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REVIEW

Aplastic anemia during pregnancy: a review of obstetric and anesthetic considerations

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Abstract: Aplastic anemia is a hematologic condition occasionally presenting during pregnancy. This pathological process is associated with significant maternal and neonatal morbidity and mortality. Obstetric and anesthetic management is challenging, and treatment requires a coordinated effort by an interdisciplinary team, in order to provide safe care to these patients. In this review, we describe the current state of the literature as it applies to the complexity of aplastic anemia in pregnancy, focusing on pathophysiologic aspects of the disease in pregnancy, as well as relevant obstetric and anesthetic considerations necessary to treat this challenging problem. A multidisciplinary-team approach to the management of aplastic anemia in pregnancy is necessary to coordinate prenatal care, optimize maternofetal outcomes, and plan peripartum interventions. Conservative transfusion management is critical to prevent alloimmunization. Although a safe threshold-platelet count for neuraxial anesthesia has not been established, selection of anesthetic technique must be evaluated on a case-to-case basis.

Keywords: aplastic anemia, platelets, high-risk obstetrics, obstetric anesthesia, pregnancy

Background

Aplastic anemia (AA) is a life-threatening disorder[1] that tends to worsen during pregnancy. This disorder consists of pancytopenia as a result of hypocellular bone marrow in the absence of an abnormal infiltrate or bone-marrow fibrosis.[2,3] The diagnosis of AA during pregnancy is associated with significant fetal, neonatal, and maternal morbidity and mortality.[4] Growth restriction affects the fetus, and neonatal sepsis is more prevalent among babies from mothers with AA.[5] A causal relationship between pregnancy and AA has not been conclusively established;[6] however, women with AA can become pregnant, since there is no compromise of fertility. In these cases, obstetric and neonatal complications range between 12% and 33%.[7,8] Furthermore, in the presence of thrombocytopenia, hemorrhagic complications during the peripartum period requiring blood transfusions have been reported to have incidence as high as 75%.[9] Anesthetic, hematologic, and obstetric care during pregnancy is discussed in this paper from an interdisciplinary standpoint. Therapy during the peripartum period is also approached in the context of a review of recent literature.

Review of literature

Acquired AA is an uncommon disorder characterized by progressive pancytopenia caused by altered bone-marrow function. Incidence is estimated to be one to two cases per million per year.[10] Given the complexity of AA and the limited experience by most providers, new guidelines by the British Society for Standards in Haematology on the diagnosis and management of adult AA were recently published.[3] Pathogenic

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mechanisms underlying this disease are likely to be immuno-mediated, and include the overproduction of bone-marrow-inhibiting cytokines elicited by abnormal T-cell response in a genetically predisposed individual.[11] Pregnancy in association with AA is a rare but serious condition that poses serious maternal and fetal risks. Unfortunately, most of the current literature has been limited to case reports, with few studies exploring risk factors and perinatal complications.[12,13]

Pathophysiology of aplastic anemia

Acquired AA is more common than the hereditary form. Typically, this disorder affects young adults who present with peripheral pancytopenia in the absence of other hematological diseases.[14] Classification of AA determines indication for treatment, and depends on etiology and severity (Table 1).[2] AA in the adult can be idiopathic (>80% of cases) or induced by pharmacologic agents, infections (particularly hepatitis), or hereditary forms with late-onset manifestations (eg, related to telomeropathies). Therapy is indicated in symptomatic disease, severe and very severe cases, and patients classified as nonsevere in whom severe cytopenia of at least one cell line requiring transfusions is present.

Although the hematologic stem-cell (HSC) compartment is affected in all types of AA, in the acquired form, the damage is extrinsic and involves direct and indirect mechanisms. Direct injury can be caused by radiation therapy and cytotoxic agents, whereas indirect damage involves immunoeffector pathways, which are responsible for idiopathic cases and present in those preceded by a history of hepatitis.[15,16] Cross-reactive marrow antigen recognition by T cells is postulated as the causative mechanism in most idiopathic cases of the disease (Figure 1).[17] Evidence supporting the role of the immune system in HSC injury includes serologic and cytokine data and the dramatic clinical response to therapy with immunomodulatory agents in animals.[18–20]

The HSC/progenitor cell is the target of immune attack by activated T cells. The antigens responsible for autoimmunization remain elusive; however, autoantibodies have been identified in serum of patients with AA.[21] The association between human leukocyte antigens (HLAs) and susceptibility to develop AA has been widely studied. Nakao et al isolated a population of CD4+ T cells able to target hematopoietic cells positive for HLA-DRB1*0405, supporting the hypothesis that certain HLA alleles may play a role in activation of T-cell clones in AA.[22] On the other hand, it has been postulated that certain HLA alleles might confer protection against autoreactive T-cell activation.[23]

In addition to individual susceptibility, T-cell dysregulation is necessary for AA to develop. Transcriptional analysis has shown altered regulation of CD4+ and CD8+ T cells, whereas abnormal expansion of T-helper (T_H)-1, T_H2, and T_H17 cell populations and underexpression of the T_{reg} immunophenotype occur consistently in AA.[24,25] Autoreactive T-cells produce proinflammatory cytokines, including TNFα and IFNγ.[26,27] Both cytokines induce apoptosis, reducing colony formation of hematopoietic progenitor cells.[28] Furthermore, intracellular expression of these cytokines predicts response to immunotherapy and is associated with poor clinical outcome.[29,30] Aside from abnormal cellular immunity, other factors have been implicated in the pathogenesis of AA, including the role of innate immunity via depressed NK cells[31] and mutations in telomerase-complex genes that lead to decreased proliferation and survival of hematopoietic progenitor cells.[32–34]

Paroxysmal nocturnal hemoglobinuria (PNH) has been considered a late clonal disease occurring in patients recovering from AA, and sometimes these two disorders overlap.[35] As is the case with AA, PNH is linked to HLA antigens, and immunosuppressive therapy is useful to control the disease. Complement inhibitors, such as the monoclonal antibody eculizumab, have proven useful for treatment of PNH, highlighting the underlying mechanism of red-blood-cell destruction and bone-marrow suppression. This therapy has been used with success in pregnancy.[36]

Pathophysiology in pregnancy

The first report of AA was published by Ehrlich in 1888. Incidentally, his patient was pregnant and died 1 month after delivery, due to postpartum hemorrhage.[37] The causal relationship between pregnancy and AA is still unclear.[38] Earlier studies found no correlation between the conditions, and a retrospective study comparing the frequency of pregnancy in 35 newly diagnosed patients with the expected frequency in the general population found no significant difference.[38,39] Other reports endorse a direct association between pregnancy and AA,[40] and pregnancy is even included as a cause of AA in some reviews.[41]

Hemorrhage and sepsis are the major reasons for death in pregnant women with AA.[9] When AA is present before

Table 1 Classification of aplastic anemia based on severity

Cells	Nonsevere*	Severe	Very severe
Neutrophils	<1×10⁹ cells/L	<0.5×10⁹ cells/L	<0.2×10⁹ cells/L
Platelets	<50×10⁹ cells/L	<20×10⁹ cells/L	<20×10⁹ cells/L
Reticulocytes	<20×10⁹ cells/L	<20×10⁹ cells/L	<20×10⁹ cells/L

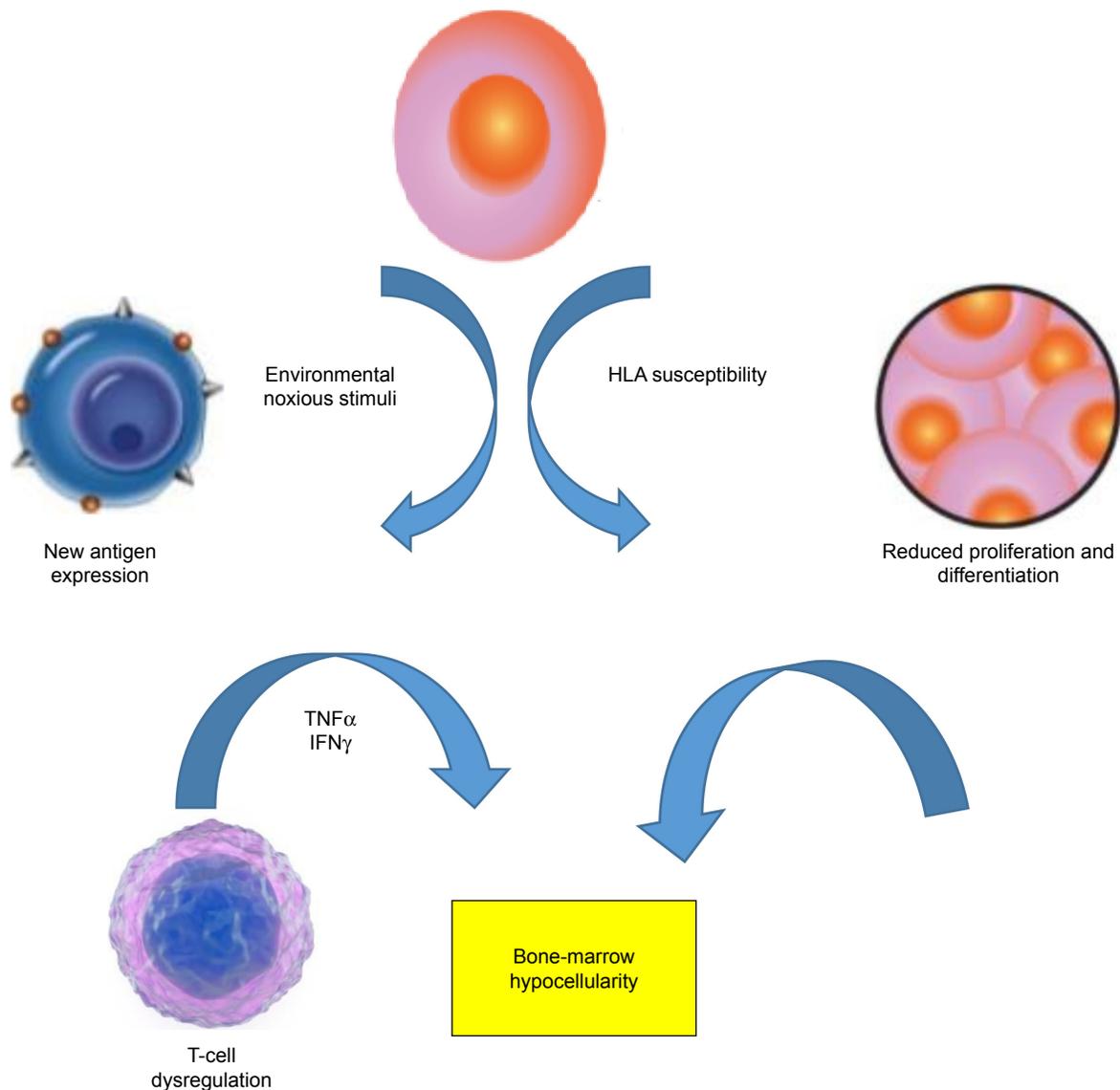**Note:** *In addition to <25% bone marrow cellularity.

Figure 1 Pathophysiologic mechanisms of aplastic anemia.
Abbreviation: HLA, human leukocyte antigen.

conception, it usually worsens during pregnancy,[42] and most series have reported a significant decrease in platelet count in almost all women with AA preceding pregnancy.[9,43] Some authors have reported remission of AA after delivery, and others have suggested that termination of pregnancy should be considered for AA in pregnancy, especially in those patients with severe disease.[44]

Pathophysiological mechanisms underlying the association between AA and pregnancy have not been clearly elucidated. It is known that estrogens increase plasma volume in pregnancy more than red-blood-cell production, resulting in anemia of pregnancy. It has been postulated that hormonal influences may contribute to worsening of blood counts in pregnant patients with AA, but the exact mechanism

and causes are still unclear.[45,46] Animal models have provided some insight into mechanisms for altered maturation and proliferation of blood cells in pregnancy. In a murine model, Zoller et al showed that injection of 17β-estradiol inhibits the development of developing thymocytes.[47] Zhdanov et al demonstrated enhanced proliferative activity of erythroid precursors in bone marrow that was increased by concomitant administration of iron.[48] According to one theory, a population of primitive $CD34^+$ progenitors responsible for cellular proliferation and regeneration is produced in maternal bone marrow in response to interaction with umbilical cord blood cells via immunologic signals.[49] Pregnancy is also sometimes accompanied by gestational thrombocytopenia and relative leukocytosis. The factors responsible for the observed

thrombocytopenia in pregnant patients with AA are yet to be definitively elucidated.[50]

Maternal and fetal considerations in aplastic anemia in pregnancy
Treatment of aplastic anemia in pregnancy

Principles of AA treatment during pregnancy include identification of any underlying cause and treatment of cytopenias, while minimizing maternal and fetal side effects of therapy. Termination should be considered if a triggering factor causing bone-marrow suppression, such as drug reaction or infection, is detected, and the medication cannot be discontinued or the microorganism cannot be adequately treated if pregnancy continues. Waiting for spontaneous resolution without further treatment is not recommended, as it places the patient at risk of complications related to pancytopenia.[51] Pregnancy termination should also be considered for patients with severe pancytopenia, given the high likelihood of life-threatening maternal and fetal complications. Furthermore, in a recent series of 61 women with AA, those with more severe thrombocytopenia had a sixfold-higher complication rate related to one of the composite pregnancy outcomes – preeclampsia/eclampsia, preterm delivery, intrauterine growth restriction, and fetal and neonatal death – and an elevenfold increase in the composite outcomes, which included transfusion dependence after delivery, sepsis, and bone-marrow transplant.[9]

The most common complications of AA in pregnancy, in addition to postpartum hemorrhage, include premature rupture of membranes, endometritis, growth restriction, subchorionic hematoma, and placental abruption. Management of AA starts with accurate diagnosis, definition of severity, and a comprehensive assessment, followed by supportive treatment. Some therapies recommended for AA in the non-obstetric population include hematopoietic stem-cell transplantation (HSCT) and use of immunosuppressive regimens.[52] HSCT, albeit associated with significant 5-year survival rates in nonpregnant patients,[53] is contraindicated in pregnancy, due to teratogenicity associated with pretransplant immunosuppressant agents.[54] Termination of pregnancy in order to perform HSCT is not usually recommended, because of the relatively favorable prognosis for mother and fetus when medical therapy is optimally used.[55] HSCT can be performed in the postpartum period. Immunosuppressant agents are excreted in breast milk, and some practitioners do not recommend breastfeeding while on those medications in the context of HSCT; however, reports of successful immunosuppression in breastfed infants are encouraging, and

the informed decision to recommend breastfeeding must be individualized.[56] Additionally, reduced fertility is a common clinical manifestation after HSCT, due to gonadal damage secondary to myeloablative conditioning. Fertility prospects must be discussed with the patient before making the decision to proceed with HSCT in the postpartum period.[57]

The optimal treatment for AA depends on different factors, including patient age, neutrophil count, and presence of comorbid conditions. In the nonobstetric population, mild cases can be either observed or treated with specific colony-stimulating factors, antithymocyte globulin (ATG), cyclosporine, and methylprednisolone.[58] In pregnancy, supportive management with transfusions to hemoglobin >8 g/dL and platelet count >20×10^9/L is recommended.[6] Additionally, there are reports of patients successfully treated with prednisolone, cyclosporine, and GCSF.[5,59] Regarding the use of ATG in pregnancy, there is little published experience. A retrospective analysis of a group of 26 patients, including two pregnant women, reported an overall response rate to treatment of 46% and 45% survival at 2 years, without special mention of outcome of pregnancy.[60] Aitchison et al reported a case series of five pregnant patients with AA treated with ATG. In his series, four patients were treated during the postpartum period and only one before delivery, receiving the medication at 23 weeks. The baby was delivered at 36 weeks, weighing 1,700 g. The patient died 2 months postpartum as a result of an episode of pneumonia without recovery from her AA.[54] ATG is a relatively safe medication, with side effects mostly related to allergic reactions, vein irritation, nausea, vomiting, and diarrhea. There are no reports of fetal adverse effects attributable to ATG in humans, and low birth weight might be the result of comorbid conditions, rather than drug toxicity.[61] Kutzler et al reported the successful use of ATG to treat kidney-transplant rejection in a pregnant patient.[61] In an animal study, antithymocyte therapy caused toxic effects, manifested as decreased placental development in a murine model.[62] There is very limited experience using ATG in pregnancy, and risks and benefits of this therapy are not clear.

If corticosteroids are used, those unable to cross the placenta, such as prednisone, prednisolone, and hydrocortisone, are preferred, in order to minimize fetal brain exposure and the slight association of orofacial malformations.[63] All corticosteroids may increase the risk of glucose intolerance, gestational diabetes, and premature rupture of membranes, and their benefit is limited in AA compared to immunorelated causes of cytopenias that result from cell destruction (eg, hemolytic anemia and idiopathic thrombocytopenic purpura). Finally, cyclosporine, an immunosuppressant recommended

for treatment of AA, seems to be associated with premature delivery and low-birth-weight infants, although it is difficult to sort out whether this is due to the medication or an underlying maternal condition. Because cyclosporine has not been shown to be consistently effective, it should be carefully considered by the treating physician.[64] Although some authors have reported an increase in neutrophil count during pregnancy,[65] in some instances severe thrombocytopenia can occur. The use of GCSF was shown to be a safe and effective therapy in a retrospective analysis of 38 pregnant patients, and can be recommended when the disorder is accompanied by significant neutropenia.[66,67]

Transfusion of blood products is the mainstay of supportive treatment in AA associated with pregnancy; however, it may lead to complications, including hemochromatosis and (most concerning) HLA alloimmunization.[68] Alloantibodies against human platelets cause platelet-transfusion refractoriness (PTR).[69] There are two types of clinically relevant platelet alloantigens: type I antigens are shared with other blood cells and tissue, which include glycoconjugates of the blood-group system and the polymorphic HLA class I molecule; and type II antigens are specific to platelets (human platelet antigens [HPAs]). Alloantibodies to both types of antigens are responsible for PTR.[70] If PTR is detected in a pregnant patient who has received blood transfusions, then HLA- and/or HPA-compatible platelet transfusions are indicated.[71]

When treating pregnant patients with AA, clinicians encounter significant ethical challenges. Therapy for maternal AA may put the fetus at risk secondary to exposure to medications, whereas maternal complications occurring if AA is left untreated may also affect the developing fetus. The biomedical ethical principles of autonomy, beneficence, nonmaleficence, and justice provide a guideline to make therapeutic decisions in these cases. In general, two rules apply to most ethical dilemmas: the maternal right to autonomy must be granted, and risks, benefits, and alternatives must be presented to the patient for her to make an informed decision. From the legal point of view, it is clear that the rights of the mother prevail over those of the fetus.[72]

Perinatal implications of aplastic anemia

Pregnancies complicated by AA require a multidisciplinary-team approach. Collaboration between high-risk obstetricians, hematologists, anesthesiologists, and transfusion-medicine specialists is necessary. Antepartum management includes frequent monitoring for clinically significant depletion of blood cell lines, with the goal of being conservative in terms of transfusion practices. Fetal growth surveillance should be performed by 28 weeks of gestation, and antenatal testing should also be offered by 30–32 weeks, due to the high prevalence of growth restriction.

Mode of delivery should be carefully considered.[6] Vaginal delivery is preferred, because even with significant thrombocytopenia, hemostasis can typically be achieved with appropriate uterine contraction after delivery.[73] A platelet count $>20\times10^9$/L is deemed acceptable[74] for vaginal delivery and $>50\times10^9$/L for cesarean delivery.[75] Availability of cross-matched blood products can be difficult with a history of previous transfusions and alloimmunization. Multiple transfusions in patients with AA can lead to significant HLA alloimmunization, especially if nonleukocyte reduced blood products have been used. This presents significant problems, given the risk of maternal bleeding at the time of delivery and the potential need for platelets to achieve hemostasis. HLA-matched platelets can be expensive and have limited availability.

Addressing permanent or long-acting reversible contraception is of critical importance, given that AA does not appear to decrease fertility, but is likely to progress or relapse with subsequent pregnancies. Another relevant aspect to consider in the context of AA is the risk of neonatal thrombocytopenia in mothers exposed to platelet transfusions. Neonatal alloimmune thrombocytopenia occurs when maternal antibodies directed against HPAs cross the placenta. Clinically significant neonatal thrombocytopenia associated with HLA alloimmunization has been suggested;[76,77] however, one prospective study was unable to find this association.[78]

Anesthetic implications of aplastic anemia

The anesthetic management of a pregnant patient with diagnosis of AA requires coordinated interaction with other care teams, including the blood bank, hematology, obstetrics, interventional radiology, nursing staff, and neonatology.[79] A comprehensive anesthetic plan should incorporate different aspects, including the presence and degree of cytopenias, infectious and bleeding complications, systemic effects of anemia, and side effects of therapy.

The presence of severe thrombocytopenia, which per se confers poor prognosis in the context of AA,[9,80,81] puts the patient at risk for surgical bleeding, and may contraindicate the use of neuraxial techniques for labor and delivery. Platelet counts $>50\times10^9$/L are generally considered safe by

surgeons to perform a cesarean section;[73] however, there is no absolute number for platelet count unanimously accepted by anesthesiologists to perform a neuraxial block.[82] The risk of spinal hematoma following epidural and spinal anesthesia is estimated to be 1:168,000 and 1:200,000, respectively.[83,84] In a review of 61 case reports of spinal hematoma after neuraxial anesthesia between 1906 and 1984, Vandermeulen et al found that 68% of the cases were receiving heparin, and only four cases had thrombocytopenia, with one also being on heparin and another being a chronic alcoholic. This review also suggests that the risks of placing and removing epidural catheters are equivalent.[85] A retrospective chart review of nonpreeclamptic thrombocytopenia ($<100\times10^9$/L) reported 47 patients, of whom 91.9% received regional anesthesia with platelet counts of $80–99\times10^9$/L and 48.1% with counts of $50–79\times10^9$/L, with no neurologic complications.[86] Another study retrospectively evaluated safety of lumbar puncture in children with acute lymphoblastic leukemia and thrombocytopenia. The authors found that 29 patients with platelet counts $<100\times10^9$/L, 170 with counts of $11–20\times10^9$/L, and 742 with counts of $21–50\times10^9$/L underwent the procedure with no serious complications. The 95% CI for serious complications when platelet counts were 20×10^9/L or less was 0–1.75%, and was 0–0.37% when the count was 50×10^9/L or less.[87]

Overall, in light of the heterogeneous etiology of thrombocytopenia in retrospective studies and case reports published to date, and recognizing that some patients might have low platelet counts, but normal or even enhanced platelet function, no recommendation regarding a specific threshold of platelet count can be made, and experience of anesthesiologists as well as institutional protocols must be considered to make the decision to perform a neuraxial block in a patient with AA.

The role of the anesthesiologist in management of anemic parturients with AA is critical, and encompasses preoperative assessment, determining need for transfusion, and devising strategies to optimize oxygen consumption:demand ratio. The preoperative assessment must include evaluation of the degree of anemia and determination of signs of cardiovascular compensatory response and compromised organ perfusion. The decision to transfuse should not be based on a "trigger" hemoglobin level, but on evidence of poor organ perfusion, hemodynamic instability despite fluid resuscitation, coexisting diseases, presence of continuing blood loss, and fetal well-being.[88] Risks of blood transfusions must be balanced against benefits of increasing oxygen delivery in the peripartum setting.[89] Regarding the use of platelet transfusions prior to epidural analgesia/anesthesia, there

is currently no evidence from randomized trials to endorse this practice.

Other aspects related to anesthetic care of AA patients deserve mention, since neuraxial techniques may be contraindicated. The anesthesia-care provider must be ready to use general anesthesia if the patient is to undergo cesarean section. Postoperative pain relief with a multimodal approach is reasonable to facilitate early ambulation and breastfeeding.[90] Adequate pain management also reduces systemic oxygen consumption, which is critical in the context of anemia. Additionally, inadequate postpartum pain control has been associated with chronic pain and depression.[91,92] Infection is a risk in AA patients, especially when neutropenia is present.[93] Precautions must be taken when performing such procedures as venous access, tracheal intubation, and neuraxial blocks. Antibiotic administration before surgical incision is also part of the anesthesiologist's responsibilities.[94]

Systemic analgesia can be obtained with inhaled nitrous oxide and intravenous (IV) opioids. Nitrous oxide administration requires special equipment and patient cooperation. Few good-quality studies have addressed labor analgesia with nitrous oxide, and research on effectiveness, satisfaction, and adverse effects is still needed.[95] Systemic opioid labor analgesia is widely used around the world; however, the use of narcotics in the obstetric setting has been associated with significant side effects and inferior efficacy when compared with neuraxial techniques. Remifentanil has been used for labor analgesia based on its short context-sensitive half-life. The use of IV patient-controlled analgesia (PCA) with remifentanil has been associated with hypoxic episodes, as well as cardiac and respiratory arrest during labor.[96] IV PCA remifentanil warrants one-to-one nursing and continuous monitoring of oxygenation, capnography, and patient responsiveness. IV PCA with fentanyl is another alternative for labor analgesia. Miyakoshi et al compared IV PCA fentanyl with no analgesia, showing longer labor in the fentanyl group with no difference in neonatal outcomes and patient satisfaction of 72%.[97] Fentanyl is a safe and clinically acceptable analgesic option in labor, especially in nulliparous women.[98]

Conclusion

AA is a complex disorder that warrants a comprehensive multidisciplinary-team approach, in order to devise an obstetric, hematological, anesthetic, and neonatal plan and anticipate complications during the peripartum period. Conservative transfusion strategies are necessary to avoid complications related to alloimmunization. Close monitoring

of fetal well-being and adequate growth has to be carried out by the maternofetal specialist, and planning for delivery needs to be discussed, with the vaginal route being the preferred mode. Anesthetic management has to be individualized, and should include considerations related to the degree of blood cell line compromise, as well as possible complications that have an impact on the anesthetic technique. An absolute number of circulating platelet count necessary to perform a safe neuraxial block cannot be recommended at this time, and the choice of the anesthetic technique depends largely on thorough clinical evaluation leading to a judicious balance of risks and benefits on a case-by-case basis. Multimodal labor and postoperative analgesic techniques, including but not limited to the use of systemic opioids, should be considered. Effective contraception is important in light of progression and relapse of AA during pregnancy.

Disclosure

The authors report no conflicts of interest in this work.

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