Fetal and Neonatal Alloimmune Thrombocytopenia

A Management Algorithm Based on Risk Stratification

Luis D. Pacheco, MD, Richard L. Berkowitz, MD, Kenneth J. Moise, Jr, MD, James B. Bussel, MD, Janice G. McFarland, MD, and George R. Saade, MD

Fetal and neonatal alloimmune thrombocytopenia constitutes the most common cause of severe thrombocytopenia in fetuses and neonates and of intracranial hemorrhage among term newborns. The cornerstone of therapy involves the use of steroids and intravenous immunoglobulins. Despite the risk of potentially devastating consequences to the fetus, fetal blood sampling has typically been used to document response to therapy. We propose a therapeutic algorithm based on risk stratification with individualized treatment optimization without the use of fetal blood sampling.

(Obstet Gynecol 2011;118:1157–63)
DOI: 10.1097/AOG.0b013e31823403f4

From the Divisions of Maternal Fetal Medicine and Surgical Critical Care, Departments of Obstetrics & Gynecology and Anesthesiology, The University of Texas Medical Branch at Galveston; Division of Maternal fetal Medicine, Department of Obstetrics & Gynecology, Columbia University Medical Center; Department of Obstetrics & Gynecology and Reproductive Sciences, University of Texas School of Medicine, Houston, Texas; Department of Obstetrics & Gynecology and Pediatrics, Weill Medical College of Cornell University, New York, New York; Division of Hematology-Oncology, Department of Medicine, Medical College of Wisconsin, and Platelet and Neutrophil Immunology Laboratory, BloodCenter of Wisconsin; Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology, The University of Texas Medical Branch at Galveston.

The authors thank the Ob/Gyn Publication, Grant, and Media Support Department director and staff for editorial and graphic assistance, including R.G. McConnell, LeAnne Garcia, and Alan Sheffield.

Corresponding author: Luis D. Pacheco, MD, The University of Texas Medical Branch at Galveston, 301 University Blvd., Galveston, TX 77555-0587; e-mail: ldpachec@utmb.edu.

Financial Disclosure
Dr. Bussel has received clinical research support from Amgen, Cangene, GlaxoSmithKline, Genzyme, IgG of America, Immunomedics, Ligand, Eisai, Inc., Shionogi, and Sysmex. He has participated in advisory boards for Amgen, GlaxoSmithKline, Ligand, Shionogi, and Eisai. He has had a 1-day consult with Portola. The other authors did not report any potential conflicts of interest.

© 2011 by The American College of Obstetricians and Gynecologists. Published by Lippincott Williams & Wilkins.
ISSN: 0029-7844/11

Fetal and neonatal alloimmune thrombocytopenia is the most common etiology of severe thrombocytopenia in fetuses and neonates and of intracranial hemorrhage in term newborns.[1–5] From prospective studies, the incidence of this disease has been estimated to be 1 out of 1,000 live births. This condition results from incompatibility between parents for platelet-specific antigens. The most frequently involved antigen is human platelet antigen-1a (HPA-1a), followed by HPA-5-b, HPA-1b, and HPA-15.[6] These antigens are inherited in the fetus in an autosomal codominant fashion. Fetal-maternal passage of platelets leads to the development of specific antibodies to the exposed antigen in the pregnant patient. Unlike Rhesus disease, these antibodies may cross the placenta and cause severe fetal thrombocytopenia, even during the index pregnancy.[7–9] The most significant complication of fetal and neonatal alloimmune thrombocytopenia is intracranial hemorrhage; the latter occurs in 10–20% of affected pregnancies, with 75% of these occurring before birth.[10]

Because of the low prevalence of this disorder and inability to predict the severity of cases at potential risk, screening for platelet antigens or antiplatelet antibodies during pregnancy is not cost-effective. The diagnosis is usually made after an affected pregnancy when either severe unexplained thrombocytopenia presents in a neonate, or fetal or neonatal intracranial hemorrhage is diagnosed in the presence of thrombocytopenia. Once the condition is suspected, confirmation of the diagnosis requires both demonstration of platelet-specific antigen incompatibility between the parents or between the mother and the neonate, and the presence of maternal antibodies against the involved antigen. Because the majority of intracranial hemorrhages occur before the onset of labor, treatment must be instituted antenatally to prevent them.[11] The cornerstone of therapy has been maternal admin-

Copyright© American College of Obstetricians and Gynecologists

istration of steroids and intravenous immunoglobulin (IVIG).[12]

Fetal and neonatal alloimmune thrombocytopenia has a wide spectrum of severity ranging from isolated mild thrombocytopenia to lethal intracranial hemorrhage.[2] In most cases, the severity of the disorder in the current pregnancy appears to be directly proportional to that in preceding pregnancies, which means that therapy regimens have to be individualized based on the patient's history. The need to stratify therapy in this disorder is necessary because the therapy required is expensive and can be associated with significant side effects. Undertreatment may result in disastrous fetal outcomes, whereas overtreatment can cause unnecessary maternal problems and be excessively costly for our society. Furthermore, response to therapy has traditionally been evaluated by means of fetal blood sampling to determine platelet counts. Not surprisingly, serious complications requiring emergent delivery have been noted after this procedure in a number of cases, and some have resulted in death in utero.[12]

Two recent publications have addressed the concept of stratified management of fetal and neonatal alloimmune thrombocytopenia.[13,14] These studies indicate that patients with this disorder should be subdivided into groups according to the presence or absence of an intracranial hemorrhage in their prior affected pregnancy and, if present, the timing of its occurrence. Intensity of therapy should be tailored accordingly, and the role of fetal blood sampling should be minimized because of the potential morbidity associated with that procedure.

The purpose of this article is to establish a simplified management algorithm that includes all strata of risks. Management options for four possible clinical categories will be presented, and recommendations regarding fetal blood sampling, route of delivery, peripartum considerations, and treatment regimens will be addressed. It should be noted, however, that many of the recommendations made in this presentation are based on the authors' experience, as well as review of the largest existing published studies, and are not solely based on the highest levels of evidence-based data. The acquisition of further knowledge may require alterations in the diagnostic and management recommendations included in this article.

STRATUM 1

History of previous fetus or newborn with thrombocytopenia or intracranial hemorrhage of unknown etiology. Paternal incompatibility for human platelet antigens may be documented, but specific anti-HPA antibody is not present.

These patients cannot be classified as having fetal and neonatal alloimmune thrombocytopenia but have the potential to develop specific antiplatelet antibodies not previously detected as the pregnancy progresses. These women do not require empiric therapy early in the pregnancy, but we believe should be followed with maternal anti-HPA antibody screening (testing against panel platelets expressing HPA antigens implicated in cases of alloimmune thrombocytopenia like HPA 1–6,9,15) and cross matching with paternal platelets at 12, 24, and 32 weeks of gestation. Cross matching paternal platelets with maternal serum is performed to detect rare antigens that may only be present on paternal platelets. Management of this stratum is described in Figure 1. If those antibody studies remain negative, the fetus is very unlikely to be affected by fetal and neonatal alloimmune thrombocytopenia, and no therapy is necessary. If, however, anti-HPA antibodies are detected, the patient should be treated according to the regimen described in Figure 2.

A very small number of these cases may involve rare HPA antigen incompatibilities that are not currently detectable by the usual screening techniques. Therefore, if a complete diagnostic work-up has been performed and there is no evidence of any platelet antigen incompatibility between the patient and the father of the fetus or of a maternal anti-HPA antibody, we recommend performing a single antibody screening study which includes crossmatching of maternal and paternal platelets at 30 weeks of gestation. If that study is negative, no further evaluation or therapy is necessary.

STRATUM 2

History of previous fetus or newborn with serologically confirmed fetal and neonatal alloimmune thrombocytopenia having only thrombocytopenia and no evidence of an intracranial hemorrhage. Once the diagnosis has been confirmed according to Figure 1, therapy should be initiated at 20 weeks of gestation and modified at 32 weeks of gestation according to Figure 2. Previous data utilizing this treatment modality coupled with fetal blood sampling at 32 weeks of gestation prevented intracranial hemorrhage in all 73 patients involved in that series.[13] Expanded data from this series indicate that there have been only three cases of grade 1 intracranial hemorrhage out of almost 100 cases, which is what would be expected for a similar group of normal term neonates.

We propose avoiding fetal blood sampling owing to its inherent risk and instead instituting salvage

Copyright© American College of Obstetricians and Gynecologists

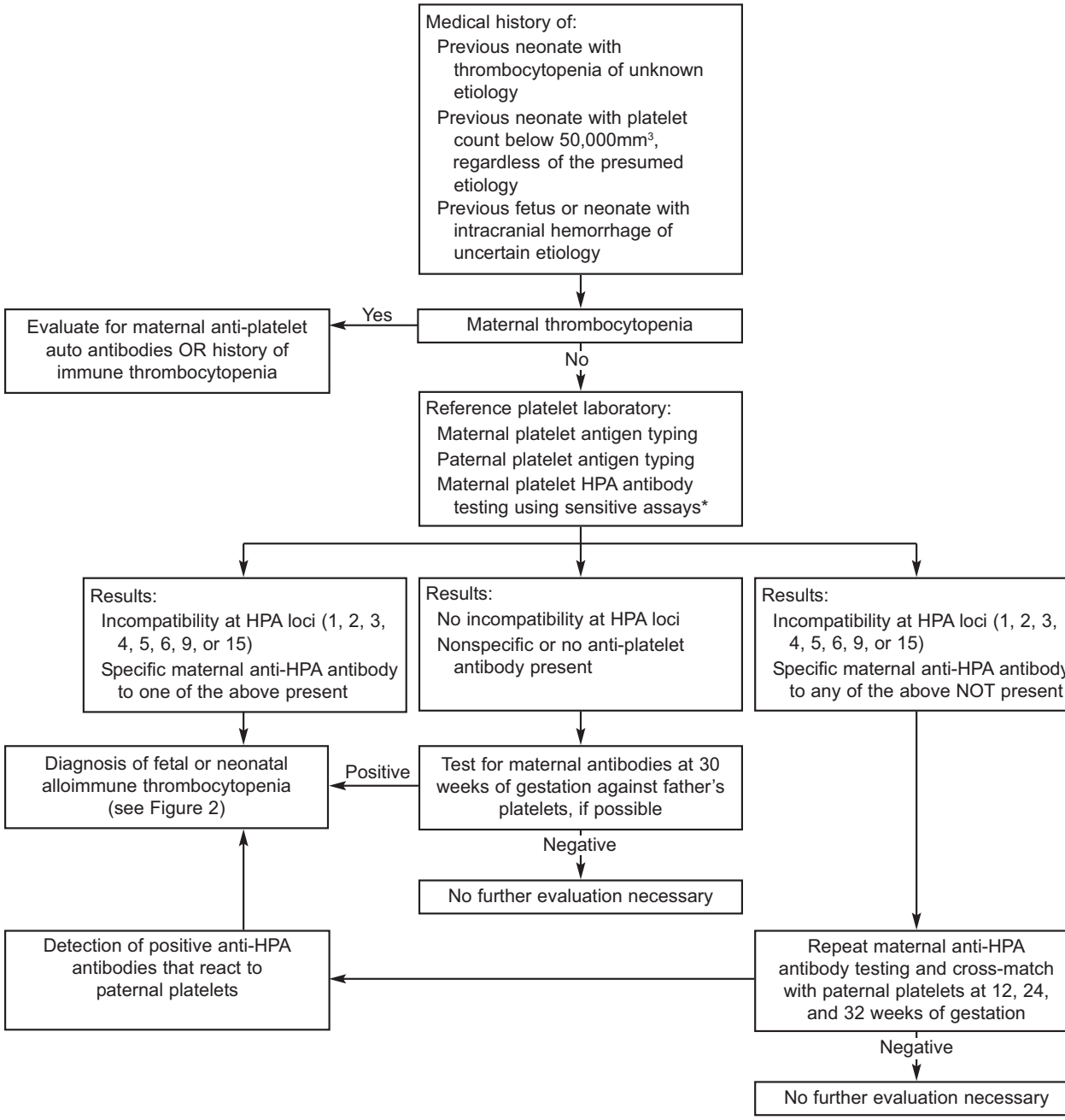

Fig. 1. Platelet alloimmunization algorithm 1. *Examples of sensitive assays include MACE (modified antigen capture enzyme-linked immunosorbent assay [ELISA]) and MAIPA (monoclonal antibody immobilization of platelet antigens). HPA, human platelet antigen.

Pacheco. Fetal and Neonatal Alloimmune Thrombocytopenia. Obstet Gynecol 2011.

empiric therapy in all cases at 32 weeks of gestation. Because the actual fetal platelet count remains unknown until after birth, these women should have an elective cesarean delivery at 37–38 weeks of gestation after documentation of fetal lung maturity. For those patients who would like to deliver vaginally, fetal blood sampling can be performed after 32 weeks of gestation to determine the fetal platelet count after a discussion of the risks associated with that procedure. If the platelet count is found to be higher than 100,000 mm^3, vaginal delivery at 37–38 weeks of gestation appears to be safe. An alternative approach might be to perform fetal blood sampling at 37–38 weeks of gestation in a patient with an inducible cervix, with a

Copyright© American College of Obstetricians and Gynecologists

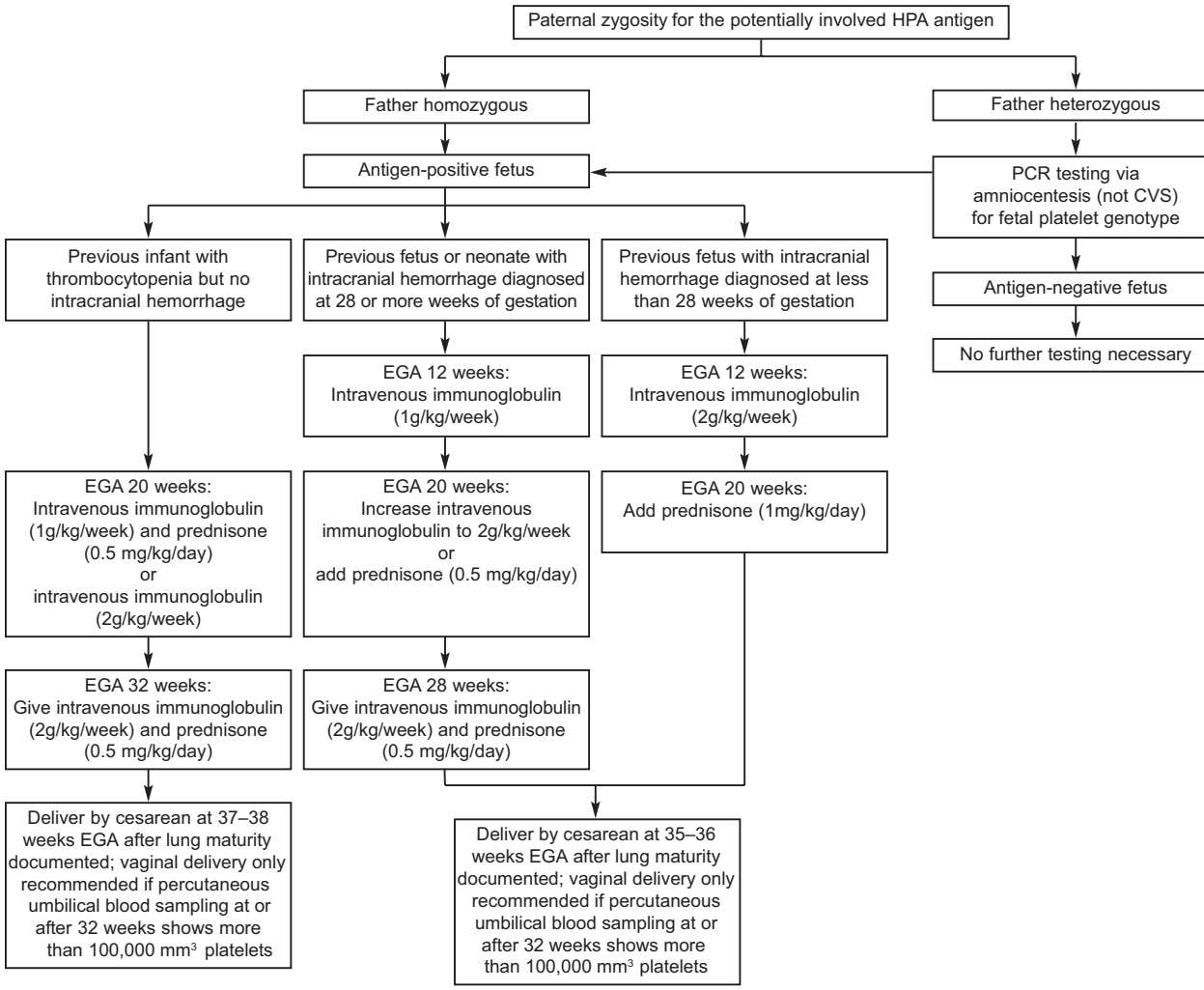

Fig. 2. Platelet alloimmunization algorithm 2. HPA, human platelet antigen; PCR, polymerase chain reaction; CVS, chorionic villus sampling; EGA, estimated gestational age.
Pacheco. Fetal and Neonatal Alloimmune Thrombocytopenia. Obstet Gynecol 2011.

plan to administer a fetal transfusion of gamma irradiated, volume reduced platelets (either from a HPA-typed donor file or the mother) if the platelet count is found to be between 30,000 mm^3 and 80,000 mm^3. In that case, the induction should be commenced immediately after completion of the procedure. It should be noted, however, that only anecdotal information exists regarding the safety and efficacy of this approach.

STRATUM 3 (HIGH RISK)

History of serologically confirmed fetal and neonatal alloimmune thrombocytopenia and previous fetus or newborn with intracranial hemorrhage at 28 weeks of gestation or more (includes peripartum and neonatal intracranial hemorrhage). Treatment in this stratum should start at 12 weeks of gestation using IVIG 1 g/kg/wk with augmentation of therapy at 20 weeks of gestation by either increasing the IVIG to 2 g/kg/wk or adding 0.5 mg/kg/d of prednisone to the initial dose of IVIG. Further augmentation of therapy is recommended for all patients in this category at 28 weeks of gestation so that they will then each receive IVIG 2 g/kg/wk plus prednisone 0.5 mg/kg/d until delivery (Fig. 2). In a previous series of patients in this category, intracranial hemorrhage was noted in 2 of 12 cases, both of which started treatment after 20 weeks of gestation.[14]

The rationale for these recommendations is that virtually all the women in the previous study who were given prednisone at a dose of 1 mg/kg/d were extremely displeased with the side effects of that regimen. Expanded data from a continuation of that

Copyright© American College of Obstetricians and Gynecologists

study, however, indicate that 10–20% of the women in this stratum who underwent fetal blood sampling while taking either IVIG 2 g/kg/wk or IVIG 1 g/kg/wk plus prednisone 0.5 mg/kg/d had fetal platelet counts lower than 50,000 mm^3. This suggests that neither of those regimens is adequate in itself without further augmentation. This regimen represents a compromise between providing maximally intensive therapy while avoiding the unpleasant side effects of prolonged administration of prednisone at a dose of 1 mg/kg/d.

STRATUM 4 (EXTREMELY HIGH RISK)

History of serologically confirmed fetal and neonatal alloimmune thrombocytopenia and previous fetus with intracranial hemorrhage at less than 28 weeks. This group has the highest risk of having a recurrent early intracranial hemorrhage in subsequent pregnancies. Aggressive therapy starts at 12 weeks of gestation with IVIG 2 g/kg/wk, and all patients should receive additional therapy with prednisone 1 mg/kg/wk at 20 weeks of gestation for the remainder of the pregnancy (see Fig. 2). Although there are few published data to guide therapy, lower-dose IVIG at 1 g/kg/wk plus prednisone 1 mg/kg/d starting as early as 12 weeks of gestation was ineffective in preventing intracranial hemorrhage in one patient in this group. When IVIG was increased to 2 g/kg/wk starting at 12 weeks of gestation, no further intracranial hemorrhages were noted among the seven cases treated in this fashion, and the birth platelet count was higher than 50,000 mm^3 in all of the neonates.[14] Therefore, despite the unpleasant side effects mentioned above, we feel that women in this exceptionally high risk group should be taking high-dose IVIG starting at 12 weeks of gestation and maximal therapy from 20 weeks of gestation until delivery.

FETAL BLOOD SAMPLING

Fetal blood sampling has traditionally been included in the management of alloimmune thrombocytopenia to evaluate the response to therapy and identify those fetuses that might benefit from more intense treatment.[7] Unfortunately, serious complications during fetal blood sampling in the setting of alloimmune thrombocytopenia have been reported in 0–8% of the cases.[8,9,12,15] We therefore propose early empiric implementation of optimized therapy according to risk of recurrence based on severity stratification as opposed to undertaking fetal blood sampling to identify which patients need additional therapy.

We currently believe that fetal blood sampling should be reserved for patients who are interested in having a vaginal delivery. In those cases, the procedure would be performed after 32 weeks of gestation to document that the fetal platelet response to therapy has been adequate enough to safely permit a vaginal delivery to occur, and late enough in gestation to emergently deliver a viable newborn if any complications occur.

If fetal blood sampling is to be performed, we recommend the following: an experienced operator, use of a small-diameter sampling needle (22-gauge), performance in an operating room setting in the event that an emergent delivery is required, immediate access to an automated hemocytometer so that a rapid platelet count can be obtained (preferably available in the operating room), and the availability of antigen-negative platelets for transfusion if the fetal platelet count is less than 50,000 mm^3.

PERIPARTUM AND DELIVERY CONSIDERATIONS

Ideally, maternal plateletpheresis or platelet donation via whole blood should be undertaken 3 days before planned delivery to have antigen-free platelets immediately available for the neonate. All maternal screening for infectious markers required before blood donation (hepatitis screening and cytomegalovirus) should be undertaken several days before the planned platelet harvest. Communication with the blood bank is fundamental. Platelets are stored at room temperature and therefore have only a 5-day shelf life. In addition, these platelets may require concentrating to minimize the quantity of maternal antiplatelet antibody before being infused into the neonate. Any additional handling of the platelets should be kept to a minimum and performed immediately before their use because they may be activated by these procedures.

In some cases, maternal IVIG therapy will result in false-positive infectious markers that will preclude a mother from donating her own platelets. Ideally, the mother should be tested for all relevant markers required by the blood bank before instituting IVIG therapy (eg, HIV1/2, HTLV1, and hepatitis B and C). This will make it much easier to identify cases of falsely positive markers of infection. In cases where either the mother is not allowed to donate platelets or another donor is preferred, further consultation with regional blood bank services will identify a specific platelet donor through their "rare donor" files.

If fetal blood sampling is not performed, we recommend delivery by cesarean at 37 to 38 weeks of gestation for patients with no history of an intracranial hemorrhage in a prior pregnancy (stratum 2), and at 35 to 36 weeks in those with a prior affected newborn

Copyright© American College of Obstetricians and Gynecologists

or fetus with an intracranial hemorrhage (strata 3 and 4), after documentation of fetal lung maturity in all cases. If a patient strongly desires a vaginal delivery, we recommend that fetal blood sampling be performed after 32 weeks of gestation, and only those cases where the fetal platelet count is above 100,000 mm^3 should be allowed a trial of labor.[13] Regardless of the mode of delivery, clinicians should avoid the use of forceps or vacuum except in extreme circumstances.

THERAPEUTIC AGENTS

Oral prednisone is typically used in fetal and neonatal alloimmune thrombocytopenia in a dose of 0.5–1 mg/kg/d. Obstetricians are generally familiar with the use of steroids during pregnancy. Common side effects include hypertension, fluid retention, hyperglycemia, diabetes, immunosuppression, mood swings, acne, and osteoporosis. Patients treated with steroids should be screened for gestational diabetes monthly and supplemented with calcium (1 g/d) and vitamin D (400 units/d).

Intravenous human immunoglobulin has been the most successful treatment in fetal and neonatal alloimmune thrombocytopenia.[13] It is prepared from plasma pooled from thousands of donors.[16] Different products are available, each with specific infusion recommendations. The latter has created confusion in administration patterns. In general, however, all of these preparations usually can be infused at a dose of 1 g/kg over 4 to 5 hours. The initial infusion may need to be administered more slowly and should always be given in the hospital. Subsequent infusions can be given more rapidly in a variety of settings, including the patient's home.

The infusion recommendations of currently available IVIG preparations are shown in Table 1. Common side effects of IVIG include headache, flushing, myalgia, low back pain, nausea, hypotension, wheezing, and fever or chills. When IVIG is used to treat fetal and neonatal alloimmune thrombocytopenia, headaches are the most common side effect and may range from being mild to severe (ie, aseptic meningitis). Corticosteroids offer the best prophylaxis for headaches, with doses of methylprednisolone ranging from 10–20 mg orally to 1 g intravenously given before the infusion of IVIG, but many of these reactions can also be ameliorated or prevented by premedicating patients with acetaminophen (650 mg) and dyphenhydramine (25–50 mg). Other maneuvers include hydration with intravenous fluids (before, during, and after administration) and slowing the infusion rate.[17] If headaches occur despite premedica-

Table 1. Currently Available Intravenous Immunoglobulin Preparations

	Gamunex (Talecris Biotherapeutics)	Privigen (CSL Behring)	Gammagard (Baxter)	Flebogamma (Grifols Biologicals, Inc.)
IgG content (%)	98 or higher	98 or higher	98 or higher	97 or higher
Concentration (%)	10	10	10	5
Dilutent	None	None	None (if 5% dilution is desired, dextrose in water should be used)	None
Flushing compatibility	Dextrose	Saline or dextrose	Saline or D5W	Saline
Form	Liquid	Liquid	Liquid	Liquid
IgA content	46 micrograms/mL	Less than 25 micrograms/mL	37 micrograms/mL	Less than 50 micrograms/mL
Initial infusion rate	0.01 mL/kg/min (1 mg/kg/min) for first 30 min	0.5/mg/kg/min	0.8 mg/kg/min	0.5 mg/kg/min
Maximum infusion rate	0.08 mL/kg/min (8 mg/kg/min)	4 mg/kg/min	8 mg/kg/min	5 mg/kg/min
Sucrose content	None	None	None	None
Contraindications	IgA deficiency	IgA deficiency	IgA deficiency, anaphylactic or severe systemic reaction to human immunoglobulin	IgA deficiency, anaphylactic reactions to blood-derived products, intolerance to any component of Flebogamma
Pricing ($/g)	64.73	66.50	137.92	72.50

Ig, immunoglobulin; D5W, 5% dextrose in water.
Other products such as Hizentra and Vivaglobin (both CSL Behring) are not included because route of administration is subcutaneous. Octagam (OCTAPHARMA) was not available at the time of this writing.

Copyright© American College of Obstetricians and Gynecologists

tion with the regimens described above, prednisone 10 mg orally plus acetaminophen 650 mg given every 4 to 6 hours for a maximum of five doses will usually provide relief. True anaphylactic reactions are rare, albeit more frequent in sensitized women with IgA deficiency.[16] The latter group will benefit from IVIG preparations that are very low or deficient in IgA. Rarely aseptic meningitis, acute kidney injury, arterial or venous thrombosis, hemolytic anemia, and stroke may occur.

As mentioned above, the first infusion must be performed in a hospital setting or medical office with experience in dealing with the side effects of this medication. Specialized home health care agencies are available for subsequent infusions to minimize the effect on the patient's lifestyle. If a patient is receiving IVIG twice a week, we recommend that the infusions not be administered on consecutive days.

CONCLUSION

In conclusion, despite fetal and neonatal alloimmune thrombocytopenia's being a rare disease, it is still the most common cause of severe thrombocytopenia in the fetus or neonate and it is the most common cause of intracranial hemorrhage in term newborns. Recurrence of this disease may be prevented by implementing timely and adequate therapy to the mother. The management algorithms presented here should help clinicians in the management of this important condition by stratifying cases according to the severity of the patient's history and differentiating therapeutic intensity according to those categories.

REFERENCES

1. Hohlfeld P, Forestier F, Kaplan C, Tissot JD, Daffos F. Fetal thrombocytopenia: a retrospective study of 5,194 fetal blood samplings. Blood 1994;84:1851–6.
2. Bussel JB, Zabusky ME, Berkowitz RL, McFarland JG. Fetal alloimmune thrombocytopenia. N Engl J Med 1997;337:22–6.
3. Mao C, Guo J, Chituwo BM. Intraventricular hemorrhage and it's prognosis, prevention, and treatment in term infants. J Trop Pediatr.1999;45:237–40.
4. 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.
5. Turner M, Bessos H, Fagge T, Harkness M, Rentoul F, Seymour J, 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.
6. Davoren A, Curtis BR, Aster RH, McFarland JG. Human platelet antigen specific alloantibodies implicated in 1162 cases of neonatal alloimmune thrombocytopenia. Transfusion 2004; 44:1220–5.
7. Bussel JB, Berkowitz RL, Lynch L, Lesser ML, Paidas MJ, Huang CL, et al. Antenatal management of alloimmune thrombocytopenia with intravenous gamma-globulin: a randomized trial of the addition of low dose steroids to intravenous gamma-globulin. Am J Obstet Gynecol 1996;174: 1414–23.
8. Kanhai HH, Porcelijn L, van Zoeren D, Klumper F, Viëtor H, Meerman RH, et al. Antenatal care in pregnancies at risk of alloimmune thrombocytopenia: report of 19 cases in 16 families. Eur J Obstet Gynecol Reprod Biol 1996;68:67–73.
9. Silver RM, Porter TF, Branch DW, Esplin MS, Scott JR. Neonatal alloimmune thrombocytopenia: antenatal management. Am J Obstet Gynecol. 2000;182:1233–8.
10. Pearson HA, Shulman NR, Marder VJ, Cone TE Jr. Isoimmune neonatal thrombocytopenic purpura: clinical and therapeutic considerations. Blood 1964;23:154–77.
11. Bonacossa IA, Jocelyn LJ. Alloimmune thrombocytopenia of the newborn: neurodevelopmental sequelae. Am J Perinatol 1996;36:426–31.
12. Berkowitz RL, Kolb EA, McFarland JG, Wissert M, Primani A, Lesser M. Parallel randomized trials of risk-based therapy for fetal alloimmune thrombocytopenia. Obstet Gynecol 2006; 107:91–6.
13. Berkowitz RL, Lesser ML, McFarland JG, Wissert M, Hung C, Bussel JB. Antepartum treatment without early cordocentesis for standard-risk alloimmune thrombocytopenia. Obstet Gynecol 2007;110:249–55.
14. Bussel JB, Berkowitz RL, Hung C, Kolb EA, Wissert M, Primiani A, 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.
15. Sainio S, Teramo K, Kekomaki R. Prenatal treatment of severe fetomaternal alloimmune thrombocytopenia. Transfus Med 1999;9:321–30.
16. Lemm G. Composition and properties of IVIg preparations that affect tolerability and therapeutic efficacy. Neurology 2002;59:S28–32.
17. Grillo JA, Gorson KC, Ropper AH, Lewis J, Weinstein R. Rapid infusion of intravenous immune globulin in patients with neuromuscular disorders. Neurology 2001;57:1699–701.

Copyright© American College of Obstetricians and Gynecologists