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INSULIN RESISTANCE AND MICROBIOTA DYSBIOSIS IN THE PATHOGENESIS OF PRETERM BIRTH: AN INTEGRATIVE REVIEW OF METABOLIC, INFLAMMATORY, AND MICROBIAL MECHANISMS

D.O. Temirova
Trainee Assistant, Asian International University
dtemirova177@gmail.com
ORCID: 0000-0008-1590-9176

Abstract

Preterm birth remains one of the most significant challenges in modern obstetrics and perinatology because of its substantial contribution to neonatal morbidity, mortality, long-term disability, and healthcare expenditure. Current evidence indicates that preterm birth is a heterogeneous and multifactorial syndrome involving infectious-inflammatory mechanisms, immune dysregulation, neuroendocrine activation, metabolic abnormalities, oxidative stress, placental dysfunction, and changes in the maternal microbiota. In recent years, increasing attention has been directed toward insulin resistance and disturbances of the intestinal and vaginal microbiota as potentially interconnected components of preterm birth pathogenesis. Insulin resistance is associated with compensatory hyperinsulinemia, endothelial dysfunction, oxidative stress, and enhanced production of pro-inflammatory mediators, whereas microbial dysbiosis may promote local and systemic inflammation, activation of innate immunity, prostaglandin synthesis, cervical remodeling, and weakening of fetal membranes. These processes may converge at the level of the maternal–placental–fetal unit and contribute to premature activation of labor pathways. The present review summarizes current concepts concerning the etiopathogenetic role of insulin resistance, inflammatory activation, oxidative stress, and intestinal and vaginal microbiota alterations in preterm birth. Particular attention is given to the potential value of early metabolic and microbiological assessment for risk stratification, prediction, and prevention. Further studies integrating metabolic, inflammatory, endocrine, and microbiome-related biomarkers may improve individualized approaches to the prevention of preterm birth.

Keywords: preterm birth, insulin resistance, microbiota, dysbiosis, pregnancy, systemic inflammation, oxidative stress, vaginal microbiome, intestinal microbiota, prediction.

INTRODUCTION

Preterm birth, generally defined as delivery before 37 completed weeks of gestation, remains a major global problem in obstetrics and perinatal medicine. Despite substantial advances in neonatal intensive care, respiratory support, fetal surveillance, and the management of extremely low-birth-weight infants, the overall burden of preterm birth remains considerable. Preterm infants are at increased risk of respiratory distress syndrome,

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intraventricular hemorrhage, neonatal sepsis, bronchopulmonary dysplasia, retinopathy, neurodevelopmental impairment, and long-term cognitive and neurological consequences. The condition therefore has not only medical but also substantial demographic, psychological, social, and economic significance. Contemporary evidence increasingly supports the concept that preterm birth is not a single disease entity but rather a syndrome resulting from the interaction of multiple maternal, fetal, placental, infectious, metabolic, immunological, genetic, and environmental factors. Among the most widely studied mechanisms are ascending genital tract infection, intrauterine inflammation, cervical remodeling, premature rupture of membranes, placental insufficiency, maternal–fetal stress-axis activation, and endocrine disturbances. More recently, metabolic abnormalities including obesity and insulin resistance have attracted growing interest as potential contributors to spontaneous preterm birth. Insulin resistance may affect pregnancy through several pathways, including chronic low-grade inflammation, endothelial dysfunction, oxidative stress, altered placental perfusion, and changes in immune regulation. At the same time, research into the human microbiome has demonstrated that both intestinal and vaginal microbial communities are dynamic components of maternal physiology and may influence pregnancy outcomes. Vaginal dysbiosis may facilitate ascending infection and inflammatory activation within the reproductive tract, while intestinal dysbiosis may contribute to systemic metabolic inflammation, altered immune signaling, and metabolic endotoxemia. These observations support the hypothesis that metabolic dysfunction and microbial imbalance may not act independently but may interact through common inflammatory and immunometabolic pathways. In Uzbekistan and other regions with a substantial prevalence of maternal anemia, chronic pyelonephritis, metabolic disorders, recurrent reproductive tract infections, and limited preconception care, the identification of modifiable risk factors is particularly important. The purpose of this review was to analyze current concepts regarding the role of insulin resistance and alterations of the intestinal and vaginal microbiota in the pathogenesis of preterm birth and to evaluate their potential importance for early prediction and prevention.

MATERIALS AND METHODS

The present work was designed as a narrative analytical review of scientific literature addressing the pathogenesis of preterm birth, with particular emphasis on insulin resistance, maternal metabolic dysfunction, systemic inflammation, oxidative stress, intestinal microbiota, vaginal microbiota, and their potential interactions. The analysis included international and regional scientific sources, clinical guidelines, textbooks, monographs, and published studies addressing epidemiology, infectious-inflammatory pathways, placental dysfunction, maternal metabolic disorders, endocrine mechanisms, immune dysregulation, microbial dysbiosis, and predictive markers of preterm birth. Particular attention was given to evidence concerning inflammatory mediators such as interleukin-1, interleukin-6, tumor necrosis factor-alpha, prostaglandins, C-reactive protein, matrix metalloproteinases, and markers of endothelial dysfunction, as well as to studies describing insulin resistance and microbiota disturbances during pregnancy. The reviewed evidence was synthesized qualitatively because of heterogeneity in study design, population characteristics, gestational age, diagnostic criteria, biological samples, microbiological methodology, and metabolic assessment. No pooled statistical analysis or meta-analysis was performed. The principal objective was to identify recurring

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pathogenetic mechanisms and to evaluate whether metabolic and microbiota-related pathways can be integrated into a unified conceptual model of preterm birth.

RESULTS

Analysis of the available evidence confirms that preterm birth is associated with a complex interaction of infectious, inflammatory, endocrine, metabolic, placental, and genetic pathways. One of the most consistently described mechanisms is infection-induced inflammation. Ascending microorganisms from the lower genital tract may reach the cervix, decidua, chorion, amnion, and amniotic cavity. Microbial components, including endotoxins and lipopolysaccharides, activate maternal immune cells such as macrophages, neutrophils, and decidual cells and stimulate the production of pro-inflammatory cytokines, particularly interleukin-1, interleukin-6, and tumor necrosis factor-alpha. This inflammatory cascade enhances prostaglandin synthesis within the decidua and fetal membranes, leading to increased myometrial contractility and premature activation of labor. Activated neutrophils and other inflammatory cells also release matrix metalloproteinases that degrade collagen within the cervix and fetal membranes. As a result, cervical shortening and ripening may occur prematurely, while weakening of the fetal membranes increases the risk of preterm prelabor rupture of membranes. Under physiological conditions, pregnancy requires tightly regulated maternal immune tolerance toward fetal alloantigens. Disruption of the balance between pro-inflammatory and anti-inflammatory pathways may therefore facilitate pathological activation of parturition. Elevated systemic inflammatory markers, including C-reactive protein and other mediators, have been proposed as potential indicators of increased obstetric risk. Neuroendocrine mechanisms also contribute to preterm labor. Chronic psychological stress, hypoxia, placental dysfunction, and maternal systemic disease may activate the maternal–placental–fetal hypothalamic–pituitary–adrenal axis. Increased placental corticotropin-releasing hormone may stimulate fetal adrenal production of cortisol and dehydroepiandrosterone sulfate, contributing to changes in estrogen synthesis, progesterone responsiveness, myometrial sensitivity to oxytocin, and activation of labor-associated pathways. Metabolic abnormalities represent another important component. During normal pregnancy, a physiological decline in insulin sensitivity occurs to ensure adequate substrate availability for the growing fetus. However, excessive insulin resistance may become pathological and is frequently associated with obesity, metabolic syndrome, gestational diabetes, endothelial dysfunction, and chronic low-grade inflammation. Compensatory hyperinsulinemia can promote oxidative stress and increase the production of pro-inflammatory mediators. These effects may adversely influence uteroplacental circulation, contribute to placental ischemia, and create an inflammatory metabolic environment that favors adverse pregnancy outcomes. Endothelial dysfunction associated with insulin resistance may also reduce nitric oxide bioavailability, impair vascular adaptation to pregnancy, and increase placental vascular resistance. Thus, insulin resistance may contribute to preterm birth through indirect mechanisms involving inflammation, oxidative stress, endothelial injury, and placental insufficiency rather than through a single independent pathway. The intestinal microbiota may further modulate these metabolic processes. Intestinal dysbiosis can alter intestinal permeability and increase the translocation of bacterial products into the circulation, a phenomenon often described as metabolic endotoxemia. Circulating microbial components may stimulate Toll-like receptors and other innate immune

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pathways, enhancing systemic inflammation and potentially worsening insulin resistance. This mechanism provides a biologically plausible link between intestinal microbial imbalance, metabolic dysfunction, and pregnancy complications. The vaginal microbiota is even more directly related to reproductive tract health. A Lactobacillus-dominant vaginal ecosystem is generally associated with maintenance of an acidic environment and suppression of potentially pathogenic microorganisms. Reduction in protective lactobacilli and expansion of anaerobic or opportunistic bacteria may disrupt this protective environment and facilitate ascending infection. Vaginal dysbiosis may therefore promote local cytokine production, cervical inflammation, degradation of extracellular matrix, and premature rupture of membranes. The association between microbial imbalance and preterm birth appears particularly relevant in early and very early gestational deliveries, where infectious-inflammatory mechanisms are frequently prominent. The interaction between metabolic dysfunction and vaginal or intestinal dysbiosis is also of interest. Insulin resistance, obesity, and hyperglycemia may alter the composition of microbial communities through changes in immune function, nutrient availability, hormonal signaling, and epithelial barrier function. Conversely, dysbiosis may intensify metabolic inflammation and insulin resistance. This bidirectional relationship suggests the possibility of an immunometabolic–microbial axis contributing to the development of preterm labor. Oxidative stress may represent another connecting mechanism. Excessive production of reactive oxygen species can damage placental endothelial cells, alter mitochondrial function, promote inflammatory signaling, and accelerate senescence of fetal membranes. Insulin resistance and chronic inflammation both enhance oxidative stress, whereas dysbiosis may further increase inflammatory activation. Thus, metabolic, microbial, inflammatory, and oxidative pathways may converge on common final mechanisms including placental dysfunction, prostaglandin activation, cervical remodeling, and membrane weakening. Genetic susceptibility may modify the individual response to these exposures. Polymorphisms affecting cytokines, matrix metalloproteinases, hormone receptors, and immune-regulatory pathways may influence vulnerability to inflammatory and metabolic stressors. Epigenetic regulation may further contribute by altering gene expression in response to environmental, nutritional, inflammatory, and microbial signals during pregnancy.

DISCUSSION

The findings of this review support the current concept of preterm birth as a heterogeneous syndrome rather than a disease with a single etiological factor. Infectious-inflammatory mechanisms remain among the most strongly supported pathways, but increasing evidence suggests that metabolic abnormalities, particularly insulin resistance, may substantially modify the maternal inflammatory and vascular environment. This is especially important because insulin resistance during pregnancy exists on a continuum, ranging from physiological adaptation to clinically significant metabolic dysfunction. When excessive, insulin resistance is accompanied by hyperinsulinemia, endothelial impairment, increased oxidative stress, and inflammatory activation, all of which may contribute to placental dysfunction and premature activation of labor-related pathways. The role of microbiota should be interpreted within this broader framework. Vaginal dysbiosis has a plausible direct relationship with preterm labor because altered microbial communities may facilitate ascending infection and local inflammation. Intestinal

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dysbiosis may influence pregnancy through more systemic pathways, including altered immune responses, metabolic endotoxemia, oxidative stress, and modulation of insulin sensitivity. The simultaneous presence of insulin resistance and microbial dysbiosis may therefore create a more pronounced pro-inflammatory state than either factor alone. This concept is clinically relevant because traditional prediction of preterm birth is based largely on obstetric history, cervical length, symptoms of uterine activity, and selected biochemical markers. These methods identify important aspects of risk but may not fully capture metabolic and microbiological heterogeneity. Combining conventional obstetric assessment with indicators of insulin resistance, inflammatory activity, oxidative stress, and microbiota composition may improve early identification of high-risk pregnancies. However, such an approach requires careful validation. Microbiota composition varies according to ethnicity, diet, geographic region, antibiotic exposure, sexual behavior, hygiene practices, gestational age, and laboratory methodology. Similarly, assessment of insulin resistance during pregnancy is complicated by physiological gestational changes in glucose metabolism. Therefore, universal diagnostic thresholds cannot be assumed without population-specific investigation. This is particularly relevant in Uzbekistan, where regional differences in nutritional patterns, anemia prevalence, chronic urinary tract disease, obesity, metabolic disorders, and access to preconception care may influence both metabolic and microbial profiles. Future studies should therefore include well-characterized local cohorts and standardized assessment protocols. Prospective longitudinal designs would be especially valuable because they could determine whether changes in insulin sensitivity and microbiota precede clinical manifestations of threatened preterm labor. Simultaneous analysis of fasting glucose and insulin, markers of insulin resistance, inflammatory cytokines, oxidative stress parameters, vaginal microbiome profiles, intestinal microbiota characteristics, cervical length, and placental function could provide a more comprehensive model of risk. Modern molecular techniques, including 16S ribosomal RNA sequencing and metagenomic analysis, may improve characterization of microbial communities compared with traditional culture-based methods. Nevertheless, molecular detection of microorganisms should not automatically be interpreted as evidence of pathological dysbiosis, because microbial composition must be evaluated within the clinical and ecological context. Another important consideration is causality. Most existing studies identify associations between dysbiosis, metabolic dysfunction, and adverse pregnancy outcomes, but association alone does not establish that these abnormalities directly cause preterm birth. Reverse causation is also possible: inflammatory or hormonal changes preceding preterm labor may themselves alter the microbiota or maternal metabolism. Therefore, mechanistic studies and longitudinal observations are required to clarify the temporal sequence of these events. Preventive strategies should also be evidence-based. Correction of maternal obesity, improvement of metabolic health before conception, appropriate management of gestational diabetes, treatment of clinically significant infections, and reduction of modifiable inflammatory risk factors are biologically reasonable components of comprehensive prenatal care. However, routine use of probiotics, antibiotics, or other microbiome-modifying interventions solely for the prevention of preterm birth requires stronger evidence regarding patient selection, timing, safety, and efficacy. The available evidence therefore supports an integrative rather than isolated interpretation of insulin resistance and microbiota changes. Their clinical

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significance is most likely determined by interaction with maternal immune status, placental function, genetic susceptibility, endocrine regulation, and environmental exposures.

CONCLUSION

Preterm birth is a complex multifactorial obstetric syndrome in which infectious-inflammatory processes, immune imbalance, neuroendocrine activation, placental dysfunction, insulin resistance, oxidative stress, and microbial dysbiosis may interact within a common pathogenetic network. Insulin resistance may contribute to preterm birth through endothelial dysfunction, chronic low-grade inflammation, oxidative stress, and impairment of uteroplacental circulation. Vaginal dysbiosis may directly facilitate ascending infection and local inflammatory activation, whereas intestinal microbiota disturbances may influence systemic immune and metabolic pathways. The potential bidirectional relationship between insulin resistance and microbiota alterations supports the concept of an immunometabolic–microbial axis in the pathogenesis of preterm birth. Early identification of these abnormalities may have prognostic value, particularly when combined with established obstetric risk factors and markers of inflammation and placental dysfunction. However, current evidence remains insufficient to establish universal microbiota or metabolic screening algorithms for prediction of preterm birth. Future prospective studies should evaluate insulin resistance, vaginal and intestinal microbiota, inflammatory biomarkers, oxidative stress, and placental function simultaneously and at several stages of gestation. Such an integrated approach may contribute to more accurate risk stratification and the development of individualized strategies for preventing preterm birth and improving maternal and neonatal outcomes.

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