

Immune thrombocytopenia in the newborn

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Abstract

The leading cause of moderate or severe thrombocytopenia in otherwise healthy appearing neonates is immune thrombocytopenia. Immune thrombocytopenia in the fetus or newborn may result from platelet alloantibodies against paternal antigens inherited by the fetus (alloimmune thrombocytopenia) or platelet autoantibodies in the mother with immune thrombocytopenic purpura (ITP). Only 10% of human platelet antigen (HPA)-1a negative mothers who are exposed to HPA-1a positive fetal platelets during pregnancy develop HPA-1a alloantibodies, and 30% of fetuses/neonates will develop thrombocytopenia and 20% of these cases being severe. The most serious complication of severe fetal and neonatal alloimmune thrombocytopenia (FNAIT) is intracranial hemorrhage (ICH), which is detected in 10-20% of affected fetuses/neonates, with most cases occurring antenatally. ICH leads to neurological sequelae in 20%, and deaths in 5-10% cases. There is no evidence-based optimal treatment strategy. Platelet antibody titration in maternal plasma is not helpful for decision-making. The best indicator for current pregnancy is the outcome of the previous pregnancy. The risk of recurrence among subsequent HPA-positive sibling is close to 100% where the previous sibling was affected with antenatal intracranial ICH. The risk of ICH becomes higher with more severe and earlier onset in each subsequent pregnancy. Serial platelet counts should be obtained for the first 5-7 days of delivery to keep the platelet counts higher than 30,000/ μL without active bleeding and higher than 50,000-100,000/ μL with active bleeding. Intravenous immunoglobulin (IVIG) is not alternative to platelet transfusions, since platelet counts don't rise before 24-48 h. In platelet-transfused patients, IVIG can be given to potentially prolong the survival of the incompatible platelets. ITP during pregnancy is not considered a serious risk of perinatal bleeding, but may cause a moderate thrombocytopenia in neonate. In mothers with ITP, the risk of thrombocytopenia is only 10%, with no more than 1% risk of *in utero* ICH.

Keywords

Alloimmune, autoimmune, newborn, pathogenesis, thrombocytopenia, treatment.

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Introduction

Platelets are the second most abundant cell type in circulation after red blood cells. In addition to their vast numbers, the small size of platelets (approximately 2-3 μm in diameter) gives them an important role as circulating controllers of the integrity of the vessel wall. The fundamental role of platelets in hemostasis and thrombosis was first described by the Italian pathologist Giulio Bizzozzero (1846-1901) in 1882 [1]. In mammals, the blood pressure is high so that blood loss from injury is very rapid. Therefore, hemostasis must be very rapid, which is met by platelet aggregation in less than 100 ms. Platelets serve as the “band-aids” of the blood stream and respond to vessel injury by aggregating to form a platelet clot (thrombosis). Although platelets lack a nucleus and genomic DNA, they contain mRNA required for protein synthesis. Therefore, platelets markedly potentiate thrombin generation (coagulation) after thrombosis, and are also involved in vascular repair, angiogenesis, inflammation, and immune responses, with the synthesis of more than 300 proteins [2-5].

Platelets are released from bone marrow megakaryocytes with unknown mechanisms. A single megakaryocyte can give 10,000-30,000 platelets, and circulate for approximately 8-10 days. The normal peripheral blood platelet count is 150,000-400,000/ μL , which is only two thirds of all available platelets, as the rest is sequestered by the spleen. Under conditions of hemostatic need, platelets move from the spleen to the peripheral blood.

The lower range (5th percentile) for infants born < 32 weeks of gestation is 104,000/ μL , and 123,000/ μL for late preterm and term neonates. At birth, the incidence of thrombocytopenia defined by a platelet count < 150,000/ μL is 0.12-0.24% of all neonates. About 0.1-2% of all infants develop thrombocytopenia during the neonatal period.

18-35% of infants admitted to NICUs exhibit thrombocytopenia at least once. In extremely low birth weight neonates (< 1,000 g), the incidence of thrombocytopenia is more than 70%, and severe thrombocytopenia (< 50,000/ μL) is 40% [6].

There are two main causes of neonatal thrombocytopenia: decreased production and increased destruction (consumption) of platelets. Specific maternal/placental disorders (e.g. preeclampsia and gestational diabetes) usually cause mild and self-limiting neonatal thrombocytopenia. Leading causes of moderate or severe thrombocytopenia are infections (in sick neonates) and immune thrombocytopenia (in otherwise healthy appearing neonates). Immune thrombocytopenia in the fetus or newborn may result from platelet alloantibodies against paternal antigens inherited by the fetus, or platelet autoantibodies in the mother with immune thrombocytopenic purpura (ITP) or systemic lupus erythematosus.

Fetal and neonatal alloimmune thrombocytopenia

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is the most common cause of severe thrombocytopenia in the fetus and otherwise healthy newborn, and intracranial hemorrhage (ICH) in term infants. In FNAIT, the mother produces IgG antibodies against fetal antigens inherited from the father. These antibodies can cross the placenta, destroy fetal platelets and may induce severe thrombocytopenia.

Incidence

FNAIT is a rare disease with the incidence of one in 1,000-2,000 live births. Severe FNAIT (platelet count < 25,000/ μL) is thought to be much more uncommon (1/10,000). It represents 3% of all neonatal thrombocytopenia. It is the most common (27%) cause of severe thrombocytopenia (< 50,000/ μL) in the fetal and neonatal period [7-12].

Clinical findings

Most cases of FNAIT are diagnosed incidentally. In mild cases of thrombocytopenia it may be asymptomatic. Petechiae shortly after birth can be the first finding. Therefore FNAIT should be suspected in a thrombocytopenic neonate with extensive petechiae after the differential diagnosis of more common causes

of thrombocytopenia, including maternal ITP and intrauterine viral infections. Gastrointestinal bleeding and hematuria can also be detected. After delivery, the greatest risk of bleeding is in the first 96 hours of life. Neonatal deaths can occur up to 5-10% of cases [9].

The most serious complication of severe FNAIT is ICH, which is detected in 10-20% of affected fetuses/neonates. As many as 75-80% of cases occur antenatally, with most of them occurring before 28 weeks. ICH may be either intraparenchymal or intraventricular, and leads to neurological sequelae in 20%, and deaths in 5-10% of cases [9].

Diagnosis

Diagnosis is based on clinical and serological findings, including a low platelet count and alloimmune antibodies. In addition, determination of the human platelet antigen (HPA) genotype of the mother, father and, if needed, of the child (or fetus) is needed to confirm the diagnosis, especially in cases without detectable antibodies [7]. Parental genotyping is required: if the father is heterozygous, the risk is 50% in fetus, however it is 100% if the father is homozygous. Routine screening for FNAIT in all pregnant women is not recommended, because of high cost, unavailability of practical tests, presence of high frequency of other HPA-antigens discordancy (20%), and no available prophylactic treatments [9].

Pathogenesis

The main contributors to the pathogenesis and factors affecting the severity of FNAIT are (a) fetomaternal incompatibility, (b) maternal exposure to these antigens, (c) maternal alloimmunization with production of IgG antibodies against foreign HPAs, (d) placental transfer of anti-HPA antibodies, and (e) destruction of fetal (and neonatal) platelets [9, 10].

Feto-maternal incompatibility

The platelets carry a still growing number of HPAs, which are further defined according to the frequency in the population as “HPA-a” being high-frequency, and “HPA-b” being low-frequency.

HPAs are located on the platelet membrane glycoprotein (GP) structures. GPIIb (integrin α IIb β) and GPIIIa (integrin β 3) form GPIIb/GPIIIa

(integrin α IIb β 3), and GPIIb α , GPIIb β , GPIIX and GPV form GPIIb-IX-V complex. These GPs serve as receptor for specific ligands (e.g. fibrinogen and von Willebrand factor), and play an important role in platelet adhesion and aggregation [10]. Absence or dysfunction of GPIIb α IIb β 3/IIIa and GPIIb/IX/V are known as Glanzmann's thrombasthenia and Bernard-Soulier disease respectively [9, 10].

Approximately 80% of pregnancies affected by FNAIT are caused by maternal antibodies against HPA-1a, which is the most common HPA haplotype in population. 98% of Caucasian women express HPA-1a (genotypes HPA-1a/1a or HPA-1a/1b). Overall frequency of HPA-1b/1b genotype in mothers is 2%. HPA-1a is carried on the β 3 component of the α IIb β 3 complex (GPIIb/GPIIIa complex), also called the fibrinogen receptor. It is the most abundant molecule on the surface of platelets, and it plays a central role in the formation of thrombosis by binding to fibrinogen, von Willebrand factor, fibronectin and vitronectin, which are all required for hemostasis. The second (10-15%) most common HPA causing FNAIT in Caucasians is HPA-5b, which is expressed on the α 2 subunit of α 2 β 1 (GPIa/IIa), followed by HPA-1b and HPA-15 [9].

In at risk pregnancies, mothers are commonly HPA-1b/1b, and the genotypes of fathers are either HPA-1a/1a or HPA-1a/1b. After an index pregnancy (alloimmunization occurred), 85% of couples are at risk for FNAIT in subsequent pregnancies. However only 10% of HPA-1a negative mothers who are exposed to HPA-1a positive platelets during pregnancy become immunized and develop HPA-1a alloantibodies. Only 30% of fetuses/neonates will develop thrombocytopenia, with 20% of these cases being severe. The risk of recurrence among subsequent HPA-positive sibling is close to 100% where the previous sibling was affected with antenatal ICH. The risk of ICH becomes higher with more severe and earlier onset in each subsequent pregnancy [7, 9, 11, 12].

In addition to HPAs, a large number of antigens present at the cell surface of platelets. Some of them are shared with other blood cells such as the human leukocyte class I antigens (HLA class I) and red cell AB0 blood group antigens. HLA antibodies are adsorbed by fetal HLA antigens in the placenta, and these antibodies do not cause thrombocytopenia. However anti-A or anti-B of the IgG class can cause mild neonatal thrombocytopenia. Interestingly, the presence

of both anti-HPA-1a antibodies and anti-HLA antibodies directed against paternal antigens on platelets do not intensify thrombocytopenia in FNAIT [13].

Maternal exposure to these antigens

Fetal platelets express HPA-1a as early as 16 weeks of gestation. However there are no reports demonstrating the transfer of fetal platelets to maternal circulation during a normal pregnancy. Maternal exposure to platelets probably occurs at delivery, and 0.5-1 ml fetal blood enters the maternal circulation in normal, uncomplicated deliveries. Unlike D sensitization, 40-60% of cases occur in the first pregnancy [7, 9]. This suggests previous maternal exposure to HPA-1a through blood transfusion, prior undetected pregnancies, transfer of fetal platelet, trophoblast or trophoblast particles early in the current pregnancy [10].

Platelets, like other cells, generate extracellular vesicles in diameters of 50-150 nm with plasma membrane budding. These microparticles participate in all platelet functions, mediate cell-to-cell communication, and express surface platelet antigens [14]. Hypothetically, platelet microparticles can pass the placenta and cause alloimmunization.

GPIb α and GPIIb (the α II β subunit of the α IIb β 3 integrin) are expressed only on the platelets and their precursor megakaryocytes. However, GPIIIa (the β 3 subunit of the α IIb β 3 integrin) may also express α V subunit (i.e. α V β 3 integrin) on other cells, including trophoblast and endothelial cells and their progenitors, which mediate vascular (angiogenesis) and placental development [15]. In animal studies, anti-GPIIb β 3 can induce miscarriage through impairment of angiogenesis, which may be the major cause of embryonic hemorrhage, spontaneous miscarriage due to extensive fibrin deposition, and apoptosis and necrosis in mice with anti-GPIIb β 3 antibodies [16-18]. This finding may increase suspicion in the real incidence of FNAIT with increased numbers of undiagnosed fetal losses.

Maternal immunization

HPA antigen incompatibility alone is not sufficient to induce maternal alloimmunization, since only 10% of HPA-1a incompatible pregnancies result in maternal HPA-1a sensitization. One explanation for this unexpected finding is related

to HPA-1a antigen presence and the associated immune response. Antibody production depends on T helper cell activation resulting from interaction between T cell receptor and HLA class II peptide complex. HLA class II antigen DRB3*01:01 present on T cells provides a binding groove which shows better avidity for β 3 peptides (i.e. HPA-1a) [19]. Therefore 99% of HPA-1b/1b women that produce HPA-1a antibody express DRB3*01:01. In other terms women who are HLA DRB3*01:01 have a 25 times higher risk of HPA-1a sensitization compared to women who lack this allele [20]. HPA-1a antibody levels in women who are DRB3*01:01 negative are lower than those in women who are DRB3*01:01 positive [21].

Maternal-fetal antibody transfer

Fetal rather than maternal Fc receptor plays a key role in the maternal-fetal transfer of immunoglobulin G (IgG) antibody. Placental syncytiotrophoblasts internalize maternal IgG by binding neonatal Fc receptor (FcRn) expressed on membrane into endosomes, then transferring them to the fetal circulation. Absence of FcRn or maternal treatment with antibodies blocks IgG transfer [22].

Each Ig molecule contains two oligosaccharide groups linked to a glycan-bound peptide at the Fc domain. Addition of fucose residue to this position (core fucosylation) modulates the affinity of IgG-Fc for the Fc γ RIII receptor expressed on phagocytes. IgG molecules lacking a core-fucose residue bind more tightly to Fc γ RIII and exhibit enhanced cellular immune function. Up to 30% of IgG molecules in normal serum lack a core-fucose residue. Decrease in core fucosylation is more common in women immunized to HPA-1a positive fetus. Neutrophil phagocytosis of platelets coated with maternal HPA-1a antibodies increases as IgG-Fc core fucosylation decreases, and there is a significant positive correlation between lower HPA-1a antibody core fucosylation and lower neonatal platelet counts and more severe clinical outcome [23].

Treatment

Antepartum management

Intravenous immunoglobulin (IVIG) is the mainstay of FNAIT management. Animal models of thrombocytopenia show that maternal adminis-

tration of IVIG reduces levels of both $\beta 3$ and GPIIb α -specific antibodies in maternal and fetal blood, and ameliorate FNAIT [24, 25].

Prophylactic interventions in pregnant women or those with a history of FNAIT are only indicated if fetal platelets carry the HPA. In approximately 30% of cases, the father is heterozygous for the HPA-1a allele (genotype HPA-1ab), and the likelihood that the fetus will inherit the HPA-1b is 50%. In this case, there is no risk of FNAIT, and there is no indication for prophylactic IVIG therapy. The fetal HPA type can be determined by amniocentesis or fetal blood sampling (FBS), which carries the risk of miscarriage and/or a boosted humoral response in the mother [26]. Methods for noninvasive genotyping of HPA alleles with the use of maternal plasma cell-free DNA have been developed to screen HPA status in suspected cases [27].

Repeated fetal ultrasounds beginning early in the pregnancy are indicated in suspected cases. There is no evidence-based optimal treatment strategy. Platelet antibody titration in maternal plasma is not helpful for decision-making. The best indicator for current pregnancy is the outcome of the previous pregnancy, although severe FNAIT in a previous child is not always associated with severe FNAIT in the subsequent child [8].

Presence and time of ICH during previous pregnancy determine the risk of FNAIT. Standard care is given to pregnant women where a previous sibling had no ICH. If a previous sibling had ICH after 28 weeks of gestation or after birth, the risk is high. Very-high-risk pregnancies are those where a previous pregnancy had ICH before 28 weeks or complicated with *in utero* death.

IgG alloantibodies can cross the placenta as early as 14 weeks of gestation, and fetal platelet membrane glycoproteins are expressed as early as 16 weeks of gestation. Therefore treatment should be initiated early in the pregnancy, especially in high-risk and very-high-risk fetuses.

In the standard risk group, treatment is initiated at 20 weeks of gestation with IVIG (2 g/kg/wk) alone or IVIG (1 g/kg/wk) plus prednisolone (0.5 g/kg/day). FBS is recommended at 32 weeks to determine the fetal platelet count. If the platelet count is less than 30,000-50,000/ μ L, prednisolone is added to the IVIG regimen, or IVIG dose increased to 2 g/kg/wk in IVIG plus prednisolone regimen. Another approach is delaying FBS to 36 weeks without knowledge of fetal platelet counts, in order to determine the mode of delivery.

In the high-risk group, treatment is recommended starting at 12 weeks with IVIG 1 g/kg/wk. At 20 weeks IVIG dose is increased to 2 g/kg/wk, and prednisolone (1 g/kg/day) is added. FBS at 32 weeks may be performed. Delivery after 32 weeks is an option if indicated.

In the very-high-risk group, treatment should start at 12 weeks with IVIG (2 g/kg/wk). Prednisolone (1 mg/kg/day) is added to this regimen at 20 weeks. FBS is performed at 32 weeks for additional therapy, fetal platelet transfusion or delivery [9].

Serial FBS to monitor platelet counts with platelet transfusions and *in utero* IVIG administration is not safe because of high risk of the procedure-related complications including fetal hemorrhage and fetal death due to severe thrombocytopenia. Serial FBS and weekly intrauterine transfusions of maternal platelets may not only further sensitize the mother, but may also aggravate thrombocytopenia in the fetus through the passage of maternal anti-platelet antibodies during platelet transfusions [13].

In practice, IVIG with or without prednisolone is given empirically without knowing fetal status [19]. Although about 20% of fetuses do not respond to IVIG treatment, which exposes them to the risk of ICH, blind treatment with IVIG without FBS is safe and effective [13].

There is no consensus about the mode of delivery in women who previously gave birth to a child with FNAIT. In some centers FBS is recommended as mentioned above. Vaginal delivery is safe in standard care pregnancies [8]. For those in the high-risk and very-high-risk groups who desire vaginal delivery, FBS is recommended at 32 weeks. If platelet count is higher than 100,000/ μ L, the patient should continue therapy, and induction of delivery at 37-38 weeks. If the patient does not accept FBS at 32 weeks, FBS is delayed to 36-37 weeks. If the platelet count is higher than 50,000/ μ L, a vaginal delivery can be performed [26]. For those in the very-high-risk group, elective cesarean section prior to 38 weeks is usually recommended regardless of platelet count [8, 9].

An estimated rate of effectiveness near to 75% when IVIG combined with prednisolone [17]. High maternal alloantibody levels before delivery, and multigravida are predictive of poor response to antenatal therapy. HPA-1a negative pregnant women carrying both HLA-DB3*01:01 and HLA-DB4*01:01 shows a reduced response to IVIG treatment in comparison to women bearing HLA-DB3*01:01 only. This may be related to the

lower binding avidity of HPA-1a epitome of the $\beta 3$ integrin to HLA-DB3*01:01 [13].

Neonatal management

Serial platelet counts should be obtained for the first 5-7 days after delivery to keep the platelet counts higher than 30,000/ μ L without active bleeding and higher than 50,000-100,000/ μ L with active bleeding [8]. If the neonate presents with clinical bleeding or the platelet count is less than 30,000/ μ L, platelet transfusion is indicated.

Maternal platelets or HPA-compatible donor platelets are used. The mother is the best donor, because transfused platelets are not destroyed. Finding HPA-1a and HPA-5b negative donors is impractical [7]. All platelets should be washed and irradiated, however both procedures can reduce platelet functions. Washing and irradiation of platelets also take considerable time, which makes maternal platelets not the best option when an emergency treatment is needed. In addition it is not appropriate to wait for the laboratory confirmation of the diagnosis in suspected cases.

Random donor platelet (AB0 compatible, reduced volume, cytomegalovirus negative and irradiated) transfusion is given in a dose of 10 mL/kg where 1 mL platelet suspension usually increases platelet count by 5,000/ μ L at least transiently [9]. This increase in platelet count reduces the likelihood of bleeding even when they are incompatible with the maternal antibody [7].

Current use of platelet transfusions is heterogeneous and primarily based on expert opinion. Whether more liberal platelets transfusion thresholds prevent hemorrhage is unclear. In addition, unnecessary platelet transfusion could be detrimental because of pro-inflammatory factors, which are secreted by the platelets during the storage or preparation. Increased inflammatory response may be responsible for an association between platelet transfusions and increased neonatal mortality [6].

IVIg is not alternative to platelet transfusions, since the action of IVIg is observed after 18 hours, and platelet counts don't rise before 24-48 h [8]. During this time severely thrombocytopenic neonates remain at risk of bleeding. However, neonates with moderately severe thrombocytopenia (30,000-50,000/ μ L) without obvious bleeding can be treated with IVIg alone in a total dose of 2 g/kg are given over 2-5 days. In platelet-transfused patients, IVIg at 0.4-1 g/kg/day for 2-5 days can

be given to potentially prolong the survival of the incompatible platelets [7].

Prognosis

All thrombocytopenic neonates with FNAIT should be monitored until platelet counts reach normal levels [20]. Platelet counts may continue to fall for some days after delivery. But the day of the lowest platelet count differs from patient to patient. Platelet counts return to normal after 1-2 weeks because the half-life of platelets is 8-10 days [7]. The duration of thrombocytopenia in treated cases ranges between a few days and some weeks [8]. In rare cases, thrombocytopenia may persist for up to 8-12 weeks. This persistent neonatal thrombocytopenia may be related to the transfer of maternal IgA type antiplatelet antibodies by breastfeeding [28].

Cranial ultrasonographic examination is indicated for every newborn with significant thrombocytopenia to exclude ICH. In the absence of ICH, prognosis is favorable. Many children with ICH have very low platelet counts, but low platelet counts are not a good predictor of ICH [29]. There is no correlation between the severity of thrombocytopenia and ICH, and maintaining a platelet count greater than 150,000/ μ L during the first week of life does not decrease the incidence of ICH [2, 7]. Temporal lobe intraparenchymal hemorrhage is the most commonly seen location of ICH [30].

Neither thrombocytopenia nor deficiency in blood coagulation (fibrinogen deficiency) is crucial for the development of ICH, particularly *in utero* in FNAIT animal models, which take into account the contribution of other factors. The integrin α IIb β 3 is the most abundant glycoprotein on platelets. The β 3 subunit is also coexpressed with the α V subunit (i.e. α V β 3) on proliferating endothelial cells during angiogenesis. Anti-platelet β 3 antibodies inhibit angiogenesis and induce ICH in the brain of murine fetuses and neonates, and can be prevented with IVIg given to the mother. Murine anti-platelet β 3 integrin antisera and human HPA-1a immunoglobulin purified from mothers with FNAIT children have similar effects on cultured human endothelial cells inhibiting cell proliferation. This study shows that impairment of angiogenesis rather than thrombocytopenia likely causes FNAIT-associated ICH [31].

Concentrations of vascular endothelial growth factor, platelet-derived growth factor and

transforming growth factor $\beta 1$, which are stored in α granules, increase in plasma during the platelet storage period. Whether these exogenous growth factors transfused with the platelets have an impact on the vascular stability of cerebral and retinal vessels, which may increase the predisposition for developing ICH and retinopathy of prematurity [2, 11].

Future

NAITgam

NAITgam (anti-HPA-1a immunoglobulin prepared from the hundreds of women previously immunized by a FNAIT-affected pregnancy) given within the first six hours to an HPA-1a negative woman who has given birth to an HPA-1a positive child is on Phase I/II trials (2011 PROFNAT, a European Union Project), and will be on market in 2018. NAITgam is similar to Rh immunoglobulin, which for almost 50 years has proven safe and effective in almost eliminating a related condition, hemolytic disease of the fetus and newborn [32].

Recombinant monoclonal antibodies

Recombinant monoclonal antibodies directed against $\beta 3$ integrin and FcRn are under development. Since the fetal FcRn is responsible for transplacental of maternal IgG, anti-FcRn monoclonal antibodies was found to be 200-fold more efficient in comparison to the common IVIG in an animal model [33]. Recombinant HPA-1a specific antibodies with lower affinity to FcRn are also being developed. These antibodies block the binding of maternal HPA-1a antibodies to fetal platelets and reduce the clearance of fetal platelets in a mouse model of FNAIT [34-37]. This study extended to human volunteers [38], and may be used to reduce the severity of disease. However, as HPA-1a antibodies also bind to endothelial cells through $\alpha V\beta 3$, they may potentially inhibit endothelial cell proliferation and cause serious side effects [37].

Thrombopoietin mimetics

Thrombopoietin is the cytokine that induces platelet production in the bone marrow. Two thrombopoietin receptor agonists or synthetic thrombopoietin mimetics, eltrombopag (daily orally) and romiplostim (weekly subcutaneously)

have been licensed for use in very refractory ITP or in an inherited thrombocytopenia (e.g. Wiskott-Aldrich syndrome). However both agents would cross the placenta and affect the fetus. The risk of thrombosis and induction of malignancies in certain adult patients as well as the lack of efficacy data have led to avoidance of these drugs during pregnancy [39]. The use of thrombopoietin mimetics in newborns also seems unlikely. Because serum thrombopoietin levels are not reduced and both agents take several weeks of treatment to be effective, these drugs are useless in emergencies [40].

Phagocytosis inhibitors

Fc γ receptors on mononuclear phagocytes recognize autoantibodies, primarily IgG1 subclass, that coat platelets in affected individuals, resulting in their phagocytosis. Fc γ receptor blockade and inhibition of platelet phagocytosis are the principal mechanisms of IVIG in immune thrombocytopenia. IVIG manufactured from thousands of donors is too expensive and has several side effects. Several pyrazole-containing derivatives that inhibit phagocytosis by human monocytes have a strong potential to become first line therapy in immune cytopenias [41].

Infants of mothers with immune thrombocytopenic purpura

ITP during pregnancy is not considered a serious risk of perinatal bleeding, but may cause moderate thrombocytopenia in neonate. In mothers with ITP, the risk of thrombocytopenia is only 10%, with no more than 1% risk of *in utero* ICH. The incidence of ITP is estimated at 0.1-1 in 1,000 pregnancies. In one-third of cases, ITP presents during pregnancy. In the majority of patients, asymptomatic thrombocytopenia is detected in tests obtained for other reasons. In more severe cases, petechiae and easy bruising may be noticed [42].

The risk of neonatal thrombocytopenia is greater for mothers with higher thrombocytopenia during pregnancy. The platelet count may fall during the first 3-5 postnatal days before recovering spontaneously. IVIG usually corrects severe thrombocytopenia ($< 30,000 /\mu\text{L}$) [43].

ITP is considered to be caused by autoantibodies against platelet antigens, although these antibodies cannot be detected in all women with ITP. Therefore, hypothesis on platelet destruction with

transported maternal antibodies cannot explain pathophysiology of all cases with fetal/neonatal thrombocytopenia [43].

In FNAIT, most cases (75-95%) have maternal alloantibodies to fetal β_3 integrin, and few cases to fetal GPIIb/IIIa. However, in ITP the prevalence of anti-GPIIb/IIIa antibodies is 20-40%. Autoantibodies against the other antigens may also be determined. However, antiplatelet antibodies are not different between gestational thrombocytopenia and ITP, and high levels of antiplatelet antibodies may be found in gestational thrombocytopenia. Differential diagnosis can be made with history and severity of thrombocytopenia. The presence of thrombocytopenia before pregnancy makes the ITP diagnosis more likely. In the absence of data on the platelet count before pregnancy, thrombocytopenia early in the first trimester and continuous decline to severe thrombocytopenia during pregnancy is more consistent with ITP. Mild thrombocytopenia developing at the end of the second or in the third trimester in a healthy pregnant woman will lead to the diagnosis of gestational thrombocytopenia [42].

The management of ITP during the first and second trimesters is the same as that of non-pregnant individuals. Pregnant women with a platelet count lower than 30,000/ μ L, bleeding or with a planned procedure should receive either prednisolone (10 mg daily) and/or IVIG (1 g/kg). Anti-D, which is used in refractory ITP, is contraindicated in pregnancy due to acute hemolysis and anemia in fetus/neonate [44].

It is unknown whether steroid therapy and IVIG are equally efficient in titrating anti-GPIIb/IIIa versus anti- α IIB β 3-mediated thrombocytopenia, since anti-GPIIb/IIIa may cause platelet destruction through an Fc-independent pathway, which is resistant to IVIG therapy. Recently anti-GPIIb/IIIa antibodies have been found causing platelet desialylation, which are cleared in the liver via Ashwell-Morell receptors, that is a significantly different process from Fc-Fc receptor-dependent macrophage phagocytosis in the spleen in anti- α IIB β 3-mediated thrombocytopenia [45].

Because of concerns of hemorrhage, cesarean section was recommended for all pregnant women with ITP. Mode of delivery should be based on obstetric indication. It is usually recommended that the platelet count should be greater than 50,000/ μ L at the time of delivery. For spinal anesthesia, platelet count should be greater than 80,000/ μ L [46].

Severe thrombocytopenia (8-13%) and its complications such as ICH (0-2.9%) are more

rare in infants of mother with ITP compared to FNAIT [43]. Maternal splenectomy for resistant ITP, history of previous siblings with severe thrombocytopenia and maternal platelet counts at delivery are the main indicators to predict severe thrombocytopenia in the newborn infant. Maternal platelet counts during pregnancy and delivery, presence of detectable antiplatelet antibodies in maternal serum, and maternal treatment with IVIG and/or corticosteroids do not correlate with neonatal platelet count at birth [38-40].

In every baby born to a mother with a pregnancy-associated thrombocytopenia, even in the case of confirmed gestational thrombocytopenia, platelet counts in umbilical cord blood should be closely monitored, because platelet counts are not always normal in babies born to mothers with incidental gestational thrombocytopenia. Since it has been hypothesized that gestational thrombocytopenia may be a mild form of ITP, follow-up of mothers long after delivery would be useful [47].

In these infants, platelet counts decline to the lowest level at postnatal day 3-5, after then they rise spontaneously. Optimal treatment (platelet transfusions, IVIG and/or prednisolone) is not evident. The effect of platelet transfusions is often short with frequent recurrence to low platelet count, requiring additional transfusions and/or IVIG treatment. When a platelet transfusion fails to result in a stable increase of platelet counts, further platelet transfusions are not advised without IVIG [43].

Declaration of interest

The Author declares that there is no conflict of interest.

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