Neonatal Thrombocytopenia as a Consequence of Maternal Preeclampsia

Ram R. Kalagiri, MD1,2  Saiara Choudhury, BS2  Timothy Carder, MD, MS2  Vinayak Govande, MD3  Madhava R. Beeram, MD1,2,3  M Nasir Uddin, PhD, FAHA2,3,4,5

1 Department of Neonatology, Baylor Scott & White Healthcare, Temple, Texas
2 Baylor Scott & White Healthcare and Texas A&M Health Science Center College of Medicine, Temple, Texas
3 Department of Pediatrics, Baylor Scott & White Healthcare, Temple, Texas
4 Departments of Obstetrics & Gynecology, Baylor Scott & White Healthcare, Temple, Texas
5 Department of Internal Medicine, Baylor Scott & White Healthcare, Temple, Texas

Address for correspondence M. Nasir Uddin, PhD, FAHA, Scott & White Memorial Hospital (Building 1) Room 352, 2401 South 31st Street, Temple, TX 76508 (e-mail: MNUDDIN@sw.org).

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...
age of 40 or older, preexisting renal disease, and possible genetic factors.\(^1\) With the increasing incidence of preE, it is important to make pregnant mothers aware of the possible risk factors and advise them to be monitored for possible signs of preE.

**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.\(^1\) 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 vasconstriction 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 stimuli in preE women. A study by Gant et al found that in preE patients, there was loss of vascular refractoriness 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, 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

Influences

and Roberts demonstrated in pregnancies complicated by 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, 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. 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. 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. 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. The most
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/μL, (2) to stable preterm infants if the counts fall below 30,000/μL, and (3) to all with a birth weight less than 1,000 g if the platelet counts less than 50,000/μL during the first postnatal week. A threshold of 50,000/μL 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/μL. Platelet transfusion is also given before major surgery and exchange transfusion if the platelet count is less than 100,000/μL.

Fig. 2 Diagnostic approach of neonatal thrombocytopenia secondary to preeclampsia (preE) and other causes. There can be four groups of infants based on whether the infant is symptomatic or not and platelet count is above or below 50,000/μL. It can also be early- or late-onset type of thrombocytopenia depending on the time of onset before or after 72 hours of life. No further intervention if platelets are > 50,000/μL and the infant is asymptomatic. Further evaluation is needed to find out other causes in case if it is not due to preE. (Adapted from Chakravorty and Roberts.)
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.
References

1. Lin S, Leonard D, Co MA, et al. Pre-eclampsia has an adverse impact on maternal and fetal health. Transl Res 2015;165(4):449–463
2. Uddin MN, Allen SR, Jones RO, Zawieja DC, Kuehl TJ. Pathogenesis of pre-eclampsia: marionobufagenin and angiogenic imbalance as biomarkers of the syndrome. Transl Res 2012;160(2):99–113
3. Wang Y, Adair CK, Weeks JW, Lewis DF, Alexander JS. Increased neutrophil-endothelial adhesion induced by placental factors is mediated by platelet-activating factor in preeclampsia. J Soc Gynecol Investig 1999;6(34):136–141
4. Gant NF, Chand S, Worley RJ, Whalley PJ, Crosby UD, MacDonald PC. A clinical test useful for predicting the development of acute hypertension in pregnancy. Am J Obstet Gynecol 1974;120(1):1–7
5. Laskowska M, Laskowska K, Oleszczuk J. Elevated maternal serum sP-selectin levels in preeclamptic pregnancies with and without intrauterine fetal growth restriction, but not in normotensive pregnancies complicated by isolated IUGR. Med Sci Monit 2013;19(118):124
6. Bevilacqua MP. Endothelial-leukocyte adhesion molecules. Annu Rev Immunol 1993;11:767–804
7. Backes CH, Markham K, Moorehead P, Cordero L, Nankervis CA, Giannone PJ. Maternal preeclampsia and neonatal outcomes. J Pregnancy 2011;2011:214365
8. Bhat YR, Cherian CS. Neonatal thrombocytopenia associated with maternal pregnancy induced hypertension. Indian J Pediatr 2008;75(6):571–573
9. Wiedmeier SE, Henry E, Sola-Visner MC, Christensen RD. Platelet reference ranges for neonates, defined using data from over 47,000 patients in a multihospital healthcare system. J Perinatol 2009;29(2):130–136
10. Ulusoy E, Tüfekçi O, Duman N, Kumral A, Irken G, Oren H. Thrombocytopenia in neonates: causes and outcomes. Ann Hematol 2013;92(7):961–967
11. Gunnink SF, Vlug R, Fijnvandraat K, van der Bom JG, Stanworth SJ, Lopriore E. Neonatal thrombocytopenia: etiology, management and outcome. Expert Rev Hematol 2014;7(3):387–395
12. Roberts I, Murray NA. Neonatal thrombocytopenia: causes and management. Arch Dis Child Fetal Neonatal Ed 2003;88(5):F359–F364
13. Sola MC, Del Vecchio A, Rimsza LM. Evaluation and treatment of thrombocytopenia in the neonatal intensive care unit. Clin Perinatol 2000;27(3):655–679
14. Burrows RF, Andrew M. Neonatal thrombocytopenia in the hypertensive disorders of pregnancy. Obstet Gynecol 1990;76(2):234–238
15. Chakravorty S, Roberts I. How I manage neonatal thrombocytopenia. Br J Haematol 2012;156(2):155–162
16. Pritchard JA, Cunningham FG, Pritchard SA, Mason RA. How often does maternal preeclampsia-eclampsia incite thrombocytopenia in the fetus? Obstet Gynecol 1987;69(3 Pt 1):292–295
17. Tsao PN, Teng RJ, Chou HC, Tsou KI. The thrombopoietin level in the cord blood in premature infants born to mothers with pregnancy-induced hypertension. Biol Neonate 2002;82(4):217–221
18. Zook KJ, Mackley AB, Kern J, Paul DA. Hematologic effects of placental pathology on very low birthweight infants born to mothers with preeclampsia. J Perinatol 2009;29(1):8–12
19. Litt JS, Hecht JL. Placental pathology and neonatal thrombocytopenia: lesion type is associated with increased risk. J Perinatol 2014;34(12):914–916
20. Brazy JE, Grimm JK, Little VA. Neonatal manifestations of severe maternal hypertension occurring before the thirty-sixth week of pregnancy. J Pediatr 1982;100(2):265–271
21. Castle V, Andrew M, Kelton J, Giron D, Johnston M, Carter C. Frequency and mechanism of neonatal thrombocytopenia. J Pediatr 1986;108(5 Pt 1):749–755
22. Weiner CP, Williamson RA. Evaluation of severe growth retardation using cordocentesis—hematologic and metabolic alterations by etiology. Obstet Gynecol 1989;73(2):225–229
23. Baschat AA, Gembruch U, Reiss I, Gortner L, Weiner CP, Harman CR. Absent umbilical artery end-diastolic velocity in growth-restricted fetuses: a risk factor for neonatal thrombocytopenia. Obstet Gynecol 2000;96(2):162–166
24. McDonald TP, Cottrell MB, Clift RE, Jackson CW. Effects of hypoxia on megakaryocyte size and number of CSH and BALB/c mice. Proc Soc Exp Biol Med 1992;198(3):287–290
25. Sola-Visner M, Saxophone MA, Brown RE. Neonatal thrombocytopenia: what we do and don’t know. Early Hum Dev 2008;84(8):499–506
26. Carr R, Kelly AM, Williamson LM. Neonatal thrombocytopenia and platelet transfusion - a UK perspective. Neonatology 2015;107(1):1–7
27. Gibson BE, Todd A, Roberts I, et al; British Committee for Standards in Haemotherapy Transfusion Task Force: Writing group. Transfusion guidelines for neonates and older children. Br J Haematol 2004;124(4):433–453
28. Christensen RD, Carroll PD, Josephson CD. Evidence-based advances in transfusion practice in neonatal intensive care units. Neonatology 2014;106(3):245–253
29. Mouzinho A, Rosenfeld CR, Sanchez PJ, Risser R. Effect of maternal hypertension on neonatal neutropenia and risk of nosocomial infection. Pediatrics 1992;90(3):430–435
30. Koenig JM, Christensen RD. Incidence, neutrophil kinetics, and natural history of neonatal neutropenia associated with maternal hypertension. N Engl J Med 1989;321(9):557–562