

Azoospermia in Male Infertility

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Abstract Azoospermia is one of the leading causes of male infertility, characterized by the absence of sperm in the ejaculate. It can be caused by obstructive or non-obstructive factors, including hormonal disorders, genetic abnormalities, or damage to the spermatic ducts. Diagnosis and treatment depend on the underlying cause, with options ranging from surgical and pharmacological interventions to assisted reproductive technologies. Azoospermia is one of the most severe forms of male infertility, characterized by the complete absence of sperm in the ejaculate. This condition affects approximately 1% of all men and 10–15% of men seeking infertility treatment. The causes of azoospermia are diverse and include obstructive factors (blockage of the spermatic ducts) as well as non-obstructive factors associated with impaired spermatogenesis. The diagnosis of azoospermia requires a multi-step approach, including hormonal evaluations, genetic testing, and imaging of the reproductive system. Modern treatment methods, including surgical, pharmacological, and assisted reproductive technologies such as ICSI, enable many men with this diagnosis to achieve fatherhood. This review utilized a retrospective method of literature analysis. Articles, theses, dissertations, and abstracts published in international databases, including PubMed, Elsevier, Google Scholar, and CyberLeninka, were examined. Special attention was given to studies focusing on the causes, diagnosis, and treatment of azoospermia. A comparative analysis of the data was conducted to summarize current approaches to the diagnosis and therapy of this condition. The review demonstrated that azoospermia is classified into obstructive and non-obstructive forms, each requiring specific diagnostic and treatment approaches. Key diagnostic methods include hormonal evaluations, genetic testing, and imaging of the reproductive organs. Modern therapeutic approaches encompass pharmacological and surgical treatments, as well as the use of assisted reproductive technologies, such as ICSI. Azoospermia requires a comprehensive approach to diagnosis and treatment, including the use of modern methods such as ICSI, to successfully restore fertility.

Keywords Azoospermia, Male infertility, Diagnosis, Obstruction, Non-obstruction, Spermatogenesis

1. Introduction

Azoospermia, as one of the most severe forms of male infertility, is characterized by the absence of sperm in the ejaculate, making natural conception impossible. This pathological condition occurs in approximately 1% of all men and 10–15% of men seeking assistance for infertility. Azoospermia is classified into two main forms: obstructive, associated with impaired patency of the spermatic ducts, and secretory, caused by a disruption of spermatogenesis in the testes.

2. Materials and Methods

The materials for this study included articles, theses, and abstracts obtained from medical databases such as PubMed,

Elsevier, Google Scholar, and CyberLeninka. A retrospective analysis of these sources was conducted.

Azoospermia (absence of sperm and spermatogenic cells in the ejaculate) is an indication for performing testicular biopsy. Azoospermia and severe oligozoospermia occur in 10-20% and 15-20% of all cases of severe spermatogenesis disorders, respectively [1]. Azoospermia affects 1% of all men, and among infertile men, its prevalence reaches 10-15% [2-3]. Azoospermia is associated with a number of irreversible dysfunctions of testicular tissue, including dysfunctions of Leydig cells and Sertoli cells, which play key roles in regulating spermatogenesis and hormonal balance. Disorders in Leydig cell function lead to insufficient testosterone production, which is necessary to maintain normal sperm maturation, while Sertoli cell dysfunction hampers the nourishment and development of sperm within the seminiferous tubules. These pathological changes may be caused by genetic factors, varicocele, endocrine disorders, infections, or toxic exposure, resulting in impaired spermatogenesis and decreased fertility [4].

According to statistical data, about 50% of infertility cases are attributed to male factors, with 30-40% of these cases

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remaining idiopathic. The main causes of male infertility include urogenital infections, genetic anomalies, cryptorchidism, varicocele, hypogonadism, ejaculation disorders, various systemic and general diseases, immunological factors, as well as idiopathic infertility [5,6]. Despite the high relevance of this issue, there are several challenges in the diagnosis and treatment of male infertility, such as the lack of standard tests for fertility assessment, insufficient understanding of the pathophysiology of this pathology, the shortage of qualified specialists in andrology, and limited technical capabilities. Additionally, there is a lack of scientific data on the effectiveness of pharmacotherapeutic treatments for subfertility. As a result, assisted reproductive technologies (ART) are one of the main therapeutic options for male infertility [7]. As a first-line ART, intrauterine insemination (IUI) is sometimes used, which is indicated when the partner's fertility is normal and there are at least 1×10^6 motile sperm in the partner's semen after preparation. If pregnancy does not occur after 3-6 cycles of IUI, in vitro fertilization (IVF) may be recommended. In cases where the number of progressively motile sperm is less than 0.5×10^6 , or sperm is surgically retrieved from the testicle or epididymis, intracytoplasmic sperm injection (ICSI) is applied [8].

The effectiveness and long-term outcomes of assisted reproductive technologies (ART) vary across different countries, such as Russia, the USA, Europe, and Asia. According to data from the European Association of Reproductive Medicine in 2010, more than 290,000 ART cycles were performed in Europe, over 110,000 in the USA, and about 10,000 annually in Russia [9]. The overall effectiveness of ART (the number of live births relative to the number of transferred embryos) is approximately 25.5%. ART success also depends on the region where treatment is performed. For example, in South Korea, 30,410 ART cycles were performed with oocyte retrieval, of which 27,683 were successfully fertilized [10]. In 8,826 fresh embryo transfer cycles, clinical pregnancy was confirmed by ultrasound. The pregnancy rate after embryo transfer with ovarian stimulation was 33.2%, and 30.6% for other cases. The most embryos transferred using frozen embryos were three (38.1%), followed by two (34.7%) and one (14.3%). Despite a decrease in clinical pregnancy rates compared to the previous year (31.1% vs. 35.4%), the overall cycle success rate increased (33.2% vs. 32.9%) [11].

Currently, the primary methods of ART are IVF and/or ICSI. ICSI is a good alternative to IVF in cases where infertility is related to male factors. In a study conducted by M. Eftekhari et al. in 2012, a comparative evaluation of these two methods in cases of infertility not related to male factors was conducted. The results showed that in the IVF group, fertilization and implantation rates were significantly higher (66.22% and 16.67%, respectively) than in the ICSI group (57.46% and 11.17%). Chemical and clinical pregnancy rates were also higher in the IVF group (42.9% and 27.3% vs. 35.7% and 21.5% in the ICSI group). The authors concluded that ICSI does not improve fertilization, implantation, or clinical pregnancy rates and is not recommended for use

when infertility is due to female factors [12].

Studies show that various factors, such as lifestyle, physical activity, body mass index (BMI), diet, smoking, and diseases of various origins, affect the outcomes of assisted reproductive technologies (ART) in infertile couples [13]. It is believed that BMI has a significant impact on ART cycle outcomes, however, A.M. H. Koning et al. (2012) questioned this influence. In a review of 14 studies, no significant link was found between ART outcomes and BMI [14]. Most researchers agree that sperm quality deteriorates with advancing paternal age. However, there is no convincing evidence that this decline affects ART reproductive outcomes. Some authors argue that male age has no significant impact on ART outcomes, and any negative effects are related to female age (Y. Kumtepe et al. [15], J.E. Stern et al. [16]). At the same time, a study conducted by authors from the University of Montpellier (France) between 2010 and 2015 showed that paternal age indeed has a negative impact. In the analysis of 859 IVF cycles and 1,632 ICSI cycles, men older than 51 and women older than 37 showed a decrease in pregnancy rates, although it is difficult to exclude the influence of female age [17].

It should also be noted that in smoking men, sperm volume, pH, sperm concentration, viability, and the levels of zinc, copper, and superoxide dismutase in seminal plasma were significantly lower compared to non-smokers, and were negatively correlated with the duration and intensity of smoking ($p < 0.01$). This indicates that smoking may reduce the chances of a successful ART outcome. However, other studies have not found a clear connection between smoking and the deterioration of sperm parameters [18]. It can be confidently stated that smoking has a negative effect on fertility in both men and women, as well as on ART outcomes [19].

Varicocele is also one of the factors negatively affecting fertility. Studies show that in patients who underwent varicocelectomy, the sperm count obtained by TESE (testicular sperm extraction) increases, and the clinical pregnancy rate after IVF/ICSI is 18.9% compared to 13.6% in those who did not undergo varicocelectomy. This suggests that varicocelectomy before ICSI improves pregnancy outcomes [20]. Additionally, varicocelectomy reduces sperm DNA fragmentation, which enhances ART effectiveness [21]. In men with unilateral cryptorchidism, fatherhood is not dependent on age, preoperative testicular location, or its size [22]. However, a history of unilateral cryptorchidism may reduce fertility and increase the time to pregnancy in the partner. In bilateral cryptorchidism, oligo- or azoospermia occurs in 31% and 42% of cases, respectively, and fatherhood occurs in only 35–53% of men. In cases of bilateral cryptorchidism and azoospermia, orchiopexy performed even at adulthood can lead to the presence of sperm in the ejaculate [23,24].

A.G. Brzhozovsky et al. report that seminal plasma may be a promising source of biomarkers for male infertility, including markers of residual spermatogenesis in patients with azoospermia. An important advantage is that the

collection of seminal plasma usually does not require invasive procedures, making it a convenient material for analysis. The use of non-invasive tests to identify men with focal spermatogenesis can improve the accuracy of patient selection for microdissection testicular sperm extraction (microTESE) and enhance patient counseling [27].

S.N. Kulikov *et al.* note that the absence of sperm in the ejaculate is a common issue, accounting for 10–15% of all male infertility cases among men seeking medical help for this issue. Azoospermia affects approximately one in every hundred men suffering from infertility. The causes of azoospermia are quite diverse: in 41% of cases, it is due to obstruction, and in 59% — due to non-obstructive disorders. About 40% of male infertility cases remain of unknown etiology, making them idiopathic. This highlights the need to optimize diagnostics to more accurately determine the nature of azoospermia, its etiology, and prognosis [28]. Additionally, an important aspect is the choice of the best treatment methods and surgical techniques for sperm extraction, which allows overcoming infertility through IVF-ICSI procedures [29,30].

3. Results and Discussion

The review highlights that azoospermia is a multifactorial condition, classified into obstructive and non-obstructive types, each requiring tailored diagnostic and therapeutic approaches. Hormonal evaluations and genetic testing are crucial for identifying underlying causes, while imaging and biopsy help distinguish between forms. Treatment options range from surgical interventions to restore ductal patency to pharmacological therapies aimed at stimulating spermatogenesis. Assisted reproductive technologies, particularly ICSI, offer significant potential for achieving conception in affected individuals. Advances in diagnostics and personalized treatments are improving outcomes and providing new opportunities for managing male infertility due to azoospermia.

4. Conclusions

Azoospermia is a complex condition and one of the leading causes of male infertility, requiring a comprehensive diagnostic approach that includes hormonal evaluations, genetic testing, and assessment of the spermatid ducts. It is crucial to distinguish between obstructive and non-obstructive forms of the condition, as this determines the choice of treatment methods. Modern therapeutic approaches encompass both pharmacological and surgical methods aimed at restoring ductal patency or stimulating spermatogenesis. Assisted reproductive technologies, such as ICSI, play a pivotal role in the treatment of patients with azoospermia. The development of new diagnostic and therapeutic methods offers promising prospects for more effective management of this condition and improving outcomes for infertile couples.

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