

Fetal and Neonatal Alloimmune Thrombocytopenia: A Concise Review

Abstract

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a rare disease resulting from the effect of maternal alloantibodies on fetal human platelet antigens HPAs which could lead to severe haemorrhage. An antibody from mother reacting against a defined platelet alloantigen has been identified as the aetiology of platelet destruction in an infant with this condition and several other platelet-specific antigens were implicated to be capable of initiating maternal immunization during pregnancy leading to fetal platelet destruction. However, in most cases of maternal sensitization the exposure to fetal blood usually occurs during delivery, resulting to thrombocytopenia in the newborn. Current management of fetal and neonatal alloimmune thrombocytopenia in the next pregnancy involves administration of intravenous immune globulin and steroids during antenatal for mothers with previous history or those at risk. Some advances have been suggested in the line of management and these 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 and the development of neonatal Fc receptor inhibitors to replace the current medical therapy administered to pregnant women with an affected fetus.

FNAIT is a devastating complication of pregnancy that can present with difficult diagnostic and treatment challenges. 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 disorder¹ and is the leading cause of severe thrombocytopenia in fetuses and neonates”.² “It is also a major cause of intracranial hemorrhage in full-term infants”.¹ “No significant explanation for the discovered thrombocytopenia after other possible cause has been ruled out, including evaluation for bacterial and viral infection, disseminated intravascular coagulation, and other congenital conditions associated with the severe low platelet level”.³ “In severely affected neonate, common presentation include florid petechial hemorrhages and purpura with a significant low platelet levels. FNAIT is an uncommon pregnancy sequelae with

asignificant risk of severe fetal and/or neonatal morbidity and has been identified as the major cause of primary hemorrhagic morbidity and mortality in fetuses and neonate”.¹

“The role of platelets in hemostasis and thrombosis is very crucial. At the site of vascular injury platelet activation, adhesion and aggregation lead to the formation of a temporary plug to secure hemostasis”.⁴“However, accumulation of activated platelets at inappropriate sites may lead to thrombus formation and vascular obstruction. Also, negatively charged phospholipids (e.g., phosphatidylserine) may be generated on the surfaces of activated platelets which promote formation of thrombin and fibrin clot”.⁴“Although this procoagulant activity enhances hemostasis however may also facilitate the severity of thrombotic disorders”.⁵ There is a paucity of reportson whether placenta thrombosis may be involved in the pathogenesis of FNAIT and contributing to the pregnancy loss observed in this disease condition.

“FNAIT is has been reported as an important adverse sequela of pregnancy presenting with diagnostic difficult and challenges with management or unexplained neonatal death even within a few hours of birth”.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 is estimated at 0.5–1.5 in 1,000 livebirths”.⁵“This excluded cases of pregnancy wastages caused by this rare disease, reason been that the rate of fetal losses in affected pregnant women has not been adequately documented”.⁵“The mechanisms leading to such loss in these women is not clearly cut and few is known about the appropriate preventive protocol of this devastating consequence”.⁵

“Fetal and neonatal alloimmune thrombocytopenia is caused by maternal alloantibodies directed against the human platelet antigens 1a or 5b of the fetus leading to severe haemorrhage. 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“Due to 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 haemorrhage”.⁶

“In contrast, immunization against platelet alloantigen can occur during a first pregnancy and the first child could be affected as well, as opposed maternal immunization against fetal red cell antigens”.^{2,7}“The antigens causing FNAIT are present on platelet membrane glycoproteins (GPs) GPIb-V-IX (von Willebrand receptor), GPIIb/IIIa (α IIb/ β 3 integrin, fibrinogen receptor) GPIa/IIa (collagen receptor) and CD109, a glycosylphosphatidylinositol (GPI)-anchored protein. These GPs interact with extracellular matrix proteins and coagulation factors to enhance hemostasis”.⁴

“There are two possible mechanisms 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 β 3 integrin with few reported cases of FNAIT associated with anti-GPI antibodies”.⁸

“It has been noted that a maternal antibody produced against a particular platelet alloantigen causes platelet destruction in neonate with this condition and several other platelet-specific antigens were implicated in the maternal sensitization or immunization during pregnancy leading fetal platelet destruction in utero”.⁹“However, most cases of maternal immunization may be initiated by exposure to fetal blood at the time of birth consequently leading to neonatal thrombocytopenia”.⁹

Current Management

“The current management of FNAIT is geared towards essential fetal care via timely recognition of pregnancies at risk through routine antenatal screening”.¹“However, due to lack of definitive screening tool for FNAIT, the condition remains unsuspected until an apparently healthy fetus or neonate manifests unexplained thrombocytopenia or bleeding. Therefore, the clinical management of FNAIT in subsequent pregnancies mostly rely on past obstetric history of a confirmed or suspected FNAIT”.¹⁰ The management involves administration of intravenous immune globulin and prednisone during antenatal period to prevent a repeat episode of severe fetal thrombocytopenia or complications like secondary intracranial hemorrhage in utero. Although this intervention is highly effective however, it is associated with maternal side effects.¹ and not cost effective especially in low resource countries.

“This treatment is non-invasive involving weekly administration of intravenous immunoglobulin doses of 0.5 or 1.0g/kg early in the second trimester for high-risk cases or at the end of the second trimester for low-risk mothers”.¹¹

The neonatal treatment depends on the clinical features and the platelet count which gives the pictures of the like event sequelae in utero. Fresh platelet transfusion is the first given in severe low platelets value or active haemorrhage in worsening clinical condition despite platelet transfusions, intravenous immunoglobulin doses of 1.0-2.0g/kg can be administered to the baby.¹¹

Advances in Management

In pregnant women with a history of FNAIT, prenatal intervention in subsequent pregnancies may be required. Some invasive and non-invasive modalities have been noted.¹² These include fetal genotyping via amniocentesis, fetal blood sampling for platelet count, platelet transfusions in utero, and administration of maternal intravenous immunoglobulin with or without giving corticosteroid. 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.¹²

Another advance suggested in the line of management is the non-invasive testing of cell-free fetal DNA obtained from maternal blood to determine the fetal HPA genotype; these antigens which can initiate FNAIT are present on platelet membrane glycoproteins.¹ Hence their detection will help in the prompt treatment or prevention of complications of FNAIT.

Furthermore, another advance made was the development of neonatal Fc receptor inhibitors. The Fc receptor recycles and increases the half-life of plasma immunoglobulin G which is capable of crossing the placental barrier from the maternal to the fetal circulation. The inhibition of neonatal Fc receptor helps to prevent maternal immunoglobulin G antibodies from causing FNAIT especially in fetus at risk.¹

Lastly, the production of a prophylactic substance or a platelet equivalent of Rhesus immunoglobulin. In the past years, hemolytic disease of the fetus and newborn caused by antibodies against Rhesus D substance has now been prevented in subsequent pregnancy by administration of anti-D immunoglobulin to RhD-negative women during antenatal period and or after childbirth.

Similarly, a hyperimmune anti-HPA-1a immunoglobulin G (NAITgam) is being developed for the prevention of FNAIT.¹⁰ The licensing of NAITgam for FNAIT prophylaxis will be an improved management modality for FNAIT treatment 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 responding for causing FNAIT. Understanding the pathogenesis of FNAIT made it possible to develop a novel strategy to treat this disorder.¹⁴ Currently, a recombinant monoclonal antibodies against the $\beta 3$ integrin and Fc receptors have been tested in a mouse subject with FNAIT, the response appeared to be promising.^{13,14} It is yet not certain if this novel treatments will eventually replace the conventional high-dose IgG administered in women with FNAIT.

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 high with up to three million stillbirths and three million neonatal deaths yearly.¹⁶ Achievement of Millennium Development Goals (MDG) 4 and 5 were focused perinatal and maternal care. 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.

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