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THE INFLUENCE OF METABOLIC SYNDROME COMPONENTS ON THE DEVELOPMENT OF FETAL MACROSOMIA

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ABSTRACT

Fetal macrosomia, commonly defined as a birth weight of ≥4000 g or above the 90th percentile for gestational age, remains a frequent and clinically significant complication of pregnancy worldwide. Maternal metabolic syndrome (MetS), characterized by central obesity, insulin resistance or hyperglycemia, dyslipidemia, and arterial hypertension, is increasingly recognized as an important risk factor for excessive fetal growth. This review synthesizes current evidence on the pathophysiological mechanisms and clinical associations linking individual components of maternal MetS with fetal macrosomia and examines their combined predictive value. A narrative review of PubMed/MEDLINE and Scopus-indexed literature was conducted, focusing on cohort and case-control studies, systematic reviews, and meta-analyses published over the past two decades. The evidence indicates that maternal hyperglycemia and compensatory fetal hyperinsulinemia constitute the central pathogenic pathway of macrosomia, consistent with the Pedersen hypothesis. Maternal obesity independently and synergistically increases this risk through chronic low-grade inflammation, dysregulation of leptin and adiponectin, and enhanced placental nutrient transport. Elevated maternal triglycerides and altered lipid indices may further contribute to fetal overgrowth through glucose-independent mechanisms. In contrast, the relationship between hypertensive disorders and macrosomia is more heterogeneous and may be influenced by placental insufficiency, which can attenuate fetal growth. The coexistence of multiple metabolic syndrome components is associated with a substantially greater risk of macrosomia than the presence of individual risk factors alone. Overall, maternal metabolic syndrome components contribute to fetal overgrowth through overlapping but distinct mechanisms, with hyperglycemia, insulin resistance, and dyslipidemia demonstrating the most consistent associations. Early identification and integrated metabolic risk stratification during the first and second trimesters may improve the prediction and prevention of macrosomia-related perinatal complications.

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Keywords: *metabolic syndrome, fetal macrosomia, gestational diabetes mellitus, insulin resistance, maternal obesity, dyslipidemia, large for gestational age.*

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Introduction

Fetal macrosomia, which is defined as a birth weight of 4000 g or more regardless of gestational age, or an estimated fetal weight above the 90th percentile for gestational age, complicates approximately 5-20% of pregnancies in published studies and is increasingly important in the setting of rising maternal

obesity and gestational diabetes mellitus (GDM) (Gaudet et al., 2014; Sourinejad et al., 2019). Macrosomic infants are more likely to experience shoulder dystocia, birth trauma, perinatal asphyxia, neonatal hypoglycemia, and cesarean delivery, and they are also more likely to develop childhood obesity, insulin resistance, and type 2 diabetes later in life, perpetuating an intergenerational cycle of metabolic disease (Gaudet et al., 2014; Mou et al., 2023). Metabolic syndrome (MetS) in pregnancy is defined by the presence of central obesity, poor glucose tolerance or insulin resistance, dyslipidemia (high triglycerides and low high-density lipoprotein cholesterol), and raised blood pressure. Each of these components has been linked to fetal growth abnormalities, while their combined and interacting effects have increasingly been studied as a clustered metabolic phenotype (Sourinejad et al., 2019). Understanding how individual and clustered metabolic disorders affect fetal growth trajectories is critical for establishing effective early detection tools and tailored preventive interventions during prenatal care. The purpose of this review is to summarize and critically analyze the current evidence regarding the role of individual metabolic syndrome components - obesity/adiposity, hyperglycemia and insulin resistance, dyslipidemia, and hypertensive disorders - in the pathogenesis of fetal macrosomia, as well as to discuss their combined predictive and clinical significance.

Materials and methods.

A narrative literature review covering papers from 2005 to 2025 was undertaken using the PubMed/MEDLINE, Scopus, and Google Scholar databases. The search phrases included “metabolic syndrome,” “fetal macrosomia,” “large for gestational age,” “gestational diabetes,” “insulin resistance,” “maternal obesity,” “dyslipidemia,” and “pregnancy.” Original cohort and case-control studies, peer-reviewed reviews, systematic reviews, and meta-analyses that investigated the link between at least one metabolic syndrome component and fetal birth-weight outcomes were included. For Uzbekistan-specific epidemiologic context, relevant conference and institutional publications were also consulted when national peer-reviewed data were unavailable. Case reports and studies not relevant to human pregnancy were excluded. Data were summarized narratively based on the primary pathophysiological route addressed by each component.

Normal pregnancy is associated with progressive physiological insulin resistance in the second and third trimesters, which is triggered by placental hormones such as human placental lactogen, progesterone, cortisol, and prolactin, which divert maternal energy sources to the developing baby (Hernández-Baraza et al., 2025). In women with underlying metabolic syndrome, this physiological adaptation is exacerbated, resulting in persistent maternal hyperglycemia, hyperlipidemia, and a chronic low-grade pro-inflammatory state. The Pedersen hypothesis proposes that excess glucose, free fatty acids, and amino acids enter the placenta and induce fetal pancreatic β-cell hyperplasia, resulting in fetal hyperinsulinemia. This mechanism explains faster fetal adipose and somatic growth (Desoye & Carter, 2022; Hernández-Baraza et al., 2025). Hyperinsulinemia raises fetal oxygen consumption and basal metabolic rate and can be followed by relative fetal hypoxemia, erythropoietin overproduction, and polycythemia, linking metabolic and hematological issues in macrosomic pregnancies (Desoye & Carter, 2022). Pre-pregnancy body mass index (BMI) is one of the most reliable predictors of fetal macrosomia. Maternal obesity is associated with approximately a twofold increase in the odds of fetal macrosomia compared with normal-weight pregnancy, with insulin resistance providing an important mechanistic link even in the absence of overt GDM (Gaudet et al., 2014). A prospective study of women meeting metabolic syndrome criteria in the first trimester found significantly higher BMI, waist-to-hip ratio, and neonatal birth weight compared with healthy controls. Maternal BMI above 24.5 kg/m² was identified as the strongest independent predictor of fetal macrosomia (Migda et al., 2016). Obesity-related adiponectin deficiency is accompanied by higher levels of leptin, E-selectin, and inflammatory cytokines (Migda et al., 2016). Gestational diabetes mellitus is widely regarded as a major metabolic syndrome-related driver of macrosomia, with the risk of large-for-gestational-age (LGA) birth reported to increase approximately five-fold in GDM and up to ten-fold in pregestational diabetes despite good glycemic control (Eslamian et al., 2013). A systematic review and meta-analysis of 17,711 women with GDM found that elevated glycated hemoglobin (HbA1c) at 24-28 weeks of gestation was associated with an increased risk of macrosomia and LGA, indicating potential value as a predictive biomarker (Mou et al., 2023). Elevated fasting glucose, together with reduced insulin

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sensitivity, has also been associated with adverse perinatal outcomes from early pregnancy (Migda et al., 2016).

Maternal dyslipidemia, particularly hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C) levels, has been identified as a significant and partially glucose-independent factor contributing to fetal overgrowth. Placental lipases hydrolyze elevated maternal triglycerides into free fatty acids and glycerol, which can support fetal nutrient supply and growth (Firatligil et al., 2025). Large prospective cohort studies in China involving tens of thousands of pregnancies found that high maternal triglyceride levels mediate a measurable proportion of the association between pre-pregnancy overweight/obesity and macrosomia, including in non-diabetic women (Song, Chen, Zhang, Liu, Wei, Sun, et al., 2022; Song, Chen, Zhang, Liu, Wei, Wang, et al., 2022; Wan et al., 2023). Composite lipid indices, such as the triglyceride-to-HDL cholesterol ratio and the triglyceride-glucose (TyG) index, have been linked to neonatal macrosomia and are being studied as accessible, low-cost prognostic markers in non-diabetic pregnancies (Firatligil et al., 2025). Preconceptional obesity has also been linked to different trajectories of maternal lipid profiles during gestation, including greater triglycerides, reduced HDL-C, and elevated inflammatory markers such as high-sensitivity C-reactive protein, regardless of GDM status (Bozkurt et al., 2016). The link between the hypertensive component of metabolic syndrome and fetal growth is more complicated and, at times, contradictory. Hypertensive disorders of pregnancy, particularly when severe or complicated by placental insufficiency, are more commonly associated with fetal growth restriction than overgrowth. When hypertension coexists with obesity and hyperglycemia as part of a broader metabolic syndrome phenotype, neonatal size may reflect the combined metabolic profile rather than blood pressure alone (Sourinejad et al., 2019). This heterogeneity emphasizes the need to analyze metabolic syndrome as a constellation of interacting factors rather than simply screening hypertension.

Several studies have found that the presence of multiple metabolic syndrome components is more strongly and consistently associated with macrosomia than any single component alone. Women who met metabolic syndrome criteria in early pregnancy had significantly higher neonatal birth weights and a higher frequency of macrosomic neonates (>4000 g) than metabolically healthy controls, as well as elevated inflammatory and reduced anti-inflammatory adipokine profiles (Migda et al., 2016). Biomarker panels that combine clinical characteristics (pre-pregnancy BMI, gestational weight gain, parity), glycemic parameters, and lipid fractions have achieved high predictive accuracy (area under the receiver operating characteristic curve approaching 0.97) for GDM-related macrosomia, highlighting the importance of a multi-component metabolic risk assessment rather than relying solely on a single marker such as fasting glucose (Yuan et al., 2023). The cumulative evidence suggests that antenatal screening protocols should include a broader metabolic risk profile, including early-pregnancy BMI, waist-to-hip ratio, fasting glucose, HbA1c, triglycerides, and HDL cholesterol, rather than relying solely on the standard oral glucose tolerance test for GDM. Early detection of clustered metabolic abnormalities may allow for timely lifestyle and nutritional interventions, more frequent glycemic and lipid monitoring, and individualized decisions about delivery timing and mode, potentially lowering the incidence of macrosomia-associated birth trauma and long-term metabolic sequelae in offspring (Eslamian et al., 2013; Mou et al., 2023). Given the high and modifiable contribution of maternal adiposity to this pathway, preconception counselling and weight management before pregnancy remain important preventive measures (Gaudet et al., 2014).

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Table 1

Metabolic Syndrome Components and Their Associations With Fetal Macrosomia

MetS component	Common diagnostic threshold in pregnancy	Principal mechanism linking to fetal overgrowth	Direction/strength of association with macrosomia
Central obesity/adiposity	Pre-pregnancy BMI >24.5-25 kg/m²; increased waist-to-hip ratio	Chronic low-grade inflammation, hyperleptinemia, hypoadiponectinemia, enhanced placental nutrient transfer, and insulin resistance independent of GDM	Strong and consistent; obesity is associated with about twofold higher odds of macrosomia (Gaudet et al., 2014; Migda et al., 2016).
Hyperglycemia /insulin resistance (GDM)	Elevated fasting glucose; abnormal OGTT; HbA1c measured at 24-28 weeks	Pedersen pathway: maternal hyperglycemia → fetal hyperinsulinemia → accelerated adipogenesis and somatic growth	Strong association; LGA risk has been reported to rise about five-fold in GDM and ten-fold in pregestational diabetes (Eslamian et al., 2013; Mou et al., 2023).
Dyslipidemia	Elevated fasting triglycerides (e.g., ≥90th percentile); reduced HDL-C; elevated TyG index or TG:HDL-C ratio	Placental lipid handling increases fetal exposure to free fatty acids and glycerol, providing a partly glucose-independent nutrient pathway	Moderate and partly mediating; high maternal triglycerides explained about 3.8-11.1% of the obesity-macrosomia association in one large non-diabetic cohort (Song, Chen, Zhang, Liu, Wei, Sun, et al., 2022).
Hypertension/vascular dysfunction	Blood pressure ≥130/85 mmHg or gestational hypertensive disorder	Endothelial dysfunction may alter placental transfer, but hypertensive placental insufficiency can favor growth restriction	Heterogeneous; effects depend on severity and co-occurring metabolic components (Sourinejad et al., 2019).

Note. BMI = body mass index; GDM = gestational diabetes mellitus; HbA1c = glycated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LGA = large for gestational age; MetS = metabolic syndrome; OGTT = oral glucose tolerance test; TG:HDL-C = triglyceride-to-high-density lipoprotein cholesterol ratio; TyG = triglyceride-glucose index.

The link between maternal metabolic disorders and excessive fetal growth is especially noteworthy in Uzbekistan, where gestational diabetes mellitus (GDM), overweight, obesity, and other metabolic risk factors are increasingly recognized as important issues in antenatal care. Although complete nationwide data on fetal macrosomia related to maternal metabolic syndrome are scarce, available regional evidence indicates that the metabolic risk profile of pregnant women in Uzbekistan warrants further clinical attention. The prevalence of GDM is a key local indicator. Between 2017 and 2020, a screening project in the Samarkand, Khorezm, and Ferghana regions examined 1,211 pregnant women aged 18 to 40 years who were 16 to 30 weeks' gestation. Anthropometric evaluation, specialist examination, fetal ultrasound, fasting

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venous glucose measurement, and a 75-g oral glucose tolerance test (OGTT) were used, with results interpreted according to IADPSG criteria. A total of 108 women were diagnosed with GDM, giving a reported prevalence of 8.9%; the regional distribution was 22 cases in Samarkand, 54 in Khorezm, and 32 in Ferghana (Ibragimova & Tojieva, 2020). The OGTT was completed in 898 of the 1,211 women screened, highlighting both the feasibility of systematic screening and the importance of consistent implementation. The same Uzbekistan report identified several clinically important risk factors among pregnant women with GDM: maternal age above 33 years in 23.1%, a previous macrosomic child (>4,000 g) in 12.8%, a family history of type 2 diabetes in 19.4%, overweight in 26.8%, obesity in 26.8%, excessive gestational weight gain of more than 15-20 kg in 10.1%, and arterial hypertension or pre-eclampsia in 2.7% (Ibragimova & Tojieva, 2020). These findings are relevant to the metabolic-syndrome concept because they show that hyperglycemia commonly coexists with other metabolic and obstetric risk factors rather than occurring as an isolated abnormality. The Uzbek findings therefore reinforce the central premise of this review: fetal overgrowth should not be seen solely as a result of hyperglycemia. Maternal overweight and obesity, excessive gestational weight gain, past macrosomia, family history of diabetes, and hypertension may occur in the same patient and may interact to increase the likelihood of excessive fetal growth. This is consistent with the broader evidence reviewed here, which suggests that clustered metabolic abnormalities may pose a higher risk than any one component alone. For pregnant women in Uzbekistan, a central clinical challenge is to identify high-risk women early. GDM can develop without obvious symptoms, allowing clinically significant abnormalities in glucose metabolism to remain unrecognized. If hyperglycemia is identified only after excessive fetal growth has occurred, opportunities for preventive intervention may be limited. This is especially relevant because the Pedersen pathway links maternal hyperglycemia with increased fetal glucose exposure, fetal pancreatic hyperinsulinemia, and accelerated fetal growth (Hernández-Baraza et al., 2025).

The clinical significance of macrosomia goes beyond birth weight alone. Excessive fetal growth increases the risk of difficult labour, shoulder dystocia, birth trauma, surgical delivery, and neonatal metabolic problems (Gaudet et al., 2014; Mou et al., 2023). These complications are especially important when a large fetus is not identified accurately before delivery. Local clinical evidence shows that fetal macrosomia is an important issue in Uzbek obstetric practice. A study conducted at Samarkand State Medical University included 200 women in labour with fetal macrosomia, with 78 managed actively and 122 managed expectantly (Zakirova et al., 2022). Although this study does not provide a nationwide prevalence estimate, it demonstrates that macrosomia is sufficiently common in regional obstetric practice to require specific pregnancy and labour management considerations. It is critical, however, to differentiate between the prevalence of macrosomia and GDM. Uzbekistan currently has far less robust nationwide epidemiological data on macrosomia specifically connected with metabolic syndrome than some other countries. The existing Uzbek evidence is primarily regional or institution-based. As a result, it would be incorrect to assert that 8.9% is the national prevalence of macrosomia; rather, 8.9% is the reported prevalence of GDM in the three-region screening initiative (Ibragimova & Tojieva, 2020). This distinction is critical to ensuring the article's scientific accuracy.

Conclusion. Fetal macrosomia should not be viewed as a single obstetric result, but rather as a complex syndrome heavily influenced by maternal metabolic health. The evidence reviewed in this study shows that hyperglycemia, insulin resistance, maternal obesity, and dyslipidemia are the most consistent metabolic determinants of excessive fetal growth, acting through interconnected pathways such as fetal hyperinsulinemia, altered placental nutrient transport, chronic inflammation, and abnormal lipid metabolism. The presence of many metabolic syndrome components appears to enhance the risk of macrosomia more significantly than any individual factor alone, underlining the significance of an integrated rather than single-marker approach to risk assessment. Preventive interventions should start before conception and last throughout pregnancy and the postpartum period. Preconception counselling, appropriate weight management, balanced nutrition, safe physical activity, timely gestational diabetes screening, adequate glycemic control, and individualized fetal growth monitoring can all help to reduce the risk of excessive fetal growth and its associated maternal and neonatal complications. For women with

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various metabolic risk factors, multidisciplinary care from obstetricians, endocrinologists, nutritionists, and other healthcare providers may give extra benefits. At the same time, additional multicenter prospective studies in Uzbekistan are required to produce nationally representative estimates, explain the combined impact of metabolic syndrome components on fetal macrosomia, and construct population-specific predictive models. This integrated strategy could lead to earlier intervention, more personalized antenatal care, and better maternal outcomes.

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