

MEDICINAL PREPARATION OF A MAN FOR CONCEPTION

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Abstract. Infertility is an actual and socially significant problem. In about half of the cases, when examining couples who sought medical help in connection with unsuccessful attempts to conceive, factors are identified that indicate a decrease in male fertility. The urgency of the problem of male reproductive health is growing - over the past decades, the total number and concentration of sperm in the ejaculate in men in the developed countries of the world has decreased by 50-60%, and in Bukhara from 2012 to 2022. There was a two fold increase in the total number of male patients diagnosed with male infertility.

Key words: infertility, conception, fertiwell, IVF

Introduction: It is known that infertility in men can be associated with the presence of congenital anomalies in the development of the genitourinary system, as well as be the result of a number of diseases (infectious-inflammatory, endocrine, autoimmune, oncological, etc.) or dysfunctions (erectile, ejaculatory). At the same time, in 30–60% of patients, the results of a clinical examination did not allow us to identify the cause of a decrease in reproductive function, and therefore such infertility was classified as idiopathic.

Further studies in this area have shown that idiopathic male infertility, as a rule, is caused by pathological processes that are not recognized during the basic clinical examination, leading to disruption of the functioning of the hypothalamic-pituitary-gonadal system and spermatozoa, pathological changes in the integrity of the chromosomal apparatus and the formation of genetic defects, etc. According to experts, oxidative stress is often observed in men with idiopathic male infertility, caused by the formation of reactive oxygen species (ROS) and insufficiently effective functioning of the antioxidant system.

Of particular interest are works that have demonstrated that normal regulation of spermatogenesis in the testicles, in which proteins and peptides (proteome, peptide) play an important role, is necessary to ensure male fertility. The authors of these publications were able to establish that this regulation is provided by several thousand biologically active protein molecules that can affect the expression of genes encoding spermatogenesis, and changes in the ratio and concentration of peptides can lead to reduced fertility and are often observed in patients in infertile marriages. A key role in maintaining an equilibrium proteomic environment is played by Sertoli cells, in which the synthesis of proteins necessary for the formation of cell membranes and regulatory peptides occurs; however, information exchange mediated by polypeptide molecules with testosterone-producing Leydig cells is also important.

Recent studies have shown that a decrease in a man's ability to conceive can also be observed under the influence of adverse chemical and physical environmental factors (pesticides, biphenyls, heavy metals, high temperatures, ionizing radiation, air pollution, etc.), lifestyle (alcohol abuse, smoking, drug use, nutrition with insufficient vitamins, etc.), as well as concomitant systemic diseases accompanied by disorders of carbohydrate and fat metabolism. These factors can have a negative impact on the mechanisms of regulation of spermatogenesis in the male body, promote excessive production of reactive oxygen species (ROS), disrupt the function of Sertoli cells, spermatozoa, lead to fragmentation of the DNA molecules contained in them, they can also lead to disruption of the proteomic environment, which, in turn, can reduce the quality of sperm and the likelihood of pregnancy.

The influence of factors unfavorable for the reproductive system can be suspected at the stages of anamnesis and objective examination of men, however, in recent years, new methods of extended and in-depth laboratory diagnostics of ejaculate have also appeared, which make it possible to draw a conclusion about the functional characteristics of spermatozoa and the quality of their chromosomal apparatus. According to guidelines released under the auspices of the World Health Organization in 2021, many of these tests are not yet recommended for widespread use in clinical practice. Obviously, as the experience of their use in scientific research is accumulated and the acquired knowledge is systematized, it will gradually become possible to obtain the levels of evidence required for their inclusion in clinical recommendations. In addition, in the conditions of assisted reproductive technologies (IVF) laboratories, it became possible to perform genetic testing of embryos at the stage prior to transfer, which made it possible to reduce the risk of transmitting genetic diseases to off spring.

Along with the improvement of diagnostic methods aimed at identifying the causes of reduced fertility and functionally viable gametes and embryos, specialists in reproductive medicine widely use various methods of preparing men for conception (preconception preparation), and are also looking for new ways to treat men aimed at increasing their reproductive potential. According to clinical guidelines, all men who have been diagnosed with fertility-limiting conditions during an infertility screening should be treated to help restore their ability to conceive naturally. These include patients with hypogonadism, varicocele, infectious and inflammatory diseases of the genitourinary system, as well as systemic diseases accompanied by disorders of carbohydrate and fat metabolism. Preconception preparation is also necessary for men who have identified adverse lifestyle and environmental factors, the elimination or neutralization of the impact of which can lead to an improvement in ejaculate parameters, in particular, the functional state of spermatozoa.

In men with hypogonadotropic hypogonadism, normalization of reproductive function is possible during treatment with chorionic gonadotropin and menotropins, however, it should be taken into account that it may take 1-2 years of

treatment to initiate spermatogenesis and obtain indicators in the ejaculate that allow one to count on conception naturally. Therapy for hypogonadism is carried out under the supervision of an endocrinologist, if necessary, dosages and the regimen of drug administration are adjusted. Therapy with testosterone preparations in male infertility and in men interested in maintaining reproductive function is contraindicated, since it suppresses the secretion of gonadotropic hormones. Men with suspected thyroid dysfunction and hyperprolactinemia are examined and, if indicated, treated by an endocrinologist. In addition, patients with overweight and obesity, which can negatively affect a man's ability to conceive, need consultation with this specialist. In recent years, more and more evidence has been obtained of the relationship between a decrease in the quantitative indicators of ejaculate and the appearance of abdominal obesity and other components of the metabolic syndrome - dyslipidemia, arterial hypertension and insulin resistance. Preconception training of men with high body mass index and prescribing drug therapy aimed at correcting metabolic disorders and increasing fertility is also recommended in interdisciplinary cooperation with endocrinologists and nutritionists.

Surgical treatment for varicocele can be used to increase the likelihood of conception both naturally and with IVF. Despite the fact that, from the standpoint of evidence-based medicine, the existence of a causal relationship between the presence of a varicocele and male factor infertility has yet to be established, most researchers confirm that surgical correction of a clinically significant varicocele can lead to an increase in the number, mobility, proportion of normal forms of spermatozoa and a decrease in fragmentation. the DNA molecules they contain. It should be noted that drug treatment - the appointment of drugs with an antioxidant effect: L-carnitine, vitamins C and E, folic acid, zinc-containing mineral supplements after surgical treatment for varicocele increased the likelihood of normalization of spermogram parameters. In this regard, at present, specialists continue to study the possibilities of preconception preparation of men with varicocele without the use of surgery, counting on the suppression of pathogenetic mechanisms of inhibition of spermatogenesis, reducing the effect of ROS and increasing reproductive potential.

It is known that about a third of infertile men report that they have previously had diseases caused by sexually transmitted infections, while such patients often show a decrease in ejaculate values. Works have been published confirming the negative impact of pathogens of these diseases on male fertility, which can be realized through various pathological mechanisms that disrupt the normal functioning of the hypothalamic-pituitary-gonadal system, sperm transport, spermatogenesis and viability of spermatozoa, which indicates the need to be vigilant in this category of patients by assigning them an appropriate examination. Many specialists who have studied the reproductive function of men with chronic prostatitis noted that against the background of this widespread disease, there is an inhibition of the viability of spermatozoa, as well as a decrease in their overall and

progressive motility. At the same time, it turned out that leukospermia in the absence of infection is not accompanied by a decrease in ejaculate parameters or the likelihood of pregnancy.

Modern ideas about the prevalence of excessive ROS production in men in infertile marriages have contributed to the accumulation of knowledge about the use of antioxidants in order to restore fertility - vitamins, minerals, amino acids and other organic compounds, which, due to increased metabolic processes, activation of nuclear cytoplasmic transport, reducing inflammation activity and attenuating autoimmune responses can reduce oxidative stress. Despite the large number of publications devoted to the study of the effect of antioxidants on male fertility, insufficient data have been accumulated to make strong recommendations based on a high degree of certainty regarding the dosage, frequency and duration of administration of each of them. Due to the fact that a large selection of drugs containing several antioxidants in different dosages is available for clinical use, the search for the optimal composition to restore the reproductive potential in men with various causes of reduced fertility and infertility diseases continues.

In 2022, andrologists in reproductive medicine, in the arsenal of drugs for the complex treatment of spermatogenesis disorders accompanied by impaired fertility in men, received the drug Fertiwell, a complex of regulatory polypeptides with a molecular weight of not more than 10 kDa, isolated from the testes of mature cattle and having organotropic action on the male gonads. Fertiwell underwent preclinical studies, during which data were obtained on the absence of toxicity, carcinogenic, embryotoxic, mutagenic, immunotoxic and teratogenic properties, local irritating and allergenic effects. In addition, its tissue-specific action was confirmed (a significant increase in the growth zone of testicular explants and no effect on organotypic cultures of other organs). In an experimental model of radiation aging in animals, the drug restored impaired spermatogenesis, significantly increased the number of spermatozoa and increased their fertilizing capacity. Subsequent phase I clinical studies in healthy male volunteers and phase II studies in patients with impaired spermatogenesis confirmed the ability of the drug to increase the concentration and motility of spermatozoa in the ejaculate, as well as the safety of its use.

According to the results of a randomized, double-blind, placebo-controlled, prospective, multicenter clinical trial of the efficacy and safety of Fertiwell, conducted under the supervision of Academician of the Russian Academy of Sciences Д.Ю.Пушкаря an increase of at least 20% in the concentration and / or proportion of progressively motile forms of spermatozoa in the ejaculate compared with baseline) in 78% of patients during Fertiwell therapy and in 32% in the placebo group. At the same time, during treatment with Fertiwell, an increase in sperm concentration by more than 3 times was noted (with a difference in effects between the drug and placebo groups in terms of average relative changes in sperm concentration in the ejaculate by 5 times), as well as more than 2 times significant

an increase in the absolute number of progressively motile forms of spermatozoa and a 2.6-fold increase in morphologically normal forms of spermatozoa.

An important result of the study is the demonstration of the preservation of the therapeutic effect after the completion of the course of treatment for at least 3 weeks, which is probably associated with the regulatory effect of the introduced peptides, which trigger a cascade of reactions and signaling processes involving Sertoli cells and Leydig cells, continuing after the end of treatment. It is recommended to administer the drug intramuscularly once a week for 10 weeks, since it is this duration of therapy that makes it possible to guarantee the presence of the drug throughout all stages of sperm maturation and to improve ejaculate parameters.

Conclusion: Thus, at present, in the context of widespread factors that negatively affect male reproductive health, specialists providing medical care to men in infertile marriages have a significant arsenal of tools, the use of which allows us to count on improving ejaculate indicators and conception as naturally, and as a result of the use of ART. It is obvious that the continuation of research in this area and, in particular, the study of the effectiveness of Fertiwell in men with various causes of infertility will help expand the understanding of the possibilities of preconception drug preparation of men for conception and overcoming the problem of infertility in general.

References

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