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VARICOCELE AND INFERTILITY: ETIOPATHOGENESIS AND PATHOGENETIC ASPECTS

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Abstract

Male infertility is a significant medical and social problem affecting a considerable proportion of married couples of reproductive age. Varicocele is one of the leading causes of male infertility and is considered the most common pathology that can potentially be corrected surgically. Currently, varicocelectomy remains the only intervention proven to restore sperm in the ejaculate in some patients and improve key parameters of spermatogenesis. Despite the accumulated clinical data, the pathogenesis of varicocele is multifactorial and includes haemodynamic disorders, heat stress, hypoxia, and immunoinflammatory processes. Particular importance is attached to oxidative stress caused by an excess of active oxygen species, which can damage sperm membranes and increase DNA fragmentation. Sperm DNA fragmentation is considered a promising marker that influences the likelihood of natural conception and the effectiveness of assisted reproductive technologies.

Keywords: Varicocele, male infertility, spermatogenesis, varicocelectomy, spermogram, reactive oxygen species, oxidative stress, sperm DNA fragmentation, immunoinflammatory mechanisms of infertility, microbiome, microRNA, assisted reproductive technologies, pregnancy, reproductive outcomes.

Introduction

Infertility remains one of the most pressing issues in modern reproductive medicine, as it affects not only the physiological aspects of procreation, but also the emotional state of the couple, social adaptation, quality of life and

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psychological well-being. According to the World Health Organisation, infertility is diagnosed when pregnancy does not occur within 12 months of regular sexual intercourse without contraception. The prevalence of infertility among couples is about 15%, with male factors playing a role in almost half of cases. Consequently, the diagnosis and treatment of male reproductive disorders are no less important than the correction of female factors and require a comprehensive interdisciplinary approach [2].

One of the most common causes of male infertility is varicocele, a pathological enlargement of the veins of the pampiniform plexus, accompanied by venous reflux and impaired local microcirculation. Historically, varicocele was considered the most common cause of male infertility that could be corrected surgically. However, in recent years, views on the role of this pathology have become more balanced. New studies show that varicocele can also be detected in healthy men without reproductive disorders, which emphasises the heterogeneity of clinical manifestations and the need for a differentiated approach to the choice of treatment tactics [4].

Modern urological practice is based on the principles of evidence-based medicine, where varicocelectomy is considered the most effective treatment for patients with clinically significant varicocele and abnormal spermogram parameters. The correct selection of patients is of particular importance, as intervention may not be justified in all clinical situations. For example, in cases of severe sperm DNA fragmentation, a long history of infertility, or repeated unsuccessful attempts at assisted reproductive technology, a more careful assessment of the appropriateness of surgery and its predicted benefits is required. [2, 5]

The mechanisms through which varicocele leads to impaired spermatogenesis continue to be actively studied. Key pathogenic factors include venous congestion, increased scrotal temperature, tissue hypoxia, inflammatory changes, endocrine disorders, and the accumulation of toxic metabolites. Oxidative stress associated with an excess of reactive oxygen species (ROS) occupies a central place in modern concepts. ROS can damage sperm cell membranes, reduce their motility and viability, and cause DNA strand breaks. This leads to an increase in the level of sperm DNA fragmentation, which is directly associated with a

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decrease in the likelihood of natural conception and a deterioration in the results of assisted reproductive technology (ART) programmes [8].

At the same time, research is being conducted on the role of immune-inflammatory mechanisms and the microbiome. Infectious agents and microflora imbalance can activate the production of pro-inflammatory cytokines, stimulate the formation of antisperm antibodies and form biofilms, thereby disrupting normal spermatogenesis. Given the complexity of the pathogenesis, it is clear that male infertility associated with varicocele cannot be considered solely as a local vascular problem [9].

Molecular research aimed at finding biomarkers that can improve diagnosis, prognosis and personalisation of treatment opens up additional prospects. Of particular interest are microRNAs, small regulatory molecules capable of controlling gene expression and participating in the regulation of germ cell development. Changes in the microRNA profile may reflect the degree of spermatogenesis impairment and potentially be used as non-invasive diagnostic tools [6, 8].

Thus, varicocele is a multifactorial pathology closely associated with various mechanisms of reproductive disorders. Systematisation of current data on surgical options, oxidative stress, immune processes, and molecular biomarkers is an important step towards improving the diagnosis and treatment of male infertility.

The effectiveness of varicocelectomy in azoospermia and the restoration of spermatozoa in ejaculate. Varicocele correction remains the only surgical method proven to be effective in restoring spermatozoa in ejaculate in some patients. The results of recent reviews show that varicocelectomy can lead not only to improved laboratory sperm parameters, but also to clinically significant changes, including increased sperm concentration and increased pregnancy rates. Even if these outcomes were not directly assessed in all studies, the observed increase in spermatogenesis suggests that a certain proportion of men may avoid the financial costs, emotional stress and time loss associated with assisted reproductive technology (ART). However, additional well-organised prospective studies and randomised controlled trials are needed to definitively confirm the benefits of this intervention in specific patient groups [4].

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However, it should be emphasised that the clinical effectiveness of varicocelectomy is not absolute and may vary significantly depending on the initial state of spermatogenesis, the severity of varicocele, the patient's age, the duration of infertility, and the presence of concomitant factors. A number of studies have noted that improvement in spermogram parameters after surgery does not always lead to the expected increase in the frequency of pregnancy, which is associated with the multifactorial nature of reproductive disorders. In addition, evaluating treatment outcomes takes time, as the spermatogenesis cycle takes several months, and early results may not reflect the real effect of the intervention [3].

The choice of the optimal treatment strategy is particularly difficult in patients with borderline sperm parameters, subclinical varicocele, or additional causes of infertility. In such cases, surgical treatment may be less justified, and preference may be given to dynamic observation, lifestyle correction, elimination of inflammatory processes, and, if necessary, the use of ART. It is important to note that even with the same clinical picture, the response to varicocelectomy may be individual, which makes it relevant to search for prognostic factors that allow predicting the likelihood of improved spermatogenesis and pregnancy [4].

In recent years, there has been increasing discussion of the need for expanded diagnosis of male infertility, including assessment not only of standard semen analysis parameters, but also of additional markers of sperm functional status. Such markers include indicators of oxidative stress, the level of sperm DNA fragmentation, and signs of immunoinflammatory changes in the urogenital tract. This approach allows for a more complete assessment of a man's reproductive potential and determines whether varicocele is the leading pathogenetic factor or merely a concomitant finding [1, 9].

Thus, varicocelectomy retains an important place in the treatment of male infertility, but its use requires strict patient selection and a comprehensive assessment of risk factors. That is why further research should be aimed not only at confirming the overall effectiveness of surgical intervention, but also at refining the criteria for predicting the clinical benefit of surgery in a particular patient.

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Conclusion

Varicocele remains one of the most common and clinically significant causes of male infertility, with its role in reducing fertility determined by a complex combination of vascular, metabolic, inflammatory, and molecular mechanisms. To date, varicocelectomy is the only surgical intervention that has been shown to restore the presence of sperm in the ejaculate in some patients and improve spermatogenesis parameters, including sperm concentration and potentially the frequency of pregnancy. However, the heterogeneity of the clinical manifestations of varicocele, as well as the presence of pathology in some healthy men without reproductive disorders, emphasise the need for strict patient selection and individualisation of the treatment strategy.

Current data indicate the key role of oxidative stress and reactive oxygen species in sperm damage, which manifests itself in reduced sperm quality and increased DNA fragmentation. Sperm DNA fragmentation is an important additional marker of reproductive prognosis, as it is associated with a reduced likelihood of natural conception and decreased ART effectiveness. Surgical treatment of varicocele has the potential to normalise the oxidative-antioxidant balance and reduce DNA damage, but there is still a need to further refine the clinical criteria under which such improvements lead to a real increase in the frequency of pregnancy and live birth.

Additional areas of research, including the study of the microbiome, immunoinflammatory cascades, and regulatory microRNAs, open up prospects for the development of new diagnostic tests and non-surgical therapies. However, existing data still have limitations related to differences in study design, population heterogeneity, and a lack of randomised controlled trials. In the future, the most promising approach is to conduct large prospective studies that will clarify the pathogenesis, determine the most effective treatment strategies, and improve the quality of medical care for patients with varicocele-related infertility.

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