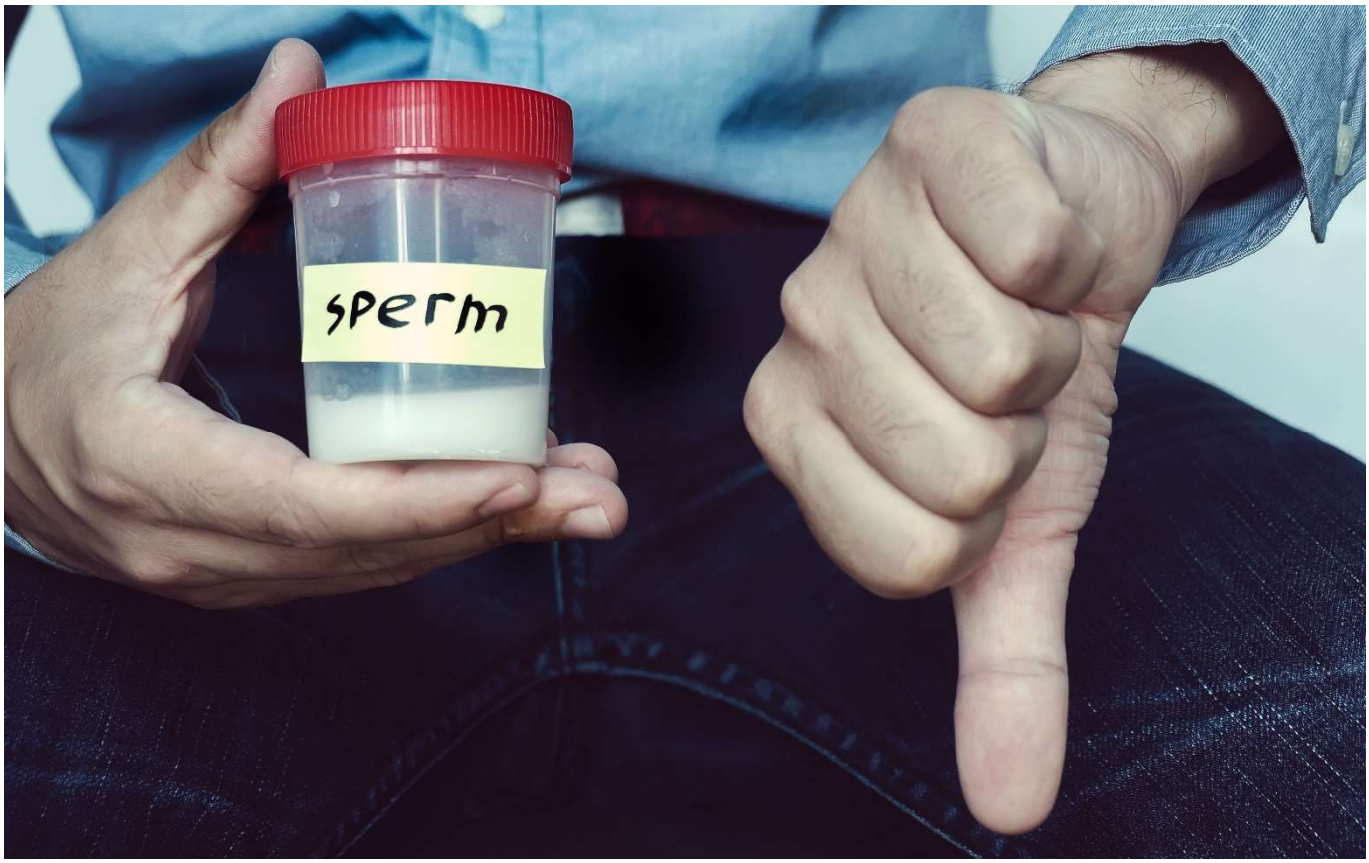

MALE INFERTILITY – CAUSES, DIAGNOSIS AND MANAGEMENT. A REVIEW

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ABSTRACT

The World Health Organization defines infertility as an inability to get pregnant after a year of regular intercourse, 3-4 times a week, without use of preventive methods. The problem of infertility concerns about 15% of the population, in 20-30% of cases the cause is on the male side, in 20-35% couples struggle with female infertility, and in 25-40% of cases fertility problems concern both partners. Male infertility is defined as the inability of a man to cause pregnancy in a fertile woman. Male infertility is caused by change in sperm concentration and/or motility and/or morphology in at least one sample of two semen analyses. The reasons for male infertility can be divided into four main groups: primary testicular defects in spermatogenesis, endocrine and systemic disorders, sperm transport disorders, idiopathic male infertility. There are also many reasons that worsen semen quality, resulting in difficulty in conceiving offspring, we can distinguish neurological disorders, obesity, smoking, autoimmune diseases or intensive sports. The causes of infertility can lie on both the male and female side, therefore it is important to examine both partners. Diagnosis of male infertility usually includes: medical history, physical examination, semen analysis, scrotal and transrectal ultrasound, hormonal tests, testicular biopsy. Further diagnosis and treatment depends on the results of semen analysis. Much of the causes of male infertility are idiopathic, however if the cause is determined, treatment is targeted and results in high success rate. Both conservative methods and surgical procedures are used in therapy. It should also be borne in mind that male infertility is often a multifaceted problem; supportive therapy is necessary in addition to targeted therapy.

BACKGROUND

Infertility is a common condition with significant psychological, economic, demographic and medical consequences. Male infertility is defined as the incapacity of a man to cause pregnancy in a fertile woman. Male infertility is caused by change in sperm concentration and/or motility and/or morphology in at least one sample of two semen analyses, collected at an interval of 1 and 4 weeks. It affects about 7% of all men [1, 2].

Men, whose semen parameters are below the normal values, defined by the World Health Organization (WHO), are infertile. The most common disturbances in the quantity and quality of semen include: oligospermia (<15 million spermatozoa/mL), azoospermia (no sperm count in the ejaculate), asthenospermia (<40% motile spermatozoa) or teratozoospermia (<4% normal forms). The origin of male infertility can arise from genetic disorders, disturbances in sperm transport, may have autoimmune background or other, often idiopathic cause [1, 2].

This article presents the most common causes of male infertility, methods of their diagnosis, as well as the treatment options.

CAUSES OF MALE INFERTILITY

The reasons for male infertility can be divided into four main groups: primary testicular defects in spermatogenesis – 65-80%, endocrine and systemic disorders – 2-5%, sperm transport disorders – 5%, idiopathic male infertility – 10-20% [3].

PRIMARY TESTICULAR DEFECTS IN SPERMATOGENESIS

The causes of primary testicular defects are usually unknown, defined as idiopathic. A significant group of infertile men have congenital and developmental disorders resulting in primary testicular defects in spermatogenesis. The most common congenital reasons are described below.

Klinefelter syndrome (KS) (47, XXY) is the most common chromosomal disorder in men (1: 650 born boys). It involves the presence of at least one additional X chromosome. Patients often have small testes and male gonads are unable to produce sperm (azoospermia) or produce them in a reduced amount (oligospermia) [4].

Cryptorchidism, undescended testes, are characterized by the absence of one or both testes in the scrotum. Men with the history of cryptorchidism have oligozoospermia or azoospermia and lower sperm quality [5]. Infertility is much more common in cases of bilateral undescended testes, in unilateral cases fertility is affected less often. The study of Kobayashi et al. found that sperm density was decreased in about 30% of men with unilateral cryptorchidism, in cases of bilateral undescended testicles about 50% of patients presented reduced sperm density [6]. Patients with unilateral cryptorchidism were characterized by rates of paternity within the normal ranges and showed normal sperm concentration in comparison to only 2 out of 15 men with bilateral cryptorchidism in the past, managing to obtain offspring [6].

Miotonic dystrophy is an autosomal dominant disease, one of most common of human muscular dystrophies. This condition involves progressive myopathy and myotonia, which are often associated with hypogonadism. Men may have small testicles and sperm production may be reduced [7].

Androgen biosynthesis disorders are relatively rare causes of sexual ambiguity in men (46, XY). The inherited decrease in testosterone synthesis and secretion is caused by a mutation in genes that encode the enzymes of the testosterone synthesis pathway (StAR) and the steroidogenic enzymes (P450scc, P450c17, 3betaHSDII, 17betaHSDIII, and 5alpha-reductase). For each of these enzymes, abnormalities lead to male pseudohermaphroditism [8]. Many acquired causes such as varicocele, infections, drugs, environmental toxins, testicular torsion can cause primary testicular defects in spermatogenesis. Genetic disorders (Y chromosome microdeletions, autosomal and X chromosome abnormalities, mutations leading to severe spermatogenesis defects) are responsible for approximately 5% of infertility cases. Abnormalities in spermatogenesis may also be caused by systemic diseases such as renal failure, hepatic cirrhosis, cancer, and sickle cell disease [8].

ENDOCRINE AND SYSTEMIC DISORDERS

Hypothalamus and pituitary gland disorders may cause hypogonadotrophic hypogonadism, a deficiency in gonadotrophin releasing hormone (GnRH) or gonadotropin deficiency, and thus cause infertility. The most frequent causes of hypogonadotropic hypogonadism are presented below.

Congenital hypogonadotrophic hypogonadism (CHH) is a rare disease characterized by the delay or lack of sexual maturity and infertility. This condition is caused by insufficient production, secretion or activity of gonadotrophin releasing hormone (GnRH). In the majority of cases, the disease is accompanied by anosmia or hyposmia. This presentation is called Kalmann's syndrome [9]. Mutations of the gonadotropin subunit may also cause hypogonadotropic hypogonadism. M. Grigorowa et al. in their study showed that genetically conditioned, low levels of follicle-stimulating hormone (FSH) can have a significant impact on testicular function, reduce testicular hormone levels, and thus reduce male reproductive potential [10]. Male infertility may also result from acquired disorders of the hypothalamus and pituitary gland such as tumors, sarcoidosis, histiocytosis, injuries, surgeries or intracranial radiation. These diseases can cause damage to GnRH neurons in the hypothalamus, gonadotrophic cells of the pituitary gland and lead also to the disruption of hypothalamic-pituitary circulation [3].

Endocrine disorders which can lead to hypogonadism include hyperprolactinemia, estrogen excess, glycocorticosteroids and androgens excess as well as hypo and hyperthyroidism [11]. Hyperprolactinemia is a relatively common endocrine disorder resulting in hypogonadotropic hypogonadism. Prolactin excess leads

to disturbances in lutropin and follicle stimulating hormone secretion, which results in spermatozoa and testicles endocrine function suppression [11]. Excessive secretion or exogenous administration of androgens or steroids results in negative hypothalamic-pituitary axis feedback and inhibits the secretion of FSH and luteinizing hormone (LH). Infertility associated with excess of these hormones results in oligozoospermia or azoospermia [12]. Thyroid disease can decrease libido, cause erectile dysfunction or delay ejaculation [13].

SPERM TRANSPORT DISORDERS

Infertility may result from the absence or bilateral obstruction of semen pathways. It may be congenital (cystic fibrosis, vascular aplasia, Yong's syndrome) or acquired (epididymitis, seminal vesicles). Cystic fibrosis (CF) is the most common autosomal recessive disease in the Caucasian population due to mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The intravital section of the vas is hypoplastic in men or may not develop. There is also a disturbance in the structure of seminal vesicles - hypoplasia and cystic changes, which lead to low sperm volume. Congenital absence of the vas defects is also possible [14]. Young's syndrome is a rare disease characterized by infertility as a result of obstructive azoospermia and chronic bronchitis. Azoospermia results from blocking the epididymis with protein masses. In males, there are disturbances in the structure of centriole and dynein proteins, which causes disturbances of motility of sperm and cilia in the epididymis and respiratory tracts [15]. The primary ciliary dyskinesia (PCD) is also responsible for disturbances in semen transport. It is a congenital disorder characterized by functional or structural ciliary disorders. Patients with PCD have frequent infections of the upper and lower respiratory tract and about 50% have sperm immunities [16]. Obstruction of the semen leading pathways may occur in congenital diseases, e.g. Muller's cyst, it may also be the result of estrogen excess, toxins or antenatal infections also infections of the male reproductive system (e.g., gonorrhea, chlamydiasis, infections by Mycoplasma or Ureaplasma) [17,18]. Iatrogenic obstruction may be the result of accidental intersection of the semen leading pathways during surgery and endoscopic procedures. It may also be caused by intentional vasectomy for contraception purposes [19].

IDIOPATHIC MALE INFERTILITY

Idiopathic male infertility refers to men in whom repeated attempts to analyse semen do not show sperm abnormalities, but they cannot achieve pregnancy with a fertile female partner despite the assessment of all possible mechanisms of male infertility.

CONDITIONS WORSENING THE SEMEN QUALITY

When discussing the causes of infertility, it is worth mentioning factors which worsen semen quality, and thus hinder the conception of the offspring.

Neurological mechanisms play an important role in proper reproductive system functioning. Their disturbances may lead to infertility due to erectile dysfunction, ejaculatory dysfunction and semen abnormalities. Disorders that cause these problems include congenital spinal defects, diabetes, pelvic and retroperitoneal surgery, multiple sclerosis and spinal cord injury [20]. Obesity which affects an increasing number of men in the reproductive age is associated with spermatogenesis defects, erectile dysfunction and decreased libido. The concentration of sex hormone binding globulin (SHBG) is lower which results in higher serum free testosterone concentration and higher free estrogen level [21,22].

The negative impact of smoking on semen quality has also been proved. Many studies have shown the decrease in sperm quality, disturbances in spermatogenesis and sperm function disorders. Disorders result from DNA damage, increased oxidative stress or apoptosis of cells due to ingredients contained in tobacco [23].

Sport is an important element of a healthy lifestyle. Sport practiced recreationally has a positive effect on the quality of semen. It reduces the risk of obesity, diabetes or cardiovascular diseases which leads to a secondary semen quality improvement. However, too much effort, professional sports, have an adverse effect on male fertility. Safarinejad et al. showed the adverse effects of intense exercises on the quality of semen along with the decrease in testosterone levels, LH and FSH hormones and the increase in prolactin and SHBG [24]. Cycling is a popular sport but it can worsen male fertility. It can cause pudendal compression syndrome and erectile dysfunction. During cycling, there is also the pressure on the vessels, which may cause hypoxia. Chronic hypoxia causes connective tissue proliferation, resulting in erectile dysfunction [25]. It is also worth mentioning that this discipline is associated with frequent injuries of the genitourinary system which may cause numerous pathological changes in the testes. Testicular injuries are also common in other athletes, especially horse riders and contact sports [26].

Autoimmune infertility is due to the presence of antibodies against sperm that may be present in serum, semen or on the sperm surface. Antibodies may cause immobilization or agglutination of sperm, as well as impaired implantation of a fertilized egg. Typical causes of autoimmune infertility include previous genital infection, testicular biopsy, testicular injury, testicular turn, and vasectomy [27].

DIAGNOSIS

Ineffective waiting for a pregnancy for one year is an indication for diagnostic process, which should always apply to both partners [27, 28].

INITIAL DIAGNOSIS

MEDICAL HISTORY

It is important to collect full medical history. Attention should be paid to history of sexual development, chronic systemic illnesses, previous infections, especially

mumps and genitourinary tract infections, which are often linked to male infertility. History of previous surgeries, especially those involving pelvic and inguinal regions and genitalia, as well as radiations covering the groin and scrotum are important. The physician should ask about medications intake, environmental exposures and sexual life (libido, erections) [27, 28].

PHYSICAL EXAMINATION

Physical examination should include a general medical examination and the results of basic laboratory tests in order to examine general health, diagnose obesity or overt signs of endocrinopathies, which may be the cause of infertility. During the examination, special attention should be paid to skin discoloration, which may occur in many congenital conditions. Particular attention is devoted to the examination of the urogenital system, especially for the presence of inflammation and varicocele, which are common causes of male infertility [27-29].

SEMEN ANALYSIS

Semen analysis is the basis for further diagnosis and treatment. Semen testing should be performed after 2-5 days of sexual abstinence. The test should be carried out in a laboratory in accordance with national quality control standards. During sperm analysis, it is important to distinguish asthenozoospermia, oligozoospermia and teratozoospermia. Sometimes these pathologies can occur together, which is known as oligo-asteno-teratozoospermia. Determination of these parameters is important for further management. If the semen parameters are in accordance with the WHO criteria, the result of one test is enough. If the test results are incorrect, semen analysis should be repeated. If semen abnormalities are present in subsequent tests, further diagnosis is necessary [27-30].

ADDITIONAL TESTS

HORMONAL TESTS

Hormonal disorders are a rare cause of male infertility. Standard tests, in case of the incorrect semen analysis result include FSH, LH and testosterone levels. Decreased testosterone levels and increased FSH levels suggest primary hypogonadism, while low testosterone levels and low levels of FSH, secondary hypogonadism. Low levels of testosterone along with low levels of LH usually justify the study of serum prolactin levels [27-30].

SCROTAL AND TRANSRECTAL ULTRASOUND

This examination enables the diagnosis of venous changes in spermatic fusions, assessment of the prostate gland and other structures of the genital system. It allows detection of obstructive azoospermia, which should be suspected especially in men with normal testicular volume, normal testosterone, FSH, LH level and azoospermia [27-30].

GENETIC TESTS

Genetic tests allow detection of hereditary and innate syndromes. These may include karyotyping, testing for Y-chromosome microdeletion, detection of mutations in the CFTR gene responsible for cystic fibrosis. These tests also allow assessment of the risk of transferring genetic abnormalities to future offspring [28, 29].

TESTICULAR BIOPSY

If the result of testicular biopsy shows that sperm production is normal, it indicates that infertility problems are associated with blockage or disturbances in semen transport [28, 29].

TREATMENT

Many cases of male infertility are idiopathic, however some of them can be detected. Depending on the cause, the most appropriate therapeutic treatment is selected, individually for each patient. It should be remembered that male infertility is often a multifaceted problem, additional therapy is needed apart from targeted therapy. This includes the control of chronic diseases (hypertension, diabetes), quitting bad habits such as smoking or alcohol abuse, and implementing regular physical activity. Treatment is a long-term process, often lasting many months, requiring patience from the patient.

MEDICAL TREATMENT

Various studies proved the positive effect of antioxidant treatment (folic acid, vitamin E, zinc, selenium) on the quality of sperm, which resulted in the improvement of spontaneous pregnancies [31,32]. None of the clinical trials showed any improvement, in case of unexplained infertility, in men after gonadotropin treatment (FSH, hMG, hCG), androgens, antiestrogens (clomifene, tamoxifen), dopamine D2 receptor agonists or steroids. Therefore, in case of patients with idiopathic infertility this type of treatment is not recommended [31,32]. Improvement in fertility after medical treatment can be obtained in men with low testosterone level (clomiphene citrate or tamoxifen), hypogonadotropic hypogonadism (treatment with gonadotropins and hCG), hyperprolactinemia (dopamine agonists) [31, 32].

SURGICAL TREATMENT

VARICOCELE

Treatment of varicocele is controversial. According to current data, varicocele causes damage to the testicles beginning in adolescence, resulting in male fertility. According to some research, the quality of semen after treatment is improved. Varicose veins treatment may be effective in adolescents. In adults with subclinical varicocelic signs, no treatment benefit was observed. The surgical treatment may be effective for men with oligozoospermia and clinical venous degeneration [31-33].

MICROSURGERY/VASOVASOSTOMY AND EPIDIDYMOVASOSTOMY

Vasectomy reversal procedure involves the removal of the scar changed section of the vas and fusion of the end to the end of the vas deferens (vasovasostomy) or the implantation of the ventral section of the vas deferens into the epididymitis head (vasoepididymostomy). These micro-surgical procedures should only be performed by experienced urologists. The chance of having a descendant is inversely proportional to the obstruction interval, it is less than 50% after 8 years. Other important factors are the quality of the sperm after the procedure and partner's age. In some cases, epididymal obstruction coexists, which is an indication for vasoepididymostomy surgery. Since this procedure has a limited effect on pregnancy rates, these procedures should be combined with microsurgical epididymal sperm aspiration (MESA), and cryopreservation of harvested spermatozoa for intracytoplasmic sperm injection (ICSI) [31, 34].

IN VITRO FERTILIZATION

If other techniques fail, in vitro fertilization (IVF) is possible. This treatment begins with stimulating ovulation in a woman. Next, under the control of USG, oocytes are collected, which is combined with selection and preparation in the laboratory sperm. The embryos obtained are then cultured for 2-5 days and introduced into the uterus via a catheter. The in vitro method is used in the case of low semen quality, unsuccessful insemination attempts, complete obstruction of the vas deferens, fallopian tubes and when the cause of infertility was not determined [35].

MESA/TESE

If in men with obstructive azoospermia vasovasostomy, vaso-epididymostomy cannot be performed or is ineffective, MESA in combination with ICSI is recommended. Percutaneous aspiration of spermatozoa from the caput epididymium (PESA) can be performed as an alternative method. If these methods fail, testicular sperm extraction (TESE) can be advised. In this method semen is prepared in the laboratory conditions with selection of the most viable and mobile sperm. Semen is injected into the uterus during natural or hormonally-stimulated ovulation. As a rule, the treatment must be repeated several times. If patient suffers from azoospermia and sperm cannot be obtained, intrauterine inseminations are performed using donor sperm [31-33]. Donor sperm is used if patient has azoospermia, significant semen pathology and lack of pregnancy despite numerous ICSI attempts. It can be also considered if there are contraindications to perform ICSI or in case of high risk of genetic disease transfer [31].

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ABBREVIATIONS

CHH – Congenital Hypogonadotrophic Hypogonadism
CF – Cystic Fibrosis
CFTR – Cystic Fibrosis Transmembrane Conductance Regulator
FSH – Follicle-stimulating Hormone
GnRH – Gonadotrophin Releasing Hormone
ICSI – Intracytoplasmic Sperm Injection
IVF – In Vitro Fertilization
KS – Klineferter Syndrome
LH – Luteinizing Hormone
MESA – Microsurgical Epididymal Sperm Aspiration
PCD – Primary Ciliary Dyskinesia
SHBP – Sex Hormone Binding Globulin
TESA – Testicular Sperm Extraction

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