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MULTIFACTORIAL DETERMINANTS OF PRETERM BIRTH: A REVIEW OF CURRENT RISK FACTORS AND PREVENTIVE STRATEGIES

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ABSTRACT

Preterm birth is one of the most serious challenges in modern perinatology, being a significant cause of morbidity and mortality in newborns and long-term health complications. PTB affects approximately 15,000,000 children worldwide each year and accounts for approximately 11% of births globally. It is responsible for a significant proportion of perinatal morbidity and mortality, as well as long-term neurological, metabolic, and developmental complications in children. The aim of this review was to summarize the current knowledge on the risk factors for preterm birth and to organize the most important ones. Preterm birth is a phenomenon with a complex etiology, and its risk results from the interaction of biological, obstetric, and environmental factors. The identification and modification of selected factors, especially those related to the mother's lifestyle and nutritional status, is a key element of prevention and prenatal care. Based on the available data, the clinical importance of early identification of risk factors and the implementation of preventive strategies and monitoring of high-risk pregnancies has been emphasized. A better understanding of the mechanisms leading to preterm birth may contribute to reducing the incidence of this complication and improving the prognosis for newborns.

KEYWORDS

Preterm Birth, Premature Delivery, Risk Factors, Maternal Smoking, Maternal Age, Birth Spacing, Assisted Reproductive Technology, Cervical Length, Cervical Insufficiency, Maternal Nutrition

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Introduction

Preterm birth, defined as the termination of pregnancy before 37 weeks of gestation, is one of the most significant challenges in modern perinatology [29][30]. The etiology of preterm birth is multifactorial and includes both obstetric and behavioral-environmental factors. Another classification refers to maternal, fetal, and environmental factors. These factors may act independently or reinforce each other.

A review of the literature shows that the most important obstetric risk factors include: previous preterm birth, cervical insufficiency, anatomical defects of the uterus, and pregnancies achieved through assisted reproductive technologies. Among behavioral and environmental factors, the following are of particular importance: smoking and the use of other stimulants, genitourinary infections, low socioeconomic status, underweight before pregnancy (BMI < 18.5 or body weight < 50 kg), inadequate diet, and maternal malnutrition. Increasing attention is also being paid to the role of inflammatory processes, immune disorders, and genetic factors in the pathogenesis of preterm birth. Despite advances in diagnosis and perinatal care, the incidence of preterm birth remains high, with no significant decline observed in many countries. The aim of this review is to present and analyze the current state of knowledge on the risk factors for preterm birth, with particular emphasis on their classification, pathophysiological mechanisms, and clinical significance. A better understanding of these factors may contribute to more effective identification of high-risk pregnancies and the implementation of preventive measures aimed at reducing the incidence of preterm birth and its negative consequences.

Methods

A review of the scientific literature was conducted to identify and summarize the risk factors for preterm birth. The analysis was based on previously published scientific studies on the epidemiological, medical, behavioral, and reproductive determinants of this phenomenon. The literature search was conducted in the PubMed, Google Scholar, and Web of Science databases. Articles published in English between 1986 and 2025 were included.

The search strategy used keywords such as: preterm birth, premature delivery, risk factors, maternal smoking, maternal age, birth spacing, assisted reproductive technology, cervical length, cervical insufficiency, and maternal nutrition. The review included studies on risk factors for preterm birth in humans, including observational, cohort, and randomized studies, as well as systematic reviews and meta-analyses.

The review included studies on risk factors for preterm birth in humans published in peer-reviewed scientific journals. Observational studies, cohort studies, retrospective studies, randomized controlled trials, as well as systematic reviews and meta-analyses were included.

Studies focusing exclusively on the consequences of prematurity without analyzing risk factors and articles with insufficient methodological description were excluded.

Based on the selected publications, information was extracted regarding the type of study, population characteristics, and risk factors analyzed. The results were then qualitatively analyzed and grouped into main categories, such as demographic factors, lifestyle, medical and obstetric factors, assisted reproductive technologies, and nutritional factors.

Results

Tobacco smoking is a global public health problem due to its wide range of negative health effects. Active smoking is a significant risk factor for many diseases, including cancer and pregnancy complications. Smoking has adverse effects on both active and passive smokers, with documented effects on the health of pregnant women and their offspring [3]. Secondhand smoke (SHS) – exposure to tobacco smoke in the environment – is associated with an increased risk of preterm birth (<37 weeks of pregnancy) and other perinatal complications [3].

Studies indicate that the risk of preterm birth correlates with the number of cigarettes smoked by the mother; women who smoke more cigarettes per day are more likely to give birth prematurely than non-smokers [2]. Smoking is also associated with a systemic inflammatory response and may increase the risk of spontaneous preterm birth for this reason. Toxic substances contained in tobacco smoke include nicotine, carbon monoxide, and more than 7,000 other chemicals that can cross the placenta, causing intrauterine damage to the fetus. Nicotine and other toxins that cross the placenta are powerful vasoconstrictors, leading to reduced uteroplacental blood flow and limited oxygen and nutrient supply. The results indicate the impact of smoking on the duration of labor, which is further confirmed by its effect on intrauterine growth retardation [5]. Meta-analyses show that smoking during pregnancy increases the risk of serious complications such as preterm birth, low birth weight and perinatal death [4]. In addition, exposure to tobacco smoke during pregnancy is also associated with the risk of developmental and health disorders in infancy and childhood. Damage occurs in the respiratory and digestive systems, but also in the neurological system. That is why it is so important to conduct educational programs and health campaigns to reduce these negative effects.

IVF/ICSI procedure

In vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) is associated with an increased risk of preterm (33rd-37th gestational week) and early preterm birth (20th-32nd gestational week) [17][28]. In vitro fertilization is another risk factor in a subgroup of women undergoing assisted reproductive technology (ART). Numerous cohort studies and meta-analyses involving large populations of women have shown that pregnancies resulting from in vitro fertilization (IVF) and assisted reproductive technologies (ART, including ICSI) are associated with an increased risk of preterm birth (before 37 weeks of gestation) compared to spontaneously conceived pregnancies [18-20]. In most analyses, the relative risk (RR) or odds ratio (OR) ranges from approximately 1.7 to 2.2, which means that the risk of preterm birth is on average several dozen to approximately 100% higher than in the general population.

The most important factor responsible for this increased risk is the higher incidence of multiple pregnancies in IVF procedures. Twin or multiple pregnancies are in themselves a very strong risk factor for preterm birth, regardless of the method of conception [20,21]. Therefore, a significant part of the observed increase in risk can be explained by the higher percentage of multiple pregnancies in the population of patients treated for infertility. The introduction of the single embryo transfer (SET) strategy has significantly reduced the frequency of multiple pregnancies and thus reduced the scale of complications associated with prematurity [21].

However, even when taking into account multiple births (i.e., analyzing only single pregnancies), many studies still observe a moderately increased risk of preterm birth in the IVF group [19]. This suggests that other factors may also influence the outcome, such as the cause of infertility, comorbidities, or the in vitro fertilization procedure itself [19]. Another study confirms the above-mentioned causes, as it showed that maternal age, multiple pregnancy, embryo reduction, and placenta previa may increase the risk of preterm birth in women undergoing in vitro fertilization/ICSI.

Maternal factors

The health of the pregnant woman plays a key role in the normal course of pregnancy and in determining the risk of preterm birth. Numerous epidemiological and clinical studies confirm that chronic diseases in the mother significantly increase the likelihood of early termination of pregnancy [1]. The most important conditions include hypertension, preeclampsia, pregestational and gestational diabetes, kidney disease, liver disease, autoimmune diseases, and severe anemia. These conditions lead to uteroplacental perfusion disorders, fetal hypoxia, and activation of a chronic inflammatory response, which can result in both spontaneous preterm birth and the need for medical induction [7].

A special clinical situation is preeclampsia, which is one of the main causes of iatrogenic prematurity. In severe cases, continuing the pregnancy may threaten the life of the mother and fetus, so it may be necessary to terminate it early [1].

The mechanism leading to preterm birth is often based on the activation of an inflammatory response. Microorganisms and their endotoxins stimulate the secretion of proinflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α), which induce the production of prostaglandins responsible for uterine contractility, cervical shortening and dilation, and premature rupture of the fetal membranes [6]. In many cases, the inflammatory process may be asymptomatic or oligosymptomatic, which significantly hinders its early diagnosis. Infections are among the best-documented risk factors for preterm birth, with particular importance attached to genitourinary infections such as bacterial vaginosis, urinary tract infections, and intrauterine infections [1].

The age of the pregnant woman is an independent factor influencing the risk of prematurity. The highest risk is observed in women under 20 and over 35 [9]. Pregnancy in teenagers is associated with an increased risk of premature birth, low birth weight, and neonatal complications, which may result from both the biological immaturity of the reproductive system and socioeconomic factors. In older women, on the other hand, chronic diseases, metabolic disorders, and placental complications are more common, which contributes to earlier termination of pregnancy [7]. Studies show that the level of education of the parents also has an impact. A higher level of education among pregnant women or their spouses and an earlier gestational age were protective factors against preterm birth [11].

One of the strongest risk factors for another preterm birth is a history of preterm birth. This risk increases with the number of previous preterm births and the lower the gestational age of the previous birth [10]. The mechanisms responsible for this phenomenon may include permanent changes in the cervix, persistent inflammatory predisposition, as well as genetic and epigenetic factors [6]. In clinical practice, women with such a history require particularly intensive obstetric supervision and the implementation of preventive measures in subsequent pregnancies.

The risk of premature birth increases significantly in pregnancies that occur shortly after the previous birth. Epidemiological studies indicate that an inter-pregnancy interval of less than 6 months can more than double the risk of premature birth compared to the optimal interval [12]. A short interval between pregnancies does not allow a woman's body to fully recover from the previous pregnancy and delivery.

The uterus needs adequate time to return to its pre-pregnancy state, both structurally and functionally. The processes of uterine muscle involution, resolution of inflammatory changes, and restoration of normal uteroplacental perfusion are crucial for ensuring the proper conditions for the development of the next pregnancy. Insufficient recovery time may contribute to implantation disorders, chronic inflammation, and premature activation of contractile activity [13].

Another important mechanism explaining the increased risk of preterm birth with a short interval between pregnancies is the maternal depletion hypothesis. It assumes that a woman's body may not have time to rebuild the reserves of vitamins, minerals, and nutrients used up during the previous pregnancy and lactation [12]. The shorter the interval between pregnancies, the less likely it is that iron and folate levels and overall nutritional status will fully normalize.

The nutritional status of a pregnant woman can be assessed using anthropometric indicators such as body mass index (BMI). Studies have shown that pre-pregnancy underweight significantly increases the risk of spontaneous preterm birth and low birth weight [14]. The mechanisms of this phenomenon may include reduced circulating blood volume, impaired uterine perfusion, and lower metabolic reserve.

Micronutrients, including iron, folic acid, and zinc, are also important. Iron is a key component of hemoglobin, enabling the effective delivery of oxygen to the placenta and the developing fetus. Iron deficiency and low ferritin levels during the preconception period and early pregnancy are associated with an increased risk of preterm birth and low birth weight [15].

Folic acid (vitamin B9) is widely accepted as a protective agent against neural tube defects in the fetus. The main sources of folic acid in the diet are folic acid-fortified foods and dietary supplements containing folic acid [22]. Folic acid plays a fundamental role in DNA synthesis, cell division, and the proper development of the fetal nervous system. Adequate supplementation before and during early pregnancy significantly reduces the risk of neural tube defects and other serious birth defects [16].

There are many potential mechanisms through which maternal nutrition can influence the occurrence of preterm birth. Inadequate nutrient supply can lead to placental dysfunction, increased susceptibility to infections, and activation of inflammatory processes. Therefore, it is extremely important to educate women planning pregnancy and to implement appropriate micro- and macroelement supplementation already at the preconception stage, which may contribute to reducing the risk of complications and ensuring optimal conditions for fetal development.

Cervical insufficiency is a clinical condition in which the cervix is unable to maintain pregnancy until term. It is characterized by painless shortening and dilation of the cervix in the second or early third trimester of pregnancy, most often between 18 and 28 weeks of gestation [22]. Under normal conditions, the cervix remains long, closed, and exhibits adequate mechanical strength until the end of the third trimester. However, in the event of insufficiency, premature structural changes occur, leading to a loss of support function.

Shortening and dilation of the cervix promotes the entry of microorganisms from the lower genital tract, which can lead to the development of inflammation in the cervix, fetal membranes, and uterine cavity. The inflammatory process activates a cascade of inflammatory mediators, including pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF- α) and prostaglandins, which participate in collagen degradation and remodeling of the extracellular matrix of the cervix. These changes result in further shortening of the cervix and induction of uterine contractions, which can lead to premature labor, often at a very early stage of pregnancy [27].

Studies show that the risk of preterm birth increases with decreasing cervical length, and is particularly high when the length is <25 mm in the second trimester of pregnancy [22]. It has been shown that the shorter the cervix and the earlier in pregnancy it shortens, the greater the likelihood of very preterm birth, especially before 28 weeks of pregnancy [23]. The presence of coexisting factors, such as intrauterine infections, multiple pregnancies, or previous cervical trauma (e.g., after conization procedures), further increases the risk of adverse pregnancy outcomes.

Population screening studies have shown that a significantly increased percentage of premature births is observed in women who have a cervical length of less than 25 mm on ultrasound examination between 18 and 22 weeks of pregnancy [22]. Pregnancy loss before 22 weeks is classified as miscarriage and is associated with a very high risk of fetal death. It should be emphasized that cervical insufficiency is usually not accompanied by typical pain or regular uterine contractions, which significantly hinders early diagnosis of the problem. Often, there is no bleeding or premature rupture of the fetal membranes.

Diagnosis is based on a detailed obstetric history, gynecological examination, and, above all, transvaginal ultrasound, which is the primary tool for assessing cervical length. This examination allows for the detection of cervical shortening even before clinical symptoms appear, enabling the implementation of appropriate preventive measures [22]. Research is currently underway on new biochemical and ultrasound markers that enable earlier prediction of the risk of preterm birth.

Treatment of cervical insufficiency includes surgical, mechanical, and pharmacological methods. Surgical methods include cervical cerclage, which can be used prophylactically or emergently in women with a shortened cervix (<25 mm) and without contractile activity [24]. A mechanical method is the use of an obstetric pessary, which changes the angle of the cervix and reduces the direct pressure of the fetal egg on the internal os, which may limit further shortening [25].

Among pharmacological methods, the use of vaginal progesterone, which has anti-inflammatory properties and inhibits uterine contractions, is particularly important. It has been shown that administering progesterone to women with a short cervix in the second trimester of pregnancy significantly reduces the risk of preterm birth [26]. The aim of these therapeutic interventions is to strengthen the supportive function of the cervix, limit its further shortening, and reduce the risk of premature dilation.

However, it should be emphasized that despite the use of available treatment methods, the risk of preterm birth in women with cervical insufficiency remains higher than in the general population. This indicates a complex, multifactorial pathogenesis of this condition, involving anatomical, inflammatory, and genetic factors [27].

Discussion

The data presented in this study confirm that preterm birth is a multifactorial phenomenon involving environmental, medical, sociodemographic, and previous pregnancy-related factors. Modifiable risk factors, such as smoking, inter-pregnancy interval, and the woman's nutritional status, are of particular importance and may constitute potential points of preventive intervention.

In terms of environmental factors, it has been clearly demonstrated that both active and passive smoking increase the risk of preterm birth and other perinatal complications [3,4]. The mechanism of this phenomenon includes, among other things, the pro-inflammatory effect of tobacco smoke, uteroplacental perfusion disorders, and chronic fetal hypoxia [5]. The dose-response relationship observed in relation to the number of cigarettes smoked [2] further strengthens the arguments for the need to intensify anti-smoking programs targeting women of childbearing age.

Another important area of contemporary perinatology is the assessment of risk in pregnancies achieved through assisted reproductive technologies. Analyses indicate that IVF/ICSI procedures are associated with an increased risk of preterm birth [17–20]. This is largely due to the higher incidence of multiple pregnancies [20,21], but even after excluding these, a moderately increased risk of prematurity is observed [19]. This suggests that the outcome of pregnancy may also be influenced by factors related to primary infertility, maternal age, and coexisting chronic diseases.

Maternal diseases are one of the best-documented risk factors for preterm birth [1,7]. Hypertension, preeclampsia, diabetes, and autoimmune diseases lead to placental dysfunction and activation of inflammatory processes, which can result in both spontaneous and iatrogenic preterm birth. The role of inflammation as a common pathogenetic mechanism in many forms of preterm birth remains particularly important [6,27].

The mother's age shows a U-shaped relationship – the highest risk is for very young women and those over 35 years of age [9]. In the younger group, biological and socioeconomic factors are important, while in the older group, the more frequent co-occurrence of chronic diseases and placental complications is significant [7]. In addition, it has been shown that a higher level of parental education may have a protective effect [11], which emphasizes the importance of social determinants of health.

A strong predictor of another preterm birth is a history of previous preterm birth [10]. This phenomenon may result from persistent structural changes in the cervix, inflammatory predisposition, and genetic and epigenetic factors [6]. In clinical practice, this requires intensive monitoring and prevention in subsequent pregnancies.

A short inter-pregnancy interval (<6 months) also significantly increases the risk of preterm birth [12]. The maternal resource depletion hypothesis suggests that a woman's body may not have time to rebuild its reserves of micronutrients and nutrients [12,13]. In this context, nutritional status, assessed by BMI, among other things, becomes important. Pre-pregnancy underweight is associated with an increased risk of prematurity [14], and iron deficiency and low ferritin levels correlate with preterm birth and low birth weight [15]. Inadequate folic acid supplementation also increases the risk of fetal malformations [16,22].

Particular attention should be paid to cervical insufficiency, which is an important anatomical factor leading to very early preterm births [22,23]. Cervical shortening (<25 mm) in the second trimester of pregnancy significantly increases the risk of preterm birth [22]. Treatment involves cerclage [24], obstetric pessary [25], and vaginal progesterone [26], but despite the implementation of therapy, the risk is not completely eliminated [27]. This indicates the complexity of the pathogenetic mechanisms and the need for further research on risk biomarkers.

Strengths and limitations of the study

This review presents a comprehensive overview of the multifactorial etiology of preterm birth, integrating medical, environmental, demographic, and nutritional determinants. A major strength of the study is the broad scope of the literature search, which included publications from 1986 to 2025 and several major scientific databases, such as PubMed, Google Scholar, and Web of Science. This approach increased the likelihood of capturing key studies relevant to the topic. Another important strength is the structured classification of risk factors into clear categories, including demographic, lifestyle, medical and obstetric factors, assisted reproductive technologies, and nutritional determinants. Such organization facilitates interpretation of the available evidence and highlights the complex interactions between different risk factors. Furthermore, the review emphasizes modifiable determinants, such as smoking, inter-pregnancy interval, and maternal nutritional status, which have important implications for prevention strategies and public health interventions. However, several limitations should be acknowledged. The review has a narrative character and

does not follow a fully systematic review methodology; therefore, detailed information regarding the study selection process, such as the number of screened and included articles or a standardized selection framework, was not provided. Additionally, the study does not include a quantitative synthesis or meta-analysis, which limits the ability to estimate the precise magnitude of associations between specific risk factors and preterm birth. Finally, the inclusion of studies with heterogeneous designs and the restriction to English-language publications may introduce potential selection and publication bias.

Conclusions

Preterm birth remains one of the most important problems in modern perinatology, being the main cause of morbidity and mortality in newborns. Its etiology is multifactorial and includes both environmental factors (smoking) [3–5], medical procedures (IVF/ICSI) [17–20], and maternal factors such as chronic diseases [1,7], age [9], previous preterm births [10], short inter-pregnancy interval [12], and nutritional status [14–16].

A common mechanism in many forms of prematurity is the activation of the inflammatory response and impaired placental function [6,27]. Identifying women at increased risk, including those with a short cervix [22], allows for the implementation of preventive measures such as progesterone therapy [26], cerclage [24], or pessary use [25].

Effective prevention of preterm birth requires an interdisciplinary approach, including health education, optimization of treatment for chronic diseases, proper pregnancy planning, and improved preconception care. Further research into molecular mechanisms and predictive factors may contribute to more effective identification of women at risk and improve the prognosis for both mothers and their children.

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