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Male infertility, metabolic syndrome and obesity

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The review article is devoted to the current understanding of the mechanisms that can have a negative impact on the reproductive function of men with metabolic syndrome and obesity. The article presents the results of clinical studies proving the existence of a relationship between the severity of metabolic disorders, copulatory activity, ejaculate parameters, the likelihood of pregnancy, as well as the health of the offspring.

Keywords: metabolic syndrome; obesity; male infertility; male reproductive health.

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Мужское бесплодие, метаболический синдром и ожирение

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Обзорная статья посвящена современным представлениям о механизмах, способных оказать негативное влияние на репродуктивную функцию мужчин с метаболическим синдромом и ожирением. Представлены результаты клинических исследований, доказывающих наличие взаимосвязи между выраженностью метаболических нарушений, копулятивной активностью, показателями эякулята, вероятностью наступления беременности, а также здоровьем потомства.

Ключевые слова: метаболический синдром; ожирение; мужское бесплодие; мужское репродуктивное здоровье.

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According to modern concepts, approximately 15% of married couples cannot achieve pregnancy despite 1 year of regular sexual activity without contraception and thus are considered infertile, while in about half of the cases, conception does not occur because of the male factor [1]. The urgency of the problem of maintaining male reproductive health is increasing, and for the period from 1973 to 2011, in men living in European countries, USA, Australia, and New Zealand, the spermatozoa count in the ejaculate decreased by 50%–60% [2]. In Russia, over the past two decades, there has been a twofold increase in the total number of men with infertility [3].

Experts have noticed that a decrease in the quantitative indicators of ejaculate and an increase in the number of couples who cannot achieve the desired pregnancy were caused by an increase in the overall prevalence of abdominal obesity and other components of metabolic syndrome (MS) such as dyslipidemia, arterial hypertension, and insulin resistance, which are noted in every fourth inhabitant of our planet in the twenty-first century [4, 5]. Severe nutrition, physical inactivity, hormonal imbalance, including androgenic deficiency, and genetic predisposition are considered factors influencing the development of MS in men. Russian and international scientists consider MS as a precursor of atherosclerosis and type 2 diabetes mellitus (T2DM) and believe that it is a risk factor for cardiovascular morbidity and results in subclinical lesions of all vital organs. Researchers also reveal evidence of a negative effect of MS on the reproductive health of men as well as on the quantitative and functional characteristics of the ejaculate, but the authors' conclusions were contradictory. Thus, this paper presents a review.

The components of MS are interconnected and interdependent, and each of them can contribute to the progression of pathological metabolic and hemodynamic processes that affect negatively a man's ability to conceive. Although the specific biochemical mechanisms that implement the relationship between MS and infertility are not fully understood, clinical evidence presents the pathogenic effect of MS on the regulation of endocrine profile and metabolism involved in gamete production [6, 7]. Published studies have confirmed the dependence of indicators, thus reflecting the reproductive health of men on the totality of their metabolic disorders. Lotti et al. [8] found significant reductions in the proportion of progressively motile and normal sperm cells, as well as a decrease in the total blood testosterone content in men with MS, regardless of age, while the differences from the normal values of these parameters were more noticeable in patients with more significant clinical manifestations of MS. A positive relationship was also found between the severity of MS and inflammation of the prostate gland, which is one of the factors that affect negatively the parameters of the ejaculate and reproductive function in general [9]. These data correspond to modern concepts of the pathophysiological mechanisms in MS, which functioning is accompanied by the production of proinflammatory cytokines [10].

Similar results were obtained by Leisegang et al. [11] in a case-control study. Compared with healthy men, patients with MS were found to have lower blood levels of free testosterone, as well as values of the concentration, total count, and motility of spermatozoa, while the degree of sperm DNA fragmentation was higher. Ventimiglia et al. [12] confirmed the findings of the frequent combination of hypogonadism and MS, but they were unable to identify differences in ejaculate parameters associated with MS in men with primary infertility. Ehala-Aleksejev and Punab [13] also drew conclusions about the absence of such differences, noted the contradictory opinions on this matter, and justified the need for further research in this field. The development of pathozoospermia due to a hypogonadal state in men with MS can also be facilitated by the concomitant obstructive sleep apnea syndrome, in which the subsequent production of testosterone is disrupted because of a disturbance in the rhythm of luteinizing hormone (LH) secretion [14].

An increase in the number of MS components in men intensifies the risk of erectile dysfunction, which also reduces the probability of conception [15]. Major population studies conducted in several countries, including Russia, have confirmed a close relationship between the components of MS and the risk of copulatory disorders [16, 17]. Russian scientists also showed that 90% of male respondents of reproductive age with MS complain of dissatisfaction with their sexual life due to erectile dysfunction of varying severities, as well as premature ejaculation. Moreover, deviations from the reference values were noted in the spermogram in 67.8% of patients with MS [18].

Many researchers believe that abdominal obesity plays a leading role in the progression of metabolic disorders and an increase in the probability of T2DM and cardiovascular diseases in patients with MS. In contrast to the subcutaneous tissue, adipose tissue, which accumulates in the mesentery and omentum, has good innervation and profuse blood supply, allowing lipid metabolism products to enter directly into the portal vein of the liver, inhibit the activity of enzymes that ensure the metabolism of carbohydrates, and thus lead to the development of insulin resistance. Moreover, visceral adipose tissue synthesizes a large number of biologically active substances involved in the regulation of metabolic processes and vital functions (such as leptin, tumor necrosis factor-alpha, insulin-like growth factor, plasminogen activator inhibitor I, angiotensinogen, angiotensin II, interleukins, prostaglandins, estrogen, adiponectin, and resistin), which presents that it is an independent endocrine organ. In this regard, in men who were obese, various pathological mechanisms

appear that can disrupt the normal functioning of the reproductive system and have a direct effect on spermatozoa [19].

Obesity, being the most significant component of MS, can negatively affect the reproductive function of men by activating several pathophysiological mechanisms, which functioning has recently been examined by many researchers.

Obesity and hypogonadism

Obesity contributes to the dysregulation of the entire endocrine system. The relationship between obesity and hypogonadism in men, due to the predominance of estrogen synthesis and the production of leptin in adipose tissue, has long been known and confirmed by many studies, including population studies [20]. Estrogens can suppress the activity of hypothalamic neurons, production of gonadotropin-releasing hormone, and subsequent release by the pituitary gland of LH, follicle-stimulating hormone (FSH), and prolactin, which affect the germ cells of the testes, which are the target organs of androgenic hormones. The production of androgens normally suppresses the production of leptin, and under conditions of androgenic deficiency, leptin can inhibit spermatogenesis [21].

In the follow-up of patients who were obese, the subsequent decrease or increase in the body mass index (BMI) is accompanied by either a normalization of the body's saturation with testosterone or an increase in the degree of androgen deficiency, which, in turn, can lead to impaired spermatogenesis and a decrease in the number of spermatozoa in the ejaculate. In men with high BMI, other disorders of the endocrine system are often recorded, which lead to a change in the FSH/LH ratio and levels of inhibin B and globulin that binds sex steroids and negatively affects the spermatogenic epithelium and functions of Sertoli cells [22]. In obesity, the activity of the cytochrome P450 system also changes, leading to excessive production of cytokines, in particular, tumor necrosis factor and interleukins, which contribute to the inadequacy of the hormone-producing function of Leydig cells [23]. Moreover, men often experience a vicious cycle; that is, with a decrease in testosterone level, an even greater deposition of visceral fat is needed. By contrast, a similar pattern can be traced in the opposite direction; in men who have lost weight, the testosterone level can normalize and reverse the functions lost in the presence of androgenic deficiency [24].

Obesity and T2DM

Obesity is one of the main risk factors for the occurrence of T2DM; therefore, both diseases can often be diagnosed in the same patient, which creates additional prerequisites for an adverse effect on the reproductive health of men, as well as difficulties for both normalizing carbohydrate metabolism and achieving normal body weight. Hyperglycemia can reduce the secretion of gonadotropins [25], as well as decrease the production of globulin that binds sex steroids in the liver, thus reducing the bioavailability of testosterone [26]. Insufficient control of glucose levels in men with T2DM is often combined with a decrease in the proportion of progressively motile spermatozoa and is accompanied by an increase in the level of DNA fragmentation [27].

Reproductive dysfunctions in men caused by obesity-related changes in body structure

In men who are overweight and obese, copulative activity is known to decrease due to the weakening of sexual impulse in the presence of hypogonadism and the difficulties in sexual intercourse caused by the excessive accumulation of subcutaneous adipose tissues [28]. Some men develop the so-called webbed penis syndrome, when, despite the normal size during an erection, a significant part of it remains in the thickness of the overhanging fatty tissue of the pubic region, which prevents intercourse [29]. The psychogenic component caused by a negative body image can significantly aggravate copulatory disorders [30]. An excess of adipose tissue on the thighs and lower abdomen in obese men can prevent the maintenance of the optimal temperature regimen of the scrotum within the range of 33°C–35°C, leading to hyperthermia and subsequent impairment of spermatogenesis [31]. This is supported by the results of scrotal thermography in men who were obese presented by Garolla et al. [32]. In some men with severe obesity, scrotal lipomatosis is noted, when adipose tissue can lead to the compression of the artery and veins of the spermatic cord, followed by the development of ischemia and impaired testicular function [33].

Influence of obesity on spermatogenesis and sperm function

Epidemiological studies conducted in many countries have revealed the negative effect of excess body weight on sperm count and reproductive function in men. Analysis of materials from a cohort of 47,835 married couples in Denmark showed that the probability of pregnancy during the year decreases by 1.53 times in men with BMI >30 kg/m^2 and by 2.75 times with concomitant obesity of the partner [34]. Comparable data were obtained by Norwegian specialists when examining 26,303 couples, where the risk of a failed pregnancy was 1.2 and 1.36 times higher for men who were overweight and obese, respectively [35]. Calculations of researchers from the USA showed that in men with BMI >25 kg/m^2, each subsequent increase in its value, i.e., 3 kg/m^2, corresponded to an increase in the risk of infertility in marriage by 1.21 times [36]. In Russia, Epanchintseva et al. [37] wrote about the prevalence of men who were overweight and obese among

those who applied to the center of reproductive medicine for infertility.

The conclusions of studies on the effect of obesity on spermatogenesis were contradictory, which was probably partly due to the collection of laboratory data mainly from men who sought medical help for infertility. Jensen et al. [38] revealed a decrease in the concentration and total spermatozoa count by 21% and 24%, respectively, in men who were overweight compared with those with BMI of 20–25 kg/m^2; they also noted similar deviations in men who were underweight. The authors of this study, based on the analysis of spermograms of 1,558 men, also noted that BMI does not affect the count of progressively motile and normal spermatozoa [38]. Moreover, Eisenberg et al. [39] could not confirm the relationship among BMI, waist circumference, and any parameters of the spermogram, with the exception of the ejaculate volume. This relationship was also not confirmed by the results of a meta-analysis of five studies published in 2010 [40]. Data obtained were subsequently included in another analysis by Sermondade et al. [41], in which a J-shaped relationship between BMI and the risk of oligozoospermia and azoospermia was revealed in a study of 31 publications on the results of examination of 13,077 men. For men who were overweight and with grade 1 and 2 obesity, this risk was 1.11, 1.28, and 2.04, respectively. This issue was most completely investigated by Campbell et al. [42] when analyzing 31 studies of 115,158 married couples who used assisted reproductive technologies (ART) for infertility treatment. Obesity in men reduced significantly the chances of having a child after using ART (odds ratio [OR] = 0.65, 95% CI 0.44–0.97), and silent miscarriage was registered in wives in 10% of the cases.

Data obtained inspired the researchers to analyze the functional characteristics of spermatozoa, as well as laboratory results of ART programs, which led to the discovery of some previously unknown patterns. Thus, in *in vitro* fertilization protocols, the frequency of ovum fertilization when using sperm from men who were overweight was higher than that in men whose BMI did not exceed 25 kg/m^2, while BMI did not have a significant effect on the indicators of embryo development under laboratory conditions, as well as the onset of biochemical and clinical pregnancy. Moreover, when using intracytoplasmic sperm injection in men who were obese, the chances of conceiving were significantly lower [43]. Moragianni et al. also wrote about this [44] and analyzed the results of treatment with ART in 4609 patients. The OR of having a child decreased consistently in men with BMI of 30–34.9, 35–39.9, and ≥40 kg/m^2 from 0.63 (0.47–0.85) to 0.39 (0.25–0.61) and 0.32 (0.16–0.64), respectively [44].

One of the mechanisms that can explain the greater number of failures in ART in men who were obese may be the termination of embryonic development associated with excessive fragmentation of sperm DNA; however, insufficient data confirm this hypothesis. In 3 of the 14 studies selected for a meta-analysis, the authors were able to demonstrate a higher level of sperm DNA fragmentation in men with BMI >30 kg/m^2 [45].

Sperm dysfunction in obesity can also be a consequence of oxidative stress, as in 30%–80% of men with infertility, an increase in the level of reactive oxygen species (ROS) is detected in the ejaculate, which can damage the membranes [46] and DNA molecules of male gametes [47, 48]. The decrease in the antioxidant activity of ejaculate in young men with post-pubertal alimentary visceral obesity was also reported by Rozhivanov and Kurbatov [49]. Although it was not always possible to draw clinical parallels between an increase in the level of ROS in sperm with spermogram parameters and the frequency of pregnancy [50], evidence showed an increase in the probability of success of ART protocols after the use of antioxidants [51], including the participation of men who were overweight. A high blood cholesterol level in obesity can also accumulate on the midpiece, leading to a change in shape, decreased motility, and loss of the ability to interact with the ovum [52].

Epigenetic effects of obesity

In recent years, studies of families, twins, and foster children in ethnically diverse populations have provided evidence of the heritability of BMI [53]. In most cases, specialists faced its variability, which is not associated with the identified single nucleotide polymorphisms but is associated with individual variability caused by the interaction of genes with the environment, that is, the so-called epigenetic factors. Several epigenetic mechanisms provide various gene expression profiles in cells of the same organism; in particular, they include DNA methylation [54], which is noted in the spermatozoa and depends on the degree of metabolic disorders [55]. Studies have shown that sperm DNA fragments involved in methylation reactions are involved in the spermatogenesis, fertilization, and subsequent development of the embryo [56, 57]; in addition, evidence shows the epigenetic effect of obesity on metabolism, morbidity, and mortality of offspring from diseases accompanied by metabolic disorders [58–60].

CONCLUSION

Currently, sufficient evidence shows the negative effect of MS and obesity on male fertility, which can cause the deterioration of ejaculate parameters and a decrease in the probability of conception and lead to metabolic disorders and development of diseases in offspring. Many pathogenetic mechanisms providing this influence are well studied, but further research is required with respect to several factors. Knowledge in this area can help

practitioners of various specialties improve the quality of medical care for married couples planning to conceive, as well as to conduct appropriate explanatory work among future parents.

ADDITIONAL INFORMATION

Conflict of interest. The authors declare no conflict of interest.

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