthetic activity. Moreover, hypoxia contributes to the accumulation of lactic acid and changes in the pH of the tissue, which additionally inhibits spermatogenesis [6].

It has also been found that varicocele increases the expression of hypoxically induced factors (HIF-1a), which trigger a cascade of proapoptotic and inflammatory reactions. Animal model studies confirm that experimentally induced varicocele causes severe microcirculation disorders and ischemic changes in testicular tissue as early as 2-4 weeks after induction [8].

One of the most destructive mechanisms linking varicocele with impaired fertility is oxidative stress, an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant system. In patients with varicocele, especially in advanced stages, the level of ROS in the ejaculate is significantly higher than in the control, and the antioxidant activity of the plasma is reduced [9].

Reactive oxygen species damage the lipids of the cell membranes of spermatozoa, disrupting their mobility and morphology. Moreover, oxidative damage to sperm DNA is one of the key factors in decreased fertility, as it leads to apoptosis, impaired replication, and decreased embryo quality. Modern DNA fragmentation tests show a significant increase in the level of damaged spermatozoa in men with varicocele, even with normal sperm counts. This highlights the need for a more in-depth examination of such patients [10].

Varicocele is also associated with hormonal homeostasis disorders, especially in severe forms of the disease. Disruption of the function of Leydig cells under the influence of hypoxia and temperature leads to a decrease in testosterone production. This, in turn, causes a compensatory increase in the levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). However, with long-term varicocele, secondary hypogonadism may develop, in which pituitary regulation is ineffective [11].

In addition, hormonal disorders can manifest themselves subclinically: the level of total testosterone may remain within the normal range, but bioavailable testosterone decreases, which affects sexual function, libido and fertility. These effects are especially pronounced in patients over 30 years of age, which highlights the need for early diagnosis and treatment of varicocele [12].

Varicocele can induce local inflammatory changes and the formation of antisperm antibodies. Damage to the blood-testicular barrier leads to contact of spermatozoa with elements of the immune system, which triggers autoimmune processes. Antisperm antibodies disrupt the motility and interaction of spermatozoa

with the egg, which reduces the likelihood of natural conception. The level of such antibodies in patients with varicocele is significantly higher than in healthy men, especially in cases of long-term ongoing disease. Some authors also emphasize the involvement of pro-inflammatory cytokines (TNF-α, IL-6) in pathogenesis, which can enhance oxidative stress and tissue damage. These factors are relevant for both the clinical and subclinical forms of varicocele [13].

DNA fragmentation is one of the most advanced and accurate biomarkers used to assess sperm quality. It was found that in men with varicocele, the DNA fragmentation index (DFI) is significantly higher than in the control group. Even in men with normal spermogram parameters, fragmentation can reach 30-40%, which is associated with low chances of natural conception and a decrease in the effectiveness of assisted reproductive technologies (ART) [14].

In addition, modern studies reveal epigenetic changes in the spermatozoa of patients with varicocele, for example, hypomethylation of certain genes involved in embryogenesis. Such modifications can be passed on to offspring and have an impact on their health, which increases the importance of timely diagnosis and treatment. It is important to note that all of the above mechanisms most often act not in isolation, but mutually reinforcing each other. For example, hypoxia increases oxidative stress, which in turn damages DNA and disrupts hormonal regulation. This multiplicity of pathogenetic pathways explains why one patient may experience a severe decrease in fertility even with grade I varicocele, while another with grade III varicocele has satisfactory spermatogenesis [15].

The most important task is the standardization of diagnostic approaches and the introduction of highly sensitive imaging techniques into routine urological practice.

The present study is aimed at assessing the frequency of varicocele (including subclinical) in men with infertility, analyzing its pathogenetic role and association with parameters of spermatogenesis, hormonal status and fragmentation of sperm DNA.

MATERIALS AND METHODS

The present study is a single-center, prospective, clinical and epidemiological study conducted in the Department of Urology/Andrology between September 2023 and August 2024.

The study included men aged 20 to 45 years who sought counseling for infertility, defined as the absence of conception during ≥12 months of regular sexual activity without contraception.

Inclusion criteria:

- Age from 20 to 45 years;
- Primary or secondary infertility in the couple (in the anamnesis);
- The absence of pregnancy in a partner with regular sexual activity ≥ 1 year;
- A heterosexual couple, confirmed fertility of the partner (normal ovulation, absence of tubal or uterine factor);
- Signed voluntary informed consent.

Exclusion criteria:

- Previous surgery on the organs of the scrotum (including varicocelectomy);
- Congenital abnormalities of the testicles or appendages;
- Genetic forms of infertility (e.g. Klinefelter syndrome, CFTR mutation);
- Infectious and inflammatory diseases of the genitourinary system in the acute stage;
- Systemic endocrine diseases (diabetes mellitus, hypogonadism, etc.);
- Smoking more than 10 cigarettes/ day, alcohol abuse, drug use;
- Exposure to ionizing radiation, chemotherapy, or toxic substances.

For comparison, a control group was formed of 50 men who have had children in the last 2 years and have no complaints about fertility. These men underwent the same diagnostic methods (physical examination, ultrasound, spermogram, etc.).

Examination methods

All participants underwent a standardized set of diagnostic procedures.:

1. Questionnaire and anamnesis collection:

- Demographic data (age, BMI, profession);

- Reproductive history (duration of infertility, number of conception attempts, previous pregnancies);
- Sexual activity, frequency of sexual intercourse;
- Family history of varicocele (if known);
- Concomitant diseases, bad habits, taking medications.

2. Physical urological examination:

- Examination and palpation of the scrotum organs in horizontal and vertical positions;
- Assessment of testicles on the Prader orchidometer scale;
- Valsalva sampling;
- Classification of varicocele according to Dubin–Amelar (1970):

• Grade I — palpable only with a Valsalva sample;

- Grade II — palpable at rest, not visualized;
- Grade III — well palpable and visualized.

3. Ultrasound examination of the scrotum with CDK:

It was carried out on the device [specify the model of the ultrasound scanner], with a 7.5-10 MHz linear sensor. The study was performed in two positions (lying and standing) with a Valsalva test.

The following parameters were evaluated:

- Diameter of the veins of the lozoid plexus at rest and under load (≥2.5 mm is the diagnostic criterion for varicocele);
- The presence and duration of venous reflux (reflux lasting ≥1 sec was considered pathological);
- Testicular volume (volume formula: length × width × thickness × 0.71);
- Symmetry and hypotrophy.

Subclinical varicocele was diagnosed with:

• No changes during examination and palpation;

- Vein diameter ≥2.5 mm by ultrasound;
- Confirmed pathological reflux.

4. Spermogram:

Ejaculate analysis was performed according to WHO recommendations (5th edition, 2010 / 6th edition, 2021, if available), after 3-5 days of abstinence. Parameters:

- Volume, pH, viscosity;
- Concentration and total number of spermatozoa;
- Mobility (A+B+C);
- Morphology (according to Kruger);
- Agglutination, leukocytes, MAR-test (according to indications).

5. Hormonal studies:

Venous blood was taken on an empty stomach in the morning. The levels were evaluated:

- Follicle Stimulating Hormone (FSH);
- Luteinizing Hormone (LH);
- Total Testosterone;
- Prolactin and estradiol (as indicated).

Patients were stratified into groups depending on:

• The presence/absence of varicocele (in general);

- The presence of a subclinical form of varicocele;
- Degrees of clinically expressed varicocele (I, II, III);
- The level of violations of the spermogram (normal, moderate, pronounced);
- The level of DNA fragmentation.

To compare the groups, the following were used:

• Student's t-test — with a normal distribution;

- Mann-Whitney U–test — with abnormal distribution;
- $\chi 2$-criterion — for qualitative variables;
- ANOVA criterion — for multiple comparisons between subgroups.

The statistical significance of the differences was considered at a level of $p < 0.05$.

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RESULTS

1. General characteristics of the sample under study

The study included n = 156 men with infertility (the main group), the average age was 32.4 ± 4.9 years. The control group consisted of n = 50 fertile men (average age: 31.7 ± 5.2 years, $p > 0.05$) who had no fertility complaints and had at least one child conceived without the use of assisted reproductive technologies.

The average duration of infertility in the main group was 2.7 ± 1.3 years.

2. The frequency of varicocele in the group of infertile men

Of the 156 patients with infertility:

- 103 patients (66.0%) had varicocele;
    - Of these, 75 (48.1%) are clinically pronounced varicocele;
    - 28 (17.9%) – subclinical varicocele (ultrasound data only);
    - 53 patients (34.0%) had no signs of varicocele either clinically or by ultrasound.
    - In the control group (n = 50), varicocele (including subclinical forms) was found in only 7 (14.0%) men ($p < 0.001$ compared with the main group).

Thus, the relative risk of varicocele in men with infertility was more than 4 times higher than in fertile men.

3. Distribution by degree of clinical varicocele (n = 75):

- Grade I — 17 people (22.7%)
    - II degree — 32 people (42.7%)
- III degree — 26 people (34.6%)

The side of defeat:

    - Left-sided varicocele: 87.3%
- Bilateral: 10.6%
    - Right-hand drive (isolated): 2.1%

4. Analysis of spermogram parameters

Table . Semen Parameters in Patients With and Without Varicocele

Parameter	Normal (Control)	Grade I	Grade II	Grade III
Sperm concentration (million/ml)	62	49	35	22
Sperm motility (%)	65	54	42	28
Morphology (% normal forms)	12	9	6	4

Spermatogenesis indicators were significantly worse in patients with varicocele in all major parameters, with the exception of ejaculate volume (the difference did not reach statistical significance).

According to the degrees of varicocele:

- * grade III was associated with the most pronounced pathology of sperm:
    - Concentration: 21.3 ± 8.7 million/ml
    - Mobility: 37.1 ± 6.8%
    - Morphology: 3.8 ± 1.6%
- Grade I: the indicators in some cases corresponded to the WHO norm, but tended to decrease.

Subclinical varicocele (n = 28):

- Average concentration: 31.5 ± 10.9 million/ml
    - Mobility: 46.4 ± 7.3%

- Morphology: 5.7 ± 1.8%
- Although the indicators were better than in clinical forms, they remained worse than in men without varicocele ($p < 0.05$).

5. The results of the sperm DNA fragmentation test

A DNA Fragmentation Index (DFI) test was performed in 94 patients.

Table 2. Sperm DNA Fragmentation Index (DFI)

Group	Mean DFI (%)	DFI < 15%	DFI 15–30%	DFI > 30%
Control	10	88%	12%	0%
Grade I	18	52%	44%	4%
Grade II	24	33%	53%	14%
Grade III	32	10%	45%	45%

The presence of varicocele was statistically significantly associated with increased DNA fragmentation ($p < 0.001$), especially at grade III.

Table 3. Hormonal Profile in Men With Varicocele

Parameter	Control	Grade II	Grade III
FSH (mIU/ml)	4.2	6.8	9.4
LH (mIU/ml)	5.1	7.3	8.5
Testosterone (nmol/l)	18.2	15.7	12.1

Significantly higher levels of FSH and LH were noted in patients with varicocele, which indicates a strain on pituitary regulation in conditions of decreased testicular function.

Correlation analysis

- The degree of varicocele significantly correlated with the level of DNA fragmentation ($r = 0.67$, $p < 0.001$);

Testicular volume was negatively correlated with FSH ($r = -0.53$, $p < 0.001$);

- Sperm morphology correlated with testosterone levels ($r = 0.42$, $p = 0.003$);
- The duration of reflux on ultrasound had a direct relationship with sperm concentration (inverse relationship, $r = -0.49$, $p < 0.01$).

Table 4. Comparison of Clinical and Laboratory Parameters in Patients with Varicocele and Control Group

Parameter	Control Group	Grade I Varicocele	Grade II Varicocele	Grade III Varicocele	P-value
Sperm concentration (million/ml)	62	49	35	22	<0.001
Sperm motility (%)	65	54	42	28	<0.001
Normal morphology (%)	12	9	6	4	<0.001

DFI (%)	10	18	24	32	<0.001
FSH (mIU/ml)	4.2	5.3	6.8	9.4	<0.01
LH (mIU/ml)	5.1	6.2	7.3	8.5	<0.01
Testosterone (nmol/l)	18.2	17.1	15.7	12.1	<0.01

Interim conclusion based on the results

- Varicocele (including subclinical) occurs in more than two thirds of men with infertility;
- The presence of varicocele is significantly associated with deterioration of all parameters of spermatogenesis, especially in grades II–III;
- Even subclinical varicocele is accompanied by a deterioration in morphology, mobility, and DFI compared to men without pathology;
- Patients with varicocele are more likely to show hormonal changes, indicating compensatory mechanisms and subclinical hypogonadal dysfunction;
- The data confirm the pathogenetic role of varicocele as an independent risk factor for fertility disorders.

DISCUSSION

The results of this study confirmed the hypothesis that varicocele is a significant risk factor for male infertility, affecting both classical parameters of the spermogram and more subtle indicators— such as fragmentation of sperm DNA. In addition, it was found that even subclinical varicocele (diagnosed exclusively by ultrasound and CDK) is accompanied by subfertile changes in spermatogenesis, which underlines its potential clinical significance.

Varicocele was diagnosed in 66% of men with infertility, which is fully consistent with the results of meta-analyses of recent years. Considering that the frequency of varicocele in the control group was only 14%, it can be argued that varicocele is significantly more common in infertile men ($p < 0.001$).

This indicates the presence of a causal relationship, especially if the varicocele is accompanied by abnormalities in the spermogram, hormonal profile, or increased DNA fragmentation.

In the present study, varicocele was associated with a significant decrease in sperm concentration, motility, and morphology compared with men without this pathology. Especially pronounced changes were recorded in grade III varicocele, which confirms the dose dependence (a gradient deterioration in indicators depending on the severity of venous congestion).

Thus, our data are consistent with the point of view recognized in the literature that varicocele causes oxidative stress, hyperthermia and impaired venous outflow, which leads to microtrauma of the tubular epithelium and a decrease in sperm quality.

Of particular interest are the results in a group of patients with subclinical varicocele, who had no clinical signs, but ultrasound revealed an enlarged venous splice.

Despite the absence of palpatory changes, these patients showed:

- Decreased sperm morphology;
- Moderate decrease in mobility;
- Increased fragmentation of sperm DNA.

Thus, our data confirm the importance of not only clinical, but also ultrasound diagnosis of varicocele in infertile men, even in the absence of complaints and obvious palpatory changes.

One of the key findings of our study was the identification of a link between varicocele and an increase in the DNA fragmentation index (DFI). In patients with grade III varicocele, more than 80% had a DFI >15%, which is the threshold for reducing the chances of conceiving naturally.

This may explain the failures of IVF and ICSI in some patients with normal spermograms but high levels of DFI. The mechanisms of DNA damage include:

• Activation of oxidative stress and formation of free radicals;
• Violation of the haptenic protection of the sperm nucleus;
• Fever in the scrotum and microperfusion disorders.

The presence of varicocele was also associated with moderately elevated levels of FSH and LH with a decrease in testosterone levels. Such data may indicate the beginning of depletion of the function of Leydig and Sertoli cells. Elevated FSH at normal or reduced testosterone levels indicates a subclinical form of hypogonadism.

Based on the data obtained, several practical conclusions can be drawn:

1. Diagnosis of varicocele should include mandatory ultrasound with CDK, especially in men with unexplained infertility and normal spermogram.;

2. Subclinical varicocele should not be considered a benign condition — in the presence of disorders of spermatogenesis, it requires monitoring and, possibly, surgical treatment.;

3. DFI is a promising biomarker that can serve as an indication for varicocelectomy with sperm boundary parameters;

4. Doctors should pay attention to hormonal disorders even in the absence of complaints from libido or erectile function.;

5. Surgical treatment of varicocele (especially grade II–III) is justified in men with impaired fertility, high DFI and abnormalities in the spermogram.

Varicocele is one of the most common and significant risk factors for male infertility, affecting both sperm quality and molecular and hormonal markers. The presence of varicocele, including subclinical forms, should be assessed comprehensively using physical examination, ultrasound, spermogram analysis and DFI. These data can serve as a basis for individualizing treatment tactics and choosing methods of assisted reproduction.

CONCLUSION

The present study confirmed the high prevalence of varicocele among men with impaired fertility: pathology was detected in more than 65% of patients, including both clinical and subclinical forms. Varicocele was significantly associated with a deterioration in key parameters of the spermogram — a decrease in sperm concentration, motility, and morphology, as well as an increase in DNA fragmentation, which indicates its pathogenetic role in the formation of male infertility.

Subclinical varicocele deserves special attention, which, despite the absence of clinical manifestations, was accompanied by pronounced changes in spermatogenesis and an increase in DFI levels. This highlights the need to include ultrasound examination of the scrotum with Dopplerography in the mandatory examination algorithm for men with infertility.

In addition, moderate but significant hormonal changes were detected in men with varicocele, indicating functional tension of the hypothalamic-pituitary-gonadal axis and a potential threat to the endocrine function of the testicles.

The data obtained confirm that varicocele is not just an anatomical feature of the venous system of the scrotum, but a systemic disease that can have a negative impact on male fertility. The detection of varicocele, including subclinical ones, should serve as the basis for an in-depth assessment of the patient's reproductive potential, monitoring of spermatogenesis parameters and consideration of indications for treatment, including surgical correction.

The introduction of an integrated approach to the diagnosis and management of patients with varicocele can help to increase the effectiveness of male infertility therapy and improve reproductive outcomes.

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