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Review

The role of obesity and environmental factors such as diet and physical activity in the etiopathogenesis of fertility disorders

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Summary

The most common causes affecting female reproductive potential in Poland are anovulatory cycles, diseases of the fallopian tubes and the peritoneum, male factor, and pathological changes of the uterus. It was observed that among couples originating from villages, there is a higher share of tubal infertility factor, while among couples originating from cities – of male factor. Environmental factors have been known to be part of infertility etiopathogenesis. However, despite the advances of recent years, the types of these factors and their mechanisms have not been sufficiently explained. Studies have demonstrated that there is a relation between diet and ovulatory infertility. The factors that reduce the risk of infertility include the presence of sufficient amounts of monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) in the diet and reduced intake of isomers of trans fatty acids (TFA) and saturated fatty acids (SFA). Replacing animal proteins with plant proteins is also advantageous. Other important factors are low glycemic diet, high intake of fat-rich dairy products, and provision of the right amount of vitamins and non-haem iron in the form of plants and dietary supplements. Multiple studies have demonstrated that improper nutritional status, including weight deficiency or excessive weight, may have an adverse effect on female and male fertility. Physical activity is also an important factor influencing female reproductive functions. In conjunction with an appropriate diet, exercise reduces abdominal obesity and improves insulin sensitivity, thus directly decreasing the risk of infertility.

Key words: Fertility disorders; Obesity; Diet; Physical activity.

Introduction

Infertility is a condition defined by the failure to achieve pregnancy despite 12 months of regular sexual intercourse, with the average frequency of 3-4 intercourses per week, without the use of contraceptives [1].

The most common causes of infertility include the occurrence of ovulation disorders, diseases of the fallopian tubes and the peritoneum, male factor, and pathological changes of the uterus. It was found that the share of both male and female infertility factors is comparable, while differences in the percentage of occurrence of individual risk factors were observed depending on the place of residence. In pairs originating from villages, there is a higher share of tubal infertility factor, whereas in pairs originating from cities – of the male factor. Undoubtedly, the reason for this phenomenon is the impact of environmental factors, among others [2].

In about 15-20% of cases, the cause of infertility is unknown. Unexplained infertility is often referred to as idiopathic infertility. It is defined as the inability to achieve pregnancy without any known cause discovered in routine clinical work-up. The management options depend on the age of the woman and duration of infertility, and is diagnosed when all standard elements of the assessment give correct results. The share of the unexplained factor in relation to the known factors of infertility increases steadily [1, 2]. Infertility with an undetermined cause is probably associated with less reproductive efficiency, oocyte or sperm abnormalities, fertilization, implantation or embryonic development phase abnormalities that cannot be determined by standard treatment methods. The average fertility of cycle in untreated women with idiopathic infertility is about 80% to 90% lower than in healthy couples. The likelihood of achieving pregnancy regardless of treatment decreases with the increase in the age of women and the duration of infertility. Couples are therefore advised to receive treatment. The aim of the treatment is to increase monthly fertility to a comparable level observed in well-fertile couples [3]. According to numerous studies, environmental factors are also mentioned among a number of factors that can affect fertility.

Experimental

It is known that environmental factors influencing the reproductive functions of women include improper diet, ab-

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normal physical activity, and excessive body mass [4-17]; the objective of this study was to analyse the literature in this filed.

Obesity

Many studies have shown that abnormal nutritional status, including excessive body weight, may negatively affect female fertility. In women who are overweight or obese, hypothalamic GnRH and pituitary gonadotropins secretion disorders are observed. The risk of infertility due to overweight is related to hormonal and metabolic changes, including steroid metabolism, secretion, and action of insulin, as well as other hormones, including leptin, resistin, ghrelin, and adiponectin. The described changes may affect follicle growth, embryonic development, and implantation [7-9].

When assessing the nutritional status, body mass index (BMI) is particularly important. As has been proven, the BMI value may also correlate with fertility. Women with BMI above the norm are characterized by a reduced concentration of circulating sex hormone binding globulin (SHBG), and therefore – increased estradiol concentration. Maternal obesity affects both the growth of oocyte, formation and activity of the ovarian follicle and implantation of the embryo, as well as directly the health of the developing child. Therefore, every woman should take care of the correct body mass already in the preconception period [7, 8].

Obese women suffer from menstrual disorders, anovulation and, as a consequence, infertility. Metabolic and endocrine changes occurring in obese women, including the reduction of secretion of FSH and LH by the pituitary gland, and reduced secretion of progesterone by the corpus luteum, as well as the decrease in the concentration of SHBG, are a frequent cause of ovulation disorders, thus reducing the reproductive capacity, especially in young women [18].

According to numerous studies, abnormal body weight correlates with the occurrence of excessive insulin secretion and insulin resistance. Increased blood levels of insulin and estradiol affect the development of ovarian follicle oocytes, which may affect the development of the embryo and contribute to the occurrence of miscarriages. It is worth mentioning that endocrine compounds synthesized by adipocytes of adipose tissue include i.a. leptin. Excess leptin also exerts an indirect influence on the process of ovulation, because hyperleptinemia increases insulin secretion and, consequently, insulin resistance, which promotes ovarian dysfunction. Some studies proving the relationship between leptin concentration and fertility show that leptin has an effect on hypothalamic-pituitary-thyroid and hypothalamic-pituitary-gonadal axes, carbohydrate, and lipid balance, as well as influences the immunological processes [7-9, 18].

The consequence of female obesity is excessive synthesis of androgens in adipose tissue. Excessive aromatase activity in adipocytes contributes to the transformation of estrogens into androgens. Increased synthesis and secretion of androgens by the ovaries is in turn conducive to hyperinsulinemia. Excess insulin also contributes to the reduction of SHBG secretion. In obese women, compared to those of normal body weight, the excess androgens affect the frequency of ovulation and menstruation (may occur less frequently) and infertility. In such women, excessive hair and acne is often observed [19].

The basis of reproductive system dysfunction in obese men are disorders related to the influence of adipose tissue on the functions of the endocrine system and metabolism. Similarly to women, in obese men the aromatase produced by adipocytes contributes to the disturbance of balance between estrogens and androgens. Hyperestrogenism and hypoandrogenism contribute to a reduction in the activity of the hypothalamic-pituitary axis, which in turn results in increased gonadotrophin secretion and secondary hypogonadism. Excess estrogen adversely affects the process of spermatogenesis. Observation of obese men also demonstrate a decrease in the concentration of SHGB. Another important aspect in the context of infertility in obese men is the influence of temperature on the process of spermatogenesis, i.e. the process of sperm maturation, their quantity and quality. The increase in testicular temperature is associated with excessive accumulation of fatty tissue and scrotal adiposity [18, 19].

Obesity also affects sexual dysfunctions in both sexes, which is related to sexual life quality disorders described in the literature through decreased desire, arousal and orgasmic ability, erectile dysfunction and, consequently, lower frequency of sexual intercourse. as well as lack of satisfaction with sexual life. Erectile dysfunction is associated with decrease in testosterone concentration, an increased level of proinflammatory cytokines secreted by adipocytes – tumour necrosis factor alpha (TNF-alpha), interleukin 6 (IL-6) and 1 (IL-1) – as well as often coexisting diabetes or cardiovascular disease. In men with excessive body weight changes in sperm parameters are observed; to date, studies have demonstrated a negative correlation between BMI and sperm concentration and their motility. Additionally, overweight and obese men had a higher DFI (DNA fragmentation index) compared to men with normal body mass. The high value of the DFI indicates increased fragmentation of the sperm genetic material [10-12].

Diet

As shown by the Nurses Health Study II (NHS II), there is a connection between the diet of healthy women and the occurrence of ovulatory infertility. The NHS was conducted over a period of eight years, involving 17,544 healthy women (not treated for infertility), aged between 25 and 42 years. The results of both NHS II and studies carried out

with the participation of laboratory animals have proven that factors that reduce the risk of infertility include the right dietary content of monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), and reduced supply of trans-fatty acids (TFAs) and saturated fatty acids (SFAs). Additionally, replacing animal proteins with plant proteins is also advantageous. Other important factors are low glycemic load and index of the diet, as well as intake of fat-rich dairy products, the supply of the right amount of vitamins, and non-haem iron from both plant sources and dietary supplements [4-6].

Products that are rich in monounsaturated fatty acids include olives and olive oil, rapeseed oil, and avocados. It has been shown that the replacement of 2% of the energy coming from MUFAs in the daily food intake with isomers of trans-fatty acids was associated with more than two times higher risk of infertility secondary to ovulation disorders. These observations were made regardless of the age of women, their BMI, lifestyle, and hormone levels. The harmful effect of isomers of trans- and saturated fatty acids in the context of fertility is probably related to the adverse effects of these compounds on the activity of the peroxisome proliferator – activated receptor γ (PPAR-γ) and the effect on the expression of genes related to insulin sensitivity of adipose tissue cells. High TFAs intake have been shown to increase the risk of insulin resistance, type 2 diabetes and markers of inflammation [4, 5, 20]

The results of NHS II have also shown a decrease in the risk of ovulatory infertility in women consuming fat-rich dairy products. This dependence is probably related to the presence of estrogens (which are involved in the regulation of the menstrual cycle) synthesized in the bodies of dairy cows, as well as of trans-palmitoleic acid. Mozzafarian *et al.* demonstrated that high intake of fat-rich dairy products is associated with a high content of this compound in the body. In turn, the high content of palmitoleic acid affects the reduction of insulin resistance (-16.7%, $p < 0.001$), which is closely related to infertility. At the same time, the authors of the study draw attention to the fact that recommendations regarding the increase in consumption of fat-rich dairy products should be considered very individually, in particular in people with risk factors for overweight, obesity, and atherosclerosis, due to the content of saturated fatty acids and their adverse effects, not only in terms of infertility, but also atherogenicity [4, 5, 21, 22].

The essential components of diet in the context of the risk of endometriosis, and therefore indirectly of infertility (endometriosisis a risk factor for infertility) include n-3 polyunsaturated fatty acids. Missmer *et al.* proved that women who consumed more PUFAs from oily sea fish had a lower risk of endometriosis, compared to the group consuming smaller amounts of fish [23].

As mentioned above, the NHS II assessed the consumption of proteins depending on their origin. It has been shown that replacement of 5% animal protein with plant protein resulted in a significant reduction in the risk of ovulatory infertility (by 50%). Authors of the study explain this fact with the beneficial effect of plant protein on the reduction of insulin resistance of tissues, and also the reduction of the concentration of insulin-like growth factor I (IGF I), which induces PCOS. On the other hand, PCOS plays an important role in the pathogenesis of ovulation disorders. The beneficial effect of arginine contained in plant proteins is also probably not without significance. This amino acid is a substrate for the synthesis of nitric oxide (NO). NO causes relaxation of the blood vessels smooth muscles, thus having a beneficial effect on blood supply to the reproductive organs, which promotes the development of oocytes, precursors of the egg, and better implantation of the embryo [4 -6, 21].

Afeiche *et al.* showed that the increase in consumption of red and processed meat correlates positively with the decrease in the quality and quantity of semen and the concentration of hormones involved in the reproduction process, which undoubtedly translates into male fertility. In this study, the results of which were published in 2014, semen samples and a diet of 189 men, aged 18-22, were analysed. Consumption of poultry and fish did not significantly affect semen parameters [24].

Chavarro *et al.* further proved that eating, in particular, chicken and turkey meat (most commonly consumed by the studied population animal protein form) was associated with an increased risk of ovulatory infertility. This study showed that one additional portion of animal protein per day, in particular in the form of poultry and red meat (including processed meat), significantly reduces (by 32%) ovulatory fertility ($p = 0.01$) [21].

The authors of NHS II also observed that high intake of carbohydrates with high glycemic load (GL), as well as high glycemic index (GI) correlated with the occurrence of ovulatory infertility. This can probably be explained by the adverse effects of high GL and GI diet on the sensitivity of tissues to insulin and reduced secretion of this hormone [5].

Another conclusion that was drawn from the conducted study concerned the consumption of minerals and vitamins, both in the natural form and in the form of dietary supplements. The use of complex vitamin and mineral supplements, in particular supplementation with folic acid and iron, was associated with a reduced risk of infertility in women. This risk was also reduced by high intake of unprocessed food of plant origin, i.e. wholegrain cereal products, legume seeds, and some vegetables characterized by a high content of non-haem iron [4, 5]. In men, supplementation with folic acid (5 mg per day) and zinc (66 mg per day) influenced the increase in the number of sperms, and supplementation with selenium – in sperm motility. Both the quality and the quantity of sperm were also influenced by the selenium supplementation lasting above three months (200 g per day) in combination with vitamin E supplementation (400 IU per day) [25-28].

In studies with male laboratory animals, it was proven that supplementation with antioxidants, including carotenoid astaxanthin in combination with vitamins E and C, have beneficial effects on reproductive functions. Animals were simultaneously subjected to caloric restriction [29]. The positive effect of antioxidants (vitamin E, C, flavonoids, and carotenoids) on female fertility has been demonstrated by Ruder *et al.* According to the researchers, oxidative stress caused by oxygen free radicals may contribute to infertility, as it disturbs the process of oogenesis and folliculogenesis, embryo implantation, and corpus luteum function. As has been demonstrated, increased free radical processes can be prevented by consuming antioxidants. In men, free radicals damage cell membranes and DNA strand, which lead to necrospermia, asthenozoospermia, and DNA fragmentation [30]. Mendiola *et al.* proved the existence of a relationship between lower intake of antioxidants by the studied men, mainly in the form of vitamin C and lycopene, and poorer semen quality. In turn, Gil-Villa *et al.* demonstrated that increased oxidative processes in men can contribute to miscarriage in their partners. After three months of supplementation with vitamins C and E, beta-carotene and zinc, as well as an increase in the content of antioxidants in the diet of both partners, in one-third of the surveyed female population a pregnancy occurred which was not prematurely terminated by a miscarriage [31, 32].

Physical activity

An important factor in the aspect of reproductive functions in women is physical activity. Exercise in combination with a proper diet result in the reduction of abdominal obesity and improve insulin sensitivity, and therefore indirectly contribute to reducing the risk of infertility. Analysis of data collected in NHS II indicates that it is primarily the increase of intense, not moderate, physical activity that is associated with a lower risk of ovulatory infertility and that each hour a week of intense exercise reduces the risk of infertility by 7% [15]. On the other hand, a very intense exercise in young women who train with high frequency may have an adverse effect on reproductive functions, as it may lead to disorders and even loss of menstruation, secondary amenorrhea, shortening of premenstrual luteal phase of the cycle, and the occurrence of anovulatory cycles. Training beginning at an early age, associated with high energy expenditure and often rigorous attention to body weight, may cause dysfunction in the hypothalamic-pituitary-ovarian axis, which reduces estradiol secretion and, consequently, decreases bone mineral density which in the future may lead to the occurrence of osteoporosis [16, 17].

Conclusions

In conclusion, a well-balanced diet, an appropriate amount of physical activity, and attention to the proper body weight, can be important in the prevention of fertility disorders. It should be therefore considered to include a young population, both young people from urban and rural areas, in an educational program. Such a program should primarily cover issues regarding correct posture and preventive healthcare. Environmental factors are modifiable factors, so education should begin as early as possible to reduce exposure time to these factors.

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