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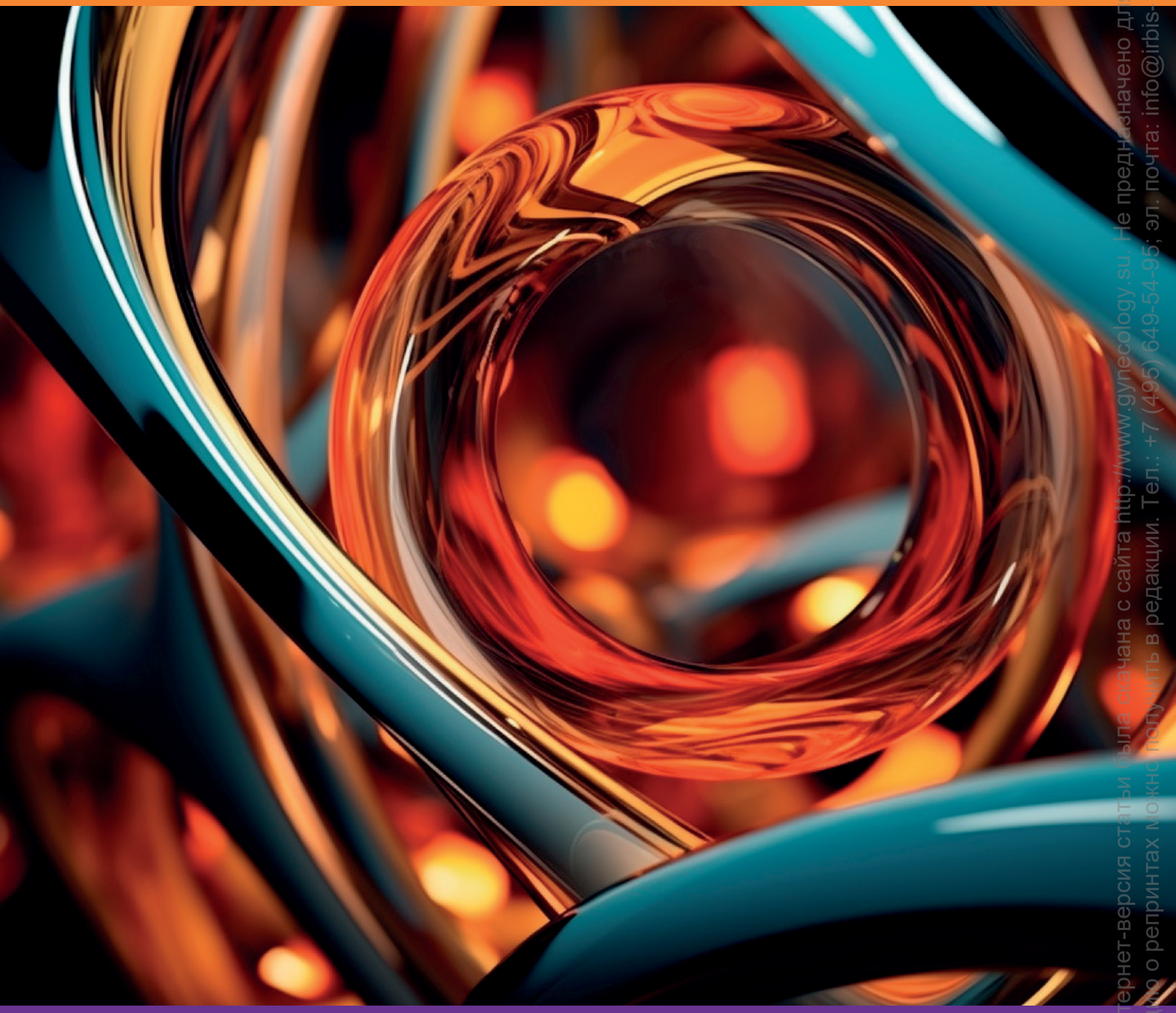

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Azoospermia: etiology, pathogenesis, prevalence of forms and algorithm for differential diagnostics

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Abstract

Introduction. Azoospermia, defined as the absence of spermatozoa in the ejaculate after centrifugation, is one of the leading causes of male infertility, affecting approximately 1,0 % of men in the general population and up to 15,0 % of infertile patients. Timely differentiation between obstructive (OA) and non-obstructive (NOA) azoospermia is critical for selecting appropriate treatment strategies, determining prognosis, and applying assisted reproductive technologies (ART).

Aim: to investigate the prevalence of different azoospermia forms in infertile men, within the context of real-world clinical practice at a non-specialized endocrine outpatient department, including personal observations, in comparison with the results of international and Russian epidemiological studies.

Materials and Methods. A comprehensive analysis of literature, clinical guidelines, and original data was performed. The study included 450 men aged 25–45 years with confirmed azoospermia. All patients underwent a comprehensive examination, including collection of anamnesis (reproductive, somatic, surgical); physical examination with assessment of secondary sexual characteristics, size and consistency of the testicles; double examination of ejaculate (centrifugation, microscopy); examination of blood hormone levels (follicle-stimulating hormone, luteinizing hormone, total testosterone, prolactin, anti-Müllerian hormone, sex hormone-binding globulin, inhibin B; if indicated – estradiol, thyroid-stimulating hormone, thyroxine); scrotum ultrasound examination with Doppler ultrasonography; genetic testing – karyotyping, testing for microdeletions of Y chromosome azoospermia factor (*AZF*) of the Y chromosome, *CFTR* (cystic fibrosis transmembrane conductance regulator) gene testing; when indicated, testicular sperm extraction (TESE) biopsy was performed.

Results. NOA and OA were identified in 63.3 % and 30,0 % of patients, respectively. Among NOA cases, the leading causes were idiopathic forms (19.6 %), Klinefelter syndrome (8.4 %), Y-chromosome microdeletions (5.8 %), and hypogonadotropic hypogonadism (6.7 %). Varicocele was associated with NOA in 12,0 % of cases. These findings are consistent with global data, although minor ethnic and methodological differences were observed.

Conclusion. Azoospermia is a clinically and etiologically heterogeneous condition. Timely differentiation between its forms and the inclusion of genetic testing improve diagnostic accuracy and help optimizing management strategies. Standardization of diagnostic algorithms and a personalized approach increase ART effectiveness and the likelihood of fertility restoration.

Keywords: azoospermia, male infertility, obstructive azoospermia, OA, non-obstructive azoospermia, NOA, hypogonadism, Klinefelter syndrome, Y chromosome microdeletions, hypogonadotropic hypogonadism, varicocele

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Азооспермия: этиология, патогенез, распространенность форм и алгоритм дифференциальной диагностики

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Резюме

Введение. Азооспермия, определяемая как отсутствие сперматозоидов в эякуляте после центрифугирования, является одной из ведущих причин мужского бесплодия, встречаясь примерно у 1,0 % мужчин в общей популяции и до 15,0 % у пациентов с нарушением фертильности. Дифференциация обструктивной (ОА) и необструктивной (НОА) азооспермии имеет критическое значение для выбора тактики лечения, прогнозирования исходов и планирования применения вспомогательных репродуктивных технологий (ВРТ).

Цель: изучить распространенность различных форм азооспермии у мужчин с бесплодием в условиях реальной клинической практики неспециализированного эндокринологического амбулаторно-поликлинического отделения в сравнении с результатами международных и российских эпидемиологических исследований.

Материалы и методы. Проанализированы литературные данные, клинические руководства и результаты собственного исследования, включающего 450 мужчин с азооспермией в возрасте 25–45 лет. Всем пациентам проводилось комплексное обследование, включавшее сбор анамнеза (репродуктивного, соматического, хирургического); физикальное обследование с оценкой вторичных половых признаков, размеров и консистенции яичек; двукратное исследование эякулята (центрифугирование, микроскопия); исследование содержания в крови гормонов (фолликулостимулирующего гормона, лютеинизирующего гормона, общего тестостерона, пролактина, антимюллерова гормона, глобулина, связывающего половые гормоны, ингибина B; по показаниям – эстрадиола, тиреотропного гормона, тироксина); ультразвуковое исследование (УЗИ) органов мошонки с доплерографией; генетическое обследование – кариотипирование, тестирование на микроделеции фактора азооспермии (англ. azoospermia factor, *AZF*) Y-хромосомы, исследование гена *CFTR* (англ. cystic fibrosis transmembrane conductance regulator; трансмембранный регулятор муковисцидоза); при показаниях проводилась биопсия яичек (англ. testicular sperm extraction, TESE).

Результаты. НОА выявлена у 63,3 % пациентов, ОА – у 30,0 %. Среди причин НОА преобладали идиопатические формы (19,6 %), синдром Клайнфельтера (8,4 %), Y-микроделеции (5,8 %) и гипогонадотропный гипогонадизм (6,7 %). Варикоцеле сочеталось с НОА у 12,0 % мужчин. Полученные данные соответствуют международным тенденциям, выявлены незначительные этнические и методологические различия.

Заключение. Азооспермия представляет собой клинически и этиологически гетерогенное состояние. Своевременная дифференциальная диагностика форм и включение генетического тестирования позволяют повысить точность диагностики и оптимизировать выбор лечебной тактики. Стандартизация алгоритмов обследования и персонализированный подход обеспечивают повышение эффективности ВРТ и вероятность восстановления фертильности.

Ключевые слова: азооспермия, мужское бесплодие, обструктивная азооспермия, ОА, необструктивная азооспермия, НОА, гипогонадизм, синдром Клайнфельтера, микроделеции хромосомы Y, гипогонадотропный гипогонадизм, варикоцеле

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Highlights

What is already known about this subject?

- Azoospermia occurs in approximately 1,0 % of men in the general population and in 10–15 % of infertile patients.
- Distinguishing between hypogonadotropic and hypergonadotropic forms of non-obstructive azoospermia determines both prognosis and treatment strategy.
- The standard diagnostic algorithm includes semen analysis, hormonal testing, ultrasound examination, genetic testing, and, if necessary, testicular biopsy.

What are the new findings?

- The forms of hypogonadism (hyper- and hypogonadotropic) and their contribution to developing azoospermia are examined in detail. Both original and international data on Klinefelter syndrome, microdeletions of the azoospermia factor (*AZF*) loci of the Y chromosome and hypogonadotropic hypogonadism are analyzed.
- An algorithm for the differential diagnosis between hypogonadotropic and hypergonadotropic azoospermia is presented.

How might it impact on clinical practice in the foreseeable future?

- Standardization of diagnostic algorithms will help reduce the number of diagnostic errors. The use of algorithms and markers for the differential diagnosis of azoospermia will enable successful application of pharmacological stimulation of spermatogenesis.
- Taking into account regional data will increase effectiveness of assisted reproductive technologies and support a personalized approach to patients with azoospermia.

Основные моменты

Что уже известно об этой теме?

- Азооспермия встречается у ~1,0 % мужчин в популяции и у 10–15 % среди пациентов с бесплодием.
- Разделение гипогонадотропной и гипергонадотропной форм необструктивной азооспермии определяет прогноз и выбор тактики лечения.
- Стандартный алгоритм обследования включает спермограмму, гормональные тесты, ультразвуковое исследование, генетическое тестирование и при необходимости биопсию тестикул.

Что нового дает статья?

- Подробно рассмотрены формы гипогонадизма (гипер- и гипогонадотропный), их вклад в развитие азооспермии. Проанализированы собственные и международные данные о синдроме Клайнфельтера, микроделециях локусов фактора азооспермии (*AZF*) Y-хромосомы и гипогонадотропном гипогонадизме.
- Приведен алгоритм дифференциальной диагностики гипогонадотропной и гипергонадотропной азооспермии.

Как это может повлиять на клиническую практику в обозримом будущем?

- Стандартизация алгоритмов обследования позволит снизить число диагностических ошибок. Использование алгоритма и маркеров дифференциальной диагностики азооспермии позволит успешно использовать методы фармакологической стимуляции сперматогенеза.
- Учет региональных данных повысит эффективность вспомогательных репродуктивных технологий и персонализированного подхода к пациентам с азооспермией.

Introduction / Введение

Azoospermia (the absence of spermatozoa in the ejaculate after centrifugation) is identified in about 1,0 % of men in the general population and in 10–15 % of men seeking medical evaluation for infertility [1, 2]. Timely differentiation between obstructive azoospermia (OA) and non-obstructive azoospermia (NOA) determines the management strategy, including microsurgical testicular sperm extraction (TESE) followed by intracytoplasmic sperm injection (ICSI), hormonal therapy in cases of hypogonadism, use of assisted reproductive technologies (ART), and assessment of future fertility potential with appropriate genetic counseling [1, 3, 4].

Current international guidelines proposed by the European Association of Urology (EAU, 2024), the American Urological Association/American Society for Reproductive Medicine (AUA/ASRM, 2024), and the World Health Organization (WHO, 2021) provide a standardized algorithm for managing such patients. However, they insufficiently address the distinct forms of non-obstructive azoospermia (hypogonadotropic and hypergonadotropic) which can markedly influence clinical decision-making and treatment strategy [1, 3, 5].

The modern azoospermia classification includes the following categories [1, 3]:

1. pre-testicular azoospermia (hypogonadotropic hypogonadism) – primarily hypothalamic or pituitary causes leading to insufficient gonadotropin stimulation;
2. testicular azoospermia – primary impairment of spermatogenesis due to intrinsic testicular pathology;
3. post-testicular (obstructive) azoospermia – obstruction or ejaculatory dysfunction in the presence of preserved spermatogenesis.

In clinical practice, NOA is more frequently represented by testicular forms rather than pre-testicular (hypogonadotropic) variants, with proportions varying across cohorts from 40 to 60 %.

The modern diagnostic algorithm for evaluating men with azoospermia includes the following steps:

1. repeat semen analysis (≥ 2 samples) with mandatory pellet assessment after centrifugation to exclude cryptozoospermia, along with evaluation of ejaculate volume, pH, and measurement of fructose and alpha-glucosidase levels [6, 7];
2. medical history and physical examination: assessment of pubertal development; use of androgens;

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exposure to gonadotoxic agents; history of infectious–inflammatory diseases; prior surgeries (hernia repair, vasectomy); evaluation for retrograde ejaculation; examination of testicular volume and consistency; assessment of epididymal status, presence of *vas deferens*, and varicocele [1, 3, 5];

3. hormonal evaluation: serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (morning sample), and prolactin; when indicated – measurement of estradiol, inhibin B, and anti-Müllerian hormone (AMH) levels [1, 3, 8, 9];

4. imaging studies: scrotal ultrasonography with Doppler assessment (varicocele, focal lesions), transrectal prostate ultrasonography (TRUS) (cysts/obstruction of ejaculatory ducts, seminal vesicles), and post-ejaculatory urinalysis when retrograde ejaculation is suspected [1, 3, 5];

5. genetic testing: karyotyping and assessment for azoospermia factor (*AZF*) microdeletions – regions of the Y chromosome long arm (Yq11) bearing genes essential for spermatogenesis (recommended in NOA or severe oligozoospermia); analysis of the *CFTR* gene (cystic fibrosis transmembrane conductance regulator) in cases of congenital bilateral absence of the *vas deferens* (CBAVD) [1, 3, 10];

6. diagnostic/therapeutic TESE: after risk stratification and counseling with the couple, TESE is performed in NOA cases [1, 3, 5].

Domestic reviews and case series highlight common diagnostic pitfalls in differentiating OA from NOA and emphasize the importance of an integrated approach (hormonal assessment + ultrasonography + genetic testing + testicular biopsy when indicated) [11]. Russia-wide studies also report a significant proportion of *CFTR*-associated CBAVD, supporting the need for routine *CFTR* testing in this patient cohort [12].

Obstructive azoospermia / Обструктивная форма азооспермии

Obstructive azoospermia occurs in approximately 30–40 % of men with azoospermia and is characterized by preserved spermatogenesis with impaired sperm transport. One of the key causes of OA is congenital bilateral absence of the *vas deferens* (CBAVD), considered a “genital form of cystic fibrosis” [1, 2]. Up to 80–90 % of men with CBAVD carry mutations in the *CFTR* gene, located on chromosome 7q31.2 [2, 3]. The most common variants include ΔF508, the 5T/7T/9T polymorphism in intron 8 (IVS8-5T), R117H, and W1282X [3, 4].

Clinical picture / Клиническая картина

Pubertal development and secondary sexual characteristics are typically normal. Ejaculate volume is often reduced (< 1.5 mL), with acidic pH (< 7.2), and fructose lacked in the ejaculate. On physical examination, the *vas deferens* is not palpable, frequently accompanied by bilateral agenesis of the seminal vesicles, which is confirmed by TRUS or magnetic resonance imaging (MRI) [5]. Spermatogenesis is preserved: testicular volume and FSH levels are generally within normal ranges.

Diagnostics / Диагностика заболевания

Confirmed by physical examination (absence of the *vas deferens*) and imaging methods (TRUS – agenesis of the seminal vesicles, cysts); *CFTR* genetic testing is mandatory. Modern diagnostic panels include more than 30 variants, as the mutation spectrum varies across ethnic groups [2, 6]. Russian cohorts demonstrate a high frequency of the ΔF508 mutation (a 3-nucleotide deletion in *CFTR* resulting in the loss of phenylalanine at position 508 the most common pathogenic variant) and the IVS8-5T allele (a variant in intron 8 of *CFTR* impairing mRNA splicing), as well as several rare variants, which justifies the use of extended sequencing approaches [7, 8].

Genetic counseling / Генетическое консультирование

Men with CBAVD may be clinically healthy but they carry *CFTR* mutations. Partner testing is essential: if both partners carry pathogenic variants, the risk of having a child with cystic fibrosis is 25 % [1, 2]. Upon such risk, preimplantation genetic testing within ART programs is recommended.

Treatment and prognosis / Лечение и прогноз

Because spermatogenesis is preserved, spermatozoa can be obtained with high efficiency using percutaneous epididymal sperm aspiration (PESA), microsurgical epididymal sperm aspiration (MESA), or testicular sperm extraction (TESE). The use of ICSI allows achieving reproductive outcomes comparable to those in men without CBAVD [9]. Long-term outcomes regarding the birth of healthy children are favorable, provided that appropriate genetic counseling is performed and bilateral carrier status in the female partner is excluded [2, 9].

Post-infectious or post-traumatic obstruction / Постинфекционная или посттравматическая обструкция

Male post-infectious and post-traumatic lesions in reproductive tract are among the most common causes of obstructive azoospermia. Damage or scarring of the *vas deferens* or epididymis may result from inflammatory diseases (epididymitis, orchiepididymitis, prostatitis, vesiculitis) caused by bacterial pathogens such as *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma genitalium*, ets., as well as genital tuberculosis. Post-inflammatory fibrosis of the epididymis

or *vas deferens* leads to impaired sperm transport despite preserved spermatogenesis.

Post-traumatic obstruction may occur after surgical procedures in the inguinal region (hernia repair, vasectomy, scrotal surgery, prostate or bladder surgery), or after pelvic or scrotal trauma. In some patients, infectious–inflammatory and traumatic factors coexist.

Diagnosis is based on medical history, palpation of the epididymis (induration, enlargement, tenderness), ultrasonographic imaging, and biochemical analysis of the ejaculate (low volume, decreased pH, absence of fructose in cases involving seminal vesicles). When required, vasography or microsurgical reproductive ducts exploration is performed.

Surgical treatment includes microsurgical reconstruction of the reproductive tract (vasoepididymostomy, vasovasostomy). When reconstruction is not feasible or is unsuccessful, sperm retrieval techniques (PESA, MESA) followed by ART are utilized [2].

Hypergonadotropic non-obstructive azoospermia / Необструктивная гипергонадотропная форма азооспермии

Hypergonadotropic (primary) hypogonadism is one of the leading causes of NOA and is characterized by azoospermia, elevated FSH/LH levels, and low serum testosterone and inhibin B [1, 4, 10].

Klinefelter syndrome / Синдром Клайнфельтера

Klinefelter syndrome (KS) is the most common chromosomal cause of male infertility, with a prevalence of ~1:600–1:800 male births [5]. More than 90 % of affected individuals present with NOA due to progressive atrophy and sclerosis of the seminiferous tubules. In mosaic forms (47,XXY/46,XY), the phenotype is milder, and severe oligozoospermia or cryptozoospermia may be found. In young adults (20–30 years), micro-TESE enables sperm retrieval in approximately 30–50 % of cases [6, 7].

De la Chapelle syndrome / Синдром де ля Шапеля

De la Chapelle syndrome (46,XX testicular disorders of sex development) is a rare form of sex-development disorder caused by translocation of the *SRY* gene (sex-determining region Y) onto the X chromosome in 46,XX males [8]. The estimated prevalence is ~1:20,000–25,000 male births.

The phenotype typically includes normal male external genitalia, small testes, hypergonadotropic hypogonadism, and infertility. Severe spermatogenic failure is characteristic, often presenting as a Sertoli-cell-only syndrome. Diagnosis is based on karyotyping (46,XX) and molecular testing for *SRY*. In most cases, treatment includes testosterone replacement therapy. Virtually no potential for sperm retrieval via TESE is reported [8].

Reifenstein syndrome / Синдром Рейфенштейна

Reifenstein syndrome results from mutations in the *AR* gene (androgen receptor) and manifests with varying degrees of androgen resistance [9]. The classic phenotype includes hypospadias, micropenis, cryptorchidism, gynecomastia, and reduced body hair. The karyotype is typically 46,XY, but the degree of virilization varies widely. In reproductive age, most affected men exhibit hypergonadotropic hypogonadism and azoospermia. Lifelong endocrine follow-up and andrological management are essential. Testosterone therapy corrects no the underlying defect and is generally ineffective [9].

Y-microdeletions (*AZFa/b/c*) / Y-микроделеции (*AZFa/b/c*)

Microdeletions within the *AZF* regions of the Y chromosome are among the most common genetic causes of male infertility and NOA.

AZFa deletions are most often associated with a Sertoli cell-only syndrome phenotype, making sperm retrieval by TESE virtually impossible and the prognosis extremely poor.

AZFb deletions typically present with complete meiotic arrest; the chance of successful sperm retrieval is also minimal.

AZFc deletions show substantial phenotypic variability, ranging from severe oligozoospermia to azoospermia. This group has the highest likelihood of successful surgical sperm retrieval (TESE), with reported success rates averaging up to 50 % in large studies.

However, sperm obtained from men with *AZFc* deletions transmit the same microdeletion to male offspring when used in ICSI, accounting for conducting mandatory thorough genetic counseling for couples [2, 10–12].

Russian studies report Y-microdeletion prevalence among men with pathozoospermia to be about 15–20%, varying depending on patient selection criteria [13, 14].

Müllerian duct persistence syndrome / Синдром персистенции мюллеровых протоков

Persistent Müllerian duct syndrome (PMDS) is a rare autosomal recessive disorder in which Müllerian duct derivatives (uterus, fallopian tubes, upper vagina) persist in genetically and phenotypically male individuals (46,XY). The primary cause is mutations in the *AMH* (anti-Müllerian hormone) gene or the *AMHR2* (anti-Müllerian hormone type 2 receptor) gene, resulting in absent or ineffective AMH activity [15]. The karyotype is 46,XY,

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with normal development of the external genitalia. The most common manifestation is unilateral or bilateral cryptorchidism, frequently accompanied by developing inguinal or abdominal masses. During surgical treatment for cryptorchidism, Müllerian structures (uterus/tubes) are often identified.

In some patients, hypergonadotropic hypogonadism develops due to testicular damage caused by cryptorchidism and fibrosis, with profound spermatogenic impairment and common secretory azoospermia. PMDS is suspected when cryptorchidism is combined with pelvic masses. Diagnosis is confirmed by laparoscopy and histological examination.

Due to cryptorchidism and testicular tissue damage, most patients exhibit severely impaired spermatogenesis. The likelihood of retrieving sperm via TESE is extremely low. The primary management goals include surgical removal of Müllerian structures (when there is a risk of malignancy), orchiopexy, and testosterone replacement therapy for hypogonadism [15].

Cryptorchidism idiopathic / Крипторхизм идиопатический

Idiopathic cryptorchidism is a pathological condition in which one or both testes fail to descend into the scrotum, with prevalence comprising 2–4 % and up to 30 % in full-term newborns and preterm infants, respectively, although in most cases spontaneous descent occurs within the first year of life. Persistent cryptorchidism is observed in about 1.0 % of adult men [16].

Idiopathic cryptorchidism is diagnosed when no genetic or anatomical cause can be identified. It is considered a polyetiological disorder resulting from impaired testicular differentiation and migration [16]. Prolonged cryptorchidism leads to progressive damage to the spermatogenic epithelium. As early as 1–2 years of age, undescended testes show a reduced spermatogonia count. In adulthood, 30–60 % of men with untreated bilateral cryptorchidism develop NOA. In unilateral cases, the risk of infertility is lower, but approximately 20 % of patients exhibit reduced fertility despite a normal contralateral testis [16].

Adult men with cryptorchidism frequently present with hypergonadotropic hypogonadism (elevated FSH, reduced inhibin B), reflecting loss of spermatogenesis. Clinical trials indicate that 50–70% of men with bilateral cryptorchidism have azoospermia, while the remainder exhibit severe oligozoospermia [16]. Early orchiopexy (before 12–18 months of age) significantly improves the likelihood of preserving spermatogenesis. In adults with idiopathic cryptorchidism, the fertility-enhancing effect of orchiopexy is limited. The probability of successful sperm retrieval via TESE in men with untreated bilateral cryptorchidism remains low (10–30 %), although in selected cases fertilization via ICSI is achievable [16].

Autoimmune orchitis / Аутоиммунный орхит

Autoimmune orchitis is a chronic testicular inflammatory disorder associated with the production of antibodies targeting antigens of spermatogenic cells (anti-testicular antibodies). Under normal conditions, spermatozoa are immunologically protected by the blood–testis barrier; however, infections (mumps, tuberculosis, human papillomavirus), trauma, scrotal surgeries, varicocele, and systemic autoimmune diseases can disrupt this barrier and trigger an autoimmune response [17].

Clinical manifestations / Клинические проявления

Primary infertility is the most common presentation. Hypergonadotropic hypogonadism (elevated FSH and LH, low testosterone) is typical. Medical history often includes episodes of epididymo-orchitis, trauma, or prior scrotal surgery. Occasionally patients report testicular pain or enlargement, but in most cases the disease is subclinical [17].

Diagnostics / Диагностика

• Semen analysis: azoospermia or severe oligoasthenoteratozoospermia.

• Detection of antisperm antibodies: MAR test (Mixed Antiglobulin Reaction test), immunofluorescence test.

• Testicular ultrasound: diffuse hypoechoic changes, focal fibrotic areas.

• Testicular biopsy: lymphocytic infiltration, seminiferous tubule sclerosis, replacement of germinal epithelium with connective tissue [17].

Prognosis and treatment / Прогноз и лечение

TESE is generally ineffective in the presence of pronounced testicular fibrosis. In selected cases, cryopreservation of spermatozoa may be possible during early disease stages. When spermatozoa are present in the ejaculate, ICSI is the method of choice, as antisperm antibodies markedly impair natural fertilization [17]. Glucocorticoid therapy may temporarily reduce antibody levels, but its clinical efficacy is limited. Immunomodulators and antioxidant therapy are used, although the evidence base is weak. For most patients, ART programs (ICSI) represent the primary route to biological fatherhood [17].

Varicocele / Варикоцеле

Varicocele is a common finding in infertile men. In some patients with NOA and clinical varicocele, micro-surgical correction may lead to the reappearance of spermatozoa in the ejaculate and improved pregnancy rates, including following TESE [18, 19]. Meta-analyses report the return of ejaculated sperm in approximately 20–45 % of men with NOA after varicocelectomy, along with an increased rate of conception (spontaneous or ART-assisted) compared with

observation alone [15]. Russian reviews confirm clinical benefit in this patient subgroup [20, 21].

Varicocele and Klinefelter syndrome / Варикоцеле и синдром Клайнфельтера

Varicocele is diagnosed in ~15–20% of men in the general population and in 30–40 % of infertile patients [1]. In Klinefelter syndrome, its prevalence reaches 20–25 % according to various series [5]. In KS patients,spermatogenic impairment is primarily attributed to chromosomal aneuploidy and seminiferous tubule atrophy. Nonetheless, varicocele may exacerbate local hyperthermia, oxidative stress, and apoptosis of spermatogenic cells, further reducing the likelihood of successful sperm retrieval during micro-TESE [5].

A few studies report that although varicocele does not modify the core pathogenic mechanism of infertility in KS, its correction may provide limited improvement in testicular function. Among young patients (mosaic karyotype or residual spermatogenesis), isolated cases of ejaculated sperm appearance have been documented after varicocelectomy, facilitating subsequent ICSI attempts. However, there is no systematic evidence showing substantial improvement in ART outcomes following varicocele repair in KS.

Most experts agree that surgical correction of varicocele in KS is justified only in the presence of prominent clinical symptoms (pain, progressive testicular atrophy), but not as a fertility-restoring intervention [5].

In Russian patient series, varicocele was present in 18–20 % of men with KS. Surgical treatment was performed in a limited number of cases and did not restore spermatogenesis but alleviated pain and slow testicular atrophy progression [22].

Hypogonadotropic non-obstructive azoospermia / Необструктивная гипогонадотропная форма азооспермии

Congenital and acquired hypogonadotropic hypogonadism / Врожденный и приобретенный гипогонадотропный гипогонадизм

Congenital and acquired hypogonadotropic hypogonadism (HGG) is characterized by insufficient secretion of gonadotropins (FSH and LH) due to dysfunction of the hypothalamic–pituitary axis. This results in decreased testosterone production by Leydig cells and impaired spermatogenesis, often progressing to azoospermia. Unlike hypergonadotropic hypogonadism, HGG manifests with low or “inappropriately normal” FSH/LH levels and reduced testosterone.

The form of the disorder accompanied by anosmia is known as Kallmann syndrome. Its etiology involves mutations in genes such as *KAL1* (Kallmann syndrome 1 sequence gene), *FGFR1* (fibroblast growth factor receptor 1), *PROKR2* (prokineticin receptor 2), *CHD7* (chromodomain helicase DNA-binding protein 7), among others, which disrupt the migration and/or function of gonadotropin-releasing hormone (GnRH)-secreting neurons [23].

Men with HGG/Kallmann syndrome typically present with azoospermia, but 60–70 % can achieve spermatogenesis with prolonged gonadotropin therapy – human chorionic gonadotropin (hCG) with or without recombinant FSH or with pulsatile GnRH administration.

Acquired vs. congenital HGG is more common and may develop at any age. The main causes include:

1. tumors of the hypothalamic–pituitary region. Pituitary adenomas (especially macroadenomas), craniopharyngiomas, and germinomas. Mechanism: compression or destruction of hypothalamic–pituitary tissue → reduced gonadotropin secretion. Clinical manifestations: decreased libido, erectile dysfunction, azoospermia, and often concomitant deficiency of other pituitary hormones;

2. hyperprolactinemia. Causes: prolactinomas; medication-induced hyperprolactinemia (antipsychotics, antidepressants, metoclopramide). Mechanism: prolactin suppresses GnRH secretion. Treatment: dopamine agonists (cabergoline, bromocriptine) → restoration of spermatogenesis is possible in the majority of patients [23];

3. systemic diseases. Hemochromatosis (iron deposition in the pituitary and testes), sarcoidosis, histiocytosis, HIV infection. These conditions frequently lead to combined hypopituitarism;

4. trauma and medical interventions. Traumatic brain injury, pituitary surgery, radiotherapy, and chemotherapy. Such insults may cause transient or permanent gonadotropin deficiency and azoospermia;

5. functional HGG. Stress, chronic systemic illness (cirrhosis, chronic kidney disease), anorexia, and excessive physical exertion disrupt GnRH secretion, resulting in hypogonadotropic azoospermia.

Diagnosis is based on low or “inappropriately normal” FSH/LH levels in the presence of low testosterone. A lack of gonadotropin elevation after GnRH stimulation points at the central defect. Pituitary MRI is mandatory to exclude tumours.

Unlike hypergonadotropic hypogonadism, congenital and acquired HGG are fundamentally distinct in that spermatogenesis can be stimulated with relevant therapy [23]. In 60–70 % of men, spermatogenesis can be induced using gonadotropin therapy (hCG ± FSH) or pulsatile GnRH administration [23].

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In HGG, hCG monotherapy stimulates Leydig cells and increases testosterone, but spermatogenesis typically is not initiated without FSH. The addition of FSH (urinary or recombinant) is essential for Sertoli cell stimulation and induction of meiosis [23]. FSH preparations: urinary FSH (containing both FSH and LH) and recombinant FSH (follitropin alfa, follitropin beta). Typical regimen: treatment begins with hCG (1500–2500 IU twice weekly) to normalize testosterone. If no spermatozoa appear following 3–6 months, FSH (75–150 IU three times weekly) is added. Total duration: 6–24 months, sometimes longer. In men with congenital or acquired HGG, successful induction of spermatogenesis is achieved in 60–80 % of cases [23]. The mean time to spermatozoa appearance in the ejaculate is 6–12 months. FSH is the key hormone in HGG therapy: without it, complete recovery of spermatogenesis is impossible. Predictors of successful FSH-based treatment in HGG-associated azoospermia larger baseline testicular volume (> 8 mL), absence of former cryptorchidism, shorter duration of hypogonadism in acquired hypopituitarism, spontaneous pubertal development [23].

Altogether, such considerations underscore the relevance of studying patient cohorts from endocrinology centers in Saint Petersburg and Tashkent to identify a target group of infertile men managed jointly by endocrinologists and urologists-andrologists in real-world clinical practice.

Aim: to investigate the prevalence of different azoospermia forms in infertile men, within the context of real-world clinical practice at a non-specialized endocrine outpatient department, including personal observations, in comparison with the results of international and Russian epidemiological studies.

Materials and Methods / Материалы и методы

Study objectives / Задачи исследования

To achieve this aim, it is necessary to summarize current epidemiological data on the prevalence of different azoospermia forms, analyze personal findings after assessing patients with azoospermia and compare them with international and Russian data, and to develop a practical algorithm for the differential diagnosis of azoospermia for routine clinical use by urologists, endocrinologists, and reproductive specialists.

Study design / Дизайн исследования

The retrospective cohort observational study enrolled 450 men aged 25 to 45 years who presented with complaints of infertility, with azoospermia confirmed by semen analysis. Examination and treatment were carried out at the following centers: MEDSI Group Clinic (Saint Petersburg, Russia), Center for Academic Medicine LLC (Saint Petersburg, Russia), Genotechnology LLC (Tashkent, Republic of Uzbekistan), and Andijan State Medical Institute (Andijan, Republic of Uzbekistan).

Inclusion and exclusion criteria / Критерии включения и исключения

Inclusion criteria: age 25–45 years; clinical diagnosis of infertility (no pregnancy in the partner after ≥ 12 months of regular unprotected sexual intercourse); azoospermia confirmed by at least two semen analyses; written informed consent to participate in the study.

Exclusion criteria: age < 25 or > 45 years; prior vasectomy or other surgical interventions intentionally causing obstruction; severe somatic or oncological disease precluding full evaluation; refusal to participate in the study.

Study methods / Методы обследования

All patients underwent a comprehensive evaluation including:

– detailed medical history (reproductive, general medical, surgical);

– physical examination by assessing secondary sexual characteristics, testicular size and consistency; duplicate semen analysis (centrifugation and microscopy) performed according to the WHO methodology [1]; serum hormone quantitation: FSH, LH, total testosterone, prolactin, AMH, sex hormone–binding globulin (SHBG), inhibin B; when indicated – estradiol, thyroid-stimulating hormone (TSH), thyroxine (T4), and hCG; scrotal ultrasonography with Doppler assessment;

– genetic testing: karyotyping, screening for *AZF* microdeletions of the Y chromosome, and *CFTR* gene analysis when congenital absence of the *vas deferens* was suspected;

– within ART programs: testicular biopsy (TESE/micro-TESE) with histological examination and sperm cryopreservation.

Results and Discussion / Результаты и обсуждение

Based on the results from the comprehensive evaluation, all 450 patients were classified into diagnostic groups presented in **Table 1**.

The data obtained confirm that non-obstructive azoospermia predominates in this cohort (63.3 %), which is consistent with international reports (60–70 %) [2, 5, 10]. Among NOA cases, idiopathic NOA accounted for the largest percentage (19.6 %), slightly lower than global estimates of 30–40 % [2].

Genetic causes were identified in a substantial number of patients. Klinefelter syndrome was diagnosed in 8.4 %,

Table 1. Prevalence of different forms of azoospermia in infertile men – comparison of own data with results of international studies.

Таблица 1. Частота различных форм азооспермии у мужчин с бесплодием – сравнение собственных данных с результатами международных исследований.

Azoospermia form **Форма азооспермии**	**Frequency according to research data, % [references]** **Частота по данным исследований, % [первоисточники]**	**Own data** **Собственные данные** **n = 450** **n (%)**
Obstructive azoospermia (total) **Обструктивная азооспермия (суммарно)**	**~30–40 [1, 2]**	**135 (30,0)**
Mucoviscidosis/*CFTR*-related CBAVD Муковисцидоз/CFTR-ассоциированная ВДОСП	1–2 [7, 8]	2 (0,4)
Post-infectious or post-traumatic obstruction Постинфекционная или посттравматическая обструкция	~25–30 [2]	133 (29,6)
Non-obstructive azoospermia (total) **Необструктивная азооспермия (суммарно)**	**~60–70 [2, 5, 10]**	**285 (63,3)**
Klinefelter syndrome (47,XXY) Синдром Клайнфельтера (47,XXY)	~10 [6]	38 (8,4)
de la Chapelle syndrome (46,XX) Синдром де ля Шапеля (46,XX)	< 1,0	10 (2,2)
Reifenstein syndrome (46,XY) Синдром Рейфенштейна (46,XY)	< 1,0	8 (1,8)
Y-chromosome microdeletions (*AZFa, AZFb, AZFc*) Y-микроделеции (*AZFa, AZFb, AZFc*)	~8–12 [7]	26 (5,8)
Persistent Müllerian duct syndrome Синдром персистенции мюллеровых протоков	< 1,0	4 (0,9)
Idiopathic cryptorchidism in history Крипторхизм идиопатический в анамнезе	~9–10 [16]	42 (9,3)
Autoimmune orchitis Аутоиммунный орхит	2–3 [17]	15 (3,3)
Varicocele (associated with non-obstructive azoospermia) Варикоцеле (сочетание с необструктивной азооспермией)	10–15 [16, 17]	54 (12,0)
Idiopathic non-obstructive azoospermia Идиопатическая необструктивная азооспермия	~30–40 [2, 5, 10]	88 (19,6)
Hypogonadotropic hypogonadism (total) **Гипогонадотропный гипогонадизм (суммарно)**	**~2–5 [5]**	**30 (6,7)**
Congenital forms (HGG/Kallmann syndrome) Врожденные формы (ГГГ/синдром Каллмана)	~1,0 [23]	12 (2,7)
Acquired forms (hyperprolactinemia) Приобретенные формы (гиперпролактинемия)	1–2 [23]	10 (2,2)
Acquired forms (post-traumatic/post-surgical hypopituitarism) Приобретенные формы (посттравматический/послеоперационный гипопитуитаризм)	1,0 [23]	5 (1,1)
Acquired forms (idiopathic HGG) Приобретенные формы (идиопатический ГГГ)	< 1,0 [23]	3 (0,7)
Total / Всего		**450 (100,0)**

Note: *CFTR – cystic fibrosis transmembrane conductance regulator; CBAVD – congenital bilateral absence of the vas deferens; AZF – azoospermia factor; HGG – hypogonadotropic hypogonadism.*

Примечание: *CFTR – трансмембранный регулятор муковисцидоза; ВДОСП – врожденное двустороннее отсутствие семявыносящих протоков; AZF – фактор азооспермии; ГГГ – гипогонадотропный гипогонадизм.*

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consistent with large cohort studies reporting 8–10 % [6]. Y-chromosome microdeletions were found in 5.8 % of men – slightly below the international range (8–12 %) [7], likely due to ethnic factors and limitations of the marker panel used. Rare etiologies – de la Chapelle syndrome (2.2 %), Reifenstein syndrome (1.8 %), and persistent Müllerian duct syndrome (0.9 %) were less prevalent, yet remain critically important for accurate diagnosis and genetic counseling.

A history of cryptorchidism was recorded in 9.3 % of patients, aligning with published data (9–10 %) [21]. Autoimmune orchitis accounted for 3.3 %, some higher than the expected 2–3 % [22], possibly reflecting variability in diagnostic criteria, as detection of anti-testicular antibodies is not always reliable. Varicocele associated with NOA was observed in 12 %, consistent with its known prevalence among infertile men [16, 17].

Obstructive azoospermia was somewhat less common in our study (30 %) than in a number of international publications (up to 40 %) [1, 2]. Among OA etiologies, post-infectious or post-traumatic obstruction predominated (29.6 %). *CFTR*-associated CBAVD was identified in only 0.4 % of patients, below the international estimate of 1–2 % [7, 8], potentially due to restricted genetic testing or population-specific factors.

Hypogonadotropic hypogonadism was found in 6.7 % of men, exceeding typical published studies (2–5 %) [5]. Both congenital forms (Kallmann syndrome – 2.7 %) and acquired forms (hyperprolactinemia, post-traumatic hypopituitarism) were represented, underscoring the need for thorough neuroendocrine evaluation in men with azoospermia [23].

Thus, the results confirm that azoospermia is a clinically and etiologically heterogeneous condition. The data for our patient cohort are consistent with global trends, but the discrepancies identified (a higher proportion of HGG, a slightly lower frequency of *CFTR*-associated CBAVD and Y microdeletions) may reflect population characteristics and methodological differences.

Practical algorithm for the diagnostic workup and management of patients with azoospermia / Практический алгоритм по обследованию и тактике ведения пациентов с азооспермией

Based on conducted study of men with azoospermia, taking into account international data, we developed an algorithm for examining men with azoospermia, which we present to readers.

1. Confirm azoospermia according to the WHO Laboratory Manual for the Examination and Processing of Human Semen.

2. Differentiate obstructive (OA) from non-obstructive azoospermia (NOA) using:

– testicular volume;
– presence or absence of the *vas deferens*;
– serum levels of FSH, LH, total (and free) testosterone, inhibin B, AMH, prolactin;
– scrotal ultrasound / transrectal prostate ultrasound;
– *CFTR* mutation testing.

3. In cases of NOA, perform extended genetic testing, including:
– karyotyping;
– *SRY* mutations;
– Y-chromosome *AZF* microdeletions;
– *AR* gene mutations.

4. Identify reversible causes of NOA, such as varicocele or hydrocele.

5. For NOA: discuss the role of micro-TESE and ART.

6. For hypogonadotropic azoospermia: induce spermatogenesis with gonadotropins (hCG + FSH); for hyperprolactinemia: initiate dopamine agonist therapy.

7. Provide genetic counseling for the couple.

Notes on the algorithm / Пояснения к алгоритму

{A} Azoospermia or oligozoospermia must be assessed only after excluding medication use that affects the reproductive system, chronic intoxications, and occupational hazards. In cases of azoospermia, differential diagnosis with obstructive azoospermia is essential, particularly in men with a history of epididymo-orchitis, vasectomy, or cystic fibrosis. Measurement of α-glucosidase (and fructose) in the ejaculate is helpful, as it is markedly reduced in obstruction.

{B} In this situation, it is necessary to differentiate among the various forms of hypogonadotropic hypogonadism. In most cases these represent congenital disorders, including idiopathic hypogonadotropic hypogonadism and Kallmann syndrome (when anosmia is present). However, hypogonadism may also result from tumors or malformations of the hypothalamic–pituitary region. If a craniopharyngioma or another neoplasm is diagnosed, neurosurgical intervention may be required.

{C} Hyperprolactinemia and prolactin-secreting pituitary adenoma (prolactinoma) are fairly common causes of male infertility. Treatment with dopamine receptor agonists (cabergoline, bromocriptine) leads to normalization of sexual function and restoration of spermatogenesis. In resistant cases, neurosurgical management may be necessary.

{D} Testicular tumors producing estrogens or hCG are increasingly encountered among men seeking medical attention for infertility. Progressive tumor growth within the testis suppresses spermatogenesis and disrupts steroidogenesis, leading to sexual dysfunction and infertility. Sperm cryopreservation is recommended, as subsequent treatment may further impair germinal epithelium or necessitate gonadectomy (in some cases, bilateral).

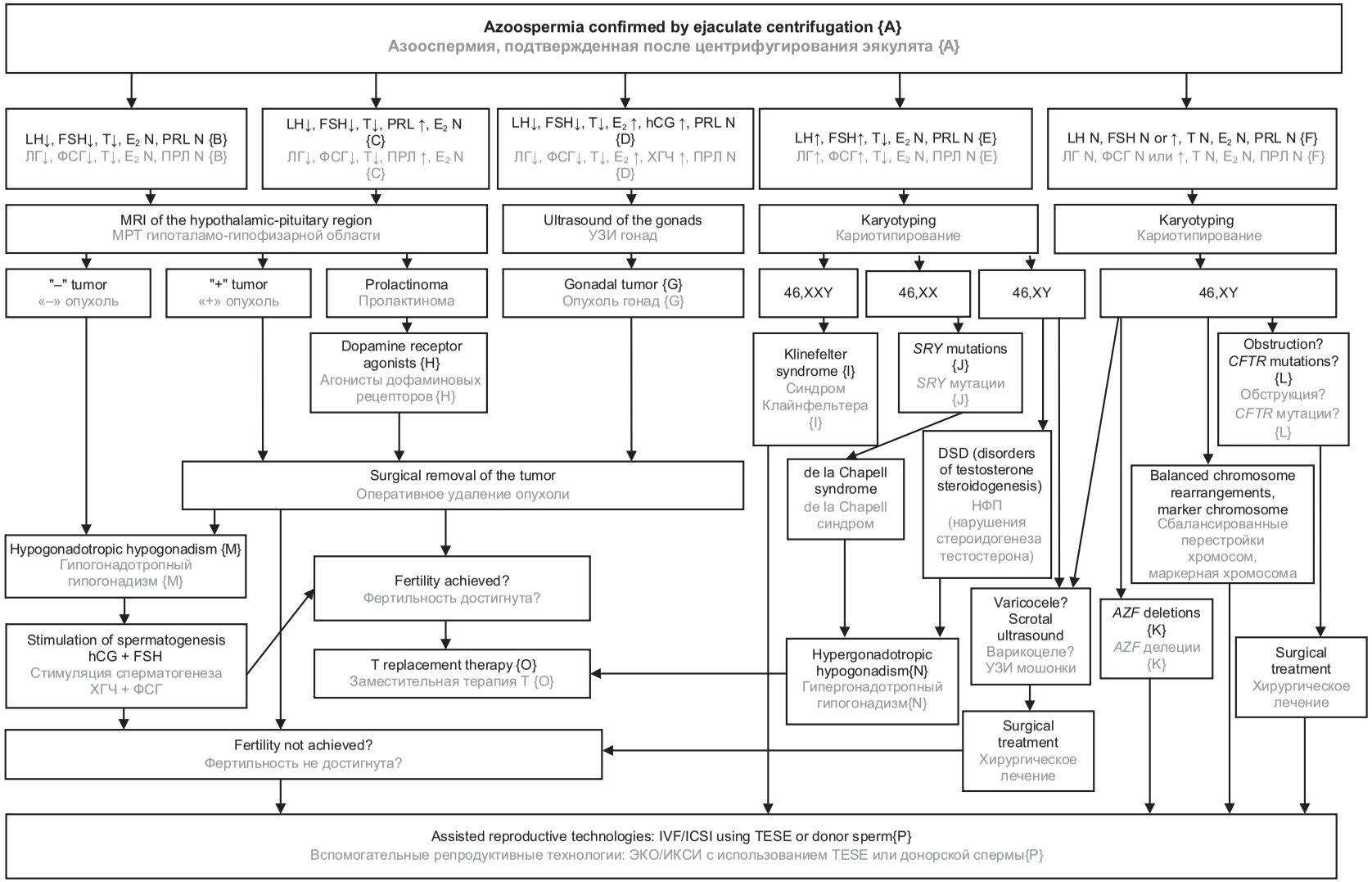

Figure 1. Algorithm for azoospermia differential diagnostics.

Note: *E_2 – estradiol; LH – luteinizing hormone; PRL – prolactin; T – testosterone; N – normal value; FSH – follicle-stimulating hormone; hCG – human chorionic gonadotropin; AZF – azoospermia factor; DSD – disorders of sex development; MRI – magnetic resonance imaging; IVF – in vitro fertilization; ICSI – intracytoplasmic sperm injection; TESE – testicular sperm extraction.*

Рисунок 1. Алгоритм дифференциальной диагностики азооспермии.

Примечание: *E_2 – эстрадиол; ЛГ – лютеинизирующий гормон; ПРЛ – пролактин; Т – тестостерон; N – нормальный показатель; ФСГ – фолликулостимулирующий гормон; ХГЧ – хорионический гонадотропин человека; AZF – фактор азооспермии; НФП – нарушения формирования пола; МРТ – магнитно-резонансная томография; УЗИ – ультразвуковое исследование; ЭКО – экстракорпоральное оплодотворение; ИКСИ – интрацитоплазматическая инъекция сперматозоида; TESE – тестикулярная экстракция сперматозоидов.*

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{E} In this case, the cause of infertility is hypergonadotropic hypogonadism, which may result from congenital (e.g., karyotype abnormalities) or acquired factors. Among the latter, scrotal disorders that provoke testicular atrophy are most prominent, including varicocele, hydrocele, trauma, and testicular torsion.

{F} Isolated elevation of FSH in infertile men most often indicates isolated damage to the germinal epithelium (spermatogenesis), which may result from both congenital and acquired causes. In congenital forms, impaired spermatogenesis is most commonly associated with Y-chromosome microdeletions (*AZF* gene deletions). Acquired forms of spermatogenic dysfunction are more often related to developing autoimmune process in the testes – autoimmune orchitis or to testicular damage resulting from varicocele or hydrocele.

{G} A twofold increase in estradiol levels or elevated hCG in the blood indicates a possible testicular tumor, which manifests with gynecomastia, reduced sexual desire, and infertility (oligozoospermia or azoospermia).

{H} Dopaminergic receptor agonists allow for to normalizing serum prolactin levels and restore spermatogenesis. If no recovery occur, the cause of infertility may be due to accompanying pituitary adenoma (more commonly a macroadenoma), development of hypogonadotropic hypogonadism, or a combination with other factors.

{I} Klinefelter syndrome most often presents clinically with infertility of varying severity: from azoospermia and hyalinization of the seminiferous tubules to oligozoospermia. Even cases of normozoospermia have been described. However, pharmacological treatment options for Klinefelter syndrome are not available. Sperm cryopreservation and ART are indicated to overcome infertility.

{J} De la Chapelle syndrome is a rare cause of male infertility, but such patients may present in the practice of endocrinologists, andrologists, and reproductive specialists. In most cases, men with a 46,XX karyotype have severe spermatogenic dysfunction: azoospermia, hyalinization of the seminiferous tubules, and treatment of such infertility is not feasible. Testicular biopsy is not recommended in these patients for sperm retrieval.

{K} Microdeletions of the Y chromosome are a common finding in infertile men. Loss of the critical *AZF* region essential for spermatogenesis leads to infertility. Pharmacological treatments are not available. ART are indicated. In patients with azoospermia, testicular biopsy (TESE) is recommended to attempt sperm retrieval.

{L} In patients with normal gonadotropin levels, differential diagnosis between OA and NOA is required. Measurement of α-glucosidase and fructose in the ejaculate may assist in diagnosis. Genetic testing for *CFTR* mutations is also indicated, as cystic fibrosis may cause infertility. The mechanism of OA formation relies on congenital underdevelopment of the *vas deferens*. Treatment of infertility is possible only with ART (IVF). Sperm retrieval is performed using TESE. If OA is caused by acquired obstruction, fertility may be restored surgically by reconstructive repair of the *vas deferens*.

{M} Treatment of infertility in hypogonadotropic hypogonadism requires the use of FSH and hCG. The duration of therapy is at least 1 year. Complete restoration of spermatogenesis has been demonstrated in these patients. However, treatment failure occurs in about 10 % of cases.

{N} Pharmacotherapy for infertility in patients with hypergonadotropic hypogonadism has not been developed. In most cases, ART is required, so that male patients should undergo sperm cryopreservation.

{O} Testosterone replacement therapy in men with hypogonadism is lifelong. Testosterone preparations suppress FSH production in the anterior pituitary and may worsen semen parameters. Therefore, sperm cryopreservation is recommended before onset of androgen replacement therapy.

{P} Assisted reproductive technologies allow infertility to be overcome in the majority of male reproductive disorders. However, the choice of method depends on the expertise of the reproductive center, its technical capabilities, and the patient's specific diagnosis. If sperm retrieval is unsuccessful, donor sperm is indicated. Genetic testing and counseling of the couple are recommended in most ART cases.

Conclusion / Заключение

Among the 450 men with azoospermia, the non-obstructive form predominated (63.3%), with idiopathic NOA being the most frequent subtype. Genetic factors (Klinefelter syndrome, Y-chromosome microdeletions, and rare disorders of sex development) were identified in nearly one out of six patients, confirming the need for mandatory genetic testing in the diagnostic algorithm for azoospermia. Obstructive azoospermia (30 %) was most often associated with post-infectious and post-traumatic changes, whereas CBAVD associated with *CFTR* mutations was less common than in international cohorts. The proportion of hypogonadotropic hypogonadism was higher than expected (6.7 %), underscoring the importance of comprehensive hormonal evaluation in all men with azoospermia.

Altogether, our results agree with international data but highlight certain regional characteristics that should be taken into consideration while developing national clinical guidelines.

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Data sharing	**Раскрытие данных**
The dataset used and/or analyzed during the current study available from the corresponding author on reasonable request.	Массив данных, использованный и/или проанализированный в ходе настоящего исследования, может быть предоставлен корреспондирующим автором по обоснованному запросу.
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References:

1. WHO laboratory manual for the examination and processing of human semen. 6th ed. *Geneva: World Health Organization,* 2021. 292 p. https://doi.org/10.1002/9781119037063.
2. EAU Guidelines. Edn. presented at the EAU Annual Congress. *Madrid,* 2025. ISBN 978-94-92671-29-5. http://uroweb.org/guidelines/compilations-of-all-guidelines.
3. Brannigan R.E., Hermanson L., Kaczmarek J. et al. Updates to Male Infertility: AUA/ASRM Guideline (2024). *J Urol.* 2024;212(6):789–99. https://doi.org/10.1097/JU.0000000000004180.
4. Flannigan R., Najafabadi B.T., Violette P.D. et al. 2023 Canadian Urological Association guideline: evaluation and management of azoospermia. *Can Urol Assoc J.* 2023;17(8):228–40. https://doi.org/10.5489/cuaj.8445.
5. Esteves S.C., Chan P. A systematic review of recent clinical practice guidelines and best practice statements for the evaluation of the infertile male. *Int Urol Nephrol.* 2015;47(9):1441–56. https://doi.org/10.1007/s11255-015-1059-0.
6. Lanfranco F., Kamischke A., Zitzmann M., Nieschlag E. Klinefelter's syndrome. *Lancet*. 2004;364(9430):273–83. https://doi.org/10.1016/S0140-6736(04)16678-6.
7. Cioppi F., Rosta V., Krausz C. Genetics of azoospermia. *Int J Mol Sci.* 2021;22(6):3264. https://doi.org/10.3390/ijms22063264.
8. Krausz C., Riera-Escamilla A. Genetics of male infertility. *Nat Rev Urol.* 2018;15(6):369–84. https://doi.org/10.1038/s41585-018-0003-3.
9. James E.R., Tasnim M., Riera-Escamilla A. et al. Genetic and epigenetic landscape of male infertility. *Trends Genet*. 2025;41(10):883–98. https://doi.org/10.1016/j.tig.2025.07.007.
10. Raman J.D., Schlegel P.N. Testicular sperm extraction with intracytoplasmic sperm injection is successful for the treatment of non-obstructive azoospermia. *J Urol*. 2003;170(4 Pt 1):1287–90. https://doi.org/10.1097/01.ju.0000080707.75753.ec.
11. Gudeloglu A., Parekattil S.J. Update in the evaluation of the azoospermic male. *Clinics*. 2013;68 Suppl 1(Suppl 1):27–34. https://doi.org/10.6061/clinics/2013(sup01)04.
12. Schlegel P.N., Sigman M., Collura B. et al. Diagnosis and treatment of infertility in men: AUA/ASRM guideline part II. *Fertil Steril.* 2021;115(1):62–9. https://doi.org/10.1016/j.fertnstert.2020.11.016.
13. Filiponi M, Zachariou A. Navigating male infertility through testicular biopsy: outcomes, predictive parameters, and surgical innovation. *Syst Biol Reprod Med*. 2025;71(1):402–15. https://doi.org/10.1080/19396368.2025.2551006.
14. Fontana L., Sirchia S.M., Pesenti C. et al. Non-invasive biomarkers for sperm retrieval in non-obstructive patients: a comprehensive review. *Front Endocrinol (Lausanne)*. 2024;15:1349000. https://doi.org/10.3389/fendo.2024.1349000.
15. Al-Shukri S.Kh., Gzgzyan A.M., Borovets S.Yu. et al. The prognostic value of AZF locus microdeletions and Klinefelter syndrome in men with azoospermia in relation to the effectiveness of testis biopsy and the outcomes of assisted reproductive technology (review of literature). [Prognosticheskaya znachimost' mikrodelecij lokusov AZF i sindroma Klajnfel'tera u muzhchin s azoospermiej v otnoshenii rezul'tativnosti biopsii yaichka i iskhodov vspomogatel'nyh reproduktivnyh tekhnologij (obzor literatury)]. *Nefrologiya*. 2016;20(4):40–6. (In Russ.).

16. Popova A.Yu., Gamidov S.I., Ovchinnikov R.I. et al. Varicocele and non-obstructive azoospermia – where to start? [Varikocele i neobstruktivnaya azoospermiya – s chego nachat'?]. *Andrologiya i genital'naya hirurgiya*. 2017;18(4):77–80. (In Russ.). https://doi.org/10.17650/2070-9781-2017-18-4-77-80.
17. Prikhodko A.V., Belyaeva L.N., Moiseeva I.V., Tyumina O.V. The efficiency of ART methods for treatment of male infertility in men of age 40 years and older with obstructive azoospermia. [Rezul'tativnost' primeneniya metodov VRT dlya lecheniya besplodiya u muzhchin starshe 40 let s obstruktivnoj azoospermiej]. *Urologiya*. 2020;(1):76–80. (In Russ.). https://doi.org/10.18565/urology.2020.1.76-80.
18. Zarezadeh R., Fattahi A., Nikanfar S. et al. Hormonal markers as noninvasive predictors of sperm retrieval in non-obstructive azoospermia. *J Assist Reprod Genet*. 2021;38(8):2049–59. https://doi.org/10.1007/s10815-021-02176-3.
19. Kaltsas A., Stavros S., Kratiras Z. et al. Predictors of successful testicular sperm extraction: A new era for men with non-obstructive azoospermia. *Biomedicines*. 2024;12(12):2679. https://doi.org/10.3390/biomedicines12122679.
20. Gamidov S.I., Shatylko T.V., Tambiev A.Kh et al. Difficulties in differential diagnosis between obstructive and non-obstructive azoospermia. [Trudnosti v differentsial'noi diagnostike obstruktivnoj i neobstruktivnoj azoospermii]. *Vestnik urologii*. 2022;10(3):19–31. (In Russ.). https://doi.org/10.21886/2308-6424-2022-10-2-19-31.
21. Gamidov S.I., Popova A.A., Ovchinnikov R.I. Non-obstructive azoospermia – clinical guidelines. [Neobstruktivnaya azoospermiya – klinicheskie rekomendatsii]. *Rossiiskii meditsinskii zhurnal*. 2015;23(11):595–601. (In Russ.).
22. Marnat E.G., Adyan T.A., Stepanova A.A. et al. Comparison of the CFTR gene variants and genotypes in Russian patients with various forms of pathozoospermia and CBAVD syndrome. [Sravnenie variantov gena CFTR i genotipov u rossijskih pacientov s razlichnymi formami patozoospermii i s sindromom CBAVD]. *Medicinskaya genetika*. 2020;19(3):93–5. (In Russ.). https://doi.org/10.25557/2073-7998.2020.03.93-95.
23. Akilov F.A., Mukhtarov Sh.T., Shomarufov A.B. et al. Assessment of semen parameters after microsurgical varicocelectomy in infertile men. [Otsenka parametrov ejakulyata posle mikrokhirurgicheskoi varikotselektomii u muzhchin iz besplodnykh par]. *Vestnik urologii*. 2023;11(3):16–22. (In Russ.). https://doi.org/10.21886/2308-6424-2023-11-3-16-22.

Литература:

1. WHO laboratory manual for the examination and processing of human semen. 6th ed. *Geneva: World Health Organization,* 2021. 292 p. https://doi.org/10.1002/9781119037063.
2. EAU Guidelines. Edn. presented at the EAU Annual Congress. *Madrid,* 2025. ISBN 978-94-92671-29-5. http://uroweb.org/guidelines/compilations-of-all-guidelines.
3. Brannigan R.E., Hermanson L., Kaczmarek J. et al. Updates to Male Infertility: AUA/ASRM Guideline (2024). *J Urol*. 2024;212(6):789–99. https://doi.org/10.1097/JU.0000000000004180.
4. Flannigan R., Najafabadi B.T., Violette P.D. et al. 2023 Canadian Urological Association guideline: evaluation and management of azoospermia. *Can Urol Assoc J*. 2023;17(8):228–40. https://doi.org/10.5489/cuaj.8445.
5. Esteves S.C., Chan P. A systematic review of recent clinical practice guidelines and best practice statements for the evaluation of the infertile male. *Int Urol Nephrol*. 2015;47(9):1441–56. https://doi.org/10.1007/s11255-015-1059-0.
6. Lanfranco F., Kamischke A., Zitzmann M., Nieschlag E. Klinefelter's syndrome. *Lancet*. 2004;364(9430):273–83. https://doi.org/10.1016/S0140-6736(04)16678-6.
7. Cioppi F., Rosta V., Krausz C. Genetics of azoospermia. *Int J Mol Sci*. 2021;22(6):3264. https://doi.org/10.3390/ijms22063264.
8. Krausz C., Riera-Escamilla A. Genetics of male infertility. *Nat Rev Urol*. 2018;15(6):369–84. https://doi.org/10.1038/s41585-018-0003-3.
9. James E.R., Tasnim M., Riera-Escamilla A. et al. Genetic and epigenetic landscape of male infertility. *Trends Genet*. 2025;41(10):883–98. https://doi.org/10.1016/j.tig.2025.07.007.
10. Raman J.D., Schlegel P.N. Testicular sperm extraction with intracytoplasmic sperm injection is successful for the treatment of non-obstructive azoospermia. *J Urol*. 2003;170(4 Pt 1):1287–90. https://doi.org/10.1097/01.ju.0000080707.75753.ec.
11. Gudeloglu A., Parekattil S.J. Update in the evaluation of the azoospermic male. *Clinics*. 2013;68 Suppl 1(Suppl 1):27–34. https://doi.org/10.6061/clinics/2013(sup01)04.
12. Schlegel P.N., Sigman M., Collura B. et al. Diagnosis and treatment of infertility in men: AUA/ASRM guideline part II. *Fertil Steril*. 2021;115(1):62–9. https://doi.org/10.1016/j.fertnstert.2020.11.016.
13. Filiponi M, Zachariou A. Navigating male infertility through testicular biopsy: outcomes, predictive parameters, and surgical innovation. *Syst Biol Reprod Med*. 2025;71(1):402–15. https://doi.org/10.1080/19396368.2025.2551006.
14. Fontana L., Sirchia S.M., Pesenti C. et al. Non-invasive biomarkers for sperm retrieval in non-obstructive patients: a comprehensive review. *Front Endocrinol (Lausanne)*. 2024;15:1349000. https://doi.org/10.3389/fendo.2024.1349000.
15. Аль-Шукри С.Х., Гзгзян А.М., Боровец С.Ю. и др. Прогностическая значимость микроделеций локусов AZF и синдрома Клайнфельтера у мужчин с азооспермией в отношении результативности биопсии яичка и исходов вспомогательных репродуктивных технологий (обзор литературы). *Нефрология*. 2016;20(4):40–6.
16. Попова А.Ю., Гамидов С И., Овчинников Р.И. и др. Варикоцеле и необструктивная азооспермия – с чего начать? *Андрология и генитальная хирургия*. 2017;18(4):77–80. https://doi.org/10.17650/2070-9781-2017-18-4-77-80.
17. Приходько А.В., Беляева Л.Н., Моисеева И.В., Тюмина О.В. Результативность применения методов ВРТ для лечения бесплодия у мужчин старше 40 лет с обструктивной азооспермией. *Урология*. 2020;(1):76–80. https://doi.org/10.18565/urology.2020.1.76-80.
18. Zarezadeh R., Fattahi A., Nikanfar S. et al. Hormonal markers as noninvasive predictors of sperm retrieval in non-obstructive azoospermia. *J Assist Reprod Genet*. 2021;38(8):2049–59. https://doi.org/10.1007/s10815-021-02176-3.
19. Kaltsas A., Stavros S., Kratiras Z. et al. Predictors of successful testicular sperm extraction: A new era for men with non-obstructive azoospermia. *Biomedicines*. 2024;12(12):2679. https://doi.org/10.3390/biomedicines12122679.
20. Гамидов С.И., Шатылко Т.В., Тамбиев А.Х. и др. Трудности в дифференциальной диагностике обструктивной и необструктивной азооспермии. *Вестник урологии*. 2022;10(3):19–31. https://doi.org/10.21886/2308-6424-2022-10-2-19-31.
21. Гамидов С.И., Попова А.А., Овчинников Р.И. Необструктивная азооспермия – клинические рекомендации. *Российский медицинский журнал*. 2015;23(11):595–601.
22. Марнат Е.Г., Адян Т.А., Степанова А.А. и др. Сравнение вариантов гена CFTR и генотипов у российских пациентов с различными формами патозооспермии и с синдромом CBAVD. *Медицинская генетика*. 2020;19(3):93–5. https://doi.org/10.25557/2073-7998.2020.03.93-95.
23. Акилов Ф.А., Мухтаров Ш.Т., Шомаруфов А.Б. и др. Оценка параметров эякулята после микрохирургической варикоцелэктомии у мужчин из бесплодных пар. *Вестник урологии*. 2023;11(3):16–22. https://doi.org/10.21886/2308-6424-2023-11-3-16-22.

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