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Epidemiological review of the association between maternal metabolic syndrome and obesity and neurodevelopmental disorders in children

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Introduction. Maternal metabolic syndrome is becoming increasingly recognized as a significant factor that can affect the health and development of children. *Aim*. This study investigates how MetS during pregnancy can increase the risk of obesity and neurodevelopmental disorders in children. *Method*. By reviewing various studies and recent data, we found that high blood sugar levels, insulin resistance, and chronic inflammation during pregnancy can lead to the stated issues. *Results*. This review paper indicates that addressing metabolic health in pregnant women early on can greatly reduce these risks and improve long-term health outcomes for their children. *Conclusion*. This study emphasizes the importance of comprehensive prenatal care that focuses on metabolic health to help prevent childhood obesity and neurodevelopmental disorders.

Keywords: Metabolic syndrome, obesity, neurodevelopmental disorders

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Introduction

Metabolic syndrome (MetS) encompasses a cluster of cardiovascular risk factors, including abdominal obesity, high blood pressure, impaired fasting glucose, elevated triglyceride levels, and low high-density lipoprotein cholesterol (HDL) levels. Additionally, it may include other conditions such as impaired kidney function, hepatic steatosis, obstructive sleep apnea, polycystic ovary syndrome, chronic inflammation, sympathetic activation, and hyperuricemia (Dobrowolski et al., 2022).

As the incidence of maternal obesity and maternal MetS continues to rise, it has become one of the most pressing health concerns during pregnancy. Obesity not only impacts the mother but also has significant implications for her offspring. It is associated with various complications during pregnancy, including gestational hypertension, diabetes, preeclampsia, premature delivery, and spontaneous miscarriage. Higher maternal pre-pregnancy body mass index (BMI) and gestational weight gain are associated with an increased risk of childhood overweight/obesity, particularly in later ages (Voerman, 2019). Analysis of published studies revealed a threefold higher risk of overweight in children born to mothers with pre-pregnancy obesity compared to those born to mothers with a normal pre-pregnancy weight (Yu, 2013). Likewise, children born to mothers with MetS are also at higher risk for developing obesity early in life, and this is partly caused by the intrauterine environment influenced by maternal metabolic conditions that affect fetal development. Studies have shown that maternal obesity and gestational diabetes mellitus (GDM) can alter fetal adiposity and metabolic set points, predisposing children to obesity and MetS themselves (Boney et al., 2005; Catalano & deMouzon, 2015). Considering the significant population impact, a key priority in preventing childhood overweight and obesity is addressing maternal weight and metabolic status before pregnancy, along with managing weight gain during pregnancy. However, there is limited evidence from human studies regarding the impact of maternal MetS during pregnancy on a child's cognitive and behavioral development.

Aim

This study aims to address the issue of increased prevalence of MetS, obesity, and gestational diabetes among women and to establish a link between these conditions and increased risk for adverse outcomes in children born to these mothers. Also, this review will present the key mechanisms and pathways that lead to this relationship and provide insight into prevention strategies.

Genetic background and risk factors for developing MetS

The Framingham study found that obese individuals without MetS did not have a significantly increased risk of type 2 diabetes or cardiovascular disease (CVD) (Hadžiabdić, 2015). However, obese individuals with MetS had a 10 times higher risk of developing type 2 diabetes and twice the risk of CVD compared to individuals with normal body weight and without MetS (Hadžiabdić, 2015). Thus, it is important to reveal factors that influence the MetS development. These factors can be genetically determined. A recent study used next-generation sequencing to explore gene variants associated with the clinical features of MetS and identified numerous variants associated with various components of MetS, such as central obesity, hyperglycemia, and hypertriglyceridemia (Le et al., 2022). Furthermore, rare recessive mutations in the genes encoding leptin and its receptor have been associated with obesity and insulin resistance (Van Der Klaauw & Farooqi, 2015). There is also a strong inherited basis for plasma levels of HDL-cholesterol (Jannuzzi et al., 2022). HDL-cholesterol levels are related to susceptibility to type 2 diabetes, and they can modulate this risk of diabetes development even in persons with a family history of type 2 diabetes (Chouery et al., 2022). Some individuals lack receptors sensitive to the taste of fat in food, leading them to consume higher amounts of fat. This is also genetically predisposed (Graham et al., 2019). Apart from genes, fat distribution is at least partly influenced by gender: with men typically having more visceral fat (internal fat) and women having more subcutaneous fat (Lazar, 2005). The harmful effects of lipid accumulation in non-adipose tissue, such as muscles and bones, are known as lipototoxicity (Engin, 2017), while chronically elevated plasma glucose levels that disrupt insulin action over a long period of time and insulin secretion lead to glucotoxicity (Del Prato, 2009).

In addition to genetic background, different energy-dense diets may lead to divergent metabolic outcomes, such as changes in body weight and insulin resistance (Liu et al., 2021). For example, the Western diet, characterized by high intakes of processed foods, red meat, high-sugar drinks, and high-fat dairy products, can negatively impact metabolism and contribute to health issues, including MetS. In a comprehensive review, Clemente-Suárez et al. (2023) discussed how the Western dietary pattern affects various aspects of health, such as metabolism, inflammation, cardiovascular health, and mental well-being, and how it can influence healthcare costs (Clemente-Suárez et al., 2023). Over-stimulation of insulin production by the Western diet might promote diseases typically associated with civilization, including MetS (Melnik et al., 2011).

Diagnosing criteria for MetS, obesity, and gestational diabetes

During pregnancy, metabolic disorders such as MetS, obesity, and gestational diabetes mellitus (GDM) have potentially adverse long-term consequences for both mother and child (Horvath et al., 2013). We have chosen the most common definitions to describe these risk factors during the gestational period.

There are no well-accepted criteria for the diagnosis of MetS in pre-pregnancy women. However, it is usually defined according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), which include at least three of the following risk factors presented in Table 1 (National Heart, Lung, and Blood Institute, 2020; Ristic-Medic & Vucic, 2013).

Table 1

Criteria for MetSy in adult women (at least 3 risk factors) according to NCEP ATP III

	Risk factors	Referencing criteria
1	Abdominal obesity	waist circumference > 88 cm
2	High triglyceride levels	≥ 1.7 mmol/L
3	Low HDL-cholesterol level	<1.3 mmol/L
4	High blood pressure	≥ 130/85 mmHg on at least two separate measurements or hypertension therapy present
5	High fasting glucose	≥ 5.6 mmol/L

Metabolic syndrome is more prevalent in women, leading to significant gender differences. Among individuals with diabetes, the prevalence of MetS is above 72%. Women have a higher prevalence of abdominal obesity and low levels of HDL-cholesterol, while men are more likely to have high blood pressure (Bhatti et al., 2016; Sigit et al., 2020). Metabolic syndrome is more common in pregnant women or during the immediate postpartum period. Risk factors include pre-gestational overweight/obesity, abnormal HDL-cholesterol levels at the 16th week of pregnancy, and abnormal triglyceride levels in the postpartum period (Lima et al., 2019).

Diabetes Federation (IDF) indicates that insulin resistance is a significant component of MetS, but its determination is not necessary because it is complicated by routine practice (Alberti et al., 2006). Insulin resistance is present in most women with MetS and in women with polycystic ovarian syndrome. However, the ATP III panel concluded that there is insufficient evidence to support the routine measurement of insulin resistance, proinflammatory states, or prothrombotic states for diagnosing MetS. Due to the complexity and variety of factors involved in MetS, accurately diagnosing and treating this condition remains challenging. Three interconnected factors are central to the etiology of MetS: chronic inflammation, abdominal obesity, and abnormalities in fatty acid metabolism (Ristic-Medic & Vucic, 2013).

The Obesity Medicine Association defines obesity as a chronic disease that alters anatomy, physiology, and metabolism. It is a relapsing, multifactorial, neurobehavioral disease, characterized by increased body fat that promotes adipose tissue dysfunction resulting in adverse metabolic, biomechanical, and psychosocial health consequences (Hampl et al., 2023). The World Health Organization (WHO) describes women's obesity with four criteria (Table 2)

Table 2

Criteria for obesity in adult women Women's body parameters: Referencing criteria

Body mass index (BMI)	≥ 30 kg/m^2
Waist circumference	≥ 88 cm
Waist to hip ratio	≥ 0,85
Body fat percentage	≥ 32%

(American Council on Exercise, 2009; National Heart, Lung, and Blood Institute, 2020; World Health Organization, 2020).

Over one-third of women in the reproductive period are obese, 4-9% have pre-existing diabetes before conception, and 2-10% of obese women are more likely to develop gestational diabetes during pregnancy (Krakowiak et al., 2012). Gestational diabetes mellitus (GDM) is abnormal glucose tolerance resulting in hyperglycemia with onset or first recognition during pregnancy. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommended the new diagnostic criteria for GDM based on the 2-h 75-g Oral glucose tolerance tests (OGTT), at 24–28 weeks of gestation (Houshmand et al., 2013, p. 742). GDM has long been associated with obstetric and neonatal complications primarily relating to higher infant birthweight and is increasingly recognized as a risk factor for future maternal and offspring cardiometabolic disease (Sweeting et al., 2022). The pooled global standardized prevalence of GDM was 14% according to the IADPSG criteria (Wang, 2022).

Table 3

ADA/ IADPSG Criteria for gestational diabetes

OGTT	Glucose levels
Fasting plasma glucose	≥ 5.2 mmol/L
1-h post 75g oral glucose load	≥ 10 mmol/L
2-h post 75g oral glucose load	≥ 8.5 mmol/L

Maternal metabolic health: Prolonged time as a crucial factor for conception, fertility challenges, and maternal well-being

Pre-conception attention to the maternal metabolic status is crucial for ensuring healthy offspring. Research has shown that MetS is linked to a longer time to pregnancy and infertility, regardless of obesity. Time to pregnancy (TTP) measures how long a couple takes to conceive, while infertility is defined as failure to achieve pregnancy after 12 months of regular unprotected sexual intercourse (World Health Organization, 2024). A recent cross-sectional study examined the association between metabolically healthy obesity (MHO) and female infertility, using data from the National Health and Nutrition Examination Survey. This study highlighted the importance of considering metabolic health in obesity when assessing risks for female infertility (Tang et al., 2023). A comprehensive analysis of MetS in reproductive health emphasized the need for screening due to its increasing prevalence and associated reproductive issues in both men and women. This study also discussed the role of high caloric intake and visceral adiposity in the pathogenesis of MetS, which can impact fertility. (Baloyi & Mokwena, 2021). Various dietary patterns, including the Western diet, characterized by high consumption of hypercaloric foods and trans fats, have been examined for their effects on fertility. A plant-based diet, particularly following Mediterranean dietary patterns rich in antioxidants and omega-3, may positively affect fertility and guard against chronic diseases associated with oxidative stress, which can impact pregnancy success (Łakoma et al., 2023).

Women with MetS have a longer time to pregnancy compared with women without MetS, whether obese or not, and they have a 62% greater risk for infertility compared with women without MetS (Grieger et al., 2019). Women with self-reported infertility were more likely to either meet the criteria for MetS or to have a cardiovascular event (Gleason et al., 2019). Another study showed that reducing HDL-cholesterol and raised triglycerides were identified as the main individual components associated with risk of infertility (Arroyo-Jousse et al., 2020; Grieger et al., 2019; Serazin et al., 2018). Importantly, adipokines such as leptin and adiponectin, altered in women with pregestational obesity, play a role in recurrent pregnancy loss and impaired fetal growth (Arroyo-Jousse et al., 2020).

Obese women often depend on hormone therapy due to difficulties with natural conception. Hyperinsulinemia, when using in vitro fertilization (IVF), has been found to negatively affect the successful implantation of embryos into the endometrium (Li et al., 2017). Additionally, these women face increased risks during pregnancy, including type 2 diabetes, gestational diabetes, preeclampsia, and premature birth (before 37 weeks). Furthermore, there is a higher likelihood of delivering newborns with a birth weight of ≥4500 g. (Surén et al., 2014).

During pregnancy, significant physiological, endocrine, and metabolic adaptations occur, leading to a pseudo-diabetogenic state characterized by progressive insulin resistance. These adaptations are necessary to meet the continuous demands of the fetus for nutrients and oxygen. As pregnancy advances, maternal glucose utilization in the peripheral tissues decreases, blood concentrations of glucose and amino acids rise, and insulin responses to various levels of glycemia diminish. (Mottola & Artal, 2016). Adipose tissue expands to support the growing fetus and the future nutritional needs; however, limited adipose tissue expandability is linked to insulin resistance due to ectopic lipid deposition. Women with GDM tend to have larger mean visceral adipocyte size compared to those with normal glucose tolerance. Additionally, mean visceral and subcutaneous capillary density are lower in GDM, suggesting impaired adipose tissue expandability (Rojas-Rodriguez et al., 2015). Furthermore, Selovic et al. (2015) found a tendency during pregnancy towards decreased accumulation of subcutaneous adipose tissue and increased accumulation of preperitoneal adipose tissue (Selovic et al., 2015).

Maternal metabolic status as a risk factor for the development of disorders in offspring

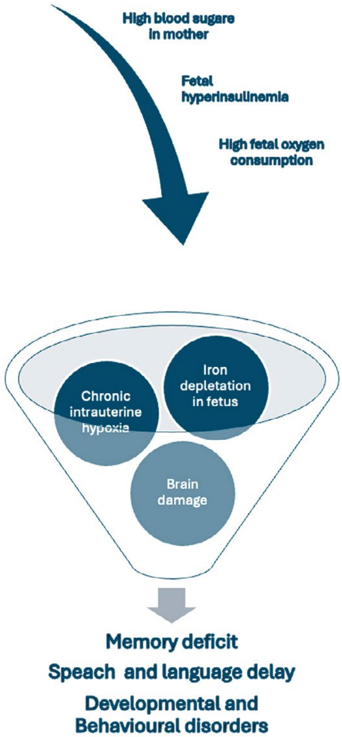
Maternal metabolic syndrome poses a significant non-genetic risk factor for cardiovascular issues, such as hypertension and diabetes mellitus, in the adult offspring. Preconceptional maternal obesity plays a crucial role in metabolic/epigenetic programming in exposed offspring, leading to cardiac abnormalities. Moreover, the post-weaning diet can exacerbate this effect, as exposure to an obesogenic diet further increases susceptibility to MetS (Loche et al., 2018). Maternal obesity was associated with an increased risk of hypertensive disorders of pregnancy, preeclampsia, stillbirth, cesarean delivery, and macrosomia in both French and Canadian cohorts compared to patients with a normal BMI (Fuchs et al., 2017; Stubert et al., 2018).

Additionally, there is a higher tendency for neonatal hypoglycemia and an increased risk for composite maternal and neonatal adverse outcomes in women with pre-gestational BMI above 25 compared to those with a BMI below 25. In participants with GDM and normal pre-pregnancy BMI, weight gain above the median for that group was also associated with adverse outcomes (Koren et al., 2019).

Prolonged effects of elevated blood sugar levels on the fetus, such as in fetal hyperinsulinemia, lead to increased fetal oxygen consumption. This results in chronic intrauterine tissue hypoxia, iron depletion in the fetus, and subsequently, memory deficits, speech development, and developmental and behavioral disorders (Li et al., 2016).

Figure 1

Influence of maternal MetS on the developing fetus



In bivariate linear regression models, maternal pre-pregnancy BMI was negatively associated with neonatal iron status (Jones et al., 2016). This deficiency can lead to prenatal brain damage and subsequent neurodevelopmental disorders in early childhood (Burg et al., 2015). Neurodevelopment primarily involves changes in neuronal myelination, neural connections, and deviations in hippocampal neuron development. Modifications in the regional, central, and occipital parts of the cerebellum can cause early developmental problems. Indicators of cerebral white matter damage also indicate an increased risk of developmental disorders (Burg et al., 2015).

The maternal status of polyunsaturated fatty acids (PUFA) needs to be evaluated because of its importance in brain plasticity in early development, as well as in regulating microglial activity and neuroinflammatory pathways during a child's brain development. Children with ASD tend to have deficient or abnormal PUFA metabolism, leading to increased production of proinflammatory cytokines, increased oxidative stress, and improper formation and activation of neurotransmitters. The metabolic interactions between omega-3 PUFAs and intestinal bacteria should be identified and recognized for their crucial effects on the immune system and the enteric nervous system, which can subsequently lead to improved behavior in children. Because of this, it is important to examine maternal diet and intake of essential nutrients like PUFA during pregnancy in order to change gut microbiota through the gut-brain axis, which can influence the occurrence of neuropsychiatric disorders (Veselinović et al., 2021).

Examination of the cognitive development of children born to mothers with GDM revealed that these children perform less favorably on tests assessing motor, cognitive, and developmental abilities (Bersain et al., 2023). Obesity in mothers affects cognitive development differently; children of mothers who were obese immediately before pregnancy have better cognitive test scores than those of mothers who were obese for a longer period, but worse than those of mothers with a normal nutritional status (Burg et al., 2015).

Exposure to maternal diabetes during pregnancy is correlated with an increased risk of ASD. Offspring exposed to maternal diabetes with antidiabetic medication have a 48% higher risk of ASD compared to those with a non-diabetic mother and a 42% higher risk compared to those with a diabetic mother not receiving medical treatment (Guo et al., 2025). Maternal health conditions during pregnancy, including obesity, diabetes, preeclampsia, and asthma, are linked to an increased likelihood of autism, both with and without gastrointestinal disturbances. (Carter et al., 2023). In addition to gestational diabetes, maternal pre-pregnancy severe obesity increases the risk of ASD and developmental disorders in children, especially in males (Matias et al., 2021). In study of Kong et al. (2018) severely obese mothers were found to have a 67% to 88% increased risk of having a child with mild neurodevelopmental disorders, attention-deficit/hyperactivity disorder, conduct disorder, psychotic, mood, and stress-related disorders, as well as for all groups of psychiatric diagnoses with onset in childhood or adolescence, compared to mothers with a normal BMI. Particularly marked effects were found for ASD, attention-deficit/hyperactivity disorder and conduct disorder, and mixed disorders of conduct and emotions (Kong et al., 2018).

Studies conducted on mice model have shown potential mechanisms for the adverse neurocognitive effects of offspring from mothers with GDM. It has been demonstrated that GDM metabolites in fetal mouse brains affect hippocampal DNA methylation and gene regulation involved in cognition and memory, impacting infants of the mothers who had GDM (Luo et al., 2022).

Unlike maternal obesity, paternal obesity is less studied. Some studies have shown that paternal obesity is related to child developmental disorders (Zhang et al., 2022). The incidence of preeclampsia, cesarean section, small for gestational age (SGA), macrosomia, and postpartum hemorrhage was significantly higher in the group of obese fathers compared to the normal BMI group. Additionally, paternal obesity is linked to alterations in fetal growth parameters and placental development, negatively impacting pregnancy outcomes (Lin et al., 2022). Sharp and Lawlor (2019) found that most studies did not investigate mechanisms linking paternal factors to offspring obesity or type 2 diabetes. However, those that did identify the most common mechanisms of paternal influence on the postnatal environment (diet, lifestyle, and socioeconomic factors), genetic imprinting, and sperm epigenetics, indicate that a significant gap in research in this field is evident (Sharp & Lawlor, 2019).

Nutritional habits during pregnancy and their influence on mother and child

Dr. David Barker was one of the first researchers who proposed the idea that many organs and their functions undergo fetal programming during embryonic and fetal development, which determines the onset of physiological and metabolic responses carried into adulthood. Therefore, any stimulus or injury during this critical developmental period can lead to structural, physiological, and metabolic changes, predisposing the individual to cardiovascular, metabolic, and endocrine diseases in adulthood. (Barker, 1990; Barker et al., 1993).

Therefore, women with a nutrient-deficient diet before and during pregnancy face an increased risk of developing metabolic disorders, such as GDM, and experiencing complications during pregnancy and childbirth (Nguyen, 2019; Ryznar et al., 2021). These complications are associated with heightened risks of maternal and fetal health issues, including stroke, slow fetal growth, premature birth, and death due to gestational hypertension, as well as development of type 2 diabetes, preeclampsia, and fetal macrosomia in women with GDM (Gresham et al., 2016).

Recent studies put maternal metabolic status and the Barker hypothesis in the spotlight, emphasizing its influence on epigenetic modifications, such as DNA methylation, which can have transgenerational effects (Ryznar et al., 2021).

High-carbohydrate diets in the pathogenesis of MetS during pregnancy

Maternal high-carbohydrate diet and lifestyle factors, such as physical inactivity, may synergistically influence gene expression by modulating genetic and epigenetic regulators during pregnancy, which further affects the development of childhood obesity and adolescent metabolic disorders in their children later in life (Akter et al., 2022). Diets leading to obesity and MetS in pregnant women often contain large amounts of refined, processed foods, resulting in the removal of dietary fiber, vitamins, minerals, phytonutrients, and essential fatty acids. A diet rich in processed carbohydrates leads to large fluctuations in blood glucose and insulin levels, and elevates free fatty acids and free radicals that contribute to fatty deposits in the arteries (Giugliano et al., 2006). It is also possible that the type of food the mother consumes during pregnancy can influence similar tendencies in the offspring through epigenetic mechanisms. If the mother can pass on a preference for fast and unhealthy food to the child in this way, it can lead to a higher risk of obesity, diabetes, and cardiovascular diseases in their children later in life. Similarly, animal studies have also shown that the consumption of foods rich in sugar, fats, and salts during pregnancy can affect the dietary preference of offspring (Teegarden et al., 2009).

High-fat diet in the pathogenesis of MetS during pregnancy

A high-fat diet (HFD) during gestation has long-term consequences, not only for mothers but also for subsequent generations. Exposure to maternal and lactational HFD sensitizes offspring to a postnatal HFD and promotes the development of features related to the MetS, including cognitive deficits and central insulin resistance (Li et al., 2017). Maternal high-fat diet (MHFD) led to cognitive disabilities and altered response to a noncompetitive receptor antagonist of the N-Methyl-D-aspartic acid (NMDA) receptor in adult MHFD offspring in both second and third generations, in a sex-specific manner. Maternal overnutrition increases the risk of developing obesity in subsequent generations as well as cognitive impairments, which affect learning and memory processes in adulthood (Sarker & Peleg-Raibstein, 2018). Additionally, adult offspring of mothers with gestational diabetes showed pronounced metabolic and cognitive dysfunction when exposed to short-term HFD (de Sousa et al., 2019).

In Chang et al. study, HFD mice with added exercise and HFD mice with no exercise had impaired glucose clearance compared to low fat diet (LFD) mice at 15 days of gestation. HFD mice who had an exercise regimen had significantly reduced visceral fat mass, serum insulin, and leptin levels, and increased HDL levels, compared to HFD-fed mice with no exercise (Chung et al., 2019). Mice from mothers fed with HFD during pregnancy showed higher weight gain later in life and decreased hippocampal expression of both the insulin receptor and leptin receptor, persisting well into adulthood, impairing spatial learning and memory function of the offspring (Cordner et al., 2019; Cortés-Álvarez et al., 2020). Specific dietary macro- and micronutrients have been shown to increase fat cell development in both in-vitro and in-vivo models and may therefore link maternal diet to increased infant adiposity, as found in the research of Shapiro et al. (2017).

Conclusion

This overview explored the connections between MetS, diabetes mellitus, and obesity both before and during pregnancy, highlighting subsequent health challenges for mothers and their offspring. Women with MetS often face prolonged conception times and an elevated risk for infertility, regardless of their weight. If pregnancy occurs, there is an increased risk for fetal hyperinsulinemia, which can lead to brain damage and the development of neurodevelopmental diseases. To mitigate these risks, maintaining a balanced and healthy diet is essential for preventing MetS and minimizing its impact on the developing fetus. It is crucial to conduct further research in order to gain better knowledge about mechanisms that link maternal metabolic syndrome, diabetes mellitus, and obesity with neurodevelopmental outcomes in offspring. A better understanding of long-term health impacts on mothers and children would lead to early screening in order to identify women at risk before conception and develop preventive strategies that would increase awareness and promote healthy lifestyles for women of reproductive age.

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Epidemiološki pregled povezanosti metaboličkog sindroma majke s gojaznošću i neurorazvojnim poremećajima kod dece

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Uvod: Metabolički sindrom majke postao je prepoznat kao značajan faktor koji može uticati na dečiji razvoj. *Cilj*: Ova studija ima za cilj da istraži kako metabolički sindrom majke tokom trudnoće može povećati rizik za razvoj gojaznosti i neurorazvojnih poremećaja kod dece. *Metod*: Pregledom najnovijih istraživanja uvidelo se kako visok nivo šećera u krvi, insulinska rezistencija i hronična inflamacija mogu dovesti do navedenih problema. *Rezultati*: U radu je prikazano da povećana pažnja o metaboličkom zdravlju majke tokom trudnoće može u velikoj meri redukovati faktore rizika i dugoročno uticati na zdravlje dece. *Zaključak*: Ovaj rad ističe značaj prenatalne nege koja se fokusira na metaboličko zdravlje majke u cilju prevencije dečje gojaznosti i neurorazvojnih poremećaja.

Ključne reči: Metabolički sindrom, gojaznost, neurorazvojni poremećaji

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