New developments in fetal and neonatal alloimmune thrombocytopenia

James B. Bussel, MD; Emilie L. Vander Haar, MD; Richard L. Berkowitz, MD

Fetal and neonatal alloimmune thrombocytopenia, the platelet equivalent of hemolytic disease of the fetus and newborn, can have devastating effects on both the fetus and neonate. Current management of fetal and neonatal alloimmune thrombocytopenia in a subsequent affected pregnancy involves antenatal administration of intravenous immune globulin and prednisone to the pregnant woman to prevent the development of severe fetal thrombocytopenia and secondary intracranial hemorrhage in utero. That therapy has proven to be highly effective but is associated with maternal side effects and is expensive. This commentary describes 4 advances that could substantially change the current approach to detecting and managing fetal and neonatal alloimmune thrombocytopenia in the near future. The first would be an introduction of a program to screen all antepartum patients in this country for pregnancies at risk of developing fetal and neonatal alloimmune thrombocytopenia. Strategies to implement this complex process have been described. A second advance is testing of cell-free fetal DNA obtained from maternal blood to noninvasively determine the fetal human platelet antigen 1 genotype. A third, in preliminary development, is creation of a prophylactic product that would be the platelet equivalent of Rh immune globulin (RhoGAM). Finally, a fourth major potential advance is the development of neonatal Fc receptor inhibitors to replace the current medical therapy administered to pregnant women with an affected fetus. Neonatal Fc receptor recycles plasma immunoglobulin G to increase its half-life and is the means by which immunoglobulin G crosses the placenta from the maternal to the fetal circulation. Blocking the neonatal Fc receptor is an ideal way to prevent maternal immunoglobulin G antibody from causing fetal and neonatal alloimmune thrombocytopenia in a fetus at risk of developing that disorder. The pertinent pathophysiology and rationale for each of these developments will be presented in addition to our thoughts relating to steps that must be taken and difficulties that each approach would face for them to be successfully implemented.

Key words: FcRn, FNAIT, HPA-1ab, intracranial hemorrhage, IVIG, NAITgam, platelet, thrombocytopenia

Introduction

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is the platelet equivalent of hemolytic disease of the fetus and newborn (HDFN). It is a rare disease, occurring in approximately 1 in 1000 births, but affected pregnancies can carry severe consequences including fetal and neonatal intracranial hemorrhage (ICH),[1] which may result in irreversible brain damage or death. FNAIT is caused by an incompatibility between the antigenic composition of the mother's platelets and those of the fetus, inherited from the father.[2,3] Approximately 80% of FNAIT cases in White people occur in a mother whose platelets express only human platelet antigen 1b (HPA-1a negative) and who conceives an HPA-1a fetus. Those fetal platelets enter the maternal circulation and cause an immune reaction, leading to maternal production of HPA-1a antibodies that subsequently cross the placenta and lead to fetal thrombocytopenia (Figure 1). Although HPA-1a discordance is the most common source of FNAIT, more than 30 other platelet antigen incompatibilities can cause this disorder,[4] although those cases are usually less severe. The HPA-1ab polymorphism is not present in patients of Chinese or Japanese descent; platelet antigen frequencies in other ethnicities are not as well defined.[5,6]

Because routine screening for the maternal platelet genotype is not currently performed in the United States, most women with this disorder are only discovered after having had an affected neonate. FNAIT is often suspected when, during the first day of life, an infant with unexpected signs of bruising or frank bleeding is found to have an abnormally low platelet count.[7] Fortunately, most cases of FNAIT are not complicated by clinically significant bleeding, but 10% to 20% of severely affected newborns will have an ICH, three-quarters of which occur in utero.[8] The current management of affected newborns with platelet counts of

From the Department of Pediatrics (Dr Bussel) and Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology (Drs Vander Haar and Berkowitz), Weill Cornell Medicine, New York, NY; and Columbia University Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, NY (Dr Berkowtiz).

Received Dec. 2, 2020; revised March 26, 2021; accepted April 2, 2021.

J.B.B. reports the following disclosures: consultant at CSL Behring (intravenous immunoglobulin manufacturer), UCB, Argenx, Momenta/Janssen (manufacturers of neonatal Fc receptor [FcRn] inhibitors), and Rallybio (company interested in screening and prophylaxis of fetal and neonatal alloimmune thrombocytopenia [FNAIT]) and Data Safety Monitoring Board at CSL Behring. R.L.B. reports the following disclosures: Momenta/Janssen (manufacturers of FcRn inhibitors) and Rallybio (company interested in screening and prophylaxis of FNAIT). E.L.V.H. reports no conflict of interest.

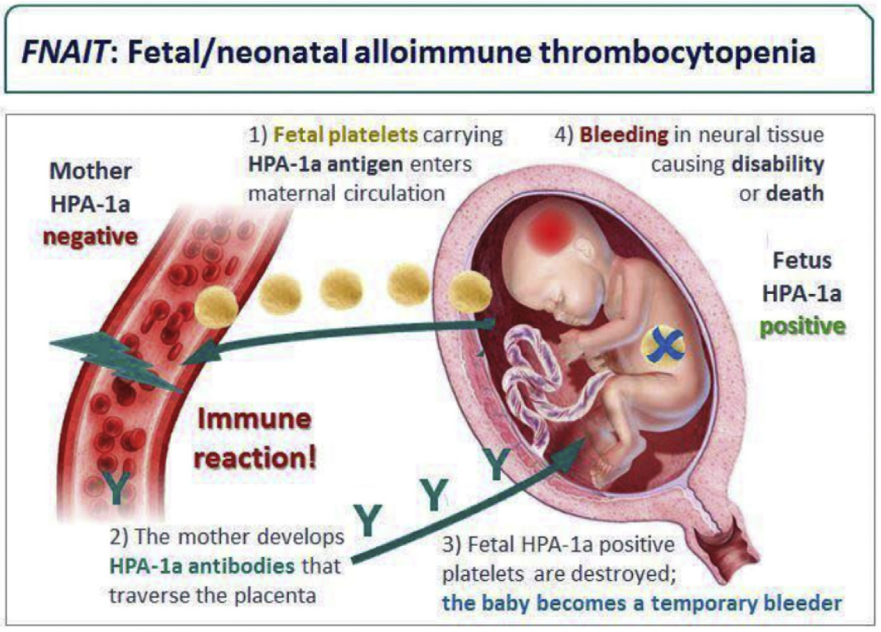
Corresponding author: James B. Bussel, MD. jbussel@med.cornell.edu

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2021.04.211


Click Video under article title in Contents at **ajog.org**

FIGURE 1
Maternal and fetal platelet antigen incompatibility in FNAIT



FNAIT is caused by an incompatibility between the antigenic composition of the mother's platelets (HPA-1b1b) and those of the fetus (HPA-1a), inherited from the father. Fetal platelets enter the maternal circulation and cause an immune reaction, leading to maternal production of HPA-1a antibodies that subsequently cross the placenta and lead to fetal thrombocytopenia. This leads to a temporary bleeding state, which can cause intracranial hemorrhage. Figure reproduced with permission from NAITbabies.org.
FNAIT, fetal and neonatal alloimmune thrombocytopenia.
Bussel. New developments in fetal and neonatal alloimmune thrombocytopenia. Am J Obstet Gynecol 2021.

<30,000/uL is to initiate treatment with a random platelet transfusion, often with concomitant intravenous immunoglobulin (IVIG),[9] along with radiologic evaluation for ICH.

In the subsequent pregnancy of a woman whose fetus is known to be carrying the offending antigen, antepartum management with IVIG and steroids is recommended to increase the fetal platelet count until delivery.[1,3,8,10–14] The anticipated severity of the disorder is related to whether, and if so when, the fetus had an ICH in the previous affected pregnancy. However, currently, the only way to assess the actual degree of fetal thrombocytopenia is to directly measure the platelet count in utero by cordocentesis, which is an invasive procedure that may have serious adverse consequences. That recognition has led to a severity-based, minimally invasive medical approach for antenatal management of affected pregnancies (Figure 2). To be certain that the fetal platelet count has achieved sufficient levels without resorting to serial cordocentesis, all patients eventually are escalated to "maximal therapy" (IVIG of 2 g/kg/wk and prednisone of 0.5 mg/kg/day).

However, this level of therapy is reached at different gestational ages according to the severity risk, and in the highest risk group, the prednisone dose administered reaches 1 mg/kg/day (Figure 2). Serial weekly platelet transfusions administered directly to the fetus is an invasive form of therapy complicated by increased fetal morbidity and mortality, which is now very infrequently used, and is not recommended.

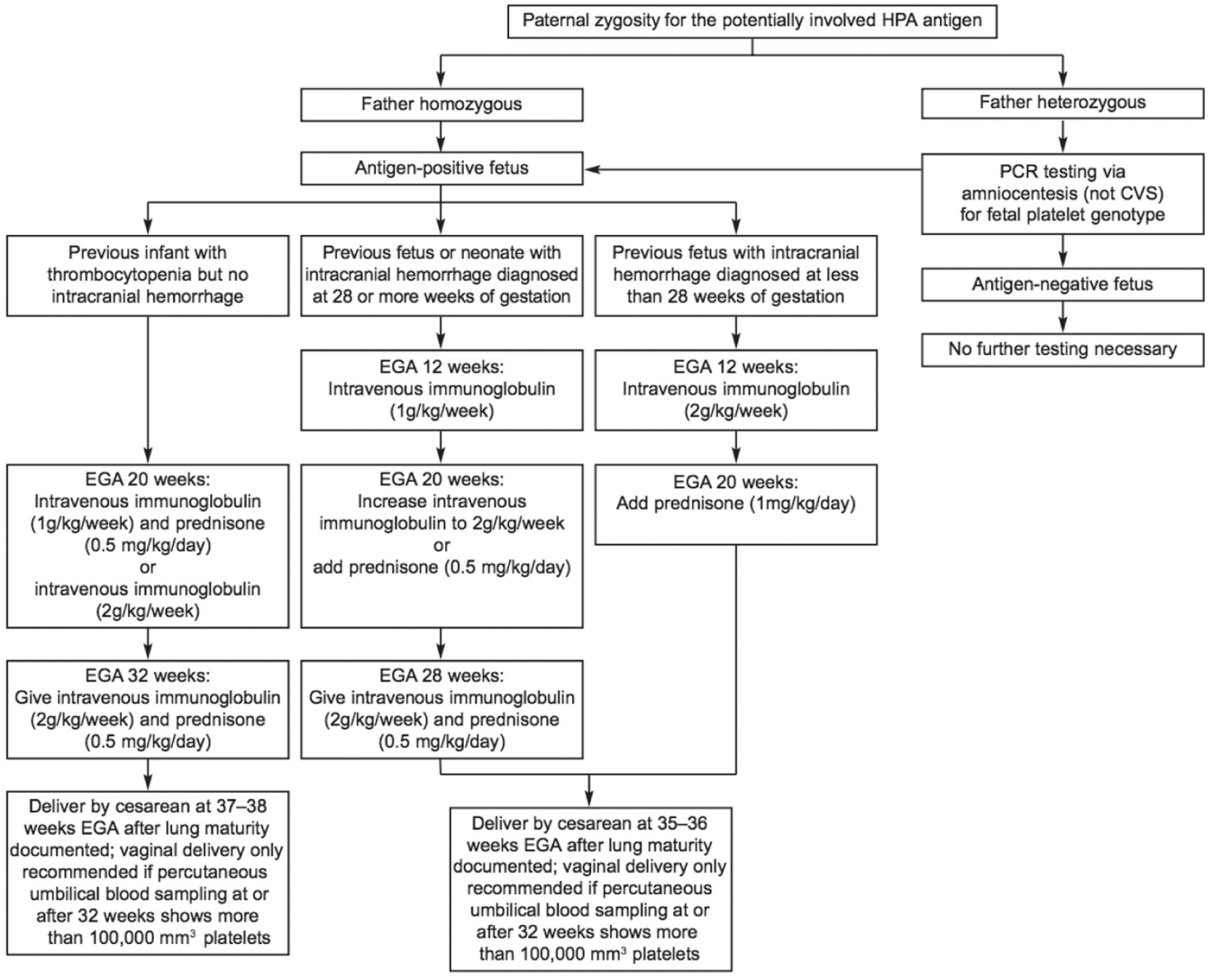
Hemolytic Disease of the Fetus and Newborn and Fetal and Neonatal Alloimmune Thrombocytopenia: 2 Peas in a Pod?

Both HDFN and FNAIT are caused by parental blood cell antigen incompatibilities in which the mother becomes sensitized by transplacental transmission of fetal cells into the maternal circulation. The mother makes immunoglobulin (Ig) G antibodies to a paternal antigen on the surface of these cells, which then cross the placenta, attack red cells or platelets, and cause fetal anemia or thrombocytopenia respectively. If severe enough, each of these effects can have fatal consequences for the fetus or newborn. Much of what we know about FNAIT has evolved based on recognizing its similarity to HDFN.

However, with the passage of time, it has become clear that there are important differences between these disorders. Among others, these include the following:

- Screening for Rh incompatibility is virtually ubiquitous in the United States, and the use of Rh immune globulin has almost entirely eliminated HDFN in this country, which is one of the most outstanding medical developments of the 20th century.[15] In contrast, there is currently no screening for patients at risk of developing FNAIT, and although that disorder is less common than HDFN, its consequences can be equally devastating.[7]
- FNAIT often becomes manifest in the first pregnancy and may be quite severe at that time,[16] whereas in HDFN, the infant in the first pregnancy is rarely affected, and fetuses become progressively more severely affected in subsequent gestations.[15,17]
- The marked severity of thrombocytopenia in FNAIT is partly caused by an inhibition of fetal megakaryocyte production by the maternal antiplatelet antibodies,[18] whereas, except for cases of Kell incompatibility, the fetal anemia in HDFN seems to be exclusively caused by the destruction of circulating red blood cells.
- HDFN causes anemia in utero which can be monitored noninvasively with serial middle cerebral artery (MCA) Doppler studies[17] whereas there are no biomarkers of fetal thrombocytopenia that can currently be assessed noninvasively before the occurrence of an ICH.[19]
- Maternally administered IVIG and steroids during the antepartum period is the way most cases of

FIGURE 2
Algorithm for management of FNAIT in women with a subsequent affected pregnancy



A severity-based, minimally invasive medical approach for antenatal management of affected pregnancies.[1]

FNAIT, fetal and neonatal alloimmune thrombocytopenia.

Bussel. New developments in fetal and neonatal alloimmune thrombocytopenia. Am J Obstet Gynecol 2021.

severely affected FNAIT pregnancies are managed in the United States, whereas in utero red cell transfusion and/or early delivery constitute standard management for severe cases of HDFN.[15,17]

- Fetal blood sampling is rarely performed in FNAIT because the medical treatment described earlier is virtually 100% effective in raising and then maintaining fetal platelet counts in a safe realm, whereas women with HDFN are followed with serial MCA Doppler studies until it is determined that they need to be transfused in utero or delivered.[15,17]
- In HDFN, the fetus and newborn can experience postnatal neurologic damage from hyperbilirubinemia caused by hemolysis and develop other sequelae resulting from prolonged hypoxia, whereas, in FNAIT, irreversible damage is almost always limited to cases complicated by ICH.[20]

In this commentary, we will describe several new developments at different stages of their evolution that we believe may, to differing degrees, potentially revolutionize how FNAIT will be diagnosed and managed in the foreseeable future.

Screening: Identifying the At-Risk Population

If screening and subsequent effective prophylaxis for FNAIT can be developed in a cost effective and safe manner, it would greatly reduce the incidence of that disorder. Several large population screening studies for FNAIT have been

successfully performed in Europe[21–23] and have demonstrated the following important findings:

- Those studies have been performed with relatively small loss to follow-up and with platelet antigen typing having a very low (<1%) error rate.
- Notably, 75% of women who were found to have FNAIT caused by the HPA-1a antigen became sensitized at delivery in their first pregnancy.[21–23] This is markedly different from cases detected by clinically documented neonatal thrombocytopenia, in which 60% are affected in the mother's first pregnancy.[16]
- Other features of FNAIT are also different if cases accessed by screening are compared with those clinically detected in neonates by documenting thrombocytopenia. For example, the incidence of severe thrombocytopenia is 3-to 5-fold higher in the clinically identified cases. In other words, population screening may be identifying much milder, asymptomatic disease.

It is important to note that approximately 28% of HPA-1a negative American women carry the DRB3*0101 HLA antigen. The latter identifies an immune response gene without which HPA-1a negative women almost never produce high levels of anti-HPA-1a antibodies.[24,25] The association of high titer anti-HPA-1a with DRB3*0101 is one of the strongest links of a specific antibody response to an immune response gene that is currently known. It is extremely rare for an HPA-1a negative woman to become substantially sensitized to her HPA-1 positive fetus in the absence of having the DRB3*0101 antigen. Therefore, detection of that antigen is an essential component of a screening program designed to detect cases at risk of developing FNAIT.

The true at-risk population for the development of HPA-1a incompatible FNAIT in screening is approximately 1 in 200 women (0.5%). This assumes that very few DRB3*0101, HPA-1a negative women being screened will have preexisting anti-HPA-1a antibodies. Approximately 85% of those women who are HPA-1a negative will have an HPA-1a potentially affected fetus. To identify this subset, the following studies would need to be performed:

1. Maternal blood (already being sent for red blood cell typing on the first prenatal visit) would also be used to have her platelet genotype determined (Figure 3). Currently maternal platelet typing has to be sent to a specialty laboratory. Whether this will continue to be necessary in the future remains to be seen. The availability of high-throughput enzyme-linked immunosorbent assay—based testing for HPA-1a may make this screening cheaper and easier to standardize,[26] but this has not undergone large-scale testing.
2. In the screened subset of HPA-1a negative women, it would also be necessary to determine the DRB3*0101 status of the mother, the genotype of the fetus using cell-free fetal DNA obtained from the maternal blood sample, and the presence or absence of anti-HPA-1A antibodies in maternal serum (Figure 3).

Therefore, the net effect of screening would be first to identify mothers at high risk of making anti-HPA-1a antibodies, that is, those who are both HPA-1a negative and DRB3*0101 positive, and then to see if they have an HPA-1a positive fetus. In addition, screening will also identify a further subset in which such a patient already has produced anti-HPA-1a antibodies. The latter group would be directly referred to an MFM specialist to undergo evaluation for antenatal therapy.

Fetal Typing: Fetal Cell-Free DNA

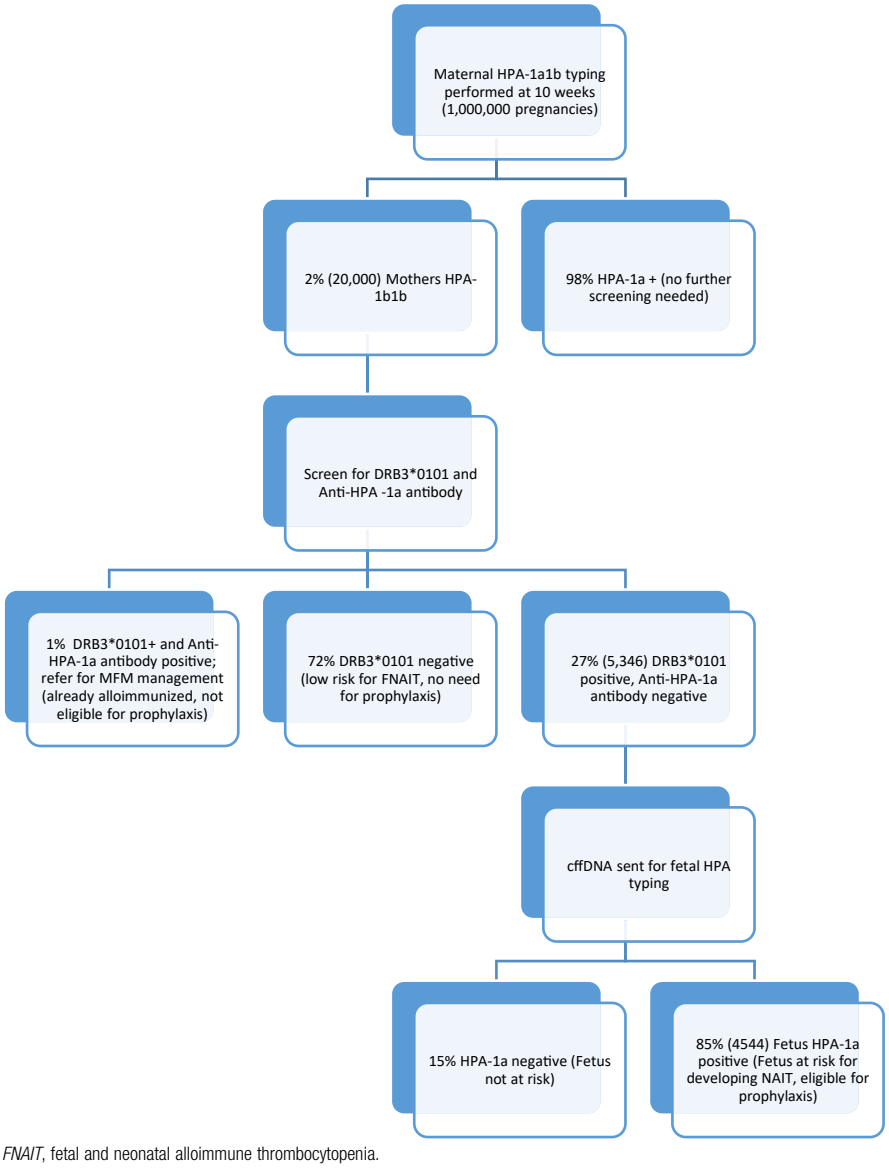
Approximately 98% of White Americans are HPA-1a positive, and 75% of those individuals are homozygous for that antigen.[27,28] However, if the father of the baby (FOB) in a pregnancy conceived with an HPA-1a negative woman is a heterozygote, which occurs in approximately 25% of cases, 50% of their conceptions will be negative for the HPA-1a antigen and thus not at risk of FNAIT. Therefore, although most pregnancies conceived by couples that include an HPA-1a negative woman and an HPA-1a positive male will have an HPA-1a positive fetus, approximately 15% will not. As a consequence, if the genotype of the FOB is not known to be HPA-1a1a, the genotype of the fetus must be determined. Previously, there were only 3 ways to perform fetal platelet antigen typing: for example, obtaining fetal cells from chorionic villus sampling, amniocentesis,[29] or fetal blood sampling. Those methods are all invasive and thus have some associated risks. Presently, fetal platelet HPA-1a antigen typing can be done reliably as early as 10 weeks' gestation using cell-free fetal DNA detection in maternal blood obtained from a venipuncture.[30] This testing is now available in the United States and Western Europe for HPA-1a1b, but not yet for other platelet antigens. This form of assessing the fetal genotype for other platelet antigens may become available in the future and, if so, will further optimize and make safer the management of those less common causes of FNAIT.

Prophylaxis: From RhoGAM to "NAITgam"

Hemolytic disease of the fetus and newborn

Prophylaxis has been remarkably successful in preventing cases of HDFN. RhD Ig (eg, anti-D, RhoGAM) is thought to prevent sensitization to RhD by blocking maternal production of her own anti-D antibodies when administered at 26 to 28 weeks' gestation, at the time of delivery, and after episodes of maternal bleeding, invasive fetal testing procedures, or maternal trauma that may be associated with fetal-maternal hemorrhage. RhD Ig is a hyperimmune anti-D gamma globulin that is manufactured by collecting the plasma of donors who have markedly elevated titers of antibody to Rh factor D.[31] In the past, these donors were highly sensitized women who had had newborns affected with HDFN. Currently, many donors are Rh negative men or women who are not capable of or have chosen not to become

FIGURE 3
Theoretical screening process for FNAIT prophylaxis



FNAIT, fetal and neonatal alloimmune thrombocytopenia.

Estimated affected pregnancies per 1,000,000 deliveries.

Bussel. New developments in fetal and neonatal alloimmune thrombocytopenia. Am J Obstet Gynecol 2021.

pregnant. Those donors are periodically given injections of Rh-positive cells to ensure that their levels of anti-D antibodies remain high. Several years ago, several studies explored whether polyclonal, plasma-derived anti-D serum could be replaced by a monoclonal anti-D antibody.[32] However, the many different structural variations in the D antigen were found to prevent a single monoclonal antibody from being highly effective in preventing the development of maternal sensitization.[33] Therefore, anti-D Ig remains a polyclonal, plasma-derived product.

"NAITgam"

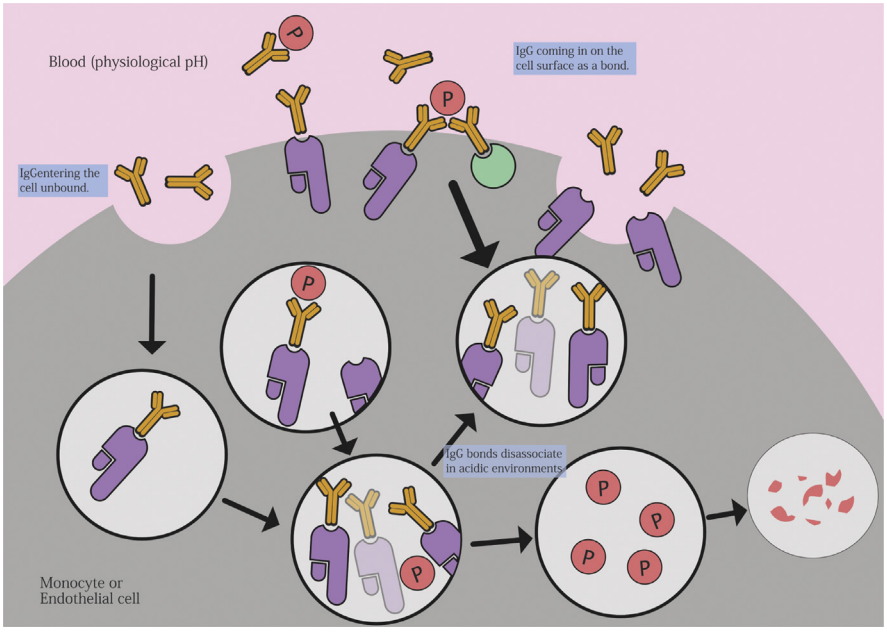
It is certainly possible that hyperimmune gamma globulin derived from the plasma of women who had previous pregnancies affected with FNAIT could provide prophylaxis in a similar fashion to that obtained with Rh Ig. One lot of such a product, called "NAITgam," has in fact been produced from plasma donations of women who have high circulating levels of antibody to HPA-1a.[34] There will soon be a "proof of principle" trial to determine whether giving that product to nonpregnant HPA-1a negative recipients who have been deliberately exposed to HPA-1a1a platelets prevents the recipients from making antibody to HPA-1a.

There are very many uncertainties as to whether "NAITgam" can actually prevent FNAIT from occurring as effectively as anti-D Ig does for HDFN. There is no reason per se to doubt this, but very little experimental work outside of limited animal studies[35] exists to support it. On the positive side, this product probably has very little maternal toxicity. However, even if "NAITgam" is shown to be highly effective in providing prophylaxis in studies of nonpregnant patients, appropriate dosing and a schedule of administration must be determined during actual gestations. This will require large-scale trials of antepartum testing to demonstrate that an experimentally verified strategy works and that "NAITgam" is safe for both the mother and the fetus. Because severe cases of FNAIT caused by HPA-1a cannot only occur in the first pregnancy but may occur as early as 18 weeks, prophylaxis for those cases would need to be started by the beginning of the second trimester[12] and likely repeated on multiple occasions throughout the pregnancy.

Treatment: inhibition of Fc receptor

Neonatal Fc receptor (FcRn) is a unique Fc gamma receptor which binds IgG only at acidic pH.[36,37] Free, unattached IgG is brought into an endothelial cell by pinocytosis from plasma and passed into an endocytic vesicle called an endosome (Figure 4). If the IgG is not "free" but has formed an immune complex with a platelet antigen, it may enter the endosome using a different pathway. The acidic pH of the endosome leads to dissociation of the immune complex. The free IgG is then able to bind to FcRn, which is located on the inner membrane of the endosome. The IgG-FcRn complex is then translocated to the cell

FIGURE 4
FcRn with free IgG and bound IgG entering cell for recycling



The FcRn is a unique Fc gamma receptor which binds IgG only at acidic pH. Free, unattached IgG is brought into an endothelial cell by pinocytosis from plasma and passed into an endocytic vesicle called an endosome. We believe that IgG bound to blood cells enters the acidified endosome via attachment to other external FcRs and then, like IgG that enters by pinocytosis, binds to FcRn on the inner surface of the acidified endosome. The FcRn then traffics the IgG to the cell surface where it detaches from FcRn because it is in neutral (extracellular) pH. Artwork by Iris Az.

FcRn, neonatal Fc receptor; *IgG*, immunoglobulin G.

Bussel. New developments in fetal and neonatal alloimmune thrombocytopenia. Am J Obstet Gynecol 2021.

surface. Because plasma has a neutral pH, the IgG dissociates from the receptor and is released back into the maternal circulation (Figure 4).[38] This recycling of IgG by FcRn results in maintenance of the normal half-life of IgG.[39,40] The same mechanism of IgG transport occurs within the placenta where it allows IgG to cross into the fetal circulation. When maternal IgG contains anti-HPA-1a antibodies, this delivery system leads to the destruction of fetal platelets containing that antigen.

The initial development of inhibitors of FcRn for clinical use was conceptualized as a therapeutic agent that should lower IgG levels, because recycling of that moiety would be markedly impaired.[36] Lowering all IgG levels would also diminish IgG autoantibody levels and, as such, would potentially have a beneficial effect on any IgG antibody-mediated disease. Although not proven, it seems that antiplatelet antibodies in immune thrombocytopenia (ITP) are reduced by FcRn inhibition to a greater extent than the levels of free IgG. Several phase 2 and 3 clinical studies have now demonstrated the efficacy and safety of FcRn inhibition as treatment in patients with IgG-mediated autoantibody disorders such as ITP,[39,40] pemphigus vulgaris,[41] and myasthenia gravis,[42] with more than 50% response rates in most of those trials.

Although when administered at a dose of 1 g/kg/wk in the antenatal management of FNAIT, IVIG is effective in maintaining a fetal platelet count of >30,000/uL in many patients, higher doses are required in more severe cases. One placental perfusion study found that only by giving IVIG at a dose of 2 g/kg/wk can 90% blockade of maternal transfer of IgG into the fetal circulation be achieved.[43] However, if FcRn blockade were complete, as can safely be achieved by appropriate dose and scheduling of FcRn inhibitors, this should totally block passage of maternal IgG across the placenta in patients affected with either HDFN or FNAIT. Therefore, the use of these inhibitors could entirely eliminate the need to employ prednisone and IVIG at any dose, with their attendant risk of substantial adverse side effects. An additional potential benefit of using FcRn inhibitors is that by substantially reducing the half-life of IgG in the maternal circulation, these agents would also markedly reduce the levels of antifetal platelet antibodies in her bloodstream.

However, a potential drawback of FcRn inhibition in pregnant women is that both maternal and fetal IgG levels would become greatly reduced. However, the mother would continue to have normal IgA and IgM levels and unimpaired T cell function.[37] Phase 3 studies using serial infusions of FcRn inhibitors will clarify whether there is any risk of that therapy causing increased maternal infection, but thus far there has been no apparent evidence of that occurring in the studies that have been performed to date.[17,18] The fetus is not thought to "need" IgG in utero. However, after birth, a neonate with hypogammaglobulinemia clearly would be at a considerably increased risk of developing sepsis.[44] One approach to deal with this issue would be to stop FcRn inhibition approximately 2 weeks before birth and then to administer high dose IVIG to the mother several days before delivery in an attempt to both reconstitute her IgG reserve and to deliver transplacental "normal" IgG to the fetus. This approach is currently being used in the HDFN study described below. An alternative, or supplemental, approach might be to administer IVIG intravenously to the neonate on the first day of life perhaps via the umbilical cord.

An ongoing study of FcRn inhibition in severely affected pregnancies affected by HDFN is currently enrolling patients at several sites worldwide (ClinicalTrials.gov NCT03842). In this study, beginning

in the second trimester, nipocalimab, an inhibitor of FcRn, is administered weekly to pregnant women with a history of severe HDFN in previous pregnancies to prevent maternal anti-D from crossing the placenta. Despite its current relative rarity, HDFN was chosen over FNAIT for this proof of concept study because the availability of a noninvasively obtainable biomarker in HDFN safely allows for frequent monitoring of the effectiveness of FcRn inhibition therapy in the at-risk fetus. In other words, if MCA Doppler studies indicate that a fetus being treated with FcRn inhibition is failing therapy and developing significant anemia, rescue therapy with intrauterine red blood cell transfusions can be administered.[15,17] No parallel noninvasive approach to fetal monitoring currently exists for FNAIT, so the need for emergent rescue therapy could not be anticipated. If this mode of treatment proves to be as beneficial as anticipated for HDFN, it should clearly be studied for FNAIT. Success in those trials could then lead to studying other maternal antifetal IgG-mediated diseases such as those caused by anti-Ro/La and antithyroid antibodies.

Conclusion

It is exciting to report that all the modalities mentioned earlier are actively being investigated, and each of them may become important to varying degrees. Testing of free fetal DNA in maternal blood to determine fetal genotype for HPA-1a is now routinely attainable in the United States. This should be used whenever possible right now to eliminate invasive procedures done exclusively for that purpose. DRB3*0101 is now well accepted as a crucial component in determining the risk of sensitization to HPA-1a and will have to be an integral part of population screening for HPA 1a. High-throughput platelet antigen screening is now possible, so the technology for instituting population screening of women at risk of acquiring FNAIT certainly exists. Studies for testing the efficacy of FNAIT prophylaxis are in the very early stages, but one lot of "NAITgam" has already been made and is being investigated in proof of concept studies. However, the likelihood of combining both screening and prophylaxis to drastically reduce the incidence of FNAIT is years away. Large-scale clinical trials will need to be performed to evaluate efficacy, safety, and cost-benefit before screening of all pregnancies and "NAITgam" prophylaxis of women at risk of developing FNAIT can become a reality.

Blocking transfer of maternal IgG to the fetus by inhibition of FcRn in HDFN is currently being studied. At least 4 different forms of this agent are also being evaluated for a number of indications in nonpregnant patients. If the studies in severe cases of HDFN prove to be safe and successful, we believe they hold great promise for revolutionizing the management of FNAIT.

What could FNAIT look like in 2030? Ideally, if screening and effective prophylaxis for this disease in HPA 1a positive women become standard of care, severe FNAIT would be almost entirely eliminated, as has occurred with Rho D incompatibility in HDFN. In those few cases of FNAIT that were subsequently identified, which occurred because of lack of screening, failure of prophylaxis, or secondary to other platelet antigens, antenatal management with an inhibitor of FcRn to block transplacental transfer of disease-causing maternal IgG would become routine. In turn, that safe and highly effective form of therapy would make treatment with IVIG and prednisone a thing of the past. However, it remains to be seen whether these aspirations can be achieved. ■

REFERENCES

1. Pacheco LD, Berkowitz RL, Moise KJ Jr, Bussel JB, McFarland JG, Saade GR. Fetal and neonatal alloimmune thrombocytopenia: a management algorithm based on risk stratification. Obstet Gynecol 2011;118:1157–63.
2. Mueller-Eckhardt C, Kiefel V, Grubert A, et al. 348 Cases of suspected neonatal alloimmune thrombocytopenia. Lancet 1989;1:363–6.
3. Lieberman L, Greinacher A, Murphy MF, et al. Fetal and neonatal alloimmune thrombocytopenia: recommendations for evidence-based practice, an international approach. Br J Haematol 2019;185:549–62.
4. Peterson JA, Gitter M, Bougie DW, et al. Low-frequency human platelet antigens as triggers for neonatal alloimmune thrombocytopenia. Transfusion 2014;54:1286–93.
5. Ohto H. [Neonatal alloimmune thrombocytopenia]. Nihon Rinsho 1997;55:2310–4.
6. Xue M, Liu YC, Wei P. [Genetic polymorphism of human platelet antigens 1-18 in Chinese Nanjing Han population]. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2012;20:1235–9.
7. Bussel JB, Zacharoulis S, Kramer K, McFarland JG, Pauliny J, Kaplan C. Clinical and diagnostic comparison of neonatal alloimmune thrombocytopenia to non-immune cases of thrombocytopenia. Pediatr Blood Cancer 2005;45:176–83.
8. Lakkaraja M, Berkowitz RL, Vinograd CA, et al. Omission of fetal sampling in treatment of subsequent pregnancies in fetal-neonatal alloimmune thrombocytopenia. Am J Obstet Gynecol 2016;215:471.e1–9.
9. Kiefel V, Bassler D, Kroll H, et al. Antigen-positive platelet transfusion in neonatal alloimmune thrombocytopenia (NAIT). Blood 2006;107:3761–3.
10. Bussel JB, Berkowitz RL, McFarland JG, Lynch L, Chitkara U. Antenatal treatment of neonatal alloimmune thrombocytopenia. N Engl J Med 1988;319:1374–8.
11. Bussel JB, Berkowitz RL, Lynch L, et al. Antenatal management of alloimmune thrombocytopenia with intravenous gamma-globulin: a randomized trial of the addition of low-dose steroid to intravenous gamma-globulin. Am J Obstet Gynecol 1996;174:1414–23.
12. Bussel JB, Berkowitz RL, Hung C, et al. Intracranial hemorrhage in alloimmune thrombocytopenia: stratified management to prevent recurrence in the subsequent affected fetus. Am J Obstet Gynecol 2010;203:135.e1–14.
13. Berkowitz RL, Kolb EA, McFarland JG, et al. Parallel randomized trials of risk-based therapy for fetal alloimmune thrombocytopenia. Obstet Gynecol 2006;107:91–6.
14. Arnold DM, Smith JW, Kelton JG. Diagnosis and management of neonatal alloimmune thrombocytopenia. Transfus Med Rev 2008;22:255–67.
15. McBain RD, Crowther CA, Middleton P. Anti-D administration in pregnancy for preventing Rhesus alloimmunisation. Cochrane Database Syst Rev 2015;(9):CD000020.
16. Jin JC, Lakkaraja MM, Ferd P, et al. Maternal sensitization occurs before delivery in severe cases of fetal alloimmune thrombocytopenia. Am J Hematol 2019;94:E213–5.
17. Moise KJ Jr, Argoti PS. Management and prevention of red cell alloimmunization in pregnancy: a systematic review. Obstet Gynecol 2012;120:1132–9.
18. Liu ZJ, Bussel JB, Lakkaraja M, et al. Suppression of in vitro megakaryopoiesis by maternal sera containing anti-HPA-1a antibodies. Blood 2015;126:1234–6.
19. Kjaer M, Bertrand G, Bakchoul T, et al. Maternal HPA-1a antibody level and its role in predicting the severity of Fetal/Neonatal alloimmune thrombocytopenia: a systematic review. Vox Sang 2019;114:79–94.

20. Ward MJ, Pauliny J, Lipper EG, Bussel JB. Long-term effects of fetal and neonatal alloimmune thrombocytopenia and its antenatal treatment on the medical and developmental outcomes of affected children. Am J Perinatol 2006;23:487–92.

21. Williamson LM, Hackett G, Rennie J, et al. The natural history of fetomaternal alloimmunization to the platelet-specific antigen HPA-1a (PlA1, Zwa) as determined by antenatal screening. Blood 1998;92:2280–7.

22. Turner ML, Bessos H, Fagge T, et al. Prospective epidemiologic study of the outcome and cost-effectiveness of antenatal screening to detect neonatal alloimmune thrombocytopenia due to anti-HPA-1a. Transfusion 2005;45:1945–56.

23. Killie MK, Kjeldsen-Kragh J, Husebekk A, Skogen B, Olsen JA, Kristiansen IS. Cost-effectiveness of antenatal screening for neonatal alloimmune thrombocytopenia. BJOG 2007;114:588–95.

24. Kjær M, Geisen C, Akkök ÇA, et al. Strategies to develop a prophylaxis for the prevention of HPA-1a immunization and fetal and neonatal alloimmune thrombocytopenia. Transfus Apher Sci 2020;59:102712.

25. Kjeldsen-Kragh J, Fergusson DA, Kjaer M, et al. Fetal/neonatal alloimmune thrombocytopenia: a systematic review of impact of HLA-DRB3*01:01 on fetal/neonatal outcome. Blood Adv 2020;4:3368–77.

26. Winkelhorst D, Porcelijn L, Muizelaar E, Oldert G, Huiskes E, van der Schoot CE. Fast and low-cost direct ELISA for high-throughput serological HPA-1a typing. Transfusion 2019;59:2989–96.

27. Fontão-Wendel R, Wendel S, Odone V, Carneiro JD, Silva L, Isfer E. A case report of neonatal alloimmune thrombocytopenic purpura: the importance of correct diagnosis for future pregnancies. Sao Paulo Med J 2005;123:198–200.

28. Kjeldsen-Kragh J. New elegant methods for maternal and fetal HPA-1a typing. Transfusion 2018;58:2253–4.

29. McFarland JG, Aster RH, Bussel JB, Gianopoulos JG, Derbes RS, Newman PJ. Prenatal diagnosis of neonatal alloimmune thrombocytopenia using allele-specific oligonucleotide probes. Blood 1991;78:2276–82.

30. van der Schoot CE, Thurik F, Scheffer PG, et al. Prenatal fetal DNA testing for predicting HDFN, FNAIT, and RhIG candidacy. Blood 2013;122.

31. Brinc D, Le-Tien H, Crow AR, Siragam V, Freedman J, Lazarus AH. Immunoglobulin G-mediated regulation of the murine immune response to transfused red blood cells occurs in the absence of active immune suppression: implications for the mechanism of action of anti-D in the prevention of haemolytic disease of the fetus and newborn? Immunology 2008;124:141–6.

32. Kumpel BM. Monoclonal anti-D development programme. Transpl Immunol 2002;10:199–204.

33. Flegel WA. The genetics of the Rhesus blood group system. Blood Transfus 2007;5:50–7.

34. Weng YJ, Husebekk A, Skogen B, Kjaer M, Lin LT, Burnouf T. Anti-human platelet Antigen-1a immunoglobulin G preparation intended to prevent fetal and neonatal alloimmune thrombocytopenia. PLoS One 2016;11:e0162973.

35. Tiller H, Killie MK, Chen P, 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 2012;52:1446–57.

36. Pyzik M, Sand KMK, Hubbard JJ, Andersen JT, Sandlie I, Blumberg RS. The neonatal Fc receptor (FcRn): a misnomer? Front Immunol 2019;10:1540.

37. Patel DD, Bussel JB. Neonatal Fc receptor in human immunity: function and role in therapeutic intervention. J Allergy Clin Immunol 2020;146:467–78.

38. Damas OM, Deshpande AR, Avalos DJ, Abreu MT. Treating inflammatory bowel disease in pregnancy: the issues we face today. J Crohns Colitis 2015;9:928–36.

39. Newland AC, Sánchez-González B, Rejtő L, et al. Phase 2 study of efgartigimod, a novel FcRn antagonist, in adult patients with primary immune thrombocytopenia. Am J Hematol 2020;95:178–87.

40. Robak T, Kaźmierczak M, Jarque I, et al. Phase 2 multiple-dose study of an FcRn inhibitor, rozanolixizumab, in patients with primary immune thrombocytopenia. Blood Adv 2020;4:4136–46.

41. Izumi K, Bieber K, Ludwig RJ. Current clinical trials in pemphigus and pemphigoid. Front Immunol 2019;10:978.

42. Menon D, Barnett C, Bril V. Novel treatments in myasthenia gravis. Front Neurol 2020;11:538.

43. Urbaniak SJ, Duncan JI, Armstrong-Fisher SS, Abramovich DR, Page KR. Transfer of anti-D antibodies across the isolated perfused human placental lobule and inhibition by high-dose intravenous immunoglobulin: a possible mechanism of action. Br J Haematol 1997;96:186–93.

44. El-Bohy M, Poowuttikul P, Secord E. Humoral immune deficiencies of childhood. Pediatr Clin North Am 2019;66:897–903.