Review Article

Fetal and Neonatal Alloimmune Thrombocytopenia; A Concise Review

Abstract

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a rare disease caused by maternal alloantibodies directed against fetal human platelet antigens HPAs and can lead to severe bleeding. A maternal antibody raised against a defined platelet alloantigen as the cause of platelet destruction in an infant with this condition has been noted and numerous other platelet-specific antigens were shown to be capable of inducing maternal immunization during pregnancy and causing fetal platelet destruction. However, most instances of maternal sensitizations may be triggered by exposure to fetal blood at the time of delivery, setting the stage for an infant to be born subsequently with thrombocytopenia. Current management of fetal and neonatal alloimmune thrombocytopenia in a subsequently affected pregnancy involves antenatal administration of intravenous immune globulin and steroids during pregnancy. Some advances suggested in the line of management include testing of cell-free fetal DNA obtained from maternal blood to determine the fetal human platelet antigen genotype, the creation of a prophylactic product;a platelet equivalent of Rhesus immune globulin andthe development of neonatal Fc receptor inhibitors to replace the current medical therapy administered to pregnant women with an affected fetus.

FNAIT is now recognized as an important complication of pregnancy that can present with difficult diagnostic and therapeutic challenges or unexplained neonatal death within a few hours of birth. Hence, a need for surveillance.

Keywords: FNAIT, Perinatal death, Alloimmune thrombocytopenia

Introduction

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) has been identified as a rare alloimmune disorder[1] and is the leading cause of severe thrombocytopenia in fetus and neonate.[2]It is also a leading cause of intracranial hemorrhage in full-term infants.[1]No other explanation for thrombocytopenia is typically discovered after evaluation for bacterial and viral infection, disseminated intravascular coagulation, and other congenital conditions associated with thrombocytopenia.[3]A severely affected infant will likely present with florid petechial hemorrhages and purpura with a profoundly low platelet count. Fetal and neonatal alloimmune

thrombocytopenia is an uncommon pregnancy complication that carries a significant risk of severe fetal and/or neonatal morbidity and has been recognized as the major cause of primary hemorrhagic morbidity and mortality in fetuses and newborns.[1]

Platelets play a critical role in hemostasis and thrombosis. Platelet adhesion, activation, and aggregation at the site of vascular injury lead to the formation of a temporary platelet plug and the subsequent arrest of bleeding.[4] However, accumulation of activated platelets at inappropriate sites may lead to thrombus formation and vessel obstruction. In addition, activated platelets may generate negatively charged phospholipids (e.g., phosphatidylserine) on their surfaces, which promote thrombin generation and fibrin formation.[4] This procoagulant activity facilitates hemostasis but may also enhance the severity of thrombotic disorders.[5]There ispaucity of reports regarding whether thrombosis in the placenta may be involved in the pathogenesis of FNAIT and contribute to the miscarriage observed in this disease.

FNAIT is now recognized as an important complication of pregnancy that can present with difficult diagnostic and therapeutic challenges or unexplained neonatal death withina few hours after delivery.[2]Therefore, this review is aimed to bring to the fore the existence of this very rare condition in fetuses which could be a pointer to unexplained intrauterine fetal death (IUFD) and earlier neonatal death.

Concise Review of Literature

Background

The incidence of FNAIT has been estimated at 0.5–1.5 per 1,000 liveborn neonates.[5] This number, however, does not include miscarriages caused by the disease, since the rate of fetal mortality in affected pregnant women has not been adequately studied.[5] Currently, the mechanisms leading to miscarriage in these women and the therapies to prevent this devastating consequence are unknown.[5]

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is caused by maternal alloantibodies directed against the human platelet antigens (mostly HPA-1a or HPA-5b) of the (unborn) baby and can lead to severe bleeding. Anti-HPA-1a-mediated FNAIT shows a severe clinical outcome more often than anti-HPA-5b-mediated FNAIT.[6]Several large prospective studies of women negative for HPA-1a, which is the most common trigger for antibodies causing neonatal alloimmune thrombocytopenia showed that between one in 1000 and one in 2000 HPA-1a-positive infants had neonatal thrombocytopenia caused by maternal antibodies.[2]Given the relatively high prevalence of anti-HPA-5b in pregnant women, the detection of anti-HPA-5b in FNAIT-suspected cases may in some cases be an incidental finding however can be associated with severe neonatal bleeding symptoms.[6]

In contrast to maternal immunization against fetal red cell antigens, it is common for immunization against platelet alloantigens to occur during a first pregnancy and for a firstborn infant to be affected likewise.[2,7]Antigens capable of triggering FNAIT are carried on platelet membrane glycoproteins (GPs) GPIb-V-IX (von Willebrand receptor), GPIIb/IIIa (αIIb/β3 integrin, fibrinogen receptor) GPIa/IIa (a collagen receptor) and CD109, a glycosylphosphatidylinositol (GPI)-anchored protein of uncertain function. Together, these platelet GPs interact with proteins of the extracellular matrix and coagulation factors to facilitate hemostasis.[4]

Two plausible mechanisms have been proposed to explain the occurrence of maternal alloimmunization in FNAIT. One mechanism involves maternal exposure to the antigen on fetal platelets due to fetomaternal bleeding or on maternal platelets due to previous platelet transfusions, and the other involves maternal exposure to integrin beta-3 on placental syncytiotrophoblast cells during pregnancy.[8]Integrin beta-3 and the GPI complex are major glycoproteins on the platelet surface and are critically required for platelet adhesion and aggregation. In FNAIT, most reported cases (75%–95%) have been characterized by maternal alloantibodies to fetal β3 integrin with few reported cases of FNAIT associated with anti-GPI antibodies.[8]

A maternal antibody raised against a defined platelet alloantigen as the cause of platelet destruction in an infant with this condition has been noted and numerous other platelet-specific antigens were shown to be capable of inducing maternal immunization during pregnancy and causing fetal platelet destruction.[9]However, most instances of maternal immunization may be triggered by exposure to fetal blood at the time of delivery, setting the stage for an infant to be born subsequently with thrombocytopenia.[9]

Current Management

Optimal fetal care can be provided by timely identification of pregnancies at risk by routine antenatal screening.[1]However, there is no definitive screening for FNAIT, and for this reason, FNAIT is not suspected until an otherwise healthy fetus or neonatemanifestsunexplained thrombocytopenia. Clinical management of subsequent pregnancies at risk of FNAIT is mostly based on the obstetric history.[10]Current management of fetal and neonatal alloimmune thrombocytopenia in a subsequently affected pregnancy involves antenatal administration of intravenous immune globulin and prednisone during pregnancy to prevent the development of severe fetal thrombocytopenia and secondary intracranial hemorrhage in utero. This therapy has proven to be highly effective but is expensive and associated with maternal side effects.[1]

The optimal antenatal therapy to prevent bleeding complications in pregnancies complicated by FNAIT is non-invasive treatment with weekly intravenous immunoglobulin (IVIG). Based on risk stratification, weekly doses of IVIG of 0.5 or 1.0g/kg are administered starting early in the second trimester in high-risk cases or at the end of the second trimester in low-risk cases.[11] The

optimal postnatal treatment depends on the platelet count and the clinical condition of the newborn. Prompt administration of compatible platelet transfusion is the first treatment of choice in case of severe thrombocytopenia or active bleeding. In case of persistent thrombocytopenia despite transfusions, IVIG 1.0-2.0g/kg can be administered.[11]

Advances in Management

The first is to screen all antepartum patients for pregnancies at risk of developing fetal and neonatal alloimmune thrombocytopenia. Strategies to implement this complex process have been described.[1]In pregnant women with a history of fetal and neonatal alloimmune thrombocytopenia (FNAIT), prenatal intervention in subsequent pregnancies may be required to prevent fetal bleeding. Several invasive and non-invasive protocols have been noted.[12]Amniocentesis for fetal genotyping, fetal blood sampling for the determination of fetal platelet count, intrauterine platelet transfusions, and weekly maternal I.V. immunoglobulin (IVIG) infusion with or without additional corticosteroid therapy. However, it has been reported that among pregnant women with FNAIT history, the use of non-invasive fetal risk determination and maternal IVIG resulted in a favorable outcome for all newborns.[12]

Another advancesuggested in the line of management is the testing of cell-free fetal DNA obtained from maternal blood to noninvasively determine the fetal human platelet antigen genotype; these Antigens capable of triggering FNAIT are carried on platelet membrane glycoproteins.[1]

Also, the creation of a prophylactic product that would be the platelet equivalent of Rh immune globulin (RhoGAM). Lastly, the development of neonatal Fc receptor inhibitors to replace the current medical therapy administered to pregnant women with an affected fetus. The neonatal Fc receptor recycles plasma immunoglobulin G to increase its half-life and , and this means immunoglobulin G crosses the placentafrom the maternal to the fetal circulation. Blocking the neonatal Fc receptor is an ideal way to prevent maternal immunoglobulin G antibodies from causing fetal and neonatal alloimmune thrombocytopenia in a fetus at risk of developing this disorder.[1]

During the last 5 decades, hemolytic disease of the fetus and newborn caused by antibodies against RhD has successfully been prevented by administration of hyperimmune anti-D IgG drug products to RhD-negative women after delivery of a RhD-positive child. Similarly, a hyperimmune anti-HPA-1a IgG (NAITgam) is under development for the prevention of HPA-1a immunization and FNAIT.[10] If NAITgam becomes licensed for FNAIT prophylaxis and national health authorities decide to include FNAIT screening in their antenatal health care programs it will be an improved tool for assessing the risk of FNAIT for early detection and prevention.[10]

The pathophysiology of FNAIT is similar to hemolytic disease of the fetus and the newborn (HDFN) than previously thought. Immunization against HPA-1a might therefore be preventable

by a prophylactic regimen of inducing antibody-mediated immune suppression (AMIS), which has been documented to be a useful prophylaxis against HDFN.[13]

New methods have been developed to facilitate the detection of common and private antibodies against HPAs triggering FNAIT. Understanding the pathogenesis of FNAIT made it possible to develop a novel strategy to treat this disorder.[14] To date, recombinant monoclonal antibodies directed against the β3 integrin and Fc receptors have been tested in a mouse model of FNAIT, and seem to be promising.[13,14] Whether those novel treatments will eventually replace the conventional high-dose immunoglobulin G in women with FNAIT is yet unknown.

Conclusion

It is distressing that, globally, about 7.5 million babies die annually during the perinatal period and 98.0% of these deaths occur in developing countries.[15]Perinatal mortality remains globally unacceptably high with up to three million stillbirths and three million neonatal deaths every year.[16]Achievement of Millennium Development Goals (MDG) 4 and 5 were focused on antenatal, intrapartum and postpartum perinatal and maternal care. These goals were linked because maternal and perinatal outcomes are inherently connected, and programs addressing improving the care of one often havean impact on the outcomes of the other. It is however pertinent to pay careful attention to rare diseases like FNAIT contributing to this global rise in natal and perinatal mortality especially in low-resource countries.

References

1. Bussel JB, Vander Haar EL, Berkowitz RL. New developments in fetal and neonatal alloimmune thrombocytopenia. Am J Obstet Gynecol. 2021 Aug 1;225(2):120–7.

2. Peterson JA, Mcfarland JG, Curtis BR, Aster RH. Neonatal alloimmune thrombocytopenia: pathogenesis, diagnosis and management. Br J Haematol [Internet]. 2013 Apr [cited 2023 Jun 1];161(1):3. Available from: /pmc/articles/PMC3895911/

3. Peterson JA, Kanack A, Nayak D, Bougie DW, McFarland JG, Curtis BR, et al. Prevalence and clinical significance of low-avidity HPA-1a antibodies in women exposed to HPA-1a during pregnancy. Transfusion (Paris). 2013;53(6):1309–18.

4. Clemetson KJ. Platelets and primary haemostasis. Thromb Res [Internet]. 2012 Mar [cited 2023 Jun 3];129(3):220–4. Available from: https://pubmed.ncbi.nlm.nih.gov/22178577/

5. Li C, Piran S, Chen P, Lang S, Zarpellon A, Jin JW, et al. The maternal immune response to fetal platelet GPIbα causes frequent miscarriage in mice that can be prevented by intravenous IgG and anti-FcRn therapies. J Clin Invest [Internet]. 2011 Nov 11 [cited 2023 Oct 16];121(11):4537. Available from: /pmc/articles/PMC3204841/

6. de Vos TW, Porcelijn L, Hofstede-van Egmond S, Pajkrt E, Oepkes D, Lopriore E, et al. Clinical characteristics of human platelet antigen (HPA)-1a and HPA-5b alloimmunised pregnancies and the association between platelet HPA-5b antibodies and symptomatic fetal neonatal alloimmune thrombocytopenia. Br J Haematol [Internet]. 2021 Nov 1 [cited 2023 Oct 16];195(4):595–603. Available from: https://pubmed.ncbi.nlm.nih.gov/34402048/

7. Jallu V, Bertrand G, Bianchi F, Chenet C, Poulain P, Kaplan C. The αIIbp.Leu841Met (Cab3a+) polymorphism results in a new human platelet alloantigen involved in neonatal alloimmune thrombocytopenia. Transfusion (Paris). 2013 Mar;53(3):554–63.

8. Fetal and neonatal alloimmune thrombocytopenia: Parental evaluation and pregnancy management - UpToDate [Internet]. [cited 2023 Jun 3]. Available from: https://www.uptodate.com/contents/fetal-and-neonatal-alloimmune-thrombocytopenia-parental-evaluation-and-pregnancy-management

9. SHULMAN NR, ASTER RH, PEARSON HA, HILLER MC. Immunoreactions involving platelet. VI. Reactions of maternal isoantibodies responsible for neonatal purpura. Differentiation of a second platelet antigen system. J Clin Invest [Internet]. 1962 [cited 2023 Jun 3];41(5):1059–69. Available from: https://pubmed.ncbi.nlm.nih.gov/13912392/

10. Kjeldsen-Kragh J, Bengtsson J. Fetal and Neonatal Alloimmune Thrombocytopenia-New Prospects for Fetal Risk Assessment of HPA-1a-Negative Pregnant Women. Transfus Med Rev [Internet]. 2020 Oct 1 [cited 2023 Oct 14];34(4):270–6. Available from: https://pubmed.ncbi.nlm.nih.gov/33039264/

11. Winkelhorst D, Oepkes D, Lopriore E. Fetal and neonatal alloimmune thrombocytopenia: evidence based antenatal and postnatal management strategies. Expert Rev Hematol [Internet]. 2017 Aug 3 [cited 2023 Oct 16];10(8):729–37. Available from: https://pubmed.ncbi.nlm.nih.gov/28644735/

12. Wienzek-Lischka S, Sawazki A, Ehrhardt H, Sachs UJ, Axt-Fliedner R, Bein G. Non-invasive risk-assessment and bleeding prophylaxis with IVIG in pregnant women with a history of fetal and neonatal alloimmune thrombocytopenia: management to minimize adverse events. Arch GynecolObstet [Internet]. 2020 Aug 1 [cited 2023 Oct 16];302(2):355–63. Available from: https://pubmed.ncbi.nlm.nih.gov/32495019/

13. Tiller H, Killie MK, Chen P, Eksteen M, Husebekk A, Skogen B, et al. Toward a prophylaxis against fetal and neonatal alloimmune thrombocytopenia: induction of antibody-mediated immune suppression and prevention of severe clinical complications in a murine model. Transfusion (Paris) [Internet]. 2012 Jul [cited 2023 Oct 14];52(7):1446–57. Available from: https://pubmed.ncbi.nlm.nih.gov/22251227/

14. Salomon O, Rosenberg N. Predicting risk severity and response of fetal neonatal alloimmune thrombocytopenia. Br J Haematol [Internet]. 2013 Aug [cited 2023 Oct 16];162(3):304–12. Available from: https://pubmed.ncbi.nlm.nih.gov/23672281/

15. Nwokoro UU, Dahiru T, Olorukooba A, Daam CK, Waziri HS, Adebowale A, et al. Determinants of perinatal mortality in public secondary health facilities, Abuja Municipal Area Council, Federal Capital Territory, Abuja, Nigeria. PAMJ 2020; 37:114 [Internet]. 2020 Oct 2 [cited 2023 Oct 16];37(114):1–12. Available from: https://www.panafrican-med-journal.com/content/article/37/114/full

16. Allanson ER, Muller M, Pattinson RC. Causes of perinatal mortality and associated maternal complications in a South African province: Challenges in predicting poor outcomes. BMC

Pregnancy Childbirth [Internet]. 2015 Feb 15 [cited 2023 Oct 16];15(1):1–7. Available from: https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/s12884-015-0472-9