Scientific Review

http://wjpn.ssu.ac.ir

Immune and Non-Immune Etiology of Thrombocytopenia: Neonatal and Maternal Causes

Mohamad Hosein Lookzadeh[1], Seyed Reza Mirjalili[1], Sedigheh Ekraminasab[1,2*]

[1] Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2] Laboratory Hematology and Blood Banking Department, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Received: 27 September 2020 **Revised:** 18 October 2020 **Accepted:** 14 November 2020

ARTICLE INFO

Corresponding author:
Sedigheh Ekraminasab

Email:
s.ekraminasab@gmail.com

Keywords:
Neonatal;
Immune Thrombocytopenia;
Gestational Thrombocytopenia;
Immune;
Non-Immune;
Etiology

ABSTRACT

Neonatal thrombocytopenia (NT) is a common hemostatic abnormalitiy among newborn in the NICU, which increases with the degree of prematurity. It is well documented that this disease has a large range of feasible etiologies. Prematurity, early and late-onset sepsis and asphyxia are the most usual causes of NT. Moreover, FNAIT is the major risk for intracranial hemorrhage in the fetus or newborn. Here, we reviewed the causes for NT, in both newborns and mothers. We demonstrated the factors associated with NT in the newborn including placental insufficiency, fetal and neonatal alloimmune thrombocytopenia (FNAIT), prematurity, sepsis, and asphyxia. The causes of thrombocytopenia in pregnant women and its impact on newborns were also described. This review showed that gestational thrombocytopenia was the most common cause of thrombocytopenia with an incidence of 70-80%, followed by preeclampsia, HELLP and ITP. But neonates born to mothers with immune thrombocytopenia (ITP) had a higher risk for NT and hemorrhagic problems. In ITP, neonatal platelets are destroyed by maternal autoantibodies. We reviewed the causes of thrombocytopenia in neonates and mothers in two groups of immune and nonimmune factors. However, it seems that immunological factors are the most severe form of NT. However, it is necessary to separate NT etiology for differential diagnosis.

Introduction

Thrombocytopenia is a condition that platelet count less than 150×10^3/L. it is one of the most common hemostatic abnormalities among newborns, particularly premature infants.[1,2] It affects 18-35% of neonates referred into neonatal intensive care units (NICU) and may lead to a high risk of hemorrhage and fatality.[2,3] Many studies demonstrated that the possibility of enhancing thrombocytopenia increases with the level of prematurity, that immature neonates were at a 2.52-fold increased risk for thrombocytopenia.[4] The etiology of thrombocytopenia is complex and both maternal and newborn factors may be implied in the development of it. Generally, Thrombocytopenia may be the only clinical apparition of alloimmune condition or an expression of other diseases, such as intrauterine growth restriction (IUGR), sepsis, or necrotizing enterocolitis (NEC). NEC is inflammatory bowel necrosis of premature infants.[5,6]

Neonatal thrombocytopenia (NT) is a common clinical issue, which enhances with the degree of prematurity. The basic causes of NT are now becoming distinct and many opinions have newly been shown to have small or no evidence to support them. We described thrombocytopenia in neonate and its etiology. Previous studies demonstrated that prematurity, placental insufficiency, sepsis, abnormal immunity, and asphyxia were the most common neonatal conditions related with NT.[7] In an otherwise healthy-appearing infant, thrombocytopenia is most probably secondary to placental inadequacy or an immune process, either autoimmune or alloimmune, in which maternal antibodies transmitted to the newborn in-utero cause the destruction of the infant's platelets.[8]

Several studies have evaluated the prevalence of thrombocytopenia during pregnancy, its etiology, and maternal and perinatal outcome. Pregnancy thrombocytopenia is a usual finding and occurs approximately in 7-10% of pregnancies. Gestational thrombocytopenia (GT), hypertensive disorders (preeclampsia; eclampsia; HELLP syndrome; and acute fatty liver of pregnancy), disseminated intravascular coagulation (DIC), consumption of drugs and vitamin B12 or folate deficiency, are the nonimmune reasons.[9,10] Overall, about 3-4% of pregnancy thrombocytopenia is related to an immune process include TTP and ITP. Immune thrombocytopenia (ITP) is an autoimmune disorder described by low platelet counts that occurs as a result of maternal autoantibodies transportation through the placenta and target platelet membrane so neonatal platelets are destroyed.[11]

Determining the causes and mechanisms of NT is the best way to develop the more appropriate treatment, including modern approaches. For example detection of NT's main causes is important to identify neonates at risk of hemorrhage and select who would benefit from platelet transfusion (PT) and to determine whether PT either abolish or intensify common neonatal problems such as sepsis, chronic lung disease, NEC, and retinopathy of prematurity.[12] In This paper we explain prevalent opinion about the reasons of NT considering fetomaternal and neonatal conditions and causes of thrombocytopenia in immune and nonimmune factors.

Causes and Mechanisms

Neonatal diseases: Almost 9.4-35% of neonates admitted to NICUs develop thrombocytopenia. Multiple disease processes can result in thrombocytopenia in neonates and these can be arranged as early-onset (< 72 hours) and late-onset (> 72 hours) NT. The significant causes of thrombocytopenia in neonates are low birth weight, sepsis, prematurity, birth asphyxia, intrauterine growth retardation, hyperbilirubinemia, and meconium aspiration syndrome. Apart from platelet counts, bleeding disorders depend on underlying diseases.[13]

Table 1. Causes of neonatal thrombocytopenias: Neonatal and maternal diseases

			Prevalence
Neonatal	Nonimmune	Placental insufficiency	-
		Perinatal asphyxia	-
		Perinatal infection	-
		DIC	-
	Immune	FNAIT	-
Maternal (pregnancy-associated causes)	Nonimmune	Gestational thrombocytopenia	70-80%
		Preeclampsia	15–22%
		HELLP	1-4 %
		Acute fatty liver of pregnancy	< 1%
		Dengue	1-2%
	Immune	ITP	2%

Apparently neonates with thrombocytopenia may develop a high risk of hemorrhage and fatality. This increased risk is associated with the important role of platelets in the whole process of hemostasis, and thrombocytopenia may lead to dysfunctional hemostasis. The differential diagnosis for thrombocytopenia is traditionally divided into disorders of decreased platelet production against those of increased platelet consumption or destruction. We arranged causes of thrombocytopenia in immune and nonimmune reasons. Decreased platelet production and increased platelet consumption (sepsis, placental insufficiency, and birth asphyxia) are the nonimmune reason, and destruction with antibodies is classified as the immune reason of thrombocytopenia (Table 1, 2).

Table 2. Comparison of early and late onset of thrombocytopenia in premature neonates

Early onset	Sepsis
< 24 hours	TORCH infection
	Birth asphyxia
	DIC
	NEC
Late onset	Sepsis
> 72 hours	Thrombosis
	DIC
	NEC
	Drug-induced

Nonimmune

Decreased platelet production: Hematopoietic stem cells (HSCs) are pluripotent cells that inhabit in the bone marrow (BM) and can differentiate into all blood cell lineages.[14] Platelet production defined as thrombopoiesis, is a convened process that results in the manufacture of thrombopoietin (TPO) as the thrombopoietic stimulus leading to the proliferation of megakaryocyte progenitors.[12,15] Megakaryocytes (MKs) in the BM generate blood platelets, necessary for thrombosis and hemostasis. MKs derive from HSCs and migrate from an endosteal niche towards the vascular sinusoids during their maturation.[16] TPO is the hematopoietic growth factor and is the major cytokine triggering platelet production. TPO contributes to the self-renewal of HSCs and also persuades transcription factors causing to the expression of proteins like CD42 or CD41 that commit HSCs to the platelet lineage.[17]

Situations increased platelet consumption

Sepsis: Sepsis is one of the major reasons of thrombocytopenia in neonates. Thrombocytopenia is presented in neonates with bacterial, fungal, viral, rickettsial and, protozoal infections. Thrombocytopenia in the very premature infant is most often secondary to sepsis, come after NEC, birth asphyxia, chronic intrauterine hypoxia, DIC and TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex) infections.[18,19] Bacterial infections can be related to thrombocytopenia or reactive thrombocytosis. The pathogenic actions complicated in thrombocytopenia are numerous and include the incidence of DIC

during sepsis, the adhesion of platelets to the activated vascular endothelium, or an increased consumption related with the formation of neutrophil extracellular catchs.[19,20] Several patients with bacterial septicemia may extend coagulopathy related to DIC. The presence of thrombocytopenia is seen mostly in early sepsis with or without laboratory evidence of obvious DIC.[21] Thrombocytopenia may quickly become very serious with the lowest platelet count extended within 24-48 hours after beginning of contamination. The significance of the relation between thrombocytopenia and sepsis was confirmed by recognizing thrombocytopenia as one of the most prognosticate and autonomous risk factors for sepsis-associated fatality in very low birth weight neonates.[7]

Placental abruption: Placental abruption, defined as the premature separation of the normally implanted placenta from the uterus, before birth and after 20 weeks of pregnancy. Placental abruption is one of the most considerable determinants of maternal morbidity as well as perinatal morbidity and fatality and complicates approximately 1% of births.[22] The incidence of concomitant DIC can cause a range of problems to both mother and neonate like as emergency cesarean transfer due to unreliable fetal condition, cerebral palsy, acute hemorrhage, uncontrollable hemorrhage requiring hysterectomy, multi-organ defeat, and maternal and fetal death.[23] Thus, placental abruption is a situation needing proper perinatal management. While primary recognition and quick cure are both necessary for making the outcomes better for mother and neonate, high-level medical facilities and improvement of the emergency patient transport system are also important.[24]

Immune

Fetal and neonatal alloimmune thrombocytopenia: Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a disorder in pregnant women. The incidence of FNAIT is approximately 1 in 1000 pregnancies.[25,26] Differences in platelet type between the fetus and the mother can result in maternal immunization and destruction of the fetal platelets, specified by maternal alloantibodies directed against the human platelet antigen (HPA). When these HPA-alloantibodies get into the fetal circulation after entering the placenta via FcRn transport, they can destruct fetal platelets as well as damage endothelial cells, which may cause haemorrhagic problems. These antibodies can lead to intracranial hemorrhage (ICH) or other great bleeding resulting in long-lasting defects or death.[27] Optimal fetal care can be provided by at the right time identification of pregnancies at risk.[28] These bleedings can alter from small skin appearances to severe ICHs or even perinatal death. In lack of population-based screening for FNAIT, cases are mostly diagnosed in case of manifestation. Consequently, FNAIT requires fast identification and therapy; following pregnancies need close monitoring and management.[29,30]

Causes of Neonatal Thrombocytopenia: maternal diseases

Thrombocytopenia during Pregnancy: Thrombocytopenia is second commonest hematological disorder in pregnancy after anemia,[9] that affects approximately 7-10% of pregnancy.[31] Most studies report a reduction in platelet count about 10% lower than the pre-pregnant values. During normal pregnancy, there is a physiological reduction in platelet count due to hemodilution, increased consumption in peripheral tissue and increased aggregation. The causes include gestational thrombocytopenia (GT) and hypertensive disorders (preeclampsia; eclampsia; HELLP syndrome; and acute fatty liver of pregnancy (AFLP)) are nonimmune. Other nonimmune causes are DIC, hemolytic uremic syndrome, consumption of drugs, vitamin B12 or folate deficiency, aplastic anemia, myelophthisis and viral infections. The most common immune diseases include

immune thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune disorders, and pseudothrombocytopenia can result from ethylenediaminetetraacetic acid (EDTA)-induced clumping of platelets, in which case, a new sample should be analyzed using citrate as an anticoagulant.[32] Thrombocytopenia during pregnancy might also give a biomarker of a coexisting systemic or gestational problems and a potential cause for a maternal intervention or treatment that possible induce hurt to the fetus.[33] It can be a diagnostic and management problem, and has numerous causes, some of this are specific to pregnancy.

Non-immune

Gestational thrombocytopenia: Gestational thrombocytopenia (GT) is the most common reason of thrombocytopenia during pregnancy and associated with moderate thrombocytopenia. GT take place in 4.4% to 11.6% of pregnancies, reporting for about 75% of all cases of thrombocytopenia in pregnancy. Platelet count < 70,000/μL excludes the diagnosis of GT. GT happens in 3rd trimester of pregnancy that is most possible from hemodilution related to an increase in plasma volume during pregnancy and possibly increased platelet clearance as mean platelet volumes, and platelet-derived cyclooxygenase products rise. Thrombocytopenia is more frequent in twin and triplet gestations. The pathophysiology entails that the fetus waste products into mothers blood increases the activity of spleen of mother which removes blood cells rapidly causing destruction of platelets. Patients generally show no alarming symptom due to GT. A subset of women with GT develop a more significant decrease in platelet count and a reduction in antithrombin III, recommending a distinct pathogenesis that depends on a sequence with the HELLP syndrome and AFLP and that may be correlated with a higher risk of relapse in subsequent pregnancies. GT needs no treatment but resolves spontaneously. The diagnosis of GT is challenging and is difficult to differentiate between ITP and GT.[34]

Hypertensive disorders: Hypertensive disorders were the 2nd most common cause of thrombocytopenia during pregnancy (15- 20%). hypertensive disorders include preeclampsia, eclampsia, HELLP syndrome, acute fatty liver of pregnancy.[35] The pathophysiologic mechanism of thrombocytopenia in hypertensive disorders is the thrombotic microangiopathy distinguish by endothelial hurt, after platelet aggregation and then formation of thrombus in small vessels. The indications of thrombotic microangiopathy are the existence of schistocytes on peripheral blood smear and increased bilirubin > 1.2 mg/ dL, reduced haptoglobin < 25 mg/dl and increased LDH.

Immune thrombocytopenia

ITP: Immune thrombocytopenic purpura (ITP), an autoimmune disease determined by the anti-platelet glycoprotein (GP) antibodies that induce the platelet destruction in the spleen, is a uncommon cause of thrombocytopenia in pregnancy. However ITP takes place only in 3- 4% of all patients of thrombocytopenia during pregnancy, it is the most current reason of a platelet count below 50×10^3 per μL indicate in the first and second trimesters. Platelet counts may reduce during pregnancy, and at least 15% to 35% of mothers need treatment even prior to management of labor and delivery. This form relies on operation patterns, so that require for treatment is probably to be more current in tertiary-care referral centers. Maternal and neonatal outcomes are commonly good.[33] differently from GT, ITP can happen anytime during gestation and almost all gravid women with ITP may have a history of thrombocytopenia previous to pregnancy. The platelet count does not automatically cure postpartum and the therapeutic reply to steroids or intravenous immunoglobulin (IVIg) contributes to the treatment of ITP. In

conclusion, a neonatal outcome with maternal ITP is generally good.

Discussion

Neonatal thrombocytopenia (NT) is one of the most common hemostatic abnormalities among newborns in the NICU and overrepresented among extremely low birth weight neonates.[36] NT has many potential etiologies and a wide range of diseases have a role in its occurrence.[6] So many studies have described different aspects of NT include causes, prevalence, clinical lab diagnostics, risk factors, risk category, time of onset, bleeding manifestation, treatment, and platelet transfusion.[37,38] There is a need to arrange and separate the etiology of it, so we evaluated neonatal and maternal causes together and described several etiologies.

The most common factors associated with NT in the newborn include placental abruption, placental insufficiency (intrauterine growth restriction (IUGR)), fetal and neonatal alloimmune thrombocytopenia (FNAIT), prematurity, sepsis (bacterial, fungal, and viral), NEC, asphyxia, meconium aspiration syndrome, DIC, hyperbilirubinemia, and anemia. The previous studies showed prematurity and sepsis and asphyxia were the most usual causes of NT.[2,12,13,37]

But, FNAIT is the serious risk for intracranial hemorrhage in the infant. Thrombocytopenia in a very immature newborn is most recurrently secondary to sepsis, subsequent by necrotizing enterocolitis (NEC), birth asphyxia, chronic intrauterine hypoxia, TORCH infections, or DIC.[39]

In this topic, we also characterized determining reasons of thrombocytopenia in pregnant women and its impact on newborns. The most current factors associated with NT in pregnancy include gestational thrombocytopenia (GT) and hypertensive disorders (preeclampsia; eclampsia; HELLP syndrome; and acute fatty liver of pregnancy (AFLP)) are nonimmune.[40] Other nonimmune causes are thrombotic thrombocytopenic purpura (TTP), DIC, hemolytic uremic syndrome, consumption of drugs, vitamin B12 or folate deficiency, aplastic anemia, leukemia, systemic lupus erythematosus (SLE) myelophthisis, and viral infections.[32] Gestational thrombocytopenia was the commonest cause of thrombocytopenia with an incidence of 70-80%, followed by preeclampsia, HELLP, and ITP.[41] GT is associated with better fetomaternal outcomes compared with other etiologies.[32] ITP diagnosed before or during pregnancy is important for both the mother and the newborn.[42] The risk of intense thrombocytopenia at delivery is more in ITP contrast with chronic ITP. Patients with GT and ITP have better maternal and perinatal outcomes as compared to hypertensive disorders include preeclampsia and HELLP syndrome.[43]

We also separated etiology in immune and nonimmune reasons. Decreased platelet production and increased platelet consumption (sepsis, placental insufficiency, and birth asphyxia) are the nonimmune reason, and destruction with antibodies is classified as the immune reason of thrombocytopenia. The most common immune diseases that have a role in NT are FNAIT and ITP. In FNAIT maternal antibodies destroyed fetal platelets that lead to hemorrhagic problems intracranial hemorrhage (ICH) or other great bleeding resulting in long-lasting defects or death.[25] Optimal fetal care can be provided by at the right time identification of pregnancies at risk. These bleedings can alter from small skin appearances to severe ICHs or even perinatal death.[38] Consequently, FNAIT requires fast identification and therapy. In ITP neonatal platelets are destructed by maternal autoantibodies. Also, in ITP is widely accepted that the frequency of intracranial hemorrhage is very rare.[44] Generally in ITP maternal and neonatal outcomes are acceptable. But in ITP The platelet count does not automatically cure postpartum and the therapeutic reply to steroids or Intravenous Immunoglobulin (IVIg) is needed.[45]

Best choice for treatment of NT according to the exact cause may be useful for clinicians. Detection of neonatal thrombocytopenia's main causes is important to identify neonates at risk of bleeding and select who would benefit from PT and to determine whether PT either abrogates or exacerbate common neonatal complications such as sepsis, chronic lung disease, necrotizing enterocolitis (NEC), and retinopathy of prematurity.[12,46] Identification is largely based on the timing of its beginning, intensity of the thrombocytopenia, and the dependent with other disorders.[34,47] There is a need for another study to compare risk factors between the neonatal and maternal group and differential diagnosis, and evaluated some other possible etiology.

Conclusion

In our study, we described different immunologic and nonimmunologic causes of neonatal thrombocytopenia. We also explained the most neonatal and maternal diseases that have roles in NT. However nonimmunologic causes are most prevalent but it seems immunological disorder is more severe than other causes. For example, several studies displayed that prematurity, sepsis, and asphyxia were the most usual factors related with NT. But in neonatal causes, FNAIT leads to hemorrhagic problems, intracranial hemorrhage (ICH), or other great bleeding resulting in long-lasting defects or death. In maternal reasons GT was the most current reason of thrombocytopenia with an incidence of 70-80%, but, it is associated with better fetomaternal outcomes compared with other etiologies. Also, thrombocytopenia is solitarily related to maternal hypertension, sepsis, and intravascular thrombosis. Optimal care of thrombocytopenia depends on the right time identification of pregnancies at risk and management etiology of it. Therefore monitoring of platelet count in pregnant women should be a routine preventive exam. The clinician should be aware of differential diagnosis findings and associated with unusual causes of thrombocytopenia that should prompt additional evaluation in the NICU.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

Not applicable.

How to Cite: Lookzadeh MH, Mirjalili SR, Ekraminasab S. Immune and Non-Immune Etiology of Thrombocytopenia: Neonatal and Maternal Causes. World J Peri & Neonatol 2020; 3(2): 78-86.
DOI: 10.18502/wjpn.v3i2.6158

References

1. Rottenstreich A, Israeli N, Levin G, Rottenstreich M, Elchalal U, Kalish Y. Clinical characteristics, neonatal risk and recurrence rate of gestational thrombocytopenia with platelet count< 100× 109/L. Eur J Obstet Gynecol Reprod Biol 2018; 231: 75-9.
2. Liu D, Wu J, Xiong T, Yue Y, Tang J. Platelet transfusion for neonates with thrombocytopaenia: protocol for a systematic review. BMJ Open 2020; 10(10): e039132.
3. Ayadi ID, Hamida EB, Youssef A, Sdiri Y, Marrakchi Z. Prevalence and outcomes of thrombocytopenia in a neonatal intensive care unit. Tunis Med 2016; 94(4): 305-8.
4. Arif H, Ikram N, Riaz S, Nafisa A. Risk factors and outcome of neonatal thrombocytopenia. J Rawalpindi Med Coll 2020; 24(3): 229-234.
5. Gordon P, Christensen R, Weitkamp J-H, Maheshwari A. Mapping the New World of Necrotizing Enterocolitis (NEC): Review and Opinion. EJ Neonatol Res 2012; 2(4): 145-72.
6. Roberts I, Murray NA. Neonatal thrombocytopenia: causes and management. Arch Dis Child Fetal Neonatal Ed 2003; 88(5): F359-64.
7. Ree IMC, Fustolo-Gunnink SF, Bekker V, Fijnvandraat KJ, Steggerda SJ, Lopriore E. Thrombocytopenia in neonatal sepsis: Incidence, severity and risk factors. PLoS One 2017; 12(10): e0185581.
8. K Peterson JA, Mcfarland JG, Curtis BR, Aster RH. Neonatal alloimmune thrombocytopenia:

Pathogenesis, diagnosis and management. Br J Haematol 2013; 161(1): 3-14.
9. Wang X, Xu Y, Luo W, Feng H, Luo Y, Wang Y, et al. Thrombocytopenia in pregnancy with different diagnoses. Med (United States) 2017; 96(29): 1-5.
10. Bergmann F, Rath W. Übersichtsarbeit: Differenzialdiagnose der Thrombozytopenie in der Schwangerschaft: Eine interdisziplinäre Herausforderung. Dtsch Arztebl Int 2015; 112(47): 795-802.
11. Melekoğlu NA, Bay A, Aktekin EH, Yilmaz M, Sivasli E. Neonatal outcomes of pregnancy with immune thrombocytopenia. Indian J Hematol Blood Transfus 2017; 33(2): 211-5.
12. Resch E, Hinkas O, Urlesberger B, Resch B. Neonatal thrombocytopenia—causes and outcomes following platelet transfusions. Eur J Pediatr 2018; 177(7): 1045-52.
13. Tirupathi K, Swarnkar K, Vagha J. Study of risk factors of neonatal thrombocytopenia. Int J Contemp Pediatr 2016; 4(1): 191.
14. Jung HE, Shim YR, Oh JE, Oh DS, Lee HK. The autophagy protein Atg5 plays a crucial role in the maintenance and reconstitution ability of hematopoietic stem cells. Immune Netw 2019; 19(2): 1-13.
15. Koltsova EM, Balashova EN, Ignatova AA, Poletaev AV, Polokhov DM, Kuprash AD, et al. Impaired platelet activity and hypercoagulation in healthy term and moderately preterm newborns during the early neonatal period. Pediatr Res 2019; 85(1): 63-71.
16. Stegner D, Vaneeuwijk JMM, Angay O, Gorelashvili MG, Semeniak D, Pinnecker J,et al. Thrombopoiesis is spatially regulated by the bone marrow vasculature. Nat Commun 2017; 8(1): 127.
17. Grozovsky R, Giannini S, Falet H, Hoffmeister KM. Regulating billions of blood platelets: Glycans and beyond. Blood 2015; 126(16): 1877-84.
18. Koltsova EM, Balashova EN, Ignatova AA, Poletaev AV, Polokhov DM, Kuprash AD, et al. Impaired platelet activity and hypercoagulation in healthy term and moderately preterm newborns during the early neonatal period. Pediatr Res 2019; 85(1): 63-71.
19. D'Atri LP, Rodríguez CS, Miguel CP, Pozner RG, Wilczyñski JM, Negrotto S, et al. Activation of toll-like receptors 2 and 4 on CD34+ cells increases human megakaryo/thrombopoiesis induced by thrombopoietin. J Thromb Haemost 2019; 17(12): 2196-210.
20. Levi M. Pathogenesis and diagnosis of disseminated intravascular coagulation. Int J Lab Hematol 2018; 40(Suppl 1): 15-20.
21. Arif SH, Ahmad I, Ali SM, Khan HM. Thrombocytopenia and bacterial sepsis in neonates. Indian J Hematol Blood Transfus 2012; 28(3): 147-51.
22. i Y, Tian Y, Liu N, Chen Y, Wu F. Analysis of 62 placental abruption cases: Risk factors and clinical outcomes. Taiwan J Obstet Gynecol 2019; 58(2): 223-6.
23. Takeda J, Takeda S. Management of disseminated intravascular coagulation associated with placental abruption and measures to improve outcomes. Obstet Gynecol Sci 2019; 62(5): 299-306.
24. Tikkanen M. Placental abruption: Epidemiology, risk factors and consequences. Acta Obstet Gynecol Scand 2011; 90(2): 140-9.
25. Regan F, Lees CC, Jones B, Nicolaides KH, Wimalasundera RC, Mijovic A. Prenatal management of pregnancies at risk of fetal neonatal alloimmune thrombocytopenia (FNAIT): Scientific Impact Paper No. 61. BJOG 2019; 126(10):e173-e185.
26. Tiller H, Husebekk A, Ahlen MT, Stuge TB, Skogen B. Current perspectives on fetal and neonatal alloimmune thrombocytopenia-increasing clinical concerns and new treatment opportunities. Int J Womens Health 2017; 9: 223-34.
27. Baker JM, Shehata N, Bussel J, Murphy MF, Greinacher A, Bakchoul T, et al. Postnatal intervention for the treatment of FNAIT: a systematic review. J Perinatol 2019; 39(10): 1329-39.
28. de Vos TW, Winkelhorst D, de Haas M, Lopriore E, Oepkes D. Epidemiology and management of fetal and neonatal alloimmune thrombocytopenia. Transfus Apher Sci 2020; 59(1): 102704.
29. Winkelhorst D, Oepkes D, Lopriore E. Fetal and neonatal alloimmune thrombocytopenia: evidence based antenatal and postnatal management strategies. Expert Rev Hematol 2017; 10(8): 729-37.
30. Lieberman L, Greinacher A, Murphy MF, Bussel J, Bakchoul T, Corke S, et al. Fetal and neonatal alloimmune thrombocytopenia: recommendations for evidence-based practice,

an international approach. Br J Haematol 2019; 185(3): 549-62.
31. Godara DS, Vyas DL, Narendra D. Prevalence of thrombocytopenia during pregnancy and its effect on pregnancy and neonatal outcome. Sch J Appl Med Sci 2020; 8(2): 681-4.
32. Gaba N, Gaba S. Etiology and fetomaternal outcomes of thrombocytopenia during pregnancy. Perinatology 2020; 21(2): 45-9.
33. Cines DB, Levine LD. Thrombocytopenia in pregnancy. Blood 2017; 130(21): 2271-7.
34. Qureshi AN, Sakina, Taqi T, Khatoon H, Ahmed I. Risk factors and fetomaternal outcome in pregnancy with thrombocytopenia. Prof Med J 2019; 26(11): 1942-6.
35. Brady CW. Liver disease in pregnancy: What's new. Hepatol Commun 2020; 4(2): 145-56.
36. Christensen RD, Henry E, Wiedmeier SE, Stoddard RA, Sola-Visner MC, Lambert DK, et al. Thrombocytopenia among extremely low birth weight neonates: Data from a multihospital healthcare system. J Perinatol 2006; 26(6): 348-53.
37. Pishko AM, Levine LD, Cines DB. Thrombocytopenia in pregnancy: Diagnosis and approach to management. Blood Rev 2020; 40:100638.
38. Bertrand G, Blouin L, Boehlen F, Levine E, Minon JM, Winer N. Management of neonatal thrombocytopenia in a context of maternal antiplatelet alloimmunization: Expert opinion of the French-speaking working group. Arch Pediatr 2019; 26(3): 191-97.
39. Sillers L, Van Slambrouck C, Lapping-Carr G. Neonatal thrombocytopenia: etiology and diagnosis. Pediatr Ann 2015; 44(7): e175-80.
40. Subtil SFC, Mendes JMB, Areia ALFDA, Moura JPAS. Update on thrombocytopenia in pregnancy. Rev Bras Ginecol Obstet 2020; 42(12): 834-40.
41. Padmawar A, Verma PG, Khadse G, Dhishana SR. Maternal and fetal outcome of pregnancies complicated with thrombocytopenia. Indian J Obstet Gynecol Res 2020; 7(4): 540-3.
42. Silva CL, Grando AC. Complications of idiopathic thrombocytopenic purpura in pregnancy: a review of literature. J Bras Patol Med Lab 2021; 57: 1-8.
43. Arora M, Goyal L, Khutan H. Prevalence of thrombocytopenia during pregnancy & its effect on pregnancy & neonatal outcome. Ann Int Med Dent Res 2017; 3(2): 4-6.
44. Hamad MNM, Idam DK, Alshazali HA. Prevalence of gestational thrombocytopenia among selected group of pregnant women attended to Soba University Hospita. AJRCPS 2017; 5(4): 144-9.
45. Kong Z, Qin P, Xiao S, Zhou H, Li H, Yang R, et al. A novel recombinant human thrombopoietin therapy for the management of immune thrombocytopenia in pregnancy. Blood 2017; 130(9): 1097-103.
46. Davenport PE, Chan Yuen J, Briere J, Feldman HA, Sola-Visner MC, Leeman KT. Implementation of a neonatal platelet transfusion guideline to reduce non-indicated transfusions using a quality improvement framework. J Perinatol 2021, 1-8.
47. Gernsheimer T, James AH, Stasi R. How I treat thrombocytopenia in pregnancy. Blood 2013; 121(1): 38-47.