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Pregorexia and its significance for physiological processes in the fetus – a review of current knowledge

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Summary

Anorexia occurring during pregnancy can have a devastating effect on the pregnant woman's physiological clinical picture, mental health and fetal development. This is because eating behaviors, the fetal programming process, and behavioral-cognitive relationships all contribute to shaping intrauterine conditions. Dysfunction at the neural level predisposes to eating disorders, reduced self-acceptance, perinatal depression, and a negative perception of body image. The health consequences of reduced energy intake in the course of anorexia during pregnancy contribute to the manifestation of maternal ketonuria, ketonemia, increased excretion of nitrogen during diuresis, decreased synthesis of gluconeogenic amino acids after starvation in pregnancy. Scientific reports confirm the destructive impact of behavioral disorders focused on significant food restriction. Medical and psychological care in pregorexia (anorexia of pregnancy) is an integral part of support during pregnancy and the perinatal period. Support includes psychoeducation as well as monitoring of weight, mental and physical health, and identified risk factors.

The interdisciplinary team taking care of a pregnant woman with anorexia should include a gynecologist, midwives, a psychiatrist, a clinical nutritionist, a psychodietitian, a psychotherapist, a psychologist and involved family members. Long-term, consecutively implemented nutrition education along with the use of dedicated diagnostic tools in the form of Eating Disorders Diagnostic Scale (EDDS) and psychodietetic intervention based on motivational dialogue should be an integral part of cognitive-behavioral therapy.

Key words: pregorexia, fetal pathophysiological changes, interdisciplinary care

Introduction

Eating disorders are classified in *The International Statistical Classification of Diseases and Related Health Problems, tenth revision* (ICD-10) [1] as behavioral

disorders and affect both women and men. However, statistics to date indicate that eating disorders are diagnosed ten times more frequently in the female population than in the male population. In the female population, special attention should be paid to pregnant women, mainly in the early stages of pregnancy, who are characterized by an increased risk of eating disorders. Psychological dysfunctions include a wide spectrum of psychosomatic symptoms. The most common female body imbalance in the course of pregnancy is pregorexia (pregnancy anorexia). However, this entity is not distinguished in either the ICD-10 criteria or in the DSM-5 classification (*Diagnostic and Statistical Manual of Mental Disorders*) [1, 2]. Pregorexia is described as a term in popular psychology that is defined as an eating disorder with a psychological basis occurring during pregnancy. This disorder disturbs the pregnant woman's perception of her body image and leads to a restrictive lowering of daily energy intake and an increase in physical exertion in relation to the physical activity index (PAL) for this population group.

The aforementioned actions are stimulated by changes specific to pregnancy. Data on epidemiology indicate that pregorexia affects 2-4% of all pregnant women, but showing specific figures is problematic. Compared with other eating disorders, pregorexia is a significant public health problem because of its impact on the developing fetus. At the same time, it is indicated that its prevalence – in relation to the prevalence of other eating disorders concerning, among others, relationships with food and disturbances at the level of the orexigenic and anorexigenic system – is quite high [2-8].

The main objective of this study was to analyze pregorexia in the light of a review of studies focused on fetal pathophysiological processes, dietary recommendations for pregnant women, and interdisciplinary therapeutic intervention. The review was prepared on the basis of a literature search of the literature available through the scientific database PubMed by searching for entries consistent with the MeSh controlled vocabulary.

The concept of intrauterine programming

Intrauterine conditions show significant effects on embryonic and fetal tissue composition and the subsequent clinical picture and nutritional status of the child in the postnatal period. Therefore, pregnant women are informed by gynecologists and midwives about numerous contraindications. Observance of these contraindications enables protection of the pregnant woman's health and proper development of the fetus. During this period, special attention should be paid to the existence of a certain critical range of substance tolerance, the so-called window of susceptibility to toxins. Exogenous factors such as: polycyclic aromatic hydrocarbons, heavy metals, endocrine disruptors (phthalates, bisphenol A, polychlorinated biphenyls, dioxins, fluoropolymers), tobacco smoke, ethanol, and pharmaceuticals, especially dangerous in unbound form, acting embryotoxically (influence on fetal binding protein level) predispose to epigenetic changes and disrupt intracellular homeostasis. This condition is defined as allostasis – an imbalance.

Scientific reports indicate that predictors of allostasis also include co-morbidities of the pregnant woman such as atopic dermatitis, endocrinopathies, neuropathies, cardiopathies, gestational diabetes, stress stimulating anxiety-neurotic states and depression.

Another factor inducing chronic changes may be lack of supplementation with essential vitamins and trace elements (especially B_9, B_{12}, cholecalciferol, iron, iodine). Nutritional deficiencies are also important in this context. These factors activate the mechanism of the metabolic/fetal programming process in response to adaptation to disturbed homeostasis of cells, tissues, and organ systems in the face of a destructive impact of exogenous conditions. These factors predispose to the process of uterine programming during the critical stage of fetal development. Moreover, according to the concept of intrauterine programming, the state of the newborn's microbiome is influenced by diet, nutritional status and exposure to harmful external factors by the pregnant woman.

In the future, it seems reasonable to undertake studies on prenatal nutrition to obtain information on the immunomodulatory effect of dietoprophylaxis acting on the microbiome of the child. In the context of microbiome formation, it is also worth extending the diagnostics with prenatal testing and a thorough medical history of both parents. Supplementation during pregnancy, the method of its termination (natural or surgical) and the method of feeding (breastfeeding/modified milk/combined feeding) may predispose to the proper formation of the microbiome and functioning of the neonate's immune system [9-15, 19].

Pathophysiological changes in the fetus

The period of pregnancy is characterized, among other things, by weight gain of the pregnant woman. The anatomical and physiological changes that occur in the body of a pregnant woman depend on the gestational age. Also the blood flow to the placenta is variable and depends on the week of pregnancy. Specialists indicate that the most important and characteristic changes during pregnancy include:

- volume and blood flow in thoracic tissue, increased cerebral blood flow,
- fetal hematocrit volume,
- composition of tissue mass in the mother and fetus,
- a decrease in serum albumin, a slight decrease in serum AAG – alpha-1-acid glycoprotein,
- successive gain of fat mass (FM) – about 4.7 kg in a term pregnancy,
- left ventricular enlargement in the third trimester of pregnancy, increase in placental chorionic area,
- decreased hematocrit (HCT), embryonic hematopoiesis and blood viscosity, increased serum volume in the second half of pregnancy.

The total average weight of all organs whose size may change during pregnancy is estimated at 57.5 kg (these organs do not include the thyroid, thymus, larynx and esophagus), while the total weight of organs and tissues in the pregnant woman's body

(average value in a healthy woman and a normally developing pregnancy) is estimated at 12.1 kg [17, 20].

Weight deficiency in women with pregorexia may contribute to disturbances of vitamin (vitamin D, vitamin B9), mineral (calcium, iron, zinc), electrolyte (especially potassium, and to a lesser extent sodium, calcium, magnesium) and nutrient (poly-unsaturated omega-3 fatty acids) metabolism due to dietary restrictions or laxative abuse. The consequence of low supply of essential exogenous components may be predisposition to iron deficiency anemia, hypocalcemia, preeclampsia, congestion of pelvic organs, decreased functioning of the immune system, inflammation of the amniotic fluid, placental dysfunction in the form of placenta previa and premature rupture of membranes [3, 18].

Pregnancy weight gain, which in healthy women with normal body weight before pregnancy should be about 8 kilograms, is the basis for normal fetal development – it enables the development of the embryo and fetus, proper development of the placenta, maintenance of the correct volume of amniotic fluid, blood, morphotic elements, and affects the adaptation process of the pregnant woman's soft tissues – the connective tissues of the uterus, glandular tissue, adipose tissue and connective tissue forming the breast [16, 17]. Table 1 shows the recommendations for weight gain during pregnancy according to the recommendations in relation to the initial category of body mass index (BMI) determined taking into account the total weight gain during pregnancy and the rate of weight gain during pregnancy [16].

Table 1. **Recommendations for weight gain in singleton pregnancy**

BMI in the preconceptional period	Total weight gain during pregnancy	Rate of weight gain in the second and third trimesters
Underweight (<18.5 kg/m^2) – singleton pregnancy	12.5-18 kg	Average – 0.51 kg/week (0.44-0.58) kg/week
Normal body weight (18.5-24.9 kg/m^2) – single pregnancy *Weight gain in twin pregnancy – 16-20.5 kg	11.5-16 kg	Average – 0.42 kg/week (0.35-0.50) kg/week
Overweight (25.0-29.9 kg/m^2) – single pregnancy	7-11.5 kg	Average – 0.28 kg/week (0.23-0.33) kg/week
Obesity (≥ 30.0 kg/m^2) – singleton pregnancy	5-9 kg	Average – 0.22 kg/week (0.17-0.27) kg/week

Own elaboration based on [16].

A caloric deficit during pregnancy contributes to the use of fat and protein stores in the pregnant woman to sustain the pregnancy. The health consequences of sustained

reduced energy intake significantly below the value of total metabolism may contribute to ketonuria, ketosis and tissue resistance to insulin (insulin resistance) in pregnant women, increased excretion of nitrogen during diuresis and decreased synthesis of gluconeogenic amino acids after starvation in pregnant women. It should also be emphasized that in the group of pregnant women with anorexia, a higher incidence of termination of pregnancy by oxytocin-induced labour and cesarean section is observed than in women with gestational weight deficiency, which is not a consequence of anorexia [16, 18].

Moreover, body mass index in the preconceptional and prenatal period is an important prognostic factor. Indeed, a BMI value below 18 kg/m^2 observed during these periods increases the risk of miscarriage or preterm delivery caused by cervical insufficiency. Body mass deficiency also contributes to bladder rupture, premature uterine contraction activity, placental abnormalities, inflammatory conditions of pregnancy more frequent than in normal weight pregnant women and abnormalities in biochemical parameters. The lower probability of achieving pregnancy by women with body mass deficiency is also important [18].

Rational nutrition of women during pregnancy and perinatal period

Pregnancy is a period of increased nutritional requirements due to the needs of the mother's body and the developing fetus. An adequate intrauterine environment reduces, as previously mentioned, the risk of adverse effects for both mother and child. The supply of adequate substrates to the fetus and placenta is essential for normal growth and development of the child. It has been proven that the growth and development of the fetus depends on the lifestyle, health status and nutrition of the woman, and this dependence is observed from the early stages of pregnancy [19]. In developing countries, maternal malnutrition is a major determinant of adverse pregnancy outcomes [20]. A woman's body weight and composition also affect nutrient availability and the maternal metabolic and hormonal response to pregnancy and associated metabolic changes [21].

Diet is one of the major environmental factors that affect pregnancy, fetal development and maternal health. Too little or too much food intake is a very important factor in the development of pregnancy. With the increasing prevalence of high calorie diets in developed countries leading to the development of overweight and obesity, it has been indicated that this is a contributing factor to adverse metabolic outcomes in the offspring later in life [20]. In addition, a diet containing high amounts of saturated fatty acids, sodium, sugar, and at the same time insufficient amounts of dietary fiber, vitamins, and minerals may weaken the metabolic profile of the mother and increase the oxidative stress and insulin resistance of the pregnant woman, and thus the fat and glucose levels of the fetus [22].

Energy requirements during pregnancy for individual women vary. In addition, the guidelines in this regard differ from country to country. According to the Polish dietary standards developed by the Food and Nutrition Institute, in the first trimester of pregnancy, the caloric intake of a pregnant woman's diet increases by 85 kcal/day.

Women in the second trimester of pregnancy should consume 285 kcal/day more than in the period before pregnancy. On the other hand, women in the third trimester of pregnancy should increase the energy content of their diet by 475 kcal/day compared to the energy content of their usual diet before pregnancy [23].

Carbohydrates should be the main source of energy for the mother's body and the developing fetus. The glycemic index (GI) of the meals consumed is also very important. A low GI guarantees a slower rate of digestion and absorption of carbohydrates from food. In turn, fiber contributes to delayed absorption of food, supports proper functioning of the maternal gastrointestinal tract, and ensures appropriate stool weight [24].

The demand for protein in the diet of pregnant women increases, which is associated with the need to ensure proper growth of the placenta, fetal tissues and is essential for proper development of the baby. The highest demand for protein is observed in the last ten weeks of pregnancy. It is during this time that the most intensive growth in fetal height and weight occurs. Protein supply during pregnancy should be 1.2g/kg bw/day, 10-20% of total energy supply. At the same time, energy from protein should not exceed 25% of daily energy requirements. Protein is a building block of both structural and functional components of cells. Protein is also an alternative source of energy when the carbohydrate intake is insufficient [24].

Fats should make up no more than 30% of the daily energy requirements of pregnant women. They support the transport of vitamins A, E, D and K as well as structural and metabolic functions. It is indicated that at least 4.5% of daily energy requirements should be covered by polyunsaturated fatty acids. Polyunsaturated fatty acids (PUFAs) are important for neurological development of the brain, nervous system and retina. Large amounts of these acids are found in fatty fish, nuts, seeds, vegetable oils and margarines. Essential fatty acids – linoleic and alpha-linolenic acids are precursors of LCPUFAs of n-6 and n-3 acids and prostaglandins. These acids are components of the inflammatory process and play an important role in inflammatory diseases. They also show importance in reproductive health. Additionally, n-3 fatty acids inhibit inflammatory processes in the body, while n-6 fatty acids may exacerbate them. Therefore, it is important to maintain the balance between these acids – the appropriate ratio of omega-6 to omega-3 acids should be between 5:1 and 2:1 [24].

In pregnant women, micronutrient requirements increase more significantly than dietary energy requirements (Table 2) [24, 25]. Micronutrients are essential vitamins and minerals that sustain and/or regulate cellular functions. Micronutrient deficiencies are associated with high reproductive risk, ranging from structural defects and fetal diseases to infertility. Among the important components in the diet of pregnant women are calcium and magnesium, whose proper supply reduces the risk of pregnancy-induced hypertension. Iron, zinc and iodine are also important in regulating the normal course of pregnancy and the development of the fetus. Zinc regulates the birth weight of the fetus and reduces the risk of prematurity. Zinc, iron, and vitamin A are also involved in the functioning of the immune system, so their deficiency can lead to potentially harmful infections. Additionally, vitamin A used in higher doses may contribute to reduced maternal mortality. At the same time, an excessive dietary supply of vitamin

A may exhibit toxic and teratogenic effects. Increasing folic acid intake during the preconceptional period may reduce the risk of fetal neural tube defects. Increasing vitamin B12 supply may reduce the risk of megaloblastic anemia in pregnant women [26].

Table 2. **Main functions of micronutrients involved in the perinatal period**

Micronutrients	Function in the body
Folate	DNA replication (cell cycle), methylation cycle
Vitamin B_{12}	Conversion of homocysteine to methionine
Vitamin B_6	Amino acid, lipid and glycogen metabolism, gluconeogenesis pathways
Vitamin A	Growth and differentiation of cells and tissues
Antioxidants	Defense system against free radicals
Iron	Hematopoiesis, nucleic acid metabolism, oxygen carrier to tissues via hemoglobin, part of important enzyme systems
Zinc	Structural, regulatory and catalytic functions
Copper	Neurotransmission, neuropeptide maturation, and defense against free radical damage
Calcium	Component of the bone skeleton, prevention of pre-eclampsia, normalization of blood pressure
Magnesium	Reduce the incidence of restricted fetal growth, preeclampsia and low birth weight infants and preterm births. Pre-partum hemorrhages are less common in pregnant women, who are also hospitalized less often
Iodine	Prevention of psychosomatic developmental disorders and attention deficit hyperactivity disorder (ADHD), prevention of hypothyroidism due to iodine deficiency

The importance of adequate vitamin D supply in women of childbearing age is also very important [20]. Humans obtain vitamin D during exposure to sunlight and from the diet by consuming animal (vitamin D3) or plant (vitamin D2) products. Due to the importance of vitamin D, there are numerous concerns about the impact of low maternal dietary supply of this vitamin on the manifestation of adverse health effects on women and their offspring. Furthermore, it has been suggested that low maternal 25-hydroxyvitamin D levels are associated with a number of adverse obstetric and neonatal outcomes [25]. Vitamin D deficiency is a modifiable factor and it is important to determine optimal levels during pregnancy in the context of growing clinical concerns about the high prevalence of vitamin D deficiency in humans worldwide [27, 28].

Physiological abnormalities in the fetus and pregorexia

The developing embryo is susceptible to changes of a physiological nature manifested by nutritional disturbances in the pregnant woman. Deficiency in the supply of nutrients to the body triggers nutritional deficiencies by interfering with the penetration of nutrients from maternal blood into the fetal circulation. The consequence of the above changes is placental weight loss, placental insufficiency, fetal growth retardation and delayed neurocognitive development [29].

Scientific reports confirm the destructive influence of negative behavioral disorders focused on significant restriction of food intake not only on the body of the pregnant woman, but also on the developing fetus. Anorexia of pregnancy can in the body of the fetus lead to: decreased head circumference, increased risk of microcephaly, spina bifida, neural tube defects, hypotrophy, lung ventilation problems, deformities, low neonatal outcome based on SGA classification and APGAR score, preterm birth, hunger center disorders, insulin resistance, diabetes mellitus, hypertension later in life, eating disorders – anorexia nervosa in the child or increased risk of death in the neonatal and infant period [31, 32, 37, 38].

Based on the results of the Norwegian Mother and Child Cohort Study (MoBa) among approximately 36,000 pregnant women with broad-spectrum eating disorders, the health consequences of pregorexia and its impact on neonatal clinical status were assessed. A significant increase in stillbirths or cesarean deliveries was observed among women with pregorexia compared to those rates observed in normal weight pregnant women without eating disorders. Newborns born to pregnant women with pregorexia were characterized by cleft palate and cleft lip more frequently than those born to pregnant women of normal weight without eating disorders. Moreover, pregnant women who abuse tobacco (active cigarette smokers) often used this habit to control food intake [23]. In a study conducted in another group of pregnant women who received epidural anesthesia during labor, it was observed that this action caused stimulation of stress hormones in women with pregorexia, thus affecting the central nervous system. Consequently, postpartum depression was observed to occur more frequently in this group than in the general population within six months of delivery [34]. On the other hand, in a population-based study involving approximately 10,000 mothers in the postpartum period, it has been shown that a depressive state contributes to long-term disorders in the offspring, even until they reach adulthood, leading to dysfunction in the child's social life [35].

The range of immunomodulatory actions also depends on the state of microbiome (genetic material of microorganisms) of the fetus, newborn and infant. Microbiota (number of microorganisms) is formed already in intrauterine conditions, and as a result of behavioral disorders of nutritional nature, its formation may be disturbed leading to dysbiosis. As a result, negative changes at the level of the gut-brain axis in the mother predispose to disorders in the fetus. Scientifically proven immunoprotective effects are characterized by psychobiotics, both in the pregnant woman and the fetus. Particularly important immunoprotective properties are demonstrated by *Bifidobacteruim longum* and *Lactobacillus helveticus* strains [11, 34-36].

Medical and psychological care in pregorexia

Perinatal care usually involves monitoring the mother's health during the first weeks of pregnancy and ends with a final assessment of health and well-being 4-6 weeks after delivery [37-39]. This is in many ways a difficult period in a woman's life, and the difficulties mentioned stem from the need to adapt to a new role, lack of time to carry out previous activities or actions, lack of motivation and/or social

support [36, 38]. Social pressure to return to the pre-pregnancy figure as soon as possible after childbirth is also important. Many women do not manage to return to their pre-pregnancy weight despite advice from doctors, dietitians or following diet and exercise guidelines, which may further exacerbate their mood disorders [39-41]. Experts also emphasize that dietary counseling and guidelines will not be successful unless the broader context of women's knowledge and psychosocial well-being is taken into account [41]. This is crucial to identify modifiable behavior that affects the normalization and maintenance of normal weight. Treatment of pregorexia is usually effective, although long-term psychological and medical support provided by a treatment team is usually necessary [42]. Such support should include psychoeducation, weight monitoring, monitoring of mental and physical health and relevant risk factors. Cooperation with other specialists and involvement of family members in the therapeutic process are also important [43].

Successful treatment of pregorexia usually involves months of medical care, regular therapy, nutritional counseling, and for some patients, pharmacotherapy. Some antidepressants can be used to treat pregorexia, although they are not always effective. To date, no antidepressant has been approved by the FDA as a pharmaceutical for the pharmacotherapy of pregorexia [44, 45]. At the same time, antidepressants should not be used as the only treatment [46]. Physicians, especially gynecologists, should pay special attention to bone mass loss, blood electrolyte levels and heart function in their pregnant patients [42]. Perinatal mental health screening and assessment is also of great importance. Through screening, it is possible to identify individuals who may be showing signs of illness, may be experiencing a particular condition or disease. This is achieved through the use of a validated test, questionnaire, survey, or other procedure that can be conducted in a low-cost, patient-safe, and rapid manner. Screening interventions aim to facilitate early identification of problems and possible treatment with the hope of reducing short – and long-term consequences [43, 44].

To date, no international criteria have been established for inpatient admission for women with pregorexia. However, it is recognized that nutritionally deficient, physiologically unstable or psychologically unstable patients are referred to the hospital for reintroducing nutrition. Reasons for admitting a patient to the inpatient unit may include: BMI lower than 75% of the value for women of a given age and specific height, hypoglycemia, electrolyte abnormalities (hypocalcemia, hyponatremia, hypophosphatemia, metabolic acidosis or alkalosis), abnormal ECG (bradycardia and other arrhythmias), acute medical complications of malnutrition (syncope, seizures, heart failure, pancreatitis), or concomitant poor mental status (severe depression, suicidal thoughts) [45].

Psychiatrists, psychologists, and other mental health professionals should help a woman with pregorexia to free herself from destructive thoughts and behaviors and to develop a positive attitude [43]. Indeed, they have a very important role in the treatment of patients with pregorexia [47]. No guidelines indicate the single most effective treatment method. Individual consultations with a psychologist should be regular, aim to reduce physical and mental health risks, encourage healthy eat-

ing and the achievement of a healthy weight and a positive body image. It is very important to create a personalized treatment plan based on the processes that seem to be useful to normalize eating problems. The patient with pregorexia should also be informed about the consequences of underweight and malnutrition [46]. Support groups can also be very helpful – if appropriately moderated by a mental health professional [42].

Nutritional therapy is another important component of treatment for eating disorders [47-49]. In the case of pregorexia, the main task of the dietitian is nutritional support aimed at improving nutritional status and normalizing body weight [46, 47]. The dietitian bases his activities on two essential elements – assessment of nutritional status and evaluation of the current diet. Thus, it is necessary to prepare an individually tailored nutritional plan, adapted to the current state of health, with appropriate energy and distribution of macro – and micro-nutrients: proteins, fats, carbohydrates, vitamins and minerals [48, 49]. Assessment of nutritional status should include anthropometric (such as body weight, BMI, measurement of skinfold thickness), biochemical (determining the degree of malnutrition) and immunological (lymphocyte count determination) tests [48, 50].

The observation of the characterized health problem also indicates that in case of the treatment of pregorexia the family can be an important support [49]. The dysfunctional behavior of one person often becomes a problem also for other family members – they may be more stressed, which may be caused by guilt, anxiety and anger. Therefore, the overriding goal of the family should be to maintain harmony, try to resolve the problems within the family, and support the patient. It is equally important for health care professionals to note how valuable the family's contribution to recovery can be [49, 51, 52].

Summary

The problem of anorexia affects an increasing number of pregnant women. It is estimated that ¼ of pregnant women struggle with abnormal body mass index, reduced self-acceptance of their figure, and consequently also with eating disorders during pregnancy. Such disorders may occur in up to 7.5% of pregnant women, while in the postpartum period (3-7 months after delivery) eating disorders may occur in 11.5% of young mothers. Current scientific reports indicate that the main obstetric and gynecological complications observed in pregnant women include abnormal nutrition, premature delivery, and postpartum depression. Expectant mothers with a positive family history of anorexia and/or a past diagnosis of this disorder are significantly more likely to develop gestational anorexia than women without these risk factors. An important aspect of cognitive-behavioral therapy is an interdisciplinary therapeutic team, using, among others, a diagnostic tool in the form of the Eating Disorders Diagnostic Scale (EDDS). A spectrum of activities with a holistic dimension allows for the identification of primary eating disorders in pregnant women. Additionally, the implementation of appropriate perinatal treatment affects the duration and effectiveness of treatment. Long-term, consecutively implemented nutrition education together

with psychodietetic intervention based on motivational dialogue should be an integral part of the therapy [36, 37].

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