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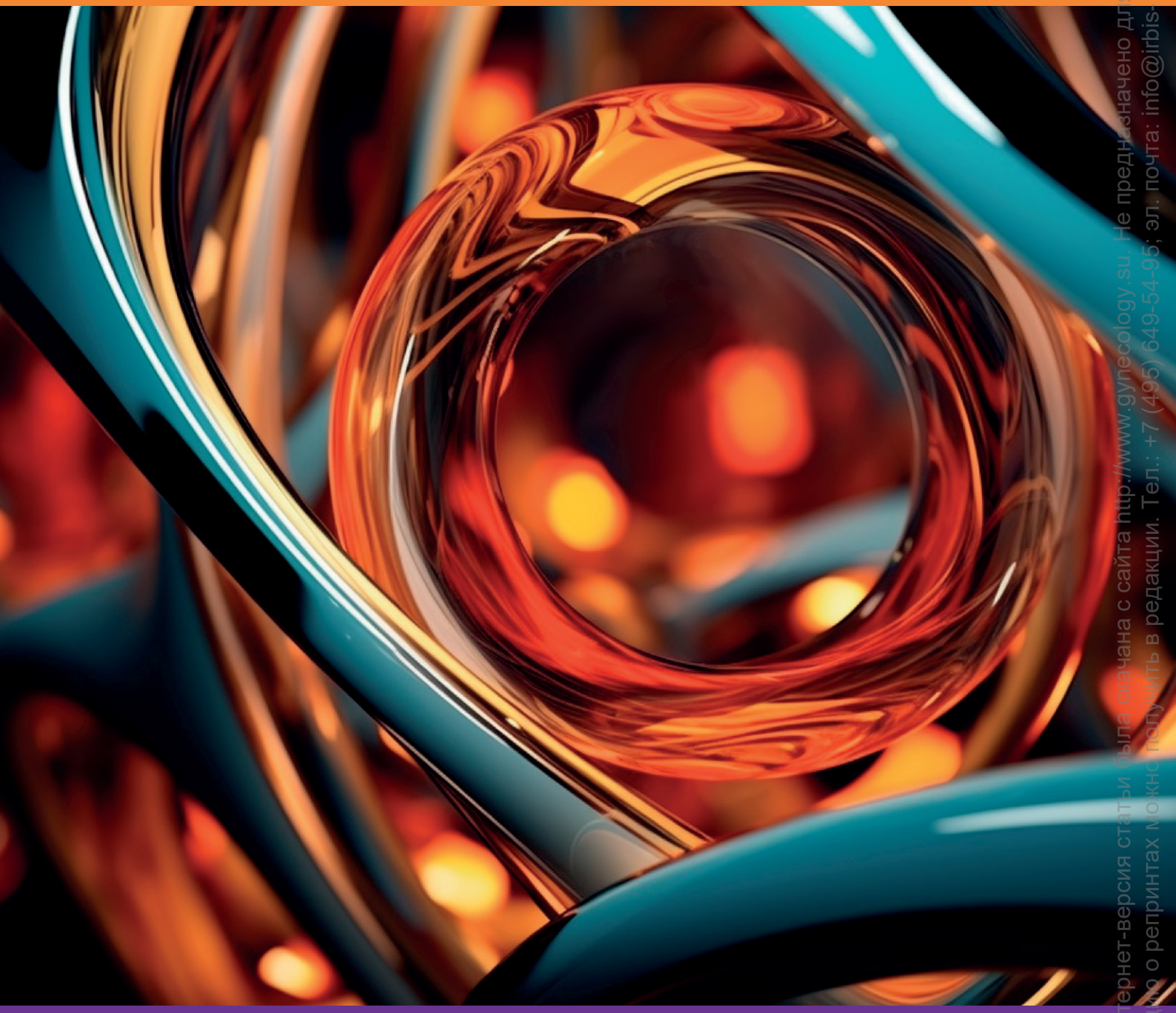

# OBSTETRICS, GYNECOLOGY AND REPRODUCTION

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# Oligozoospermia: etiology, pathogenesis, and algorithm for differential diagnostics

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**Abstract**

**Aim:** to compare international and Russian epidemiological data on the causes of oligozoospermia and to develop differential diagnostics and patient management algorithm by taking into account endocrine, genetic and immunological factors.

**Materials and Methods.** A retrospective observational study included 210 men aged 25-45 years with confirmed oligozoospermia and infertility complaints. All patients underwent semen analysis according to the World Health Organization standards (2021), blood hormone testing (follicle-stimulating hormone, luteinizing hormone, total testosterone, prolactin, thyroid-stimulating hormone, estradiol, inhibin B, anti-Müllerian hormone, 17-hydroxyprogesterone), scrotal ultrasound, as well as genetic testing (karyotyping and Y-chromosome microdeletions). The data provided by international clinical guidelines, European Association of Urology (EAU, 2024), American Urological Association/American Society for Reproductive Medicine (AUA/ASRM, 2024), publications in Russian and English retrieved from PubMed/MEDLINE, Scopus and eLibrary databases were analyzed.

**Results.** A wide spectrum of oligozoospermia causes was identified: endocrine disorders (hypo- and hypergonadotropic hypogonadism), Klinefelter syndrome, Y-chromosome microdeletions, varicocele, and obstructive forms. The pathophysiological mechanisms of hypogonadism, the clinical significance of Klinefelter syndrome, features of Y-chromosome azoospermia factor deletions, and the role of varicocele as a potentially reversible cause of male infertility are discussed in detail.

**Conclusion.** Differential diagnosis of oligozoospermia requires a comprehensive, stepwise approach. Incorporating repeated semen analysis, hormonal profiling, ultrasound, and genetic testing into the diagnostic algorithm enables identification of reversible causes (varicocele, hypogonadotropic hypogonadism) as well as timely diagnostics of genetic forms (Klinefelter syndrome, Y-chromosome microdeletions). This ensures a personalized therapeutic strategy and improves the effectiveness of assisted reproductive technologies.

**Keywords:** oligozoospermia, male infertility, hypogonadism, hypogonadotropic hypogonadism, Klinefelter syndrome, Y-chromosome microdeletions, varicocele

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# Олигозооспермия: этиология, патогенез и алгоритм дифференциальной диагностики

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**Резюме**

**Цель:** сравнить международные и российские эпидемиологические данные по причинам развития олигозооспермии и разработать алгоритм дифференциальной диагностики и ведения пациентов с учетом эндокринных, генетических и иммунологических факторов.

**Материалы и методы.** В ретроспективное наблюдательное исследование включены 210 мужчин в возрасте 25–45 лет с подтвержденной олигозооспермией и жалобами на бесплодие. Всем пациентам проведены анализы спермы по стандартам Всемирной организации здравоохранения (2021), исследования содержания гормонов в крови – фолликулостимулирующего гормона, лютеинизирующего гормона, общего тестостерона, пролактина, тиреотропного гормона, эстрадиола, ингибина B, антимюллерова гормона, 17-OH прогестерона, ультразвуковое исследование органов мошонки, генетическое обследование (кариотип, микроделеции Y-хромосомы). Для сопоставления с результатами предыдущих исследований использованы данные международных клинических рекомендаций, Европейской ассоциации урологов (англ. European Association of Urology, EAU, 2024), Американской урологической ассоциации/Американского общества репродуктивной медицины (англ. American Urological Association/American Society for Reproductive Medicine, AUA/ASRM, 2024), публикации из PubMed/MEDLINE, Scopus и eLibrary на русском и английском языках.

**Результаты.** Выявлен широкий спектр причин олигозооспермии: эндокринные нарушения (гипо- и гипергонадотропный гипогонадизм), синдром Клайнфельтера, микроделеции Y-хромосомы, варикоцеле, обструктивные формы. Подробно рассмотрены патофизиологические механизмы гипогонадизма, клиническое значение синдрома Клайнфельтера, особенности делеций фактора азооспермии Y-хромосомы, а также роль варикоцеле как потенциально обратимой причины мужского бесплодия.

**Заключение.** Дифференциальная диагностика олигозооспермии требует комплексного и поэтапного подхода. Включение в алгоритм повторных исследований спермы, гормонального профиля, ультразвуковой и генетической диагностики позволяет не только выявлять обратимые причины (варикоцеле, гипогонадотропный гипогонадизм), но и своевременно диагностировать генетические формы (синдром Клайнфельтера, Y-микроделеции). Это обеспечивает персонализированный выбор лечебной тактики и повышает эффективность применения вспомогательных репродуктивных технологий.

**Ключевые слова:** олигозооспермия, мужское бесплодие, гипогонадизм, гипогонадотропный гипогонадизм, синдром Клайнфельтера, микроделеции Y-хромосомы, варикоцеле

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## Introduction / Введение

Male infertility is one of the key medical and social challenges of modern healthcare. According to the World Health Organization (WHO), up to 15 % of couples experience infertility, with a male factor identified in approximately 40–50 % of cases [1]. Among the various forms of male infertility, oligozoospermia is of special clinical significance and is defined as a reduction in sperm concentration below 15 million/mL, the diagnostic threshold established in the latest WHO guidelines [2].

Epidemiological data evidence that oligozoospermia occurs in 7–10 % of men in the general population and in 15–20 % of patients seeking evaluation for infertility [3]. In certain cohorts, the percentage of oligozoospermia reaches 30–35 % among men with abnormal semen parameters. Russian data are consistent with the international findings, showing a prevalence of about 17–18 % among patients at specialized reproductive centers [4].

The etiology of oligozoospermia is multifactorial. The most common causes include endocrine disorders (primary and secondary hypogonadism), chromosomal abnormalities (Klinefelter syndrome), Y-chromosome microdeletions, varicocele, obstructive lesions of the seminal tract, inflammatory conditions, and idiopathic forms, which account for up to 30 % of cases [5–7].

The high prevalence, diversity of etiological factors,

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**Highlights**

**What is already known about this subject?**

- Oligozoospermia is one of the leading causes of male infertility and is diagnosed in 15–20 % of patients seeking fertility evaluation.
- The most frequent etiological factors include endocrine disorders (hypogonadism), varicocele, and genetic abnormalities such as Klinefelter syndrome and Y-chromosome microdeletions.
- International and Russian clinical guidelines provide general diagnostic algorithms including semen analysis, hormonal profiling, imaging, and genetic testing.

**What are the new findings?**

- The examination data from 210 men aged 25–45 years with confirmed oligozoospermia and infertility helps to systematize the spectrum of the underlying causes in clinical practice.
- The pathophysiological mechanisms of hypogonadism, the clinical significance of AZF locus microdeletions, Klinefelter syndrome, and hypogonadotropic hypogonadism are examined in detail.
- Special attention is paid to hypogonadism and idiopathic oligozoospermia as the most common and potentially reversible causes of male infertility.

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

- Application of a stepwise diagnostic algorithm will improve detection of reversible forms of oligozoospermia and guide timely treatment or referral for assisted reproductive technologies.
- Incorporation of genetic testing (karyotyping, Y-chromosome microdeletions) into the routine evaluation of men with severe oligozoospermia will enhance prognostic accuracy and enable personalized reproductive strategies.
- The findings may contribute to refinement of national clinical guidelines and everyday management of patients with male infertility.

**Основные моменты**

**Что уже известно об этой теме?**

- Олигозооспермия является одной из ведущих причин мужского бесплодия и выявляется у 15–20 % пациентов, обращающихся за помощью.
- Наиболее частые этиологические факторы включают эндокринные нарушения (гипо- и гипергонадизм), варикоцеле и генетические дефекты (синдром Клайнфельтера, микроделеции Y-хромосомы).
- Международные и российские клинические рекомендации содержат общие алгоритмы обследования, включающие спермограмму, гормональный профиль, инструментальные и генетические методы.

**Что нового дает статья?**

- Данные обследования 210 мужчин 25–45 лет с подтвержденной олигозооспермией и бесплодием помогли систематизировать спектр причин патологии в клинической практике.
- Подробно рассмотрены патофизиологические механизмы гипогонадизма, клиническое значение микроделеций *AZF* локусов, синдрома Клайнфельтера, гипогонадотропного гипогонадизма.
- Особое внимание уделено гипогонадизму и идиопатической олигозооспермии как наиболее распространенной и потенциально обратимой причине мужского бесплодия.

**Как это может повлиять на клиническую практику в обозримом будущем?**

- Использование комплексного алгоритма дифференциальной диагностики позволит повысить выявляемость обратимых форм олигозооспермии и своевременно направлять пациентов на лечение или вспомогательные репродуктивные технологии.
- Включение генетического тестирования (кариотип, микроделеции Y-хромосомы) в стандарт обследования мужчин с тяжелой олигозооспермией повысит точность прогноза и персонализацию репродуктивных стратегий.
- Полученные данные могут быть использованы для совершенствования национальных клинических рекомендаций и практики ведения пациентов с мужским бесплодием.

and significant reproductive consequences underscore the need for a comprehensive approach to diagnosing oligozoospermia. A key component of this approach is the comparison of international and Russian clinical guidelines, which enables the development of a standardized diagnostic algorithm and facilitates optimal management strategies for affected patients [8–10].

## Primary (hypergonadotropic) hypogonadism as a cause of oligozoospermia / Первичный (гипергонадотропный) гипогонадизм как причина олигозооспермии

Primary hypogonadism develops due to direct damage to testicular tissue, leading to reduced production of testosterone, inhibin B, and anti-Müllerian hormone (AMH), as well as impaired spermatogenesis in the presence of elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels [11]. Key etiological factors include congenital chromosomal abnormalities (such as Klinefelter syndrome), cryptorchidism, prior orchitis (including post-viral), testicular trauma, radiation and toxic exposures, as well as chemotherapy. The prevalence of primary hypogonadism among men with severe oligozoospermia reaches 15–20 % [12].

### Klinefelter syndrome / Синдром Клайнфельтера

Klinefelter syndrome is the most common chromosomal aneuploidy in males, occurring with a frequency of 1:600–1:1000 male newborns [13]. This condition is characterized by markedly impaired spermatogenesis, clinically presenting as oligozoospermia of varying severity, although in most cases azoospermia eventually develops. The principal pathophysiological mechanisms

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include seminiferous tubule atrophy, hypospermatogenesis, and Sertoli cell dysfunction in the setting of primary (hypergonadotropic) hypogonadism.

Typical clinical and laboratory features include small testicular volume (< 4 mL), elevated FSH levels, and reduced testosterone and inhibin B concentrations, reflecting profound damage to the spermatogenic epithelium. Thus, Klinefelter syndrome is considered one of the leading genetic causes of oligozoospermia and plays a critical role in differential diagnosis and management decision-making [14], second in prevalence right after Y-chromosome microdeletions.

### *AZF* (azoospermia factor) microdeletions / Микроделеции *AZF* (azoospermia factor)

Microdeletions of the *AZF* (azoospermia factor) regions on the Y chromosome long arm represent one of the most significant genetic causes of impaired spermatogenesis [15]. Their clinical relevance in oligozoospermia is particularly high, as they are detected in 8–15 % of men with severely lowered sperm concentration (< 5 million/mL), making this condition one of the key etiologies of severe oligozoospermia.

The prognostic value of the different *AZF* loci varies. *AZFa* and *AZFb* deletions are associated with profound testicular failure, in which the likelihood of retrieving sperm is virtually zero. *AZFc* deletions represent the most common form, and in men with severe oligozoospermia, sperm retrieval using micro-TESE (microsurgical testicular sperm extraction) is successful in 50–70 % of cases [16].

According to the international and Russian clinical guidelines, testing for Y-chromosome microdeletions is a mandatory diagnostic step in men with severe oligozoospermia and a normal karyotype, as the results directly influence fertility prognosis and the appropriateness of assisted reproductive technologies [17].

### Varicocele / Варикоцеле

Varicocele is a pathological dilation of the veins of the pampiniform plexus of the spermatic cord, occurring in 15–20 % of men in the general population and in up to 40 % of patients with primary infertility [18]. Varicocele is of particular importance in oligozoospermia: epidemiological studies indicate that its prevalence in this patient group reaches 35–45 %, thereby accounting for it as one of the most common and potentially reversible causes of reduced sperm concentration [19]. The presence of varicocele is associated with impaired key semen parameters, including decreased sperm concentration, motility, and normal morphology [20].

The pathogenesis of developing oligozoospermia in varicocele involves several mechanisms: an increase in testicular temperature due to venous stasis (2–3 °C above normal), which suppresses meiosis and reduces sperm production [21]; tissue hypoxia resulting from venous hypertension, leading to impaired maturation of spermatozoa; oxidative stress that damages sperm DNA and increases the DNA fragmentation index (DFI), thereby worsening the severity of oligozoospermia [22]; and reflux of renal and adrenal metabolites (cortisol, catecholamines, and components of the renin–angiotensin system), which disrupts the endocrine regulation of spermatogenesis [23].

According to the clinical guidelines [3, 4], indications for surgical treatment include abnormal semen parameters such as oligozoospermia and infertility in the couple for more than 12 months after excluding female-factor causes [24]. Meta-analyses demonstrate that in men with oligozoospermia, surgical correction of varicocele leads to significantly improved semen parameters, including increased sperm concentration, enhanced motility, and improved morphology, as well as a 10–20 % higher probability of natural conception compared with conservative management [25].

## Secondary (hypogonadotropic) hypogonadism as a cause of oligozoospermia / Вторичный (гипогонадотропный) гипогонадизм как причина олигозооспермии

### Hypogonadotropic hypogonadism / Гипогонадотропный гипогонадизм

Hypogonadotropic hypogonadism (HGG) is characterized by insufficient testicular stimulation due to a deficiency of gonadotropins (FSH and LH) resulting from dysfunctional hypothalamic–pituitary axis [11] either of congenital (e.g., Kallmann syndrome, caused by impaired migration of gonadotropin-releasing hormone–secreting neurons) or acquired (pituitary tumors, hypophysitis, craniopharyngioma, traumatic brain injury, infectious lesions) origin. HGG is one of the few forms of male infertility in which full restoration of spermatogenesis is possible with timely hormonal therapy [12]. It occurs in 1–2 % of infertile men but represents a clinically significant, reversible cause of oligozoospermia.

Therapy involves the use of human chorionic gonadotropin (hCG) to stimulate Leydig cells, added with FSH to activate spermatogenesis. Treatment duration ranges from 6 to 24 months depending on initial testicular volume and clinical history [13]. Prospective studies demonstrate that in 80–90 % of men with HGG, sperm concentration > 5 million/mL can be achieved with early therapy initiation [14].

The main therapeutic principle is as follows: hCG stimulates testosterone production by Leydig cells (substituting for LH), whereas FSH activates Sertoli cells and induces spermatogenesis [15]. Clinical studies indicate that hCG monotherapy may normalize testosterone levels but does not consistently restore fertility, as FSH plays a critical role in spermatogenesis [16]. In multicenter trials, combined hCG + FSH therapy resulted in the appearance of spermatozoa in the ejaculate in 70–90 % of cases within 6–24 months of treatment [17]. Mean sperm concentrations typically reached 5–10 million/mL, enabling both natural conception and the use of assisted reproductive technologies (ART).

The effectiveness of therapy is strongly affected by baseline testicular volume: men with testes > 8–10 mL have a substantially higher likelihood of spermatogenesis recovery compared with those with marked testicular atrophy [18]. Additionally, meta-analyses show that in men with isolated FSH deficiency, treatment with recombinant FSH (rFSH) lasting 6–12 months improves spermatogenesis parameters including sperm concentration and motility and increases the probability of partner pregnancy [19].

## Other forms of oligozoospermia / Иные формы олигозооспермии

### Idiopathic oligozoospermia / Идиопатическая олигозооспермия

Idiopathic oligozoospermia is diagnosed when sperm concentration is below 15 million/mL (according to the WHO 2021 criteria), but no endocrine, anatomical, infectious, or genetic causes are identified [20]. According to the international reviews, up to 25–30 % of oligozoospermia cases remain idiopathic even after comprehensive evaluation using modern diagnostic methods [21]. Recent Russian data indicate that idiopathic forms account for 20–28 % of infertility cases in men [22] representing the most challenging group to manage clinically, as no obvious reversible cause such as varicocele or HGG is found.

Although idiopathic oligozoospermia lacks a clearly established etiology, several hypotheses have been proposed to explain its pathogenesis: subclinical genetic defects not detectable by conventional karyotyping; epigenetic dysregulation of genes involved in spermatogenesis; Sertoli cell dysfunction with reduced inhibin B production; and relative deficiency of endogenous FSH [23].

Recent Russian studies confirm that men with idiopathic oligozoospermia more often exhibit low inhibin B levels and signs of subclinical Sertoli cell dysfunction, providing a rationale for therapy with recombinant FSH preparations [24].

FSH is a key regulator of Sertoli cell function, which supports the microenvironment necessary for spermatogenesis. Based on this concept, exogenous FSH has been proposed as a therapeutic option for idiopathic oligozoospermia. Randomized trials show that FSH therapy at a dose of 150–300 IU three times weekly for 3–6 months improves semen parameters in 30–40 % of patients [19]. Improvements include increased sperm concentration, motility, and morphology, as well as reduced DNA fragmentation.

A meta-analysis demonstrated that FSH treatment in men with idiopathic infertility increases the probability of spontaneous pregnancy and improves ART outcomes, including in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycles [19]. In Russian clinical practice, the use of recombinant FSH has similarly shown beneficial effects, including increased sperm concentration and motility and decreased DNA fragmentation, especially in men with initially low inhibin B levels [22, 24].

Idiopathic oligozoospermia remains one of the most difficult challenges in andrology. Exogenous FSH is considered one of the few pathogenetically justified treatment options. Despite its moderate efficacy, FSH therapy enables a subset of patients to achieve improvements in semen quality and to increase the likelihood of both natural conception and success in ART programs.

### Prolactinoma / Пролактинома

Prolactinoma, a hormonally active pituitary tumor secreting prolactin, is one of the most common causes of hyperprolactinemia in men. Elevated prolactin levels exert a profound inhibitory effect on the hypothalamic–pituitary–gonadal axis: secretion of gonadotropin-releasing hormone (GnRH) decreases, resulting in reduced production of LH and FSH, which leads to testosterone deficiency and diminished stimulation of Sertoli cells [21]. In a substantial proportion of men with prolactinoma, semen analysis reveals a marked reduction in sperm concentration and motility, up to severe oligozoospermia.

The pathogenesis of hyperprolactinemia-induced impairment of spermatogenesis includes: suppression of GnRH secretion → reduced FSH and LH production; testosterone deficiency leading to Leydig cell dysfunction; insufficient stimulation of Sertoli cells and disruption of spermatocyte meiosis; and associated metabolic disturbances (obesity, insulin resistance), which further exacerbate reproductive dysfunction [22].

First-line therapy consists of dopamine agonists (cabergoline, bromocriptine), which normalize prolac-

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tin levels, restore gonadotropin secretion, and re-establish testosterone production. In most patients, this is accompanied by improved semen parameters parameters and increased chances of conception. In resistant cases, surgical intervention or radiotherapy may be considered [23].

**Hydrocele / Гидроцеле**

Hydrocele is the accumulation of serous fluid between the parietal and visceral layers of the tunica vaginalis of the testis. It occurs in 1–2 % of adult men, most commonly as a complication of trauma, inflammatory processes, or surgical interventions involving the scrotum [24]. Although hydrocele is traditionally regarded as a benign condition, in some cases it may be associated with impaired spermatogenesis and the development of oligozoospermia.

The pathogenesis is not fully understood; however, several mechanisms have been proposed to explain the association with oligozoospermia: compression of the testis in large hydroceles may lead to ischemia and tissue atrophy; increased local scrotal temperature due to impaired thermoregulation can negatively affect meiosis and sperm morphogenesis; and chronic inflammation and oxidative stress further damage the spermatogenic epithelium.

When hydrocele coexists with varicocele or orchiepididymitis, the likelihood of oligozoospermia increases [25]. Patients with hydrocele frequently demonstrate reduced sperm concentration and motility. Clinical observations indicate that 20–25 % of men with long-standing or recurrent hydrocele exhibit abnormal semen parameters of varying severity, including oligozoospermia. Following surgical treatment, normalization of spermatogenesis and improvement of semen parameters are observed in most patients within 3–6 months [25].

**Autoimmune orchitis / Аутоиммунный орхит**

Autoimmune orchitis is a rare but clinically significant condition in which the immune system mounts an abnormal response against endogenous testicular antigens. The disorder may occur in isolation or as part of systemic autoimmune syndromes. According to the literature, autoimmune orchitis is identified in 2–4 % of infertile men, and in up to 8–10 % of patients with unexplained oligozoospermia [24].

The core mechanism of the disease is the loss of the testis's immunologically privileged status. Disruption of the blood–testis barrier due to infections, trauma, surgical interventions, or varicocele allows immune system exposure to antigens of the spermatogenic epithelium. This leads to the formation of antisperm and antitesticular antibodies and to the development of local inflammation [24].

The immune response results in lymphocytic and plasma-cell infiltration of the interstitium, damage to Sertoli cells and the spermatogenic epithelium, apoptosis of spermatogonia, as well as reduced sperm concentration and motility. Clinically, this manifests as oligozoospermia, often accompanied by asthenozoospermia and teratozoospermia. Recent Russian publications report that in autoimmune orchitis, medical therapy rarely results in fully recovered spermatogenesis, and ART recommended in most cases [25].

**Malignant testicular tumors / Злокачественные опухоли яичка**

Testicular malignancies are the most common solid tumors in men aged 20–40 years, with peak incidence occurring during the reproductive period. Despite excellent survival rates (over 95 % with timely treatment), testicular cancer has a significant impact on fertility, including the development of oligozoospermia and infertility [25]. Spermatogenic impairment in testicular cancer is driven by several mechanisms: tumoral infiltration of testicular tissue leading to destruction of seminiferous tubules and loss of spermatogonia; endocrine disturbances, as both the tumor and associated inflammation disrupt the secretion of testosterone, FSH, and LH; oxidative stress and local inflammation, which contribute to sperm damage; and testicular dysgenesis syndrome (TDS) – a spectrum including cryptorchidism, hypospadias, and testicular cancer characterized by an inherently reduced spermatogenic reserve [25].

Before treatment, 40–50% of men with testicular cancer already exhibit abnormal spermatogenesis, including oligozoospermia and teratozoospermia. The primary treatment modality is radical orchifuniculectomy, supplemented by chemotherapy or radiotherapy when indicated. Although survival outcomes are generally excellent, reproductive function remains compromised: up to 50 % of patients continue to experience severe spermatogenic impairment; the likelihood of natural conception declines following treatment; and the use of ART and cryopreserved sperm remains a cornerstone of fertility preservation strategies [25].

**Hypothyroidism / Гипотиреоз**

Hypothyroidism is one of the most common endocrine disorders and has a systemic impact on male reproductive function. According to the literature, subclinical and overt hypothyroidism are found in 2–5 % of men of reproductive age, and among infertile patients its preva-

lence is higher – up to 10–12 % [25]. The association between hypothyroidism and impaired spermatogenesis is explained by several mechanisms: disrupted hypothalamic-pituitary-gonadal axis, as reduced thyroid hormone levels lead to elevated thyroid-stimulating hormone (TSH) and imbalance in FSH/LH secretion, resulting in hypogonadism; decreased testosterone levels due to impaired Leydig cell stimulation; Sertoli cell dysfunction – because thyroid hormones regulate Sertoli cell proliferation and differentiation, which are essential for spermatogenesis; and metabolic disturbances (obesity, insulin resistance, hyperlipidemia), which are frequently associated with hypothyroidism and exacerbate damage to the spermatogenic epithelium [25].

Recent Russian studies confirm that hypothyroidism is an important risk factor for male infertility. According to evaluations performed at reproductive centers, 8–10 % of men with oligozoospermia exhibit signs of subclinical or overt hypothyroidism. Thyroid hormone replacement therapy with levothyroxine restores normal thyroid status and rebalances pituitary gonadotropin secretion. In several clinical observations, correction of hypothyroidism was followed by improvements in semen parameters, including increased sperm concentration and motility [25].

#### Congenital adrenal cortex dysfunction / Врожденная дисфункция коры надпочечников

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by mutations in the *CYP21A2* gene, with 21-hydroxylase deficiency being the most common form. This defect leads to impaired cortisol synthesis and compensatory hypersecretion of adrenocorticotropic hormone (ACTH). Chronic ACTH stimulation results in adrenal hyperplasia and excessive androgen production. The development of testicular adrenal rest tumors (TARTs) – ectopic adrenal tissue within the testes – occurs in 40–50 % of adult males with CAH and represents a direct risk factor for oligozoospermia and azoospermia [25]. Compression of the seminiferous tubules leads to their atrophy and impaired spermatogenesis. Hormonal disturbances (testosterone deficiency in the setting of chronic dysregulation of FSH/LH) further exacerbate damage to the spermatogenic epithelium.

Men with CAH frequently present with varying degrees of oligozoospermia, reduced sperm motility, and increased infertility rates, with 40–60 % exhibiting profound spermatogenic impairment. Glucocorticoid therapy (hydrocortisone, dexamethasone) lowers ACTH levels, inhibits the growth of ectopic adrenal tissue, and improves semen parameters [25].

#### Oligozoospermia as a side effect of chemotherapy and radiation therapy / Олигозооспермия как побочный эффект химиотерапии и лучевой терапии

Chemotherapy and radiotherapy are widely used in the treatment of malignant tumors, including testicular cancer, lymphomas, leukemias, and solid neoplasms in young men. Despite their high therapeutic efficacy, such modalities frequently lead to impaired spermatogenesis and the development of oligozoospermia or azoospermia [25].

The cytotoxic effects of chemotherapeutic agents (alkylating agents, platinum-based drugs) induce apoptosis of spermatogonia and disrupt meiosis. Radiotherapy causes direct damage to germinal epithelium cells; even doses of 0.1–0.2 Gy can reduce sperm count, and at doses > 2 Gy, the risk of prolonged or permanent azoospermia increases substantially. Oxidative stress and inflammation following therapy further deteriorate semen quality and increase DNA fragmentation levels.

Most men develop pronounced oligozoospermia in the first months post-treatment. Spermatogenesis may recover within 1–5 years depending on radiation dose and chemotherapy regimen, although in some patients the changes are irreversible. Men with initially impaired semen parameters have a higher risk of persistent oligozoospermia. Sperm cryopreservation prior to treatment is the gold standard for fertility preservation. In cases of severe oligozoospermia, ART, including ICSI and IVF, are required [25].

Thus, it is of particular interest to analyze the clinical activity profile of endocrinology centers in Saint Petersburg and Tashkent in order to identify the target group of men with infertility and oligozoospermia who are managed by both endocrinologists and urologists-andrologists within the context of “real-world” clinical practice.

**Aim:** to compare international and Russian epidemiological data on the causes of oligozoospermia and to develop differential diagnostics and patient management algorithm by taking into account endocrine, genetic and immunological factors.

## Materials and Methods / Материалы и методы

#### Дизайн исследования / Study design

A retrospective observational study included 210 men aged 25–45 years with confirmed oligozoospermia and infertility-related complaints.

#### Inclusion and exclusion criteria / Критерии включения и исключения

*Inclusion criteria:* age 25–45 years; confirmed oligozoospermia according to the WHO criteria (2021); sperm concentration < 15 million/mL; complaints of infertility

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in the couple for ≥ 12 months; providing at least 2 spermograms with an interval of 2–4 weeks.

*Exclusion criteria:* acute inflammatory diseases of the genitourinary system; drugs affecting spermatogenesis (testosterone, anabolic steroids, human chorionic gonadotropin, cytotoxic drugs) used for 6 months; cryptorchidism, previous orchidectomy; severe somatic diseases in the decompensation stage; inability to complete the diagnostic algorithm.

**Study methods / Методы исследования**

Spermograms were performed twice, 2–4 weeks apart, according to the WHO (2021) methodology, using an OLYMPUS CX43 microscope with a Makler chamber (Sefi-Medical Instruments).

FSH, LH, testosterone, prolactin, TSH, estradiol, inhibin B, AMH, and 17-OH-progesterone blood levels were measured by immunochemiluminescence assay on Architect i2000SR analyzer (Abbott Diagnostics, USA) using Abbott Diagnostics (USA) reagent kits for FSH, LH, TSH, prolactin, testosterone, and estradiol; and Beckman Coulter (USA) reagent kits for inhibin B and AMH. Blood samples were collected in the morning (8:00–9:00 AM) on an empty stomach.

An ultrasound examination of the scrotum was performed using a Samsung HS60 scanner (Samsung Medison, Korea) with a 7.5–12 MHz linear transducer. Testicular volume and structure were assessed, as well as the presence of varicoceles, signs of orchiepididymitis, cysts, and tumors.

Magnetic resonance imaging (MRI) of the hypothalamic-pituitary region was performed using a Siemens Magnetom AERA 1.5 T scanner (Siemens Healthineers, Germany).

Genetic testing: karyotyping was performed using GTG banding (400–550 bands) and MetaSystems cytogenetic kits (Germany). Y-chromosome microdeletions (*AZF*) were assessed using real-time polymerase chain reaction.

**Comparison with the results of previous studies / Сопоставление с результатами предыдущих исследований**

For comparison with data reported elsewhere, there were analyzed international clinical guidelines of the European Association of Urology (EAU, 2024), American Urological Association/American Society for Reproductive Medicine (AUA/ASRM, 2024) [1, 3, 4], as well as publications from PubMed/MEDLINE, Scopus and eLibrary in Russian and English.

## Results and Discussion / Результаты и обсуждение

Analysis of the obtained data demonstrated significant heterogeneity of etiologic factors, consistent with current understanding of the multifactorial nature of spermatogenesis disorders.

The most common cause of oligozoospermia in the study group was varicocele, detected in 44.3 % of patients (**Table 1**) that agrees with international data, which consider varicocele a key factor in spermatogenesis disorders with potential for correction.

The second most common category was idiopathic oligozoospermia (25.2 %). Despite comprehensive hormonal, genetic, and ultrasound examinations, it was not possible to determine the cause of spermatogenesis disorders in this group of patients. This is consistent with international data, where the proportion of idiopathic forms reaches 25–30 %, thereby confirming the need for further study of the subclinical genetic and epigenetic mechanisms influencing the functioning of Sertoli cells and spermatogenic epithelium.

Genetic causes – Klinefelter syndrome (10.0 %) and *AZF* microdeletions (8.6 %) also significantly contributed to the pattern of oligozoospermia. The obtained data are comparable to the results of large international cohorts. Diagnosis of these conditions is of fundamental clinical importance, as it determines the prognosis for spermatogenesis restoration and the feasibility of ART. The high incidence of *AZFc* deletions, which increase the likelihood of successful ART treatment for infertility, is particularly noteworthy.

In Klinefelter syndrome, classic signs of primary hypogonadism were observed: high FSH and LH levels along with decreased testosterone and inhibin B levels, reflecting profound loss of spermatogenic epithelium. In cases with *AZFc* deletions, the hormonal profile was more variable, confirming the heterogeneity of clinical phenotypes.

Endocrine disorders constituted a smaller, but clinically significant, proportion of cases. Hypogonadotropic hypogonadism is diagnosed in 0.95 % of patients. Despite its relatively low prevalence, this form of oligozoospermia is potentially reversible, as combined hCG and FSH therapy can restore spermatogenesis within 6–24 months.

Rare causes – prolactinoma, hypothyroidism, autoimmune orchitis, hydrocele, and the consequences of chemotherapy and radiation therapy have been identified in isolated cases but have crucial practical significance. Prolactinoma is accompanied by severely suppressed hypothalamic-pituitary-gonadal axis; hypothyroidism leads to secondary hypogonadism; autoimmune orchitis is one of the few forms of testicular damage with predominantly irreversible damage to spermatogenesis. Patients who previously received chemotherapy experienced the most severe forms of oligozoospermia, reflecting the known

**Table 1.** Prevalence of different oligozoospermia forms in infertile men – comparison of personal data with results of international studies.

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

| **Oligozoospermia form**<br>**Форма олигозооспермии** | **Frequency according to research data, % [references]**<br>**Частота по данным исследований, % [первоисточники]** | **Personal data**<br>**Собственные данные**<br>**n = 210**<br>**n (%)** |
|---|---|---|
| Idiopathic / Идиопатическая | ~25–30 [12, 13] | 53 (25,2) |
| Varicocele-associated<br>Варикоцеле-ассоциированная | ~30–40 [18, 19] | 93 (44,3) |
| Hypogonadotropic hypogonadism<br>Гипогонадотропный гипогонадизм | 1–2 [8] | 2 (0,95) |
| Hypergonadotropic hypogonadism (Klinefelter syndrome)<br>Гипергонадотропный гипогонадизм (синдром Клайнфельтера) | ~10–15 [10] | 21 (10,0) |
| Y-chromosome microdeletions (*AZFc*)<br>Микроделеции Y-хромосомы (*AZFc*) | 8–15 [15, 16] | 18 (8,6) |
| Prolactinoma / Пролактинома | ~1–2 [21, 22] | 2 (0,95) |
| Hydrocele / Гидроцеле | ~2–3 [24, 25] | 4 (1,9) |
| Autoimmune orchitis / Аутоиммунный орхит | 2–4 [24] | 4 (1,9) |
| Testicular cancer / Рак яичка | ~1–2 [25] | 2 (0,95) |
| Hypothyroidism / Гипотиреоз | ~2–5 [25] | 4 (1,9) |
| Congenital adrenal hyperplasia<br>Врожденная дисфункция коры надпочечников | ~1–2 [25] | 2 (0,95) |
| Post-chemotherapy/radiotherapy<br>После химио- и лучевой терапии | ~2–3 [25] | 5 (2,4) |

dependence of spermatogenesis on the dose and class of cytotoxic drugs.

The obtained results demonstrate the need for a comprehensive, multi-level approach to the diagnosis of oligozoospermia. An algorithm including repeated spermograms, hormonal profile, ultrasound, pituitary MRI, karyotyping, and *AZF* locus testing enables the identification of reversible forms of disorders (varicocele, hypogonadotropic hypogonadism, hypothyroidism); timely diagnosis of genetic forms requiring specific tactics (ICSI); and identification of patients requiring early referral for ART. Also, similar to the practical algorithm for examination and management of patients with azoospermia developed by our research group [26], this approach helps to methodologically substantiate a personalized therapeutic strategy.

## Algorithm for the differential diagnosis and patient management / Алгоритм дифференциальной диагностики и ведения пациентов

### Notes to the algorithm / Пояснения к алгоритму

**{A}** Oligozoospermia should be assessed only after excluding the use of medications that affect the reproductive system, chronic intoxications, and occupational harmful exposures.

**{B}** In this situation, differential diagnosis typically involves distinguishing between various forms of hypogonadotropic hypogonadism. In most cases, these are congenital conditions such as idiopathic hypogonadotropic hypogonadism or Kallmann syndrome (if anosmia is present). However, hypogonadism may also result from tumors (or malformations) of the hypothalamic–pituitary region, which would require neurosurgical intervention if craniopharyngioma or another intracranial mass is identified.

**{C}** Hyperprolactinemia and prolactin-secreting pituitary adenoma (prolactinoma) are relatively common causes of male infertility. Treatment with dopamine receptor agonists (cabergoline, bromocriptine) helps normalize sexual function and restore spermatogenesis. In some cases, neurosurgical treatment may be required.

**{D}** Testicular tumors producing estrogens or hCG are increasingly diagnosed in men presenting with 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 negatively

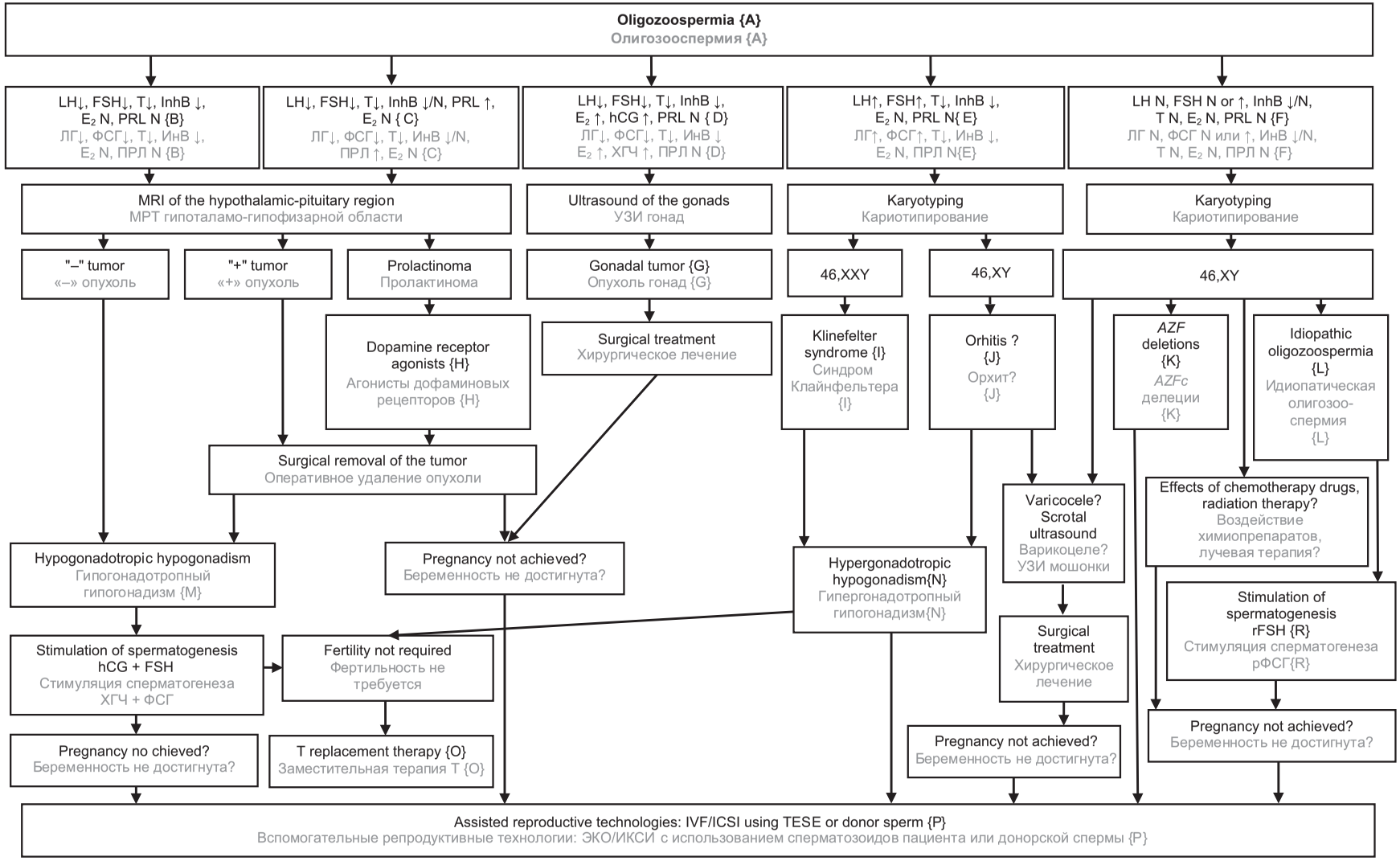


**Figure 1.** Algorithm for oligozoospermia differential diagnosis and patient management.

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

**Рисунок 1.** Алгоритм дифференциальной диагностики и ведения пациентов с олигозооспермией.

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

affect the germinal epithelium or necessitate gonadectomy (in some cases bilateral).

**{E}** In this case, the cause of male infertility is hypergonadotropic hypogonadism, which may result from congenital factors (e.g., karyotype abnormalities) or acquired conditions. Among acquired causes, scrotal pathologies leading to testicular atrophy are most prominent, including varicocele (dilation of the pampiniform plexus), hydrocele, trauma, and testicular torsion.

**{F}** Isolated FSH elevation in infertile men typically indicates selective damage to the germinal epithelium, with impairment of spermatogenesis caused by either congenital or acquired factors. Congenital forms are most commonly associated with Y-chromosome microdeletions (*AZFc* gene). Acquired spermatogenic failure is frequently linked to intratesticular autoimmune processes – autoimmune orchitis or to testicular damage resulting from varicocele or hydrocele.

**{G}** A two-fold increase in blood estradiol or elevated hCG levels suggests a potential testicular tumor, which may manifest clinically with gynecomastia, reduced libido, and infertility (oligozoospermia).

**{H}** Dopamine agonists help normalize serum prolactin levels and restore spermatogenesis. If no recovery occur, the infertility may be due to a coexisting pituitary adenoma (often a macroadenoma) causing hypogonadotropic hypogonadism, or to a combination of contributing etiological factors.

**{I}** Klinefelter syndrome in most cases presents with infertility of varying severity, ranging from azoospermia and seminiferous tubule hyalinization to oligozoospermia. However, no pharmacological treatments have been developed for patients with Klinefelter syndrome. Sperm cryopreservation and ART use are recommended to overcome infertility.

**{J}** Autoimmune orchitis is diagnosed when other causes of oligozoospermia are excluded and the patient exhibits hypergonadotropic hypogonadism. Antibodies against Leydig cells or antisperm antibodies may be detected in the ejaculate (MAR test).

**{K}** Y-chromosome microdeletions is a common finding in infertile men. Loss of the critical *AZF* region required for spermatogenesis leads to infertility. No pharmacological treatments are available. ART is recommended.

**{L}** Idiopathic oligozoospermia is diagnosed in men with normogonadotropic status after all other causes of oligozoospermia have been excluded.

**{M}** For the treatment of infertility in hypogonadotropic hypogonadism, FSH and hCG preparations are indicated. Therapy lasts at least one year. Complete restoration of spermatogenesis has been demonstrated in these patients, although treatment may be ineffective in about 10% of cases.

**{N}** Pharmacotherapy for infertility in patients with hypergonadotropic hypogonadism has not been developed. In most cases, ART is required. Sperm cryopreservation is recommended for men with this form of hypogonadism.

**{O}** Testosterone replacement therapy in men with hypogonadism is administered lifelong. Testosterone preparations suppress FSH production in the anterior pituitary and may worsen semen parameters. Therefore, sperm cryopreservation is recommended prior to initiating androgen replacement therapy.

**{P}** Assisted reproductive technologies enable the achievement of conception in the majority of male-factor infertility conditions. However, the choice of a specific technique depends on the expertise of the reproductive center, its technical capabilities, and the patient's underlying diagnosis. If sperm retrieval is unsuccessful, the use of donor sperm is indicated.

**{R}** Stimulation of spermatogenesis with FSH preparations has demonstrated effectiveness in this group of patients. Several meta-analyses have shown the efficacy of clomiphene therapy [25].

## Conclusion / Заключение

Oligozoospermia has a multifactorial nature, with causes ranging from varicocele and endocrine disorders to genetic and iatrogenic factors. The most common forms are varicocele-associated and idiopathic oligozoospermia, which together account for more than 50 % of cases.

Genetic factors (Klinefelter syndrome, Y-chromosome microdeletions) are found in about one in five patients with oligozoospermia and require mandatory diagnostic evaluation.

Reversible forms (hypogonadotropic hypogonadism, hypothyroidism, prolactinoma, varicocele, hydrocele) comprise up to one-third of cases, supporting a potential for fertility restoration upon timely diagnosis and treatment.

Management of these patients should include a comprehensive diagnostic workup (semen analysis, hormonal profiling, ultrasonography, genetic and immunological testing) and a personalized therapeutic strategy tailored to the underlying etiology.

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