Review

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Spontaneous Preterm Birth: a Fetal-Maternal Metabolic Imbalance

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Abstract

Preterm delivery is a major global health problem associated with increased neonatal morbidity and mortality. To develop effective strategies to reduce preterm birth, it is important to address the causes of and risk factors for this condition. Maternal metabolism plays a crucial role in pregnancy outcomes, as it affects the availability of nutrients, energy, and other essential factors required for fetal development and growth. Several aspects of maternal metabolism can potentially contribute to the risk of preterm delivery. Severe energy deficiency as observed in women suffering from eating disorders can affect the hypothalamic-pituitary-gonadal axis resulting in amenorrhea and infertility, suggesting that maintaining a minimum maternal weight is essential to uphold a functional reproductive system, thus ensuring a successful pregnancy. Maternal undernutrition as observed in past famine and observations and animal studies may affect fetal growth and trigger an early activation of the parturition pathway leading to preterm delivery. A correlation exists between maternal size and gestation duration. Obesity is associated with a higher likelihood of medically indicated preterm birth. Low maternal body mass index and low gestational weight gain during pregnancy have been associated with preterm birth, potentially due to fetal-maternal metabolic imbalance; however, the exact mechanism remains to be determined, thus emphasizing the importance of appropriate weight management before and during pregnancy. Addressing metabolic-related risk factors for preterm delivery requires a comprehensive approach to reduce the burden of preterm delivery and improve neonatal outcomes. This review aims to explore various aspects of fetal-maternal metabolic imbalance that could potentially contribute to preterm birth. By doing so, we suggest a novel and comprehensive approach that sheds light on the intricate connection between fetal-maternal imbalance and the susceptibility to preterm birth.

Keywords: Premature birth; Undernutrition; Obesity; Maternal BMI; Gestational length; Placental sensing; Preterm parturition

Introduction

Preterm birth is a significant public health concern, representing one of the most challenging obstetrical complications. The World Health Organization's March of Dimes report published this year that "13.4 million babies were born preterm in 2020, stated that 1 in 10 babies worldwide was 'born too soon'." The rates of preterm births remained stable at 9.9% from 2010 to 2020, reflecting that limited progress was achieved in the global burden of preterm birth, despite advanced knowledge of associated risk factors and medical interventions.[1–3] Preterm delivery is the leading cause of perinatal morbidity and mortality worldwide.[4–8] Prematurely born infants are at a heightened risk of experiencing various short-term complications including respiratory distress syndrome, necrotizing enterocolitis, and sepsis. They are also susceptible to enduring long-term neonatal morbidity, including neurodevelopmental disorders and cerebral palsy.[8,9]

Preterm parturition is a syndrome arising from diverse underlying mechanisms, encompassing factors such as intra-amniotic infection and inflammation, placental vascular disease, maternal antifetal rejection, cervical insufficiency, metabolic factors, and progesterone deficiency.[8,10,11] These mechanisms contribute to pathologic early initiation of the common pathway of parturition, involving uterine contractions, cervical thinning and opening, and decidual activation of the uterine lining. The syndromic nature of preterm parturition, along with its intricate underlying mechanisms, poses a significant challenge in identifying women at risk and developing efficacious strategies for the prevention and treatment of spontaneous preterm birth. At present, there is no single drug or intervention capable of effectively preventing or treating all cases of preterm birth.[8,10,11]

Fetal-maternal metabolic imbalance is one of the mechanisms that may lead to spontaneous preterm birth.[12,13] During pregnancy, there are many maternal physiological alterations that are essential to ensure the proper distribution of nutrients and oxygen to support the developing fetus. Extremes in maternal body mass index (BMI), including both underweight and overweight conditions leading to malnutrition, is recognized as a significant risk factor for preterm delivery.[3,14–16] As opposed to nonmodifiable risk factors such as genetics, ethnicity, and race,[17,18] nutritional status before and during pregnancy can be adjusted and should therefore command attention from both the patient and their physician, with the aim to prevent adverse prenatal outcomes, including the occurrence of preterm deliveries.[19] The existing information regarding the connection between maternal metabolism

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imbalance and preterm birth is limited and does not fully examine the role of maternal metabolism in its many aspects. In this review, we discuss the various attributes of fetal-maternal metabolic imbalances that could potentially contribute to preterm birth, including examining their impact on the female reproductive system, maternal size and length of gestation; their influence on placental and central signaling system; as well as their effects on the fetal growth. Through this, we aim to develop a new and comprehensive approach to the link between maternal-fetal imbalance and the potential risk of preterm birth.

Metabolic imbalance and female reproduction

The process of human reproduction requires adequate energy supplementation and a minimal maternal fat mass as an energy resource. The global trend toward the obesity pandemic can lead to the phenomenon of earlier menarche. Severe energy deficiency, resulting from reduced food intake, stress, or exercise, can also affect the normal functioning of the hypothalamic-pituitary-gonadal (HPG) axis. This disruption impacts the hypothalamus, leading to a reduction in the secretion of gonadotropin hormone-releasing hormone, causing decreased levels of both follicle-stimulating hormone and luteinizing hormone. This occurrence obstructs follicle formation, subsequently affecting estrogen secretion, thereby impeding ovulation and resulting in amenorrhea, a condition associated with female infertility.[20] In a woman affected by functional hypothalamic amenorrhea (FHA), these systematic changes reflect in the form of circulating concentrations of follicle-stimulating hormone and luteinizing hormone decreasing to the prepubertal-level ranges. In addition, women with stress-induced inhibition of the HPG axis often have higher levels of serum cortisol.[21] Thus, the treatment of FHA requires a balanced approach that involves managing anxiety, appropriate exercise, and achieving healthy weight gain. Clinical evidence supporting the resolution of FHA is demonstrated by the occurrence of spontaneous menstruation, an indicator of the normalized HPG axis. On average, menstrual resumption takes approximately 9 months at the 90th percentile or higher of the ideal body weight,[22] supporting the concept that a minimal maternal mass is needed for maintaining a functioning reproductive system and sustaining a healthy pregnancy.

Undernutrition and preterm delivery in animal studies

Numerous animal studies have shown the association between maternal undernutrition and the occurrence of adverse pregnancy outcomes. However, data regarding its effect on gestational length remain scarce. Moderated maternal undernutrition in the periconceptional period has been associated with an increased risk of preterm delivery in sheep.[23] In their study, a cohort of singleton-bearing ewes was randomized into a well-fed group and an undernourished group from 60 days before conception up to 30 days after. Within sheep, where a full-term pregnancy typically lasts 145 days, it is observed that despite the nutritional restrictions ending at early gestation, undernourished ewes in the periconceptional era delivered earlier than the control group.[23] Parturition initiation was linked to an increased fetal hypothalamic-pituitary-adrenal axis activity, subsequently leading to the production of prostaglandins (PGE2 and PGF2 alpha) and an elevation in the 17 β-estradiol to progesterone ratio. Therefore, in sheep, periconceptional maternal undernutrition may accelerate fetal hypothalamic-pituitary-adrenal axis maturation, triggering an early activation of the common parturition pathway and culminating in preterm delivery.[23,24]

Famine and preterm birth

Research on the Dutch famine during World War II (WW2) also effectively illustrated the association between famine and adverse pregnancy outcomes.[25] During WW2, part of the Dutch population endured famine lasting approximately 5 months. The famine had an impact on the entire population, reducing the influence of potential confounders, such as genetic inheritance or socioeconomic status.[26] This period provided valuable information into the effect of undernutrition on pregnancy outcomes. Indeed, preterm delivery rates increased in women who conceived during the famine, and exposure to famine during the third trimester was related to reduced birthweight, along with only a small decline in gestational length.[25,27,28]

Maternal size and gestational length

Viviparity imposes high metabolic demands on the mother, challenging virtually every organ and maternal system. This can be compared to the strain imposed on a non-pregnant individual by sustaining the growth of an 8-pound tumor over 9 months. Biology seems to have established a set of governing principles regarding the possibilities within mammalian pregnancy. There is an association between the size of the mother, the length of gestation, and litter size.[3] In general, larger mammals (e.g., elephants with 645 days and whales with 535 days) have longer gestation periods than rodents (rats with 22 days; mice with 19 days).[29] In humans, the considerably large size of the fetal body and brain imposes substantial metabolic challenges during pregnancy. Human pregnancy is characterized by the following: (1) deep hemochorial placentation, rather than the shallow placentation of most mammalian species[30], and (2) adaptations in the maternal-fetal immune system required to tolerate the semi-allograft nature of the fetus and placenta. These intricate adaptations, while complex, are beyond the scope of this article. Furthermore, major metabolic and endocrine physiologic adaptations are required to support fetal growth and the rapid acquisition of fetal body fat during the third trimester.

Physiologic gestational insulin resistance is crucial as the fetus relies on the mother for a continuous supply of glucose and other essential nutrients. This adaptation becomes particularly evident during the third trimester of pregnancy, a period characterized by exceptional demands for fetal growth. The fetus undergoes rapid weight gain, tripling its mass from an average of 1 kg at 27 weeks to approximately 3 kg at term. This exponential growth pattern requires the availability of glucose, amino acids, fatty acids, and other nutrients that serve as fundamental building blocks of the fetus.

Animal studies have shown that a mother's nutritional status significantly impacts her capacity to adequately support the growing and developing fetus. In 2009, the National Academy of Medicine published recommendations regarding weight gain during pregnancy.[31] Excessive gestational weight gain aligns with increased risks of adverse outcomes in both mothers and fetuses. A recent meta-analysis evaluated the association between various dietary patterns, physical activity, and pregnancy weight gain, alongside

obstetrical outcome. It showed that appropriate antenatal dietary choices were associated with a reduced risk of preterm delivery (odds ratio [*OR*], 0.43; 95% confidence interval [*CI*], 0.22–0.84).[32] The susceptibility to preterm birth is linked to maternal nutritional status and BMI.[8,33]

Maternal BMI levels

Low maternal BMI

It has been identified that low maternal weight before pregnancy is a risk factor for preterm birth.[3,34] Women with a low BMI of < 19 kg/m^2 have an increased risk of giving birth to small-for-gestational-age neonates[35] and spontaneous preterm birth.[3] A recent meta-analysis that included 23 studies and 1,309,136 women reported that GWG below the recommended guidelines of the National Academy of Medicine guidelines[31] was associated with a higher risk of preterm delivery (*OR*, 1.70; 95% *CI*, 1.32–2.02). This association was stronger in the lower prepregnancy BMI group (underweight: *OR*, 2.41; 95% *CI*, 1.01–5.73; normal weight: *OR*, 1.96; 95% *CI*, 1.17–3.29; overweight: *OR*, 1.2; 95% *CI*, 1.03–1.40)[14] (Fig. 1). Moreover, in a different meta-analysis, underweight women had an increased overall risk of preterm delivery (relative risk [*RR*], 1.29; 95% *CI*, 1.15–1.46) for both spontaneous (*RR*, 1.32; 95% *CI*, 1.10–1.57) and induced (*RR*, 1.21; 95% *CI*, 1.07–1.30) preterm birth.[8,36]

High maternal BMI

In a recent retrospective cohort study including 36,596 women, overweight or obese patients (compared with normal BMI) before pregnancy had an increased risk of preterm birth, with an *RR* of 1.22 (95% *CI*, 1.08–1.37) and 1.30 (95% *CI*, 1.01–1.69), respectively.[16] Obesity is associated with a higher likelihood of medically indicated preterm birth. According to a systematic review, overweight or obese individuals have a higher risk of induced preterm birth than those with a normal BMI, with an *RR* of 1.30 (95% *CI*, 1.23–1.37); this risk further escalated with increasing weight.[15]

Maternal metabolic syndrome and risk of preterm birth

Research on the direct relationship between metabolic syndrome and preterm delivery is limited, and the mechanisms connecting the two conditions remain unknown. In a prospective cohort study, women with metabolic syndrome were at high risk of preterm birth (*RR*, 2.93; 95% *CI*, 1.53–5.58) and the highest risk was observed for medically indicated preterm births (*RR*, 5.13; 95% *CI*, 1.97–13.38).[37] On the contrary, in a large cohort study, elevated fasting glucose or post-prandial glucose concentrations were not associated with preterm birth.[38]

A case-control study of prenatal cardiovascular risk factors and their impact on preterm birth revealed significant associations between hypertension (*OR*, 4.58), diabetes (*OR*, 3.06), and elevated low-density lipoprotein cholesterol values with substantially increased odds of preterm birth.[39]

Nutritional sensing and preterm birth

Central neural sensing refers to the ability of the central nervous system to detect and interpret signals originating from the body and the external environment. Through this mechanism, the central nervous system monitors and responds to changes in hormonal cues, nutrient levels, and other physiological parameters to ensure adequate support for fetal growth and development.[40] Central neural sensing, placental sensing, and maternal-fetal crosstalk are critical processes coordinating and regulating various physiological functions during pregnancy, entailing communications and interactions involving the maternal system, the placenta, and maternal-fetal compartments. This complex interplay helps optimize fetal growth and development while safeguarding maternal health. Disruptions or imbalances within these processes may lead to pregnancy complications and unfavorable outcomes impacting both the mother and the baby.[2,40,41]

The placenta mediates maternal-fetal exchange and plays an active role in response to maternal nutritional and metabolic signals to adapt the fetal demand to the maternal ability to supply. This mechanism, the "placental nutritional sensing,"[2,41,42] takes place at the syncytiotrophoblast layer that is exposed to maternal blood. Indeed, the syncytiotrophoblasts senses alterations in the availability of maternal nutrients to the fetus and responds by changing placental structure, size, and function, thereby leading to a change in the nutritional status of the fetus and orchestrating the hormonal and metabolic response of the fetus to these changes (Fig. 2).[2,43] Perturbation in maternal nutritional sensing can facilitate fetal growth restriction and subsequent fetal compromise.[44] On the other hand, in the case of maternal obesity, this sensing of overwhelming maternal nutrients leads the nutritional sensing mechanism to deploy a hormonal response that may lead to fetal overgrowth. Indeed, higher levels of insulin, leptin, and insulin-like growth factor 1 were reported among obese pregnant women and those who developed gestational diabetes mellitus.[45,46]

However, in pregnancies complicated by fetal growth restriction, maternal serum concentrations of insulin-like growth factor 1, insulin, and leptin were observed to be

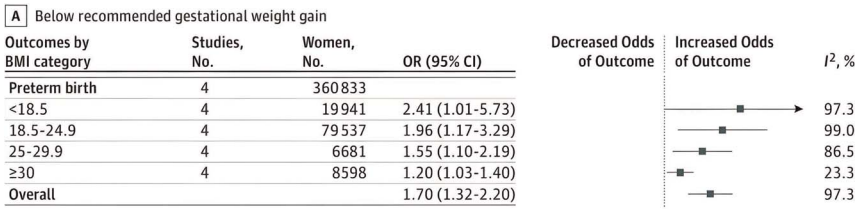

Figure 1. Summary of odds ratios for the association between gestational weight gain below the recommended guidelines of the National Academy of Medicine and adverse pregnancy outcomes. Reproduced with permission from JAMA 2017. 317(21). doi: 10.1001/jama.2017.3635. Copyright ©(2023) American Medical Association. All rights reserved.

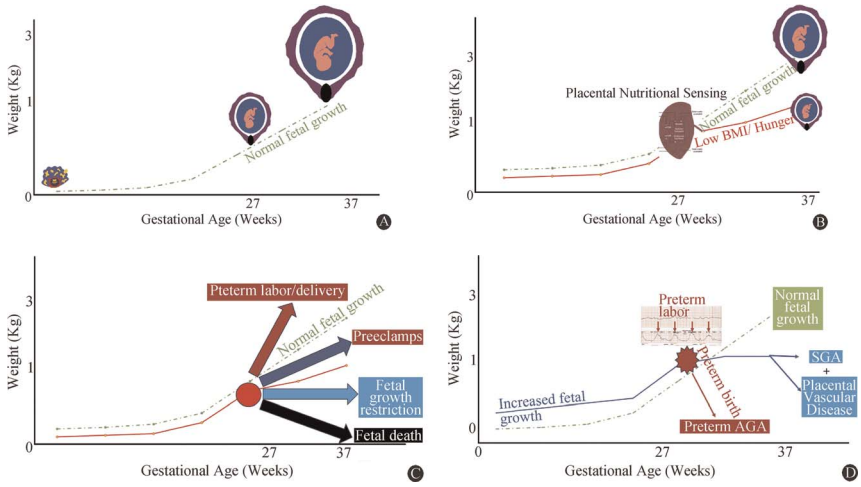

Figure 2. Fetal growth patterns, the effect of normal pregnancy (A), maternal nutrition (B), placental vascular lesions (C), and excessive fetal growth leading to preterm labor and subsequent term delivery (D).

decreased.[47] This provides evidence in favor of the hypothesis that maternal nutrition indeed impacts the functionality of the placenta and the growth of the fetus by regulating the maternal-fetal transport of nutrients. This adaptive mechanism not only ensures the mother's survival during periods of malnutrition or famine but also influences the growth of the developing fetus. Nevertheless, we postulated that this effect is not solely limited to fetal growth and can have an effect on the length of gestation, increasing the risk of preterm parturition.

Preterm parturition and perturbations in fetal growth

Previous reports have demonstrated that a subset of women who experienced preterm labor had a high fetal growth velocity before the onset of preterm parturition.[48,49] Moreover, among women in whom the pregnancy continued and culminated in a later preterm or term deliveries, there was a reduction in fetal growth trajectory[50] and a higher rate of small-for-gestational-age neonates (term delivery 21.5% *vs.* preterm delivery 12.7%) and a higher prevalence of vascular placenta lesions than those who delivered preterm.[51] A subset of patients with spontaneous preterm birth may have an abnormal angiogenic-to-antiangiogenic ratio. This suggests that preterm parturition might manifest clinically as a placental vascular disease.[52] A different observation was that fetal death was preceded by a significant reduction in fetal growth velocity (fetal growth velocity below the 50th percentile of the control group had a 4.7-fold increased risk of antepartum death).[48,49,53] Collectively, these observations suggest that the premature activation of parturition could serve as an adaptive mechanism of the fetus to a hostile uterine environment that fails to support its growth. However, failing to support fetal growth comes at a price of either rescued fetal growth, higher long-term morbidity, premature birth, preeclampsia, or, in severe cases, fetal death.[54]

Thus, we proposed that spontaneous preterm parturition may result from a fetal-maternal metabolic imbalance. In a subset of patients, the mother cannot sustain the nutritional and metabolic demands of the fetus that, in turn, activates the common pathway of parturition. Therefore, careful surveillance of fetal growth trajectory is warranted to identify such fetuses, which if not delivered, preterm may either experience restricted growth or in the more severe cases, be stillborn.

Conclusion

The success of pregnancy is a collaborative effort between the mother and her fetus, balancing the allocation of maternal resources to support and sustain fetal growth without compromising maternal well-being. Many women in their reproductive years have poor maternal nutrition in both aspects—with respect to both undernutrition and obesity. In this review, we have shown the linkage between pre- and periconceptional nutrition and maternal BMI and the risk of preterm birth. When a metabolic imbalance occurs, the fetus responds by inducing changes in the growth rates, metabolic intake, placental function, and gestational length, of all which may lead to higher rates of preterm birth.

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Conflicts of Interest

None.

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