Advances in Research on Risk Factors and Pregnancy Outcomes Related to Prematurity

Yun Liu[1], Dexiong Zhao[2*], Mengli Feng[1], Bingqian Wang[1], Tao Wang[1]

[1] College of Clinical Medicine, Qinghai University, Xining, Qinghai, China

[2] Department of Obstetrics, Qinghai Red Cross Hospital, Xining, Qinghai, China

Abstract: Preterm birth, as an important factor affecting the health of pregnant women and perinatal fetuses, is a hot issue worth long-term attention around the world. This paper will describe the risk influencing factors of preterm birth and pregnancy outcomes from the aspects of social factors, environmental factors, pregnancy-related diseases and pregnancy outcomes. In order to early identification and diagnosis of preterm birth, prevent the occurrence of preterm birth, improve pregnancy outcomes, improve the quality of fetal life.

***Keywords*:** preterm birth, related factors, pregnancy outcome, preterm infants

1. Introduction

The upper limit for the definition of preterm birth is globally standardized, defined as delivery before 37 weeks of gestation. Globally, about 15 million cases of preterm birth occur each year (10% of all births), with approximately 85% occurring between 32+0 and 36+6 weeks of gestation[1]The upper limit for preterm birth is generally set at 37+0 weeks globally, while the lower limit varies by country, influenced by socioeconomic conditions, culture, education, genetics, healthcare levels, and the capacity to treat preterm infants. In recent years, the rapid development of perinatal medicine in China has significantly improved the treatment of preterm infants. According to surveys in some regions, the survival rate of extremely premature infants at or after 26 weeks of gestation has exceeded 80%, which is significantly higher than that of extremely premature infants at or before 25 weeks of gestation, approaching the levels seen in developed countries. Depending on the cause, preterm birth can be categorized into spontaneous preterm birth and therapeutic preterm birth. The incidence of preterm birth in China is approximately 5% to 15% [2]. Pregnancy complications, including preterm birth, are common and are a significant cause of death and disability among perinatal infants and children under 5 years old. This article will discuss the risk factors associated with preterm birth and the outcomes of pregnancy.

2. Social and environmental factors of premature birth

2.1 Race

Epidemiological studies have shown that preterm birth varies by race and geography. Blacks have a significantly higher rate of preterm birth compared to whites, and women with a history of preterm birth often have a family or ethnic predisposition. Recent studies indicate that preterm birth is a polygenic hereditary disease influenced by multiple genes and environmental factors. A Meta-analysis of 94 studies found that in different geographical regions and time periods, Black and South Asian women have a higher rate of adverse outcomes, such as PTB and small for gestational age infants, compared to white women[3].

2.2 Age

Pregnant women who are too young or too old: pregnant women under 17 years of age or over 35 years of age [4], the risk of premature birth will increase.

2.3 Diet

The Developmental Origins of Health and Disease (DOHaD) theory suggests that changes in the uterine environment during development can have irreversible lifelong effects on offspring[5]. Dietary patterns, which encompass the types and quantities of daily food intake, consider the intake of various foods or nutrients to explore their relationship with health outcomes. Dietary patterns can provide a comprehensive analysis of how nutritional status during pregnancy affects the risk of premature birth[6]. Maintaining a healthy diet rich in fruits, vegetables, whole grains, and fish during pregnancy can reduce the risk of premature birth. Given that premature birth is associated with adverse health outcomes later in life, enhancing dietary nutrition education and increasing the intensity of dietary interventions during pregnancy can promote

a healthier dietary pattern[7]. CHIA 's[8] research indicates that adhering to a healthy diet can lower the risk of premature birth.

2.4 Body mass index (BMI)

In recent years, the rapid economic growth, along with changes in lifestyle and dietary patterns, has led to a significant rise in the number of overweight and obese individuals. A retrospective cohort study found that 33.16% of pregnant women were overweight, and 1.8% of these women experienced preterm birth (PTB)[9]. A prospective cohort study indicated that the risk of very early and mid-term preterm birth increases with higher Body Mass Index (BMI), with obese women having the highest risk of very early preterm birth (OR=3.34,95%CI=1.07-10.97)[10]. Wu Kaijia 's[11] research showed that pregnant women with a BMI below the normal range have a significantly higher incidence of preterm birth, low birth weight, and fetal growth restriction.

2.5 Environment

People who are more sensitive to high temperatures, such as the elderly, pregnant women, and infants[12], have been found by multiple studies both domestically and internationally to be associated with an increased risk of premature birth. For example, a systematic review from the United States reported that temperature is associated with an increased risk of premature birth (OR: 1.086,1.21) [13]. Another study in South Korea did not find that vegetation levels in the area had a moderating effect on the relationship between high-temperature exposure and premature birth[14]. Improving air quality can reduce the risk of premature birth and low birth weight. In urban areas, noise pollution is also a significant environmental factor. High noise exposure is linked to health issues such as hypertension, anxiety, and sleep disorders [15].

2.6 Others

Smoking, drinking, physical activity during pregnancy, pre-pregnancy medication use, and pre-existing conditions can all contribute to the risk of premature birth to varying degrees. Both too short and too long intervals between pregnancies can increase the risk of premature birth[16]. Liu [17] noted that women with polycystic ovary syndrome (PCOS) are more likely to experience preterm birth (PTB). For women with cervical insufficiency who become pregnant again, it is important to monitor cervical length dynamically and intervene early to reduce the risk of adverse pregnancy outcomes. Breintoft [18] found in a cohort study that women with endometriosis have a higher risk of PTB compared to those without endometriosis, with mPTB being the predominant type.

3. Pregnancy-related diseases

3.1 Multifetation

With the widespread adoption of assisted reproductive technologies and the delayed onset of childbearing age, the incidence of twin pregnancies has significantly increased, now accounting for about 2% to 3% of all pregnancies. Twin pregnancies are more prone to premature birth. The causes of premature birth in multiple births often stem from the doubled placental mass and the limited uterine expansion capacity, which prevent the fetus from growing sufficiently, leading to fetal growth restriction and resulting in preterm birth (PTB).

3.2 Gestational diabetes mellitus

The risk of preterm birth in GDM pregnant women increases by 3.45 times [19]. Premature rupture of membranes (PROM) is a significant risk factor for preterm birth in GDM pregnant women, possibly due to oxidative stress in GDM patients, which can lead to placental vascular endothelial dysfunction[20]. This dysfunction can result in premature rupture of membranes before full term, affecting the development of the membranes and causing cervical insufficiency [21]. The outflow of amniotic fluid and the reduction in uterine cavity size can cause uneven pressure within the uterus, leading to fetal malposition and increasing the risk of preterm birth. Abnormal increases in HbA1c can increase vascular permeability, and the frequent occurrence of hyperglycemia and hyperinsulinemia in GDM patients can place pregnant women in a hyperosmotic state, leading to polyhydramnios and promoting preterm birth[22].

3.3 Hypertensive disease of pregnancy

Hypertensive disorders of pregnancy (HDP) is a significant risk factor for preterm birth. Previous studies have shown that compared to women with normal blood pressure, HDP pregnant women exhibit significantly higher levels of pro-inflammatory cytokines (such as IL-6, IL-8, TNF-α) and anti-inflammatory cytokines (such as IL-4, IL-10). However, the concentration of pro-inflammatory cytokines is much higher than that of anti-inflammatory cytokines [23]. In HDP patients, the PI3K/Akt/PTEN pathway is activated, where PTEN upregulation inhibits trophoblast cell invasion, and Akt downregulation

leads to endothelial dysfunction. HDP is also characterized by placental perfusion insufficiency. Furthermore, previous research suggests that the PI3K/Akt/PTEN pathway may play a crucial role in the development of spontaneous preterm birth (spPTB) due to uterine-placental insufficiency [24]. Additionally, in HDP patients, uterine-placental insufficiency may act as a stress signal, leading to increased CRH levels, which in turn cause spPTB through downstream effects.

3.4 Anemia in pregnancy

Ghimire[25] found that anemia of pregnancy (IDA) significantly increases the risk of complications in newborns, including premature birth, low birth weight, and neonatal asphyxia. Ferritin, the protein with the highest iron content in the body, is a key indicator of iron stores. When ferritin levels drop, it indicates insufficient iron stores. If not promptly addressed, this can lead to iron deficiency in red blood cells, a reduction in the number of sideroblasts in bone marrow, and ultimately, a decrease in hemoglobin levels, resulting in anemia [26].

3.5 Merge kidney diseases

Women with kidney disease during pregnancy generally face an increased risk of adverse pregnancy outcomes. Multiple Meta analyses and clinical studies have reported that the risk of premature birth, fetal growth restriction, and small for gestational age infants is [27] higher. A large cohort study in 2021 found that women with kidney disease during pregnancy have a 9-fold higher risk of premature birth compared to those without kidney disease [28]; other studies have reported an average premature birth rate of 13% in CKD patients, which is significantly higher than the average rate of 6% in healthy control groups[29].

3.6 Genital tract infection

Healthy vaginal lactobacilli in women can produce hydrogen peroxide, which inhibits other pathogens, maintaining a dynamic balance in the vaginal micro-ecosystem. In a vaginal microenvironment with high microbial diversity, various harmful microorganisms alter the vaginal pH by secreting lipopolysaccharides from their cell membranes and endotoxins from their cells, increasing adhesion to vaginal surface cells, inducing maternal-fetal interface inflammatory responses, and promoting premature birth [30]. Xu [31]demonstrated that the vaginal pH and serum estradiol levels significantly influence vaginal microbiota, with the relative abundance of lactobacilli negatively correlated with vaginal pH. The vaginal inflammatory response and the reduction in lactobacilli are mutually reinforcing factors that contribute to disease progression, leading to ascending chorioamnionitis, premature rupture of membranes, and premature birth among other pregnancy complications [32]. GBS can cause ascending infection, leading to chorioamnionitis, which results in the secretion of proteases and the activation of cytokine-prostaglandin cascade reactions, causing spontaneous premature birth and premature rupture of membranes [33]. A systematic review found that GBS positivity at 26-28 weeks of gestation is a risk factor for preterm birth during pregnancy, and early detection of GBS is beneficial for predicting the occurrence of preterm birth [34]. A Meta-analysis based on cohort studies and cross-sectional studies found that the risk of preterm birth is significantly increased in pregnant women colonized with GBS and those with GBS bacteriuria [35].

3.7 Abnormal thyroid function

Gestational thyroid dysfunction can adversely affect fetal development, increasing the risk of miscarriage, premature birth, fetal distress, stillbirth, low birth weight, and congenital defects. Pregnant women with thyroid dysfunction (TAI) have a higher risk of miscarriage and premature birth. Women with positive thyroid peroxidase antibodies (TPOAb) have a higher risk of premature birth compared to those with negative antibodies. Maternal thyroid hormones can cross the placenta and affect the fetus, increasing the risk of adverse outcomes in newborns [36]. The mid to late stages of pregnancy are critical for placental development, and any placental insufficiency can lead to premature birth[37].

3.8 Placental implantation abnormalities (PIA)

Placental factors, such as low-lying placenta, marginal placenta, placenta previa, placental implantation, velamentous placenta, and vascular placenta, often result from injuries to the endometrium caused by surgical procedures like curettage, scarred uterus, and assisted reproductive technologies. These conditions increase the risk of preterm birth (PTB) to 26.9%,43.5%,57.7%,81.9%, and 37.5%, respectively. A large-scale population study [38]found that the rate of preterm birth due to placenta previa can be as high as 44%, and the rate of preterm birth due to placental implantation can be as high as 58%.

4. Pregnancy outcome

Premature birth is a significant cause of neonatal mortality, with the risk of complications increasing as gestational age decreases. Premature infants are more likely to have underdeveloped lungs and central nervous systems, which makes them

more vulnerable to environmental factors and increases their risk of complications[39]. Studies show that newborns with a gestational age <34 weeks have a higher incidence of respiratory distress syndrome[40]. The survival rate of newborns improves with longer gestational periods, and the incidence of severe complications decreases, leading to shorter hospital stays[41]. Therefore, it is crucial to extend gestational periods as much as possible to improve the prognosis and quality of life for newborns.

5. Summary and Outlook

Premature birth has long been a critical issue that requires global attention, as it significantly impacts the health of pregnant women and their fetuses during the perinatal period. While numerous studies have identified various factors contributing to premature birth, precise prevention remains a significant challenge. Further validation and analysis are needed to accurately apply these findings in clinical settings. By integrating multiple methods, including risk factors and predictive models, we can better predict premature birth, thereby extending gestational duration, improving neonatal outcomes, and enhancing the quality of life for newborns.

References

[1] Dagklis T, Akolekar R, Villalain C, Dagklis T, Akolekar R, Villalain C, et al. Management of preterm labor: Clinical practice guideline and recommendation by the WAPM-World Association of Perinatal Medicine and the PMF-Perinatal Medicine Foundation[J]. European Journal of Obstetrics & Gynecology and Reproductive Biology, 2023, 291: 196-205.

[2] Tian Meiling, Ma Guojun, Du Liyan, et al. Analysis of the incidence and risk factors of premature birth in Hebei Province [J]. Progress in Modern Obstetrics and Gynecology, 2023,32(06):435-437.

[3] Sheikh J, Allotey J, Kew T, Sheikh J, Allotey J, Kew T, et al. Effects of race and ethnicity on perinatal outcomes in high-income and upper-middle-income countries: an individual participant data meta-analysis of 2 198 655 pregnancies[J]. The Lancet, 2022, 400(10368): 2049-2062.

[4] Ferrero DM, Larson J, Jacobsson B, et al. Crosscountry individual participant analysis of 4.1 million singleton births in 5 countries with very high human development index confirms known associations but provides no biologic explanation for 2/3 of all preterm births[J]. PLoS One, 2016, 11(9):e0162506. DOI: 10.1371/journal.pone.0162506.

[5] FALL C,KUMARAN K.Metabolic program ming in early life in humans[J].Philos Trans R Soc Lond B Biol Sci,2019,374(1770):2018 0123.

[6] Liu Qi, Huang Xin, Shi Zumin, et al. Research progress on dietary pattern evaluation methods [J]. Journal of Nutrition, 2021,43 (6):615-618.

[7] BLENCOWE H,COUSENS S,OESTERGA ARD M Z,BLENCOWE H,COUSENS S,OESTERGA ARD M Z, et al.National,regional,and world wide estimates of preterm birth rates in the year 2010 with time trends since 1990 for se lected countries:A systematic analysis and im plications[J].Lancet,2012,379(9832):2162 2172.

[8] CHIA A R,CHEN L W,LAI J S,CHIA A R,CHEN L W,LAI J S, et al.Mater nal dietary patterns and birth outcomes:A sys tematic review and meta-analysis[J].Adv Nu tr,2019,10(4):685-695.

[9] Sobczyk K, Holecki T, Woźniak-Holecka J, et al. Does maternal obesity affect preterm birth? documentary cohort study of preterm in firstborns—Silesia (Poland)[J]. Children, 2022, 9(7): 1007.

[10] Liu K, Chen Y, Tong J, Liu K, Chen Y, Tong J, et al. Association of maternal obesity with preterm birth phenotype and mediation effects of gestational diabetes mellitus and preeclampsia: a prospective cohort study[J]. BMC Pregnancy and Childbirth, 2022, 22(1): 459.

[11] Wu Kaijia, Zhang Yongxin, and Zhang Guohua. The effect of body mass index on the outcome of delivery in primiparous women with breech presentation at term [J]. Chinese Journal of Practical Gynecology and Obstetrics, 2023,39(1):107-110.

[12] WardK,LaufS,Kleinschmit B, et al. Heat waves and urban heat islands in Europe: A review of relevant drivers. Sci Total Environ, 2016, 569-570: 527–539

[13] Bekkar B, Pacheco S, Basu R, Bekkar B, Pacheco S, Basu R, et al. Association of air pollution and heat exposure with preterm birth, low birth weight, and stillbirth in the US. JAMA Netw Open, 2020, 3: e208243.

[14] Son J Y, Lee J T, Lane K J, et al. Impacts of high temperature on adverse birth outcomes in Seoul, Korea: Disparities by individual- and community-level characteristics. Environ Res, 2019, 168: 460–466

[15] XuW,WangH,SuH,et al. Impacts of sights and sounds on anxiety relief in the high-density city. Landscape Urban Planning, 2024, 241: 104927

[16] Creinin MD, Trussell J. Interpregnancy interval after termination of pregnancy and the risks of adverse outcomes in subsequent birth[J]. Obstet Gynecol, 2017, 129(5):943944.

[17] Liu Q, Wang J, Xu Q, Liu Q, Wang J, Xu Q, et al. A retrospective cohort study of obstetric complications and birth outcomes in women with polycystic ovarian syndrome: obstetric complications and birth outcomes in women with PCOS[J]. Journal of Obstetrics and Gynaecology, 2022, 42(4): 574-579.
[18] Breintoft K, Arendt L H, Uldbjerg N, Breintoft K, Arendt L H, Uldbjerg N, et al. Endometriosis and preterm birth: a Danish cohort study[J]. Acta obstetricia et gynecologica Scandinavica, 2022, 101(4): 417-423.
[19] Mane L,Flores-le RJ,Benaiges D,Mane L,Flores-le RJ,Benaiges D, et al. Impact of overt diabetes diagnosed in pregnancy in a multi-ethnic cohort in Spain[J]. Gynecol Endocrinol, 2019, 35(4):332-336.
[20] Ren Xiaolu. Analysis of influencing factors of patients with gestational diabetes complicated with preterm birth [J]. Journal of Henan Medical College, 2022,34(1):19-23.
[21] Liu Xiaomin, Zu Xiaoxia, and Zhang Minghua. Risk factors and preventive measures for spontaneous preterm birth in pregnant women with diabetes mellitus [J]. Chinese Journal of Maternal and Child Health Care, 2020,35(9):1622-1625.
[22] Wang Haiyan, Zhang Zhongmin, Liu Yanfang, et al. The effect of HbA1c level on the clinical outcomes and maternal and infant gut microbiota in pregnant women with GDM [J]. Chinese Journal of Hospital Infection, 2021,31(4):585-58.
[23] Guan X, Fu Y, Liu Y, Guan X, Fu Y, Liu Y, et al. The role of inflammatory biomarkers in the development and progression of pre-eclampsia: a systematic review and meta-analysis[J]. Frontiers in immunology, 2023, 14: 1156039.
[24] Lien Y C, Zhang Z, Cheng Y, Lien Y C, Zhang Z, Cheng Y, et al. Human placental transcriptome reveals critical alterations in inflammation and energy metabolism with fetal sex differences in spontaneous preterm birth[J]. International Journal of Molecular Sciences, 2021, 22(15): 7899.
[25] Ghimire RH, Ghimire S (2013) Maternal and fetal outcome following severe anaemia in pregnancy: Results from noble medical college teaching hospital, Biratnagar, Nepal. Journal of Nobel Medical College 2:22-26.
[26] CHEN C L,HUANG F W,HUANG S S,et al.IGFBP-3 and TGF-β inhibit growth in epithelial cells by stimula ting type V TGF-β receptor (TβR-V)-mediated tumor suppressor signaling[J].FASEB Bioadv,2021,3(9):709 729.
[27] Gouveia IF,Silva JR,Santos C,Gouveia IF,Silva JR,Santos C, et al. Maternal and fetal outcomes of pregnancy in chronic kidney disease:diagnostic challenges,surveil lance and treatment throughout the spectrum of kidney disease[J]. Brazilian Journal of Nephrology,2021,43(1):88-102.
[28] halaf SYA,Bodunde E,MaherSukainah G,et al. Chronic kidney dis ease and adverse pregnancy outcomes:a systematic review and Me ta-analysis [J]. American Journal of Obstetrics and Gynecology, 2021,226(5):656-670.
[29] Nevis IF,Reitsma A,Dominic A,Nevis IF,Reitsma A,Dominic A, et al. Pregnancy outcomes in women with chronic kidney disease:a systematic review[J]. Clinical Journal of the American Society of Nephrology,2011,6(11):2587-2598.
[30] Ansari A,Bose S,You Y,Ansari A,Bose S,You Y, et al.Molecular Mechanism of Microbi- ota Metabolites in Preterm Birth: Pathological and Therapeutic Insights[J].Int J Mol Sci, 2021, 22(15):8145.
[31] XuJ,Bian G,Zheng M,XuJ,Bian G,Zheng M, et al.Fertility factors affect the vaginal microbiome in women of reproductive age[J].Am J Reprod Im- munol, 2020, 83(4):e13220.
[32] Chen Huayun, Wang Yujie, Huang Zhenyu, et al. Analysis of vaginal microecological differences in early pregnancy between preterm and full-term women [J]. Chinese Journal of Microecology, 2024,36(09):1086-1091. DOI:10.13381/j.cnki.cjm.202409015.
[33] BIANCHI-JASSIR F,SEALE A C,KOHLI-LYNCH M,et al. Preterm birth associated with group B Streptococcus maternal colonization worldwide:systematic review and meta-analyses[J]. Clin Infect Dis, 2017, 65(suppl 2): S133-S142.
[34] TANO S,UENO T,MAYAMA M,et al. Relationship be- tween vaginal group B streptococcus colonization in the early stage of pregnancy and preterm birth:a retrospec- tive cohort study[J]. BMC Pregnancy Childbirth, 2021, 21(1):141
[35] Stoll BJ,Hansen NI,Sánchez PJ,et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues[J]. Pediatrics, 2011, 127(5):817-826.
[36] LIU Y H, CHEN H, JING C, LIU Y H, CHEN H, JING C, et al. The association between maternal subclinical hypothyroidism and growth, development, and childhood intelligence: a meta-analysis[J]. J Clin Res Pediatr Endocrinol, 2018, 10 (2): 153-161.
[37] Tian Lei, Wang Qilong, and Liu Yafei. Advances in the study of thyroid function abnormalities during pregnancy [J]. Chinese Journal of Primary Health Care, 2022,36(8):63-65.
[38] VAHANIAN S A, VINTZILEOS A M. Placental implantation ab- normalities: A modern approach[J]. Curr Opin Obstet Gynecol, 2016, 28 (6): 477-484.
[39] Sivieri E M, Eichenwald E C, Rub D, Sivieri E M, Eichenwald E C, Rub D, et al. Carbon dioxide clearance using bubble CPAP with superimposed high-frequency oscillations in a premature infant lung model with abnormal lung mechanics[J]. Pediatric Pulmonology, 2020, 55(11): 3189-3196.
[40] Gauda EB, Mclemore GL. Premature birth, homeostatic plasticity and respiratory consequences of inflammation[J]. Resp Physiol Neurobi, 2019, 274: 103337. DOI: 10.1016/j.resp. 2019. 103337.
[41] MEKIC N, SELIMOVIC A, COSICKIC A, MEKIC N, SELIMOVIC A, COSICKIC A, et al. Predictors of ad- verse short-term outcomes in late preterm infants[J]. BMC Pedi- atr, 2023, 23 (1): 298.