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THE PREDICTIVE ROLE OF OBESITY FOR MATERNAL AND CHILD HEALTH IN THE FIRST YEAR OF LIFE

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Abstract. Over the past few decades, the prevalence of obesity worldwide has reached epidemic proportions. Obesity and overweight during pregnancy are associated with worse maternal and child outcomes. In addition, studies show that maternal obesity can lead to long-term consequences for the offspring, increasing the risk of neuropsychiatric disorders, metabolic, atopic diseases, and possible changes in the immune / inflammatory status. In addition to genetic mechanisms, a growing body of evidence suggests the induction of epigenetic changes by maternal obesity, which may influence offspring phenotype, thereby influencing later risk of obesity and cardiometabolic disease. However, the mechanisms linking the maternal environment to adverse short and long term outcomes remain poorly understood. This review presents current knowledge about the impact of maternal obesity on a child in the first year of life. Understanding these processes is key to developing therapeutic interventions to prevent future cardiovascular and metabolic pathologies in future generations.

Key words: *maternal obesity; perinatal period; metabolic syndrome; offspring of obese mothers; mother–placenta–fetus.*

ПРОГНОСТИЧЕСКАЯ РОЛЬ ОЖИРЕНИЯ ДЛЯ ЗДОРОВЬЯ МАТЕРИ И РЕБЕНКА В ПЕРВЫЙ ГОД ЖИЗНИ

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Резюме. За последние несколько десятилетий распространенность ожирения во всем мире достигла масштабов эпидемии. Ожирение и избыточный вес во время беременности связаны с ухудшением исходов для матери и ребенка. Кроме того, исследования показывают, что материнское ожирение может привести к долгосрочным последствиям для потомства, увеличивая риск развития психоневрологических расстройств, метаболических, атопических заболеваний, а также возможных изменений иммунного / воспалительного статуса. В дополнение к генетическим механизмам все больше данных свидетельствует об индукции эпигенетических изменений материнским ожирением, которые могут влиять на фенотип потомства, тем самым программируя риск ожирения и кардиометаболических заболеваний. Однако механизмы, связывающие материнскую среду с неблагоприятными краткосрочными и долгосрочными последствиями, остаются плохо изученными. В данном обзоре представлены современные знания о влиянии материнского ожирения во время беременности на ребенка в первый год жизни. Понимание этих процессов имеет ключевое значение для разработки терапевтических вмешательств с целью предотвращения будущих сердечно-сосудистых и метаболических патологий у последующих поколений.

Ключевые слова: *материнское ожирение; перинатальный период; метаболический синдром; потомство матерей с ожирением; мать–плацента–плод.*

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INTRODUCTION

Obesity is a serious medical and social problem in modern medicine, it reaches epidemic proportions worldwide. In 2022, according to the World Health Organization report on obesity in Europe, about 55.5% of adult population is overweight and obese. The prevalence of obesity in women of childbearing age is steadily increasing [1]. In 2017–2018, the prevalence of obesity in women of childbearing age in the US was about 40% [2–4], in the UK, 21.6% of women had obesity and 27.4% were overweight. In Scotland in 2021, 25.9% of women were obese by the time of pregnancy [3]. Statistical data in the Russian Federation echo the global trend. Thus, according to the results of the epidemiologic study ESSE-RF (Epidemiology of cardiovascular diseases and their risk factors in the regions of the Russian Federation) in 2013–2014, obesity was found in almost every third citizen of Russia. The second wave of the ESSE-RF program, conducted in 2017, included 17 regions and more than 26,000 participants of both sexes aged from 20 to 64 years. The results of the study showed that obesity was registered in 27.9% of men and 31.8% of women, the prevalence of obesity in women of childbearing age reached 25% [5]. Currently, the problem of obesity in women of childbearing age is urgent, according to recent studies demonstrating the adverse effect of maternal obesity on the health of offspring. Obesity significantly complicates the course of pregnancy and labor, contributing to obstetric complications 2–3 times more often than in women with normal body mass index [6–8]. In addition, women with obesity are more likely than women with normal body mass index (BMI) to have excessive gestational weight gain, which has also been shown to increase obstetric and perinatal risks [9–12].

THE IMPACT OF MATERNAL OBESITY ON FETAL GROWTH AND DEVELOPMENT. PERINATAL RISKS

Numerous studies have proven the role of maternal obesity in the formation of various complications of pregnancy and childbirth, such as pregnancy failure, preeclampsia, gestational diabetes mellitus, gestational arterial hypertension, labor anomalies, increased incidence of operative delivery, bleeding in labor and early postpartum period, maternal and fetal traumas, surgical infections, and delayed fetal intrauterine development [14–18]. In addition to complications of pregnancy and labor, perinatal risks, the mechanisms of long-term effects of maternal obesity on offspring are actively studied. Currently, there are sporadic studies investigating the impact of maternal obesity in the first year of a child's life, the influence of genetic and epigenetic factors.

During pregnancy, significant anatomical and physiological changes occur in many organs and systems of a woman's body to ensure nutrition and development of the fetus. One of the important mechanisms of physiologic adaptation of the maternal body to pregnancy is the controlled production of cytokines, inflammatory and proinflammatory factors by different cell subtypes at the maternal-fetal interface, since strict regulation of inflammatory factors is required for implantation, placentation, and continuation of pregnancy [19, 20]. Maternal obesity is associated with changes in the profile of the inflammatory response, which directly affects physiologic adaptation. Pregnancy with obesity and excessive body weight results in low-grade chronic inflammation secondary to an impaired immune cell profile, subsequently leading to activation of pro-inflammatory mechanisms. This condition has the name "metaflammation" in the current literature. Nowadays, metaflammation is recognized as a major factor affecting offspring health in early life [21, 22]. Three immunological stages based on the body's inflammatory response during pregnancy have been described [20, 23]. In the first trimester, the initial pro-inflammatory stage is important for implantation and placentation. With the onset of the II trimester, Th2-type anti-inflammatory and immune stage appears, which is necessary for fetal growth. In the III trimester, the pro-inflammatory stage and Th1-type immune activation initiate labor and delivery [20–23]. In addition to the important role of Th1 and Th2 cells during pregnancy, other T-helper cells such as T-helper 17 (Th17), T-helper 22 (Th22), follicular T-helper (Tfh) and regulatory T-cells (Treg) of the mother and fetus contribute to the continuation of a healthy pregnancy. Th17 and Th22 cells are involved in the induction of immunity against extracellular pathogens at the maternal-fetal interface [20–22]. Uncontrolled Th1 and Th17 response is associated with implantation failure and pregnancy failure [21–28]. Treg cells enhance fetal immune tolerance by suppressing excessive Th1 and Th17 activity and autoimmune response [29]. Follicular T-helper cells in the third trimester provide humoral immunity by activating B-cells to initiate an antibody response outside the follicular and germinal center [30]. Type 1 (Th1) and type 2 (Th2) T-helper cells represent the two major subsets of CD4 T-helper cells that regulate the adaptive immune response [31]. Th1 cells produce high levels of interferon-γ (IFN-γ), interleukin-2 (IL-2), tu-

mor necrosis factor (TNF) and are responsible for phagocyte-dependent inflammation as well as for defense against intracellular pathogens [31]. They also play an important role in the development of organ-specific autoimmune diseases and chronic inflammatory diseases [31]. Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13, which leads to an excessive immune response by switching B cells, activating eosinophils and inhibiting phagocytic activity [32]. Despite some inconsistent results, a lot of studies, found in the current literature, show that mothers with obesity before pregnancy have increased levels of pro-inflammatory cytokines such as IL-8, IL-6, CRP, TNF-α and IFN-γ and altered levels of adipokines [33–40]. Inflammation occurring against a background of maternal obesity leads to impaired placental development, which affects both maternal and placental inflammatory profiles [41–43]. Nowadays, the influence of cytokines on implantation and remodeling of spiral arteries has been proven. For example, abnormally high levels of TNF-α can lead to impaired remodeling of spiral arteries [44], and IL-6 increases trophoblast cell migration and invasion, while TNF-α decreases it [45–48]. Recent studies have demonstrated that maternal obesity is associated with increased placental mass and decreased placental efficiency, indicating an adaptation to increased nutrient availability to regulate fetal growth [49–54]. A linear correlation between placental mass and birth weight has also been found [49, 54]. Placental transport has a significant influence on the fetal intrauterine environment [55]. In pregnancies with a background of obesity, abnormal placental vasculature is the most common placental pathology [53, 56–59]. Placental vascular growth is regulated by angiogenic factors including VEGF, placental growth factor (PlGF) forming growth factor-β (TGF-β) and leptin, as well as anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) [7–9, 51]. By the end of the second trimester, the villous vessels begin to form loops and wriggle, dramatically increasing the surface area for nutrient and gas exchange [60]. The imbalance between pro- and anti-angiogenic factors is considered an important link in the pathogenesis of preeclampsia and intrauterine developmental delay [65]. Obesity has been proven to be associated with increased placental expression of VEGF, decreased levels of circulating PlGF and sFlt-1 [66, 67]. Thus, maternal obesity impairs the development of placental architecture, potentially jeopardizing fetal growth and survival [60].

In the early stages of physiologically normal pregnancy, insulin sensitivity is increased, which promotes glucose uptake by adipose tissue, which in turn prepares the body for increased energy requirements later in pregnancy [61]. Obese women have 50–60% higher postprandial insulin concentrations than women with normal body mass in both early and late pregnancy [62]. Women with obesity also have greater glucose tolerance compared to pregnant women with normal BMI, as evidenced by higher fasting glucose levels 1 and 2 hours after the oral glucose tolerance test (OGTT) [62]. Although glycemic values may not meet the criteria for gestational diabetes mellitus (GDM), an abnormal response to the OGTT in obese women is associated with the risk of delivering a fetus large for gestational age [63]. In addition, in obese or overweight pregnant women, increased levels of circulating cytokines in the maternal blood, such as TNF-α and IL-6, have been reported. This association has been proven in the development of insulin resistance in the first and second trimesters of pregnancy [64–66].

In studies carried out on animal models and then repeated in humans, it was found that maternal obesity leads to decreased transport of oleic acid in the placenta in male children, which is associated with decreased expression of the CD36 transporter (fatty acid translocase) and intracellular fatty acid binding protein (FABP 5) [67]. Increased lipid transfer to the fetus contributes to the development of adipose tissue, and thus the risk of developing overweight offspring [68]. Hyperlipidemia and vascular dysfunction may be an important mediator of cardiometabolic diseases observed in offspring born to obese mothers. Considering all the above mechanisms, it can be concluded that maternal obesity has deleterious effects on offspring health. Short-term adverse fetal outcomes in infants of obese mothers include increased risk of fetal overgrowth, stillbirth, and neonatal hypoglycemia [69, 70]. A meta-analysis of published data from 38 cohorts showed that maternal obesity and even small increases in BMI were associated with an increased risk of intrauterine and infant death. For women with BMI >30 kg/m^2, the absolute risk per 10,000 pregnancies was 102 and 43 intrauterine and infant deaths, respectively [71]. Pregnancies of overweight women are associated with a 2–3-fold increased risk of fetal macrosomia; this is associated with an increase in absolute fetal size and its fat mass [72–74]. Some studies suggest that the programming of obesity in offspring by maternal obesity may be partially sex-specific, basically, male offspring have a greater susceptibility to the risks of developing of obesity compared to female offspring born to obese mothers

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[75]. Fetal overgrowth is the main reason for the increased incidence of cesarean section [76, 77]. Severe neonatal hypoglycemia occurs in 10–15% of neonates and can lead to nervous system damage [78]. In maternal obesity, neonatal hypoglycemia is usually transient and occurs because of inadequate, persistent hyperinsulinemia caused by higher than normal concentrations of glucose in the womb [79].

REGULATORY FACTORS AT THE LEVEL OF MOTHER-PLACENTA-FETUS IN MATERNAL OBESITY

Data from recent studies demonstrate that adipose tissue is an important endocrine organ involved in metabolism through several mechanisms, the most important of which is the secretion of bioactive mediators by adipocytes and other cells [80–88]. These bioactive substances, collectively referred to as "adipokines", are important in the pathophysiology of insulin resistance, hyperlipidemia, inflammation, and metabolic syndrome [89–100]. Metabolic adaptation begins early in pregnancy and is accompanied by changes in maternal hormone production, including prolactin, estrogen, progesterone, and cortisol [101, 102]. Placental hormone secretion, which begins immediately after implantation and continues all pregnancy, is important for maternal metabolic adaptation through indirect modeling of endocrine axes and direct changes in maternal metabolic systems [103].

Glucose metabolism. Glucose is a major substrate for placental and fetal energy metabolism, and normal pregnancy causes marked changes in maternal glucose metabolism, including insulin resistance, activation of hepatic glucose production, and increased insulin release by pancreatic β-cells with higher plasma C-peptide levels; these mechanisms contribute to placental and fetal glucose delivery [61]. Early in gestation, fasting glycaemia levels decrease (compared with pre-pregnancy glucose levels), in part due to hemodilution associated with an increase in maternal circulating blood volume. Maternal fasting glycaemia remains consistently low in the second trimester and reaches even lower values in the third trimester: this is due to increased glucose utilization by the fetal-placental complex [62]. Maternal fasting hypoglycemia during pregnancy is compensated for by increased hepatic gluconeogenesis, which contributes to elevated blood glucose levels and helps maintain nutrient supply to the fetus [63–69]. In contrast, postprandial glucose levels progressively increase during pregnancy compared to pre-pregnancy levels [106, 107]. This is due to impaired peripheral tissue sensitivity to insulin and hence decreased maternal glucose utilization after meals [108]. Obese women have a higher glucose profile than women with normal BMI [70–73]. Maternal glycaemia is a strong determinant of fetal growth, as evidenced by the continuous association of maternal glucose levels with increasing birth weight [65–67].

Insulin. Early in pregnancy, the mother has increased secretin levels and insulin sensitivity, which stimulates lipogenesis and decreases fatty acid oxidation, causing maternal fat accumulation. In mid-pregnancy, insulin resistance develops to direct available nutrients for fetal growth and development. This state of insulin resistance is exacerbated in pregnant women with a background of GDM or obesity [68–71]. Insulin resistance in obesity leads to maternal hyperglycemia and, consequently, fetal hyperglycemia, because glucose freely passes through the placenta [72–78]. It is already known, that insulin plays a neurotrophic role for many brain regions; it inhibits neuronal apoptosis through activation of protein kinase B and protein kinase C, resulting in increased neuronal survival [79–85]. High insulin levels are essential for proper brain maturation [86]. However, chronic hyperinsulinemia, which is proven to be more common in obese mothers, corresponds to high fetal insulin levels, which contributes to fetal insulin resistance [87–94]. Maternal obesity is also associated with characteristic changes in the release of adipokines, which have systemic effects on metabolism and energy homeostasis [95–98].

Adiponectin. Adiponectin is one of the adipokines produced by adipocytes and the most abundant product of adipose tissue and accounts for 0.01% of total plasma proteins. It plays an important role in the relationship between adipose tissue and other metabolic tissues such as liver and skeletal muscle [45–47]. Adiponectin suppresses hepatic gluconeogenesis and contributes to insulin sensitization [45–59]. As opposed to other adipokines, although it is secreted by adipocytes and its plasma concentration is inversely correlated with BMI [56, 99–102]. During pregnancy, adiponectin levels decrease as the insulin resistance develops in pregnant women, which contributes to decreased glucose uptake and increased lipolysis, moving nutrients such as glucose and lipids to the fetus [103–109]. Studies in mice have shown that in maternal obesity, fetal adiponectin enhances fetal fat deposition, thereby increasing fetal body weight, proving the important role of adiponectin in the regulation of maternal meta-

bolism, placental function, and fetal development [110–114].

Leptin. Leptin is released from adipose tissue in proportion to its mass. Leptin levels increase throughout pregnancy, reaching a maximum level in the third trimester. Overweight or obese mothers have higher levels of serum leptin before pregnancy, so throughout pregnancy, leptin concentrations are higher in mother and fetus compared to mothers with normal BMI [85, 87]. Leptin involved in the development of the nervous system as it is an important trophic factor. In studies, leptin has been shown to bind to the receptors of the satiety center in the hypothalamus and form a negative feedback loop, suppressing increased food intake and thus preventing obesity [36]. It is shown in studies that have been carried out on animal models that obesity is associated with hyperleptineamia in both females and their offspring, and maternal obesity leads to the formation of resistance to leptin and, consequently, the inability of leptin to cause anorexic effects [92].

Ghrelin. Ghrelin is a gut hormone with a strong orexigenic signal. After entering the bloodstream, ghrelin circulates in two major forms: acyl ghrelin and des-acyl ghrelin. The maternal concentration of total ghrelin decreases slightly throughout pregnancy, and there is a positive correlation between the ratio of acylated to total circulating ghrelin in mothers in the third trimester of pregnancy and the baby's birth weight [106–110]. Levels of total ghrelin in cord blood are inversely correlated with neonatal birth weight [115–117]. Studies in animal models and humans have shown that maternal ghrelin regulates fetal development in late pregnancy. Administration of ghrelin to mice during the last week of gestation caused a 10–20% increase in body weight in the offspring [118]. In studies on mice, it was shown that ghrelin has an inhibitory role in the development of neural connections of hypothalamus, acting as a "break" in the balance of the neurotrophic action of leptin, and, therefore, proper expression of ghrelin in the neonatal period is important for children and in older age.

Pre-adipocyte factor. Pre-adipocyte factor (PREF-1) is a secreted protein that inhibits adipocyte differentiation both in vitro and in vivo. Pre-adipocyte factor is synthesized as a transmembrane protein whose ectodomain containing repeats of epidermal growth factor, is cleaved by tumor necrosis factor-α-converting enzyme to release a biologically active soluble form [104–108, 118]. The importance of PREF-1 in adipogenesis has been demonstrated in animal models. Mice experimentally deprived of pre-adipocyte factor had growth retardation, skeletal abnormalities, tendency to obesity, impaired insulin sensitivity and decreased glucose tolerance, which confirms the role of PREF-1 in the regulation of adipocyte differentiation [13]. During embryonic development, PREF-1 is widely expressed in numerous embryonic tissues: multipotent mesenchymal stem cells, pancreatic glandular cells, ovarian and male glandular cells, and is also involved in the differentiation of the central nervous system, hepatocytes, respiratory epithelial cells, mesodermal cells of the renal proximal tubule, and adrenal cortex [119–121]. Increased levels of PREF-1 are detected in serum, urine, and amniotic fluid during the second trimester of pregnancy [53]. After birth, PREF-1 expression ceases in most tissues and is observed in a limited number of cells: preadipocytes, pancreatic islet cells, thymus stromal cells, and adrenal cortex cells [28, 97].

Growth hormone. Growth hormone is well known for its function in stimulating cell growth, reproduction, and regeneration, so it is extremely important for development. Recent research findings suggest that the brain is an important target for growth hormone in the regulation of food intake, energy expenditure and glycaemia, especially in response to various forms of metabolic stress such as glucoprivation, food restriction and exercise [122–125]. During pregnancy, growth hormone action is associated with the regulation of maternal food intake, insulin and leptin sensitivity, suggesting that growth hormone and other gestational hormones are important in preparing the maternal body for the metabolic needs of the offspring [126]. Currently, little is known about the programming effects of maternal and/or fetal growth hormone on hypothalamic development in the offspring. There is some evidence that growth hormone regulates hypothalamic neurocircuits that control energy homeostasis [59].

Pro- and anti-inflammatory cytokines. Numerous studies show that maternal obesity further increases concentrations of pro-inflammatory cytokines such as IL-6, TNF-α, monocyte chemoattractant protein 1 (MCP-1), IL-8 and C-reactive protein in plasma, supporting the concept that the low pro-inflammatory state associated with normal pregnancy is exacerbated by maternal obesity [127]. The biological effects of pro-inflammatory cytokines are counterbalanced by anti-inflammatory cytokines such as IL-1, IL-4, IL-6, IL-10, IL-11 and IL-22 [63]. Obesity is now considered as a key factor in the development of chronic inflammation [96, 128], which is important in the pathogenesis

of pre-eclampsia, gestational diabetes mellitus [129]. Chronic inflammation has unfavorable significance for fetal programming. In a recent animal study, it was shown that the offspring of rats injected with IL-6 throughout pregnancy had more body fat compared to the control group, and male offspring had reduced insulin sensitivity [130].

Lipids. During pregnancy, in maternal organism, a lipid accumulation occurs in the I and II trimesters, and subsequently there is an increase in adipose tissue lipolysis. The catabolic state of female adipose tissue in late pregnancy is associated with hyperlipidemia, mainly corresponding to an increase in plasma triglyceride levels, and a smaller increase in phospholipid and cholesterol levels [70]. Maternal obesity is associated with increased lipid levels, higher triglyceride and very-low-density lipoprotein (VLDL) levels and lower cholesterol, high-density lipoprotein (HDL) levels than women with normal BMI [131]. Several recent studies have shown that maternal postprandial triglycerides and free fatty acids are stronger predictors of neonatal weight gain than maternal glucose levels in obese pregnancies [45]. The amount and nature of fatty acid intake during pregnancy are important for brain development and hypothalamic function in the offspring. Hypothalamic dysfunction was observed in the offspring of mice and rats born to animals that consumed increased amounts of saturated or trans fatty acids [132, 133]. Excessive nutrition usually activates hypothalamic inflammatory signaling through increased endoplasmic reticulum stress in the hypothalamus, which serves as a mechanism for the energy imbalance underlying obesity [76]. In obese pregnant women, offspring have increased level of inflammation in the hypothalamus [58] due to elevated levels of circulating fatty acids [134–138]. It has been suggested that fatty acids play an important role in the hypothalamic dysfunction observed in offspring born to mothers who consume increased amounts of saturated or trans fatty acids, and the mechanisms underlying these changes may be related to endoplasmic reticulum stress and hypothalamic inflammation.

Nowadays, the role of brain-derived neurotrophic factor and peptide YY in regulation at the maternal-placenta-fetal level in maternal obesity and their further effects on child growth and development remain poorly understood [102, 113, 139–141].

THE IMPACT OF MATERNAL OBESITY ON OFFSPRING HEALTH

In addition to adverse intrapartum and perinatal outcomes, maternal obesity is also associated with the development of chronic diseases in children later in their life. In 1990, David Barker proposed an "adult disease origins" model in which he hypothesized that exposure to a suboptimal environment early in life shapes an individual's future health [80]. Initially, he showed that adults born with low birth weight secondary to intrauterine developmental delay due to inadequate nutrient intake were at higher risk of developing metabolic and cardiovascular diseases. Conversely, conditions associated with intrauterine "overeating" and increased inflammation, such as gestational diabetes mellitus and maternal obesity, negatively impact the long-term health of the offspring. Evidence from recent studies suggests that activation of the proinflammatory state during pregnancy is associated with long-term offspring diseases, including childhood obesity, neuropsychiatric disorders, and allergic diseases [135].

Neuropsychiatric disorders. In recent years, there is increasing evidence that children born to obese mothers are more prone to neurodevelopmental and neuropsychiatric disorders. There is evidence that children born to obese mothers have lower intelligence quotient (IQ), higher rates of autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), cerebral palsy (CP), and mood disorders [45, 47, 136–138]. In studies on animal models, maternal obesity more often led to neuropsychiatric diseases in offspring, which is associated with significant changes in brain structure in the form of decreased proliferation of neural precursors in the hippocampus, reduced apoptosis in the hippocampus and neuronal differentiation in the dentate gyrus, atrophy of dendrites in the hippocampus and amygdala, and reduced myelination in the cerebral cortex in offspring (predominantly male offspring) [205–209]. It was also shown that offspring born to obese mothers had problems in education, behavioral disorders in the form of hyperactivity, anxiety, decreased sociability, addictive behavior, and food intake disorders [139]. Edlow et al. in their study found that the offspring of mice born to obese animals had increased production of TNF-α in response to polysaccharide exposure in placental CD11b cells compared to control group [140]. The increase in pro-inflammatory cytokines was more significant in male offspring, which may correlate with the prevalence of some neuropsychiatric diseases associated with maternal obesity in males [140–142]. From these findings, it has been hypothesized that it is neuroinflammation and oxidative stress, which arise through increased expression of proinflammatory cytokines,

increased lipid peroxidation and microglia activation in offspring born to obese mothers, that play an important role in adverse neurodevelopmental outcomes [26]. The pro-inflammatory environment affects the metabolism of brain-derived neurotrophic factor (BDNF), which is essential for hippocampal neurogenesis. Alterations in BDNF metabolism and tryptophan hydroxylase (TPH2) expression are associated with anxiety disorder in adulthood [29, 130].

Impact on the immune system. There is evidence that maternal obesity and chronic inflammation during pregnancy increase the risk of developing different chronic diseases in offspring. A lot of such diseases have features of altered immune/inflammatory activation [143–145]. Reviews in recent years have provided evidence of altered fetal immunity in response to maternal obesity [36–38]. In a study conducted by Enninga et al. an increased number of CD4+ lymphocytes and decreased levels of IL-12p40 and chemokines were detected in the cord blood of infants born to obese mothers [146]. In another small cohort study, cord blood from the placenta of obese mothers showed increased numbers of CD3+, CD4+, CD8+, NK and CD8 + CD25 + Foxp3 + Treg lymphocyte subpopulations, while CD34 cells were decreased [40]. Moreover, the effect of maternal obesity on decreased response of fetal monocytes and dendritic cells to toll-like receptor ligands has been proved [147]. The toll-like receptor family plays a key role in the proinflammatory response to bacterial infections; consequently, dysregulation of toll-like receptor signaling is associated with bacterial diseases, including necrotizing enterocolitis [148]. Most of these studies are performed using circulating immune cells and probably do not reflect the specificity of immune cells in different organ systems. Kamimae-Lanning investigated the effect of maternal obesity on hematopoietic stem cells (HSCs) and progenitor cells isolated from the liver of fetal mice [149]. The results showed that female mice that were continuously fed a high-fat diet exhibited not only signs of adverse fetal programming, including growth restriction, but also a decrease in HSCs and progenitor cells in the fetal liver. Despite the decrease in the total number of HSCs and progenitor cells, the proportion of B220+ lymphoid and Gr1+/Ter119+ myeloid cells in the liver was increased, indicating a tendency toward myeloid and B-cell differentiation [43].

Atopic diseases. Several studies and meta-analyses show that children born to obese mothers are at higher risk of developing atopic diseases, including atopic dermatitis and bronchial asthma [44–51]. Probably, this is due to altered function of immune checkpoints in offspring born to obese mothers that regulate development of allergy. Elevated levels of maternal TNF-α and pro-inflammatory cytokines, which are significantly elevated in obese mothers, have been associated with frequent lower respiratory tract infections and wheezing in offspring [52, 150]. In animal models, MacDonald et al. showed that the contents of bronchoalveolar lavage in offspring born to obese mice had an increased percentage of neutrophils and an increased concentration of IL-6, which allowed them to propose a theory about the role of the influence of an active proinflammatory state in reactive respiratory diseases in children born to obese mothers [151]. In the same study, increased bronchial hyperreactivity was observed during methacholine provocation test [34]. In 2019, Smoothy et al. found increased concentrations of Th1 (TNF-α) and Th2 (IL-5, IL-33) cytokines in bronchoalveolar lavage of obese mice, without any neutrophilia or eosinophilia, and it was hypothesized that these mice are more prone to hyperreactivity to further exposure to allergens or exposure to viruses [152]. Another study found that offspring born to obese mice exhibited an enhanced sensitization reaction in response to allergen (ovalbumin) administration, which was characterized by overproduction of IL-4, IL-13, TNF-α and TGF-β1 [153]. The same study demonstrated that mice born to obese mothers exhibited increased eosinophilic/neutrophilic infiltration in the parenchyma of lungs, increased collagen deposition and increased mucus hypersecretion [56]. A study conducted by Castro-Rodriguez et al. in 2020 showed an association of high levels of leptin in cord blood with a higher risk of bronchial asthma in children aged 3 years born to obese mothers [154].

Cardiometabolic diseases. The effect of maternal obesity on the risk of cardiometabolic disease in offspring in childhood and adult life has been demonstrated in human and animal models [58, 155]. Cardiometabolic diseases are a complex phenotype of cardiovascular and metabolic dysfunction characterized by insulin resistance, impaired glucose tolerance, dyslipidaemia, obesity, arterial hypertension, and cardiovascular diseases. Recent studies have demonstrated that children born to obese mothers are at higher risk of future cardiovascular disease (excluding congenital heart disease) [155], and a positive correlation was found between maternal pre-pregnancy BMI and increased blood pressure in the child, regardless of the child's BMI [23, 156]. In addition to cardio-

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vascular diseases, children born to obese mothers are susceptible to developing of obesity at early age. Evidence from observational studies of mothers and their children in Europe, North America and Australia showed that high maternal BMI before pregnancy and increased body weight during pregnancy were associated with an increased risk of overweight and obesity in offspring throughout childhood [26]. Recent studies have demonstrated the important role of levels of adipokine and leptin in the formation of obesity in children and adults. Obesity is associated with a state of hyperleptinemia and decreased tissue sensitivity to leptin, which subsequently leads to impaired regulation of energy homeostasis [69]. Leptin is secreted into the blood by adipocytes, regulates appetite, metabolism and energy homeostasis, and increases insulin secretion by pancreatic β-cells [157, 158]. During pregnancy, leptin levels regulate fetal development and growth and are positively correlated with neonatal body weight and fat mass [71–75]. Several studies have shown that low levels of cord blood leptin in children predict increased body weight and body length at 2–3 years of age [159]. Leptin and insulin control metabolism of glucose by acting at peripheral and central units [160]. Insulin is a key regulator of leptin metabolism; hyperinsulinemia leads to an increase in serum leptin concentrations [144–159]. Such infants were more resistant to insulin with a positive correlation with neonatal fat deposition [42, 94]. In the view of fact, that leptin and insulin are factors that influence the development of hypothalamus, nervous system, and involved in appetite regulation. It is shown that maternal obesity programs obesity in their offspring with occurrence of hyperphagia. The hyperphagia has been observed in several different rodent models of maternal obesity in both male and female offspring [161]. Considered, that this hyperphagic phenotype may be caused by altered development and function of hypothalamic circuits that regulate appetite and energy expenditure. The timing of the maximum level of neonatal leptin in rodents is a critical window for the development and maturation of hypothalamic neural connections, because the correct levels and timing of influences are required for proper hypothalamic development. Thus, any influences that result in under- or over-exposure to leptin during these critical periods of development may have negative consequences. In animal models, newborn rats born and obese animals have been shown to have an enhanced and prolonged postnatal leptin surge [162]. Studies both in human and animals show that maternal obesity has sex-specific effects on glucose metabolism and cardiometabolic profiles in male offspring [163]. One theory is differences in pancreatic β-cell function that are partially associated with increased oxidative stress in the islets of Langerhans and decreased plasma estradiol levels in male offspring. Maternal obesity induces insulin resistance and impairs pancreatic β-cell function, accompanied by inflammation in adipose tissue and hepatic steatosis with marked sex differences [91]. Estrogen in female offspring may play a protective role against oxidative stress induced by the effects of maternal obesity [164].

Diseases of urinary system. Recent studies have shown an association between maternal obesity and congenital abnormalities of the urinary system and reduced volume of fetal kidney in late pregnancy compared with fetal body weight [93–95]. Since kidney volume is proposed as an approximate measure of the number of nephrons, maternal obesity may be associated with a reduction in the number of fetal nephrons, potentially leading to hyperfiltration with further development of chronic kidney disease [165, 166]. In contrast, a study in animal models (rats) showed no effect on the number of fetal nephrons late in pregnancy in obese females [108]. However, there was evidence of increased cellular stress, inflammation and apoptosis in the kidneys of fetuses of obese females [167]. In the postnatal period, studies in rodent have shown that offspring from obese mothers show abnormalities in kidney structure due to oxidative stress and fibrosis [99–102, 168, 169]. A potential mechanism for programming renal dysfunction in offspring is the depression of sirtuin 1 (SIRT1) expression induced by maternal obesity [170, 171]. Sirtuin 1 is a key regulator that promotes lipid utilization and suppresses lipogenesis. It's well known, SIRT1 is reduced in cells with high insulin resistance [109, 110]. Maternal obesity during intrauterine development can lead to increased formation of glomerulosclerosis in response to inflammation with further decline in renal function [60].

Features of breastfeeding. Mother's milk realizes the connection between the health of the mother and the offspring. The triad "mother — breast milk — infant" is a unified system, the basic mechanisms of which have not yet been fully elucidated. The nature of nutrition of a pregnant woman significantly affects the development of the fetus, the state of health of the child in the future. Obese women are less likely to initiate breastfeeding than normal-weight women, and are more at risk of lactation difficulties, which may lead to discontinuation of breastfeeding [61].

Lactation function in women with obesity is affected by physiological (delayed lactogenesis or reduced prolactin production in response to suckling) and psychosocial factors [62–64]. The trophic status of a lactating woman affects the composition of breast milk and, consequently, the rate of growth and development of the infant. One of the main sources of energy is lipids. A systematic review of 11,373 publications found a positive correlation between maternal BMI and the amount of fat in breast milk. For every unit of maternal BMI, 0.56 g/L of fat was added to breast milk, and this association was observed from the 1st to the 6th month after delivery. There was no significant association between maternal BMI and the energy value of milk, lactose content and total protein [168, 169]. There is also evidence that the milk of an obese mother contributes to the formation of components of metabolic syndrome in the child in the future life.

MATERNAL OBESITY AND GUT MICROBIOTA IN CHILDREN

The hypothesis that the gut microbiota is an important factor in the pathogenesis of obesity has led to the investigation of its diversity in a group of overweight and obese individuals. The first evidence suggesting a link between the gut microbiota and obesity was suggested by Ley et al. in a study using 16SrRNA genome sequencing. In their work in animal models, they identified the two most abundant types of bacteria, *Firmicutes* (60–80%) and *Bacteroidetes* (20–40%), which differed proportionally in obese mice compared to mice with normal BMI [170]. Specifically, obese mice showed a 50% decrease in the *Bacteroidetes* population and a proportional increase in *Firmicutes*. Of particular interest were the results which revealed that after dietary treatment, the relative abundance of *Bacteroidetes* increased and *Firmicutes* decreased [171–180]. Turnbaugh et al. confirmed the increased ratio of *Firmicutes* and *Bacteroidetes* in obese mice compared to lean mice in animal models using the latest DNA metagenomic sequencing technique [176, 179]. Moreover, obese mice had a higher proportion of archaea in the microbial communities of the caecum [43]. Armougom et al. in their study evaluated the expression profiles of gut microbiota using real-time PCR and found significantly reduced levels of *Bacteroidetes* in obese individuals compared to those with normal BMI, whereas the concentration of *Firmicutes* was similar in the compared groups [173]. Species-specific variations of *Lactobacillus* in patients with obesity, such as *L. reuteri* and *L. Gasseri*, and lower concentrations of *Ruminococcus* flavefaciens, a subgroup of *Ruminococcus* flavefaciens belonging to the bacterial subdivision *Firmicutes*, were also observed in obese individuals [45, 146]. In another study investigating the relationship between gut microbiota, genotype and host's weight, Turnbaugh et al. analyzed the composition of the gut microbiota in monozygotic and dizygotic twins with normal BMI and obesity and their mothers [170]. The results showed that obesity was associated with a low proportion of *Bacteroidetes* and a higher proportion of *Actinobacteria* in obese individuals compared to lean people, but no differences in the phylum *Firmicutes* were found between groups [176, 179]. Numerous studies in recent years have focused on the dynamics of changes in the levels of the bacterial types *Bacteroidetes* and *Firmicutes* in people both with obesity and loss of weight, but there are researches linking obesity in mice to specific bacteria, particularly *Halomonas* and *Sphingomonas*, and decreased numbers of *Bifidobacteria* [180]. A special place in the genesis of obesity is also allocated to archaea — *Methanobrevibacter* is the main representative of archaea in the gut microbiota [149]. Zhang and Armougom et al. found higher numbers of *M. smithii* in obese people compared to a group of people with normal BMI [131, 138, 153, 178]. Currently, there are several putative mechanisms that contribute to the development of obesity. The first is that different strains of the gut microbiota are able to induce low-grade inflammation by stimulating the production of pro-inflammatory cytokines [181–196]. Gram-negative bacteria such as *Bacteroidetes* produce lipopolysaccharide (LPS, endotoxin), which is an important component of the cell wall [197–215]. Cani et al. described that a high-fat diet increases LPS levels, and observational studies have reported diurnal fluctuations in plasma LPS concentration, termed "metabolic endotoxemia" [216]. The pattern of weight gains, visceral and subcutaneous obesity in LPS-injected mice was similar to those observed in mice fed a high-fat diet [217]. In addition, "metabolic endotoxemia" triggered the expression of inflammatory cytokines and serum amyloid A (SAA) proteins. Overgrowth of Gram-negative bacteria such as *Veillonella* in obese individuals can lead to a higher dose of LPS in the intestine, consequently it can disrupt the intestinal barrier through activation of the TLR4/MyD88/IRAK4 signaling pathway in intestinal epithelial cells, resulting in the movement of LPS from the intestine into the bloodstream [183, 184]. When circulating systemically, LPS is able to initiate an immune response in adipose tissue and liver. LPS

first binds to lipopolysaccharide-binding protein, forming a complex with CD14, further inducing the expression of activator protein 1 and nuclear factor kappa B (NF-kB) by activating toll-like receptor 4 (TLR4), expressed on macrophages and adipose tissue, which promotes the secretion of pro-inflammatory cytokines and chemokines including TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1) [218, 219]. These cytokines can influence adipocytes and stimulate cytokine and chemokine secretion by autocrine and paracrine pathways [185–191, 220–224]. Moreover, MCP-1 overexpression in adipose tissue has been shown to be associated with increased macrophage infiltration in rodents [225].

It's known, the gut microbiota is involved in the central modulation of appetite through the production of gut hormones such as peptide YY (PYY), glucagon-like peptide-1 (GLP-1), and neurotransmitters. *Bifidobacterium* and *Lactobacillus* can produce lactate, which serves as a substrate for neuronal cells, thereby prolonging the postprandial feeling of satiety [226]. Acetate is able to activate the citric acid cycle in the hypothalamus and further alter the expression profile of neuropeptides regulating satiety [194]. Butyrate affects appetite and eating behavior of the host by activating the vagus nerve and hypothalamus, it is able to cross the blood-brain barrier [193]. Bile acids, short-chain fatty acids and indoles are closely related to the secretion of intestinal hormones by neuroendocrine cells [195–198]. GLP-1 and PYY are the potent anorexigenic hormones that can influence host appetite and eating behavior by binding to their receptors locally distributed in intestinal neurons, vagus nerve afferents, hypothalamus and brainstem [51, 199, 227–230]. The gut microbiota also leads to the production of neurotransmitters, including γ-aminobutyric acid (GABA) and serotonin [37]. GABA, as the predominant inhibitory neurotransmitter of the nervous system, has the ability to stimulate appetite, while serotonin contributes to appetite suppression through regulation of melanocortin neurons [200–204].

In addition, the gut microbiota influences the food center and eating behavior through the regulation of mood. On the one hand, gut microbiota is able to alter mood by affecting the production of bacterial metabolites, gut hormones and neurotransmitters that act as important messengers in gut-brain interactions and further regulate host appetite and eating behavior [47, 205]. On the other hand, the gut microbiota is involved in the regulation of mood and reward pathways, which presumably influence brain circuits related to eating behavior [206–210, 231].

MATERNAL OBESITY IN PREGNANCY AND CHANGES IN GUT MICROBIOTA

The composition of gut microbiota in pregnant women with obesity differs from that of pregnant women with normal BMI. Physiological shifts in the gut microbiota during pregnancy are necessary to adapt the mother to pregnancy and promote optimal fetal growth and development. During pregnancy on the background of obesity, changes in the gut microbiota may lead to metabolic disturbances of mother, which may indirectly affect the growth and development of the child and the establishment of its own gut microbiota [211–218, 232–242]. Collado et al. in their study observed significant differences in microbial composition in pregnant women depending on their BMI. They found higher numbers of *Bacteroides* and *Staphylococcus aureus* in obese women compared to women with normal BMI [187, 243, 244]. Interestingly, the composition of the microbiota varied with weight gain throughout pregnancy: *Bacteroides* showed a positive correlation both with pre-pregnancy BMI and with weight gain during pregnancy; each kilogram of weight gain was proportionally accompanied by an increase in the number of *Bacteroides* by 0.006 logarithmic units [220–235]. Various studies have shown that the gut microbiota remodels and fluctuates during pregnancy depending on gestational age [221, 236–238]. Zacarias et al. demonstrated that pregnant women with obesity have a high ratio of *Firmicutes* and *Bacteroidetes*, increased numbers of actinobacteria in the second and third trimester of pregnancy, and decreased bacterial diversity in the third trimester [239]. Santacruz et al. studied the fecal microbiota of 50 pregnant women (group 1 — overweight pregnant women, group 2 — pregnant women with normal BMI) to evaluate the relationship between changes in the composition of the gut microbiota during pregnancy and biochemical parameters depending on their BMI. It was found that higher concentration of *Staphylococcus* was significantly correlated with increased serum cholesterol levels, higher number of *Enterobacteriaceae* and *E. coli* was correlated with increased serum ferritin and decreased transferrin levels, while higher number of *Bifidobacterium* was correlated with decreased ferritin and increased transferrin and folic acid levels. The number of *Bacteroides* was associated with higher levels of cholesterol, HDL, and folic acid [240].

THE ROLE OF MATERNAL MICROBIOTA IN PROGRAMMING OF BABY'S OBESITY

It is well known that the first microbial influence on the child is exerted by the maternal microbiota during pregnancy, suggesting that the maternal gut microbiota has a direct influence on the child's gut microbiota and subsequent metabolic and immunologic programming. Both animal and human studies have shown that changes in the diversity and abundance of gut microbial composition in obese mothers were associated with changes in the gut microbiota of the offspring at early and later ages. Soderborg et al. showed in their study that germ-free mice colonized with stool microbes from the stools of two-week-old infants born to obese mothers had increased gut permeability, impaired macrophage activity, and increased inflammation compared to mice colonized with stool microbes from infants born to normal weight mothers [241]. In addition, these mice showed accelerated body weight gain at follow-up [242]. When comparing the gut microbiota in obese and normal weight children, studies have demonstrated an increased ratio of *Firmicutes/ Bacteroidetes* in the obese group [243, 244]. Recent studies also show a decrease in the level of bifidobacteria in the intestinal microbiota in obese and overweight children [245]. A study on 77 children born to obese mothers and women with normal BMI showed that the number of *Parabacteroides* spp. and *Oscillibacter* spp. in the gut microbiota was higher in children born to obese mothers. In addition, amounts of *Blautia* spp. and *Eubacterium* spp. were lower [245–251]. Vael et al. in a prospective study demonstrated high intestinal concentrations of *Bacteroides fragilis* and low concentrations of *Staphylococcus* in infants aged from three weeks to one year, which is associated with a higher risk of obesity later in life [247, 252]. Nadal et al. found significantly reduced levels of *Clostridium hystoliticum, Eubacterium rectale* and *Clostridium coccoides* correlated with weight loss in obese adolescents [253].

Changes in the gut microbiota of offspring born to obese mothers are still controversial and require further investigation.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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