Neonatal Thrombocytopenia as a Consequence of Maternal Preeclampsia

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Abstract

Introduction  Preeclampsia (preE) is pregnancy-induced hypertension affecting a significant proportion of pregnant women worldwide and can cause detrimental effects in the mother and newborn. Some of the effects in the newborn include neonatal thrombocytopenia. Pertaining specifically to neonatal thrombocytopenia, several questions remain unanswered.

Discussion  According to the current literature, neonatal thrombocytopenia due to maternal preE is highly prevalent in the general population and the incidence is reported to be around 30% worldwide. This review gives an insight into the syndrome and summarizes the possible pathological mechanisms, the diagnostic approach, complications, and therapeutic interventions of neonatal thrombocytopenia. It also identifies the involvement of other cell lines, apart from platelets in the newborns. Furthermore, we suggest a future prospective study to investigate the pathogenesis of preE and plan a study involving animal models to come up with a possible therapeutic intervention to prevent preE and its various consequences in neonates.

Keywords  ► preeclampsia  ► neonatal thrombocytopenia  ► pregnancy-induced hypertension

Preeclampsia

Preeclampsia (preE) is a clinical disorder that affects 3 to 10% of pregnancies in the United States and is a major cause of fetal and maternal morbidity and mortality. PreE causes about 60,000 maternal deaths per year worldwide.1 It is characterized by the de novo development of hypertension and proteinuria in pregnant women and is often accompanied by edema, neurological complications, and intrauterine growth restriction (IUGR). Diagnosis of preE includes a systolic blood pressure (BP) of 140 mm Hg or higher or a diastolic BP of 90 mm Hg or higher along with proteinuria of 0.3 g or more in a 24-hour urine specimen. This typically begins after 20 weeks of gestation and can eventually lead to premature delivery and poses additional risk to the mother and baby. Attempts of early diagnosis and treatment have been unsuccessful so far. However, various risk factors have been identified that increase the mother’s chances of developing preE during pregnancy. These include, among others, nulliparity, obesity (body mass index > 35 kg/m²), a pregnancy interval of more than 10 years, history of preE or gestational diabetes, preexisting hypertension, multiple pregnancies, maternal...
Pathogenesis of Preeclampsia

Even though the exact etiology of preE is not known, de novo hypertension and proteinuria in the mother may indicate the endothelium as the target tissue of the disease. Various studies have identified several factors in pregnant mothers that eventually lead to preE and endothelial dysfunction. Some of the factors include angiogenic and antiangiogenic factors such as inhibition of vascular endothelial growth factor and placental growth factor which can lead to placental hypoxia, various immunological aspects which can lead to significant inflammation in the patient, and diabetes in the mother which can lead to incomplete placental growth.²

PreE can occur through two connected pathways: dysfunction of the placental trophoblast and endothelial dysfunction within the maternal systemic vasculature. The formation of various toxic compounds, such as agents that cause vasoconstriction and altered cytokines can cause greater oxidative stress within the cells in the placenta that can lead to endothelial dysfunction.³ This may explain why several endothelial cells do not show the proper response to specific stimuli in preE women. A study by Gant et al found that in preE patients, there was loss of vascular reactivity that is normally produced in response to an increased level of angiotensin II.⁴ Possible factors that have been identified to cause endothelial dysfunction are platelet-activating factor and P-selectin, which when unregulated, favored increased platelet activity, and endothelial retraction.⁵,⁶ However, once a preE pregnancy is terminated, it has been shown that disturbances in maternal circulation resolve rapidly due to elimination of these placental factors.⁷ Furthermore, when endothelial dysfunction is combined with preexisting conditions such as vascular, renal, and metabolic diseases and other genetic factors, there is a much greater risk of developing preE. While placental pathophysiology is not the primary pathway for developing preE, it is an important contributor in the development of the disorder during pregnancy. The schematic diagram of pathogenesis of preE is depicted in – Fig. 1.

Consequences of Preeclampsia in the Newborn

PreE changes the intrauterine environment of the fetus, and the fetus has to adapt to live in the unfavorable environment. Backes et al have demonstrated that preE affects the fetus and newborn in several ways.⁷,⁸ These effects include an increased risk of fetal demise or stillbirth; increased neonatal mortality and morbidity; IUGR; premature birth; hematological abnormalities, such as thrombocytopenia, polycythemia, and neutropenia; necrotizing enterocolitis (NEC); bronchopulmonary dysplasia; adverse neurodevelopmental outcomes and fetal origin of adult disease states.⁷,⁸ The purpose of this article is to review neonatal thrombocytopenia as a consequence of preE, its pathogenesis, and management.

Neonatal Thrombocytopenia

In a large multicenter study, Wiedmeier et al defined neonatal thrombocytopenia as a platelet count less than 150,000/μL based upon the definition used in adults, which corresponds to values at or below the 5th percentile.⁹ Neonatal thrombocytopenia has been categorized into two groups depending on the time of onset: early-onset type, which is within 72 hours of life, and late onset, after 72 hours of life.¹⁰⁻¹² The degree of severity of thrombocytopenia can be further subcategorized according to platelet count in the affected individuals: Mild thrombocytopenia—platelet count 100,000 to 150,000/μL; moderate thrombocytopenia—platelet count 50,000 to 99,000/μL; severe thrombocytopenia—platelet count < 50,000/μL.⁹

The severity of neonatal thrombocytopenia related to preE is highly variable, with a small percentage of infants developing severe or clinically significant thrombocytopenia (< 50,000/μL). Severe thrombocytopenia and/or persistent thrombocytopenia (any platelet count < 150,000/μL) can result in bleeding.¹³,¹⁴ Thrombocytopenia occurring within the first 72 hours of life (early-onset type) is largely related to neonatal alloimmune thrombocytopenia, and chronic fetal hypoxia secondary to preE, though other conditions such as placental insufficiency, perinatal asphyxia, congenital infections (cytomegalovirus, toxoplasmosis), perinatal infections (i.e., Escherichia coli, group B streptococcus, Haemophilus...
Thrombocytopenia, disseminated intravascular coagulation, autoimmune disorders (immune thrombocytopenic purpura, systemic lupus erythematosus) and genetic disorders such as trisomy 13, 18, and 21 play a role. Furthermore, neonatal thrombocytopenia that occurs after 72 hours (late-onset type) is associated with NEC, postnatal infections, such as late-onset neonatal sepsis, and inherited conditions, such as thrombocytopenia with absent radii and congenital amegakaryocytic thrombocytopenia. However, some degree of overlap has been observed between the early- and late-onset thrombocytopenia, for example, in neonates with Kasabach–Merritt Syndrome or in those with metabolic diseases such as propionic and methylmalonic acidemia.\(^7\)–\(^12\) Chakravorty and Roberts demonstrated in pregnancies complicated by preE, that thrombocytopenia is generally identified at birth or within the first 2 to 3 days following delivery, with resolution by 7 to 10 days of life in most cases.\(^15\)

**Incidence and Prevalence of Neonatal Thrombocytopenia**

The rate and severity of thrombocytopenia in neonates of pregnancy-induced hypertensive mothers vary. Pritchard et al have shown that in neonates of mothers with preE, the incidence of neonatal thrombocytopenia varies widely from 9.2 to 36%.\(^5\),\(^8\),\(^16\) In another study, the incidence of thrombocytopenia associated with this disorder has been estimated at 1 per 100 live births, and it is more likely to occur in preterm and low-birth-weight infants.\(^13\) Furthermore, several studies have shown a prevalence of thrombocytopenia in 1 to 5% of all newborns born to mothers with preE; however, the prevalence varies depending upon the population studied.\(^16\) In neonates admitted to intensive care units, it has been shown that thrombocytopenia develops in 18 to 35% of all admissions. In addition, Sola et al have shown that the more premature an infant is, the more likely they are to develop thrombocytopenia.\(^13\) Roberts and Murray\(^12\) have proven that low-birth-weight infants are at 2.52 times increased risk for thrombocytopenia and Tsao et al\(^17\) concluded birth weight is negatively associated with thrombocytopenia.

**Pathogenesis of Neonatal Thrombocytopenia**

Platelets are tiny cellular fragments produced by megakaryocytes in the bone marrow. Platelet production, or thrombopoiesis, is a complex process that results in the production of thrombopoietin as the thrombopoietic stimulus leading to the generation and proliferation of megakaryocyte progenitors.\(^17\) The pathogenesis of thrombocytopenia among infants born to mothers with preE is presently unknown and a topic of current research.\(^7\),\(^16\),\(^19\) The principal mechanism postulated by Roberts and Murray is that preE and the resultant fetal hypoxia have a direct depressant effect on fetal megakaryocytepoiesis and platelet production.\(^7\),\(^12\) Castle et al have proven that the combined effect of impaired megakaryocyte formation and increased platelet activation mediated through cytokines, thrombopoietin, and interleukin-6, are said to be the most likely causative mechanisms.\(^20\),\(^21\) This is supported by studies showing that growth-restricted neonates have significant megakaryocytopenic defects without evidence of increased platelet destruction.\(^7\),\(^22\),\(^23\) Decreased production of platelets mediated by an inhibitor of platelet production is also considered as one of the mechanisms of neonatal thrombocytopenia.\(^13\) According to in vitro studies by McDonald et al regarding the stem cell competition hypothesis, there is a common precursor cell for erythroid and megakaryocytic cell lines.\(^24\) So, chronic exposure to increased levels of erythropoietin in the fetus due to fetal hypoxia may also lead to thrombocytopenia by suppressing the megakaryocytic cell line which may lead to decreased platelet production.\(^24\) Others have looked directly at the placenta as a potential cause of neonatal thrombocytopenia in infants born to mothers with preE. In a retrospective cohort study by Zook et al,\(^18\) though placental pathology was very common in infants born to mothers with preE, there was no association of placental infarction or vasculopathy with neonatal neutropenia and thrombocytopenia, suggesting that neonatal hematologic effects of maternal preE, if related to the placenta, are associated with factors other than placental histology. In a case-control study by Litt and Hecht,\(^19\) they looked to find a link between histopathological placental lesions and neonatal thrombocytopenia and whether placental lesions affecting the fetal circulation, such as fetal vascular thrombosis were associated with neonatal thrombocytopenia. They found a possible link between placental lesions and thrombocytopenia and an independent association of fetal vascular lesions such as thrombosis with thrombocytopenia.

**Diagnostic Approach to Neonatal Thrombocytopenia**

Neonates presenting with thrombocytopenia may or may not be symptomatic. In symptomatic neonates, it is important to differentiate if the symptoms are due to preE-related thrombocytopenia or secondary to other causes.\(^12\),\(^15\) Thus, the newborn should be worked up to find out the underlying cause of thrombocytopenia. In addition, in asymptomatic infants the severity of thrombocytopenia depends on the platelet count. With a platelet count less than 50,000/μL, it is important to rule out other causes of the condition.\(^12\),\(^15\) Furthermore, infants with a platelet count of more than 50,000/μL should be carefully observed and their platelet count should be monitored for a period of 7 to 10 days to note an increasing trend in the platelet count.\(^12\),\(^15\) The suggested clinical approach to diagnose neonatal thrombocytopenia in the presence or absence of preE has been schematically depicted in Fig. 2.

**Complications and Management of Neonatal Thrombocytopenia**

There are various complications that have been associated in newborns with thrombocytopenia. Risk of bleeding has been observed in approximately 5 to 15% of severely thrombocytopenic neonates in neonatal intensive care units.\(^14\) The management of neonatal thrombocytopenia is based on the level of platelet count, as well as the clinical presentation of the infants. In asymptomatic neonates with platelet counts greater than 50,000/μL, observation alone is sufficient. In symptomatic neonates, platelet transfusions may be necessary to prevent life-threatening bleeding. However, platelet transfusions may have a detrimental effect on the immune system of the newborn and should be used cautiously. In neonates with platelet counts less than 50,000/μL, platelet transfusions are indicated to prevent severe bleeding. In addition, the use of intravenous immunoglobulin (IVIG) has been shown to be effective in treating thrombocytopenia in neonates with immune thrombocytopenia. IVIG works by coating platelets, preventing their destruction by the immune system. Furthermore, steroids have also been used in the management of neonatal thrombocytopenia, particularly in cases of immune thrombocytopenia. Steroids work by inhibiting the production of antibodies that target platelets. Overall, the management of neonatal thrombocytopenia requires a multidisciplinary approach, involving pediatricians, hematologists, neonatologists, and pediatric intensivists.
important and devastating bleeding event is intraventricular hemorrhage (IVH). In addition, other less frequent bleeding events include pulmonary and gastrointestinal hemorrhage and some minor events such as petechiae, oozing at the puncture site, and bloodstained endotracheal secretions.

Apart from general measures, the only specific therapy recommended for neonatal thrombocytopenia is platelet transfusion. A recent prospective study of neonates with severe thrombocytopenia found that 91% of neonates whose platelet counts fell below $20 \times 10^9/L$ did not develop major hemorrhage, suggesting that this is a reasonably safe threshold for platelet transfusion for most neonates. However, it is recommended that prophylactic transfusion be given to (1) all neonates, term or preterm, with a confirmed count less than $20,000/\mu L$, (2) to stable preterm infants if the counts fall below $30,000/\mu L$, and (3) to all with a birth weight less than 1,000 g if the platelet counts less than $50,000/\mu L$ during the first postnatal week. A threshold of $50,000/\mu L$ is used for unstable infants, for example, in those with fluctuating blood pressure, those with a previous major bleed IVH, pulmonary hemorrhage, or other recognized risk factors (i.e., NEC). Platelet transfusion should also be considered in infants with evidence of minor bleeding such as oozing from the umbilical cord, puncture sites, or the presence of petechiae, ecchymosis, or cephalohematoma with platelet counts of less than $50,000/\mu L$. Platelet transfusion is also given before major surgery and exchange transfusion if the platelet count is less than $100,000/\mu L$. In the majority of
cases, thrombocytopenia resolves within a week with no intervention without any subsequent major sequelae. Roberts and Murray have concluded in their independent studies that the platelet count reaches a nadir around 4 days of age and resolves by 7 to 10 days. The summary of possible complications and management of neonatal thrombocytopenia, in the consequence of maternal preE, have been schematically depicted in Fig. 3.

**Other Cell Line Involvement**

In addition to the effects of preE on platelets that have been mentioned earlier, neonates delivered to women with preE have an approximately 50% incidence of neutropenia. Neutropenia is defined as an absolute neutrophil count less than 500/μL. The biological mechanism for preE resulting in neonatal neutropenia has not been fully elucidated. One potential mechanism that has been suggested by Mouzinho et al is that preE and the resultant uteroplacental insufficiency can inhibit fetal bone marrow production of the myeloid lineage manifested by a decrease in neutrophil production. Neutropenia associated with maternal preE is also associated with reduced numbers of circulating colony forming unit-granulocyte macrophage and decreased neutrophil storage pools. Neutropenia is generally self-limited although in some cases it may be severe enough to warrant therapy with granulocyte-colony stimulating factor. It has also been shown that these newborns may have polycythemia. Increased red blood cell mass results from increased erythropoietin production stimulated by chronic fetal hypoxia that is secondary to preE.

**Perspective and Conclusions**

This review article gives us an insight into preE as one of the etiologies of neonatal thrombocytopenia. With this in mind, we have initiated a retrospective study that aims to identify the prevalence of neonatal thrombocytopenia in preE mothers. Furthermore, we plan to design a prospective study that will involve monitoring patients with preE to understand the pathogenesis of neonatal thrombocytopenia as a consequence of maternal preE. Subsequently, we plan to design an interventional study in an animal model to further investigate the pathogenesis of preE and its consequences on neonates and aim to identify the possible outcomes of preE in newborns that can be used as therapeutic targets.

Conflict of Interest

The authors report no conflict of interest.
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