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Causes and Factors of Male Infertility

Сохранение репродуктивного здоровья населения — важный фактор демографической политики государства. По данным ряда авторов, от 14 до 30% супружеских пар репродуктивного возраста страдают бесплодием, при этом мужской фактор в таких браках выявляется более чем в 1/2 случаев. В последние годы отмечено значительное ухудшение состояния основных показателей репродуктивной функции мужчин. Увеличилось число андрологических заболеваний, морфологических нарушений мужской репродуктивной системы, практически вдвое снизилась продукция сперматозоидов у мужчин репродуктивного возраста. Причина, вероятно, скрывается за целым комплексом стрессогенных факторов, таких как медицинская неосведомленность, бесконтрольное и неадекватное применение лекарственных средств, метаболические нарушения, недостаток витаминов и микроэлементов, влияние промышленных поллютантов, а также рост числа аддиктивных нарушений (алкоголизм, курение и наркомания). Разные по своей этиологии и степени тяжести формы бесплодия, от незначительных изменений сперматогенеза до полной дисфункции гонад, также могут возникнуть из-за генетических нарушений. Отсутствие анализа взаимосвязи клинической и генетико-биохимической компоненты у мужчин с бесплодием не позволяет подойти к пониманию патогенетики бесплодия и оценке риска развития мужской инфертильности. Высокий уровень развития современной медицины не всегда гарантирует истинное установление причин мужского бесплодия. В статье проанализированы результаты обзора специализированной литературы по вопросам диагностики и этиопатогенеза инфертильности мужчин. Частота и клинические признаки патологии мужской репродуктивной системы зависят от комбинаторности воздействия средовых влияний, проявляющихся чаще всего во взаимоусиливающемся эффекте. Сочетание нескольких, даже слабых, но однонаправленно действующих факторов делает риск развития мужской репродуктивной патологии очень высоким. Критичность ситуации побуждает специалистов проводить дополнительные комплексные исследования репродуктивного потенциала мужского населения.

Ключевые слова: мужчины, репродуктивное здоровье, репродуктивные нарушения.

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The preservation of reproductive health of the population is an important factor of demographic policy of the state. According to some authors from 14 to 30% of couples of reproductive age suffer from infertility; male factor in such marriages is detected in more than half of the cases. As you know, in recent years there has been a significant deterioration in the main indicators of reproductive function of men. Increased the number of andrological diseases, morphological disorders of the male reproductive system, almost halved the production of sperm in men of reproductive age. The reason probably lies behind a whole range of stress factors, such as medical ignorance, uncontrolled and inappropriate use of medication, metabolic disturbances, lack of vitamins and minerals, the impact of industrial pollutants, as well as the growth of addictive disorders (alcoholism, smoking and drug addiction). The forms of infertility differ according to its etiology and severity from minor changes to complete spermatogenesis dysfunction of the gonads, and can also occur due to genetic disorders. The lack of analysis of the relationship between clinical and genetic-biochemical components in men with infertility

makes it impossible to understand the pathogenesis of infertility and to assess the risks of male infertility. High level of current medicine does not always guarantee an identification of the cause of male infertility. The article analyzes data from the review of specialized literature on the diagnosis and etiopathogenesis of male infertility. Frequency and clinical signs of pathology of the male reproductive system depend on the combinatorial effects of environmental influences, manifested most often in mutually reinforcing effect. A combination of several, seemed to be imperceptible factors makes the risk of development of male reproductive pathology very high. This situation compels specialists to conduct comprehensive studies on the men reproductive potential.

Keywords: men, reproductive health, reproductive disorders.

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Introduction

Currently the health problems of the population, fertility and demographic prospects are key problems not only in Russia but also in other countries. Unfavorable demographic indicators with a sustained negative rates of natural increase of population in recent decades has forced specialists (geneticists, morphologists, immunologists, endocrinologists, gynecologists, urologists) to analyze the factors that affect fertility rate and infertility takes an important place among these factors [1–3]. According to the statistics, the frequency of infertile marriages in many countries of the world varies from 8 to 29%. In Europe, infertility affects about 10% of couples, in the USA – 15%, in Canada – 17%, the share of infertile marriages in Russia varies from 8.2 to 19.6%. These indicators exceed the critical level (15%) and represent a state problem by having many components (social and demographic, medical, economic, etc.) [1–3]. Until recently, female reproductive disorders (90%) were mainly considered the causes of infertility in marriage. However, a more detailed recent study of childless couples have shown that in 40-60% cases the reason for children absence in a family is male infertility [3]. The number of andrology disorders, as well as morphological disorders of the male reproductive system increased. Quantitative and qualitative spermatogenesis indicators in reproductive age men have decreased by almost 2 times [4–6]. The origins of male infertility usually start in childhood. Very often boy's pathology is not revealed and therefore not treated up to the entry into the reproductive phase period. Because of that this pathology becomes so severe that it is almost not correctable [7, 8]. Based on mentioned above, it should be noted that assessment of the male reproductive health is an important research problem and it is essential not only for monitoring of the reproductive health of the population as a whole, but also for development of a complex measures aimed at early diagnosis and correction of disorders of the male reproductive system.

In accordance with resolution of the Russian scientific Congress on "Men's health", more than in 33% of somatically healthy young and middle age men claim a decrease in sexual activity [3]. The increase in the number of stressful social factors, addictive disorders (alcoholism, drug addiction, smoking), as well as the sharp deterioration of environmental conditions are the cause of this situation. In one of the first studies of sperm quality, E. Carlsen et al. (1992) indicated a decline in the semen of men living in various regions of the world from 1938 to 1990: decrease in the concentration of spermatozoids in the ejaculate, a decrease in the proportion of motile and morphologically normal ones [9]. It was found that the spermatozoids concentration for these years decreased from 113 to 66 million/ml, volume of ejaculate has decreased from 3.4 to 2.8 ml. The research conducted in 2008 confirmed the decline in semen quality in recent decades [3, 9]. Geographic and ethnic differences in sperm concentration in men were revealed [9, 10]. For example, the sperm concentration in the ejaculate in men of Finland is higher than of those living in other regions of Europe [10]. The concentration of

sperm in the ejaculate was significantly higher among men in Scotland and Finland, than in men of Japan [11]. In addition, the total number of spermatozoids reduced and percentage of motile and morphologically normal spermatozoids is lower in Japanese compared to Europeans [11]. The concentration of sperm in the ejaculate is lower among residents of Columbia than in the Americans [10], the lower concentration also shown in the Danes in comparison with Swedes or Finns [12]. Comparing semen in men from different Russian cities (Arkhangelsk, Kemerovo and Novosibirsk) it was found that the volume of ejaculate among residents of Arkhangelsk was significantly lower than in men from Kemerovo, but did not differ from that of men from Novosibirsk [3, 9]. The concentration and percentage of motile sperm in the ejaculate of the residents of Arkhangelsk was significantly higher than that of residents of Novosibirsk [13]. The concentration and percentage of motile sperm among residents of Arkhangelsk were significantly lower than in young men living in Estonia, Norway, Finland, and Latvia, but it was not different from those of the residents of Germany [13]. There is evidence that such indicators as the volume and percentage of morphologically normal sperm in residents of Novosibirsk are similar to Europe and the USA men [14]. Though significant (more than twice) differences in semen quality between the inhabitants of different countries or different areas of one country well known, but the causes of regional differences remain unidentified.

Thus, geographical and national characteristics of sperm quality can determine the regional variability of reproductive parameters and make a significant contribution to the general trend of decreasing male fertility.

Genetic markers of male infertility

It is known that genetic factors are the cause of various forms of male infertility in 30-50% of cases [15, 16].Genetic disorders can cause different infertility forms due to the occurrence and severity: from minor changes of spermatogenesis to complete dysfunction of the gonads.

The process of spermatogenesis is under the influence of a precisely controlled cascade of activation and deactivation of specific genes. There are 3 main genetic factors of male infertility: chromosomal aberrations (changes in the genetic apparatus at the chromosomes level), mutations (at the level of single or group of genes), and DNA fragmentation. According to some authors, chromosomal changes in infertile men are detected in 5-15% of cases, of which 3/4 are anomalies of X and Y sex chromosomes, the rest —anomalies of other chromosomes [17]. Other authors estimate the frequency of structural chromosome aberrations in the karyotypes of different samples of infertility men with the range of 1.6 to 4.2% [18].The most common chromosomal abnormalities are presented by Klinefelter's syndrome (1.5 per 1.000 newborns) and Y disomy (1 per 1.000 newborns). Well-known chromosomal aberrations are of two types: balanced and unbalanced. Balanced chromosome rearrangements, such as inversions, translocations, marker chromosomes, lead neither to loss nor to addition of genetic material, but only to its movement within the genome, therefore, more often carriers of these rearrangements are phenotypically normal and healthy.

In contrast, carriage of unbalanced rearrangements (deletions and duplications) is associated with significant abnormalities and is characterized by the presence of replacement of dose ratios of genes. In addition to the pathology of the karyotype, one of the most common genetic causes of male infertility is Y-chromosome microdeletions which are present in the locus AZF (Azoospermia factor region). Changes in this locus are found in 7-10% of all cases of secretory azoospermia [15, 17, 18].The presence of microdeletions of Y chromosome in the AZF locus may lead to changes in morphological and reproductive properties of spermatozoa from an insignificant decrease in spermatogenic activity (hypospermatogenesis) up to full blockage of spermatogenesis (Sertoli cell-only syndrome). Now with the help of modern assisted reproductive technologies male carriers of microdeletions of Y - chromosome can have children

of their own, however, there is a high risk that children (boys) can inherit this rearrangement, or lead to the birth of children with various forms of hermaphroditism.

AZF-locus is not the only determinant of spermatogenesis. Sterility and block of spermatogenesis can be the consequence of changes in the gene CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) and lead to a serious hereditary disease — cystic fibrosis [19]. As a result of mutations in the *CFTR* gene obstructive azoospermia is diagnosed in men, in 25% of cases resulting from single or bilateral congenital absence of vas deferens. Another important cause of male infertility is a disorder of spermatogenesis hormonal regulation. In this case the main role plays androgens, which interacts with the androgen receptors (AR), stimulating the development of male sexual signs and activates spermatogenesis. Chromosome rearrangements and point changes in the AR gene lead to either testicular feminization, or Reifenstein's syndrome and make a significant contribution (>40%) in male infertility. Functional activity of androgen receptor depends on the number of repeats of CAG (cytosine–adenine–guanine) correlating with the amount of free testosterone in the serum. The decrease in receptor sensitivity is inversely proportional to the number of CAG-repeats. Increasing the number of CAG-repeats increases the risk of the development of oligo- and azoospermia.

An example of a gene that participates in the development of the male reproductive system and sexual differentiation can be the *SRY* gene. An extensive range of phenotypic and clinical manifestations accompanies its changes: from complete sex reversal to the underdevelopment of the male gonads [20]. For example, most patients with De La Chapelle syndrome, characterized by changing of the external genitalia and absence of spermatogenesis, karyotype has translocated fragment of Y chromosome containing the *SRY* gene.

The data of some authors indicate one of the causes of male infertility may be DNA fragmentation, which identified recently and was studied intensively in the last decade. It includes double- and single-stranded DNA breaks that are associated with abnormal chromatin packaging or protamine deficiency during spermatogenesis [16, 17]. Early stages of embryo development (blastocyst formation) under the influence of fragmented DNA are particularly affected. In addition, the rate of pregnancy and a positive reproductive outcome depend on the presence of damaged DNA chains [19, 20].

Oxidative stress and sperm quality

The problem of oxidative stress of sperm cells deserves special attention [21–23]. It is known that the result of an emotional or any other stress is release of endogenous flogogenes (initiators of inflammation) into the intercellular environment; they are represented by heat shock proteins chaperones. This followed by stimulation of phagocytosis, activation of neutrophil NADPH oxidase, and in the end - the formation of reactive oxygen species (ROS) - ozone, free radicals, hydrogen peroxide [24, 25]. Due to the balance between the formation of ROS and the antioxidant in sperm there is a minimal amount of free radicals necessary for the regulation of capacitation, acrosomal reaction and fusion with the oocyte, the regulation of biochemical redox reactions of energy synthesis. Regardless of the etiological factor, imbalance between the production of free radicals and the weakening of the antioxidant defense in different parts of the male reproductive tract is a key indicator of oxidative stress, which has a positive correlation with the degree of male infertility. The pathology of the male germ cells induced by reactive oxygen metabolites observed in 30-80% of cases of male infertility [25]. Excessive ROS production, which causes membranes damage, can lead to a decrease in motility and fertilizing capacity of sperm. Excessive production of ROS also determined in such pathological conditions as inflammation of the accessory genital glands, varicocele, urogenital infections, scrotal lipomatosis that have both direct and indirect effects on the reproductive system. The same is characteristic for psycho-emotional stress, depression, diabetes, metabolic syndrome, systemic chronic inflammation, hormonal disorders and other pathological conditions [23–25]. ROS can have direct damaging effect on the chromosomes DNA; moreover, they are can initiate sperm

apoptosis mediated by endonucleases that in most cases can cause infertility. ROS — universal constraints on the number of sperm and regulators of the quality of the ejaculate from the point of view of evolution [24]. Since the main substrate for the free radical oxidation are phospholipids, the intensity of lipid peroxidation will depend on their composition and the structural organization, the violation of which can lead to decreased mobility and quality of sperm and, as a consequence, to infertility [26]. However, essential phospholipids have the ability to influence the sex cells, increasing their fertility both directly and indirectly [26]. Assessment of the level of the generation of oxygen free radicals in the ejaculate seems to be one of the important methods that allow providing the characteristic of the sperm fertility in normal - and pathospermia, as well as in infections of the genital organs [27].

According to the modern concepts, disruption of the activity of the thiol-dependent ensembles is a central feature of oxidative stress, a constant satellite of spermatogenesis abnormalities [28]. According to some authors, at infertility of unknown nature, the activity of some enzymes such as glutathione peroxidase and glutathione-S-transferase, is significantly lower than in fertile males and it does not depend on the state of spermogram [30]. Glutathione peroxidase has a unique position in the reproductive system of mammals, because it directly related to the attainment and maintenance of the sperm integrity. Unlike superoxide dismutase, which can be a pro-oxidant, glutathione peroxidase destroys other organic peroxides in addition to hydrogen peroxide even with a slight increase of their concentration, , maintaining cellular homeostasis [29-31]. Glutathione peroxidase reacts first to oxidative stress and acts as scavenger during ROS leakage and development of uncontrolled chain processes. Glutathione-S-transferase being localized on the surface of sperm cells plays the role of a trigger which starts their interaction with ligands in the *zona pellucida* on the stage of initiation acrosomal reaction. It is also an important multifunctional protein of the ejaculate providing protection from xenobiotics and ROS. That is why the determination of glutathione-S-transferase can be used not only to test the antioxidant activity of drugs, but also to determine the fertilizing capacity of sperm [32, 33]. It is also known that at chronic inflammatory diseases of the prostate, ROS accumulation with activation of free radical oxidation of biopolymers occurs. These results in sperm damage and decrease their functional activity [25, 34, 35]. Reduced number of live sperm, actively motile sperm, as well as the increase in various forms of defective sperm in the ejaculate of patients with chronic abacterial prostatitis found. The concentration of the final products (malonic dialdehyde) in these patients is higher than in the control group, and the activity of antioxidant enzymes, in contrast, is reduced. It suggested that the strengthening of the processes of polymers peroxide oxidation on the background of reduced antioxidant defense in the ejaculate is at least one of the reasons for changes in semen probes [34].

Medical and social causes of male infertility

Obesity also makes a negative contribution to the pathogenesis of male infertility [36, 37]. It is well known that adipose tissue is not only a depot for storage and accumulation of energy substrates, but it is active as an endocrine organ and is capable of producing a number of biologically active substances [38]. According to Japanese scientists, men with high body mass index are less able to conceive a child than men with normal body mass index, despite their age, lipid profile and glycated hemoglobin. The degree of obesity is positively correlates with the frequency of DNA damage of sperm chromosome when assessing the integrity of the chromatin [35]. Concurrently obesity inversely correlates with the volume of ejaculate, index of semen, and its fertility [38, 39].

Morphological damage of the epididymis and urogenital neuropathy on the background of oxidative stress and lack of nitric oxide can lead to violations of sperm transport and damage to the nuclear and mitochondrial DNA of sperm and their increased immobilization in men with type 2 diabetes [40]. Also, a decrease in fertility and semen volume were registered in men with type 2 diabetes [40].

A large number of researchers suggest that the deterioration of spermatogenesis and increasing the frequency of pathological states of the male reproductive system are related to the influence of anthropogenic pollution of the environment [14, 20, 41]. There is evidence that the reduction in the concentration of sperm in men occurs primarily in the industrialized countries of Europe and America, and is not typical of Asian and African countries [42]. It proves data of spermatogenic function research in men in various regions [9, 10, 14]. In men, living and working in industrial areas, there were determined more severe violations of indicators of semen, in contrast to the inhabitants of agricultural areas in which the deterioration of indicators of semen were absent or expressed weakly. For decades, in the result of intense human activity of industrialized countries the environment gets thousands of chemical compounds to which the organisms have not been adapted during evolution; as a consequence, adaptation mechanisms (including biochemical systems of detoxification and excretion from the body) are not fully formed. Chemical pollutants penetrate into the human body with environmentally contaminated food and water. Many toxicants of different nature have been identified in research of food, breast milk, semen, blood serum, follicular fluid [20, 42]. In some areas chemical compounds content of Russia men surpassed those of Western countries up to 10 times [42]. Especially active pathogenic action was determined for dioxins and dioxin-like compounds, pesticides, herbicides, insecticides. Violation of spermatogenesis (oligospermia), decreased of reproduction and infertility were found in men working in the production of chlordane - estrogenic insecticide [42]. Some chlorinated hydrocarbons belonging to the class of chlorinated hydrocarbons, causes significant reduction in sperm motility and inhibits acrosome reactions [42, 43]. Studies of many authors show that men working in the production of lead, more often have asteno-, oligo- and teratozoospermia and infertility [43]. A number of experimental studies noted that metals such as cadmium, lead, manganese, mercury violate the differentiation of spermatids and spermatocytes, resulting in oligo-, asteno- and teratozoospermia [43]. Carrying out work on the reproductive function in men exposed to fluorine, V.I. Tokar et al. found that hypogonadism is the primary link in the chain of violations arising from the effects of this microelement. Phosphorus is also assigned to substances which directly affect the organs of male reproductive system [44]. H. Kolstad et al. studied the concentration ratio of sperm in men who work in the shops where styrene was a negative factor. The results showed that after 6 months of their work an average sperm concentration in the examined contingent ejaculate dropped from 63.5 to 46 million / ml [45]. Among other impacts with determined damaging effects (both clinically and experimentally) on spermatogenesis (and for the whole human body) should be allocated smoking, alcohol and drugs. They certainly have an adverse effect on the reproductive system of males.

Conclusion

Analysis literature data clearly shows prove that catastrophic growth of reproductive disorders in men, observed in the last few years, is a reflection of the common comorbid predisposition of the male population. Despite the fact that currently developed methods of comprehensive laboratory examination of reproductive function of men, they are not always useful and correct in determining the true causes and factors affecting male fertility. A more detailed understanding of the mechanisms of action of various damaging factors inhibiting men spermatogenic function, will make it possible to develop effective methods of protection in case of isolated or combined harmful effects, and also determine the priority of diagnostic and preventive measures in a barren marriage. Improvement of measures of clinical, genetics and biochemical complex examination in men with impaired spermatogenesis is an important stage in the diagnosis of various forms of infertility in the male population. The reproductive health of men requires increased attention and further differentiation of approaches to a healthy lifestyle.

Conflict of interest

The authors have indicated they have no financial support / conflict of interest relevant to this article to disclose.

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