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Review

Management of immune-mediated cytopenias in pregnancy

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ABSTRACT

Immune-mediated cytopenias are a well-described complication of pregnancy. Appropriate recognition and treatment are important in order to limit maternal and fetal morbidity and mortality. First line treatment options are fairly well-established for these entities. Refractory disease may be difficult to manage because treatment choices are limited by known or unestablished risk to the fetus. While the use of new agents, such as romiplostim and rituximab, has been reported, their safety in pregnancy is not known. This article summarizes immune cytopenias seen in pregnant patients, and it also discusses management of these cytopenias, and provides practical strategies for the treatment of these challenging conditions.

Contents

1. Introduction

Normal physiologic changes in pregnancy dramatically alter the immune and hemostatic systems. There are a number of complex changes in the immune system during pregnancy in order to permit tolerance of the fetus [1,2]. These immunologic adaptations affect the course of maternal autoimmune diseases in varying ways. For example, in patients with rheumatoid arthritis, disease activity improves during pregnancy and worsens in the postpartum period [3]. In contrast, pregnancy may be associated with disease flares in patients with systemic lupus erythematosus (SLE). Pregnant patients with SLE have a higher incidence of renal and hematological involvement but decreased mucocutaneous and musculoskeletal involvement compared to non-pregnant patients with SLE [4]. Because immune-mediated cytopenias primarily affect women of childbearing age, it is not uncommon for immune cytopenias including immune thrombocytopenia (ITP), thrombotic thrombocytopenia purpura (TTP), autoimmune hemolytic anemia (AIHA), and autoimmune neutropenia (AIN) to complicate pregnancy.

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Anemia and thrombocytopenia are two of the most frequent hematologic complications of pregnancy. A relative increase in the plasma volume compared to red blood cell mass leads to a mild anemia termed "physiologic anemia of pregnancy." Hemodilution, increased platelet activation and clearance lead to a mild decrease in platelet count in normal pregnancy [5,6]. Thrombocytopenia (platelet count $< 150 \times 10^9$/l) occurs in 10% of pregnancies [7,8]. The most common etiology of thrombocytopenia in pregnancy is gestational thrombocytopenia, accounting for 70 to 80% of cases. ITP is the second most common cause of isolated thrombocytopenia in pregnancy, making up 3% of cases of thrombocytopenia in pregnancy [7,8]. Approximately half of patients with ITP have a significant platelet decline during pregnancy and 11% of patients experience worsening of ITP in the postpartum period compared to the pre-pregnancy status [9].

Changes in coagulation and fibrinolytic systems during pregnancy create a hypercoagulable state [10]. Increased procoagulant factors, decreased anticoagulant factors, decreased fibrinolytic activity, and loss of endothelial cell thrombomodulin contribute to the increased rate of acute TTP in pregnancy [11].

The clinical course and treatment of immune cytopenias is primarily based on observational studies and case reports. Careful management is important in order to limit maternal and fetal morbidity and mortality. Corticosteroids and intravenous immunoglobulin (IVIg) are considered to be safe in pregnancy and considered first line therapy. While the use of cytotoxic agents including cyclophosphamide and vinca alkaloids may be safe in the second and third trimesters of pregnancy, their use is typically reserved for use in patients with malignancies where intensive treatment is imperative [12]. Safety data on newer agents such as romiplostim and rituximab are lacking.

2. Immune thrombocytopenia (ITP)

2.1. Epidemiology

ITP, which is characterized by immune-mediated platelet destruction, occurs in 1 to 2 in 1000 pregnancies [13]. ITP is classified as secondary when it is due to an underlying disease, such as SLE, or primary when there is no precipitating cause [14,15]. The diagnosis of ITP may predate pregnancy, or ITP may be diagnosed for the first time during pregnancy [16]. In patients with new onset thrombocytopenia during pregnancy, it may be difficult to distinguish ITP from the more common gestational thrombocytopenia, especially when the thrombocytopenia is mild. Gestational thrombocytopenia tends to present as a mild thrombocytopenia in the third trimester. Although new onset ITP may present at any time during pregnancy, onset is most common in the first trimester. Thrombocytopenia (platelet count $< 100 \times 10^9$/l) that presents early and continues to decline during pregnancy is most consistent with ITP [17].

In a retrospective study of 118 pregnancies in 82 women with primary ITP, there was a significant decrease in platelet count in nearly half of pregnancies (median platelet count nadir was 66×10^9/l). Severe thrombocytopenia (platelet count $< 30 \times 10^9$/l) and/or bleeding requiring treatment occurred in 25.4% pregnancies ($n = 30$). For an additional 23.7% of pregnancies ($n = 28$), treatment was initiated only in preparation for delivery [9]. In this series, 8.5% of patients experienced bleeding prior to delivery (mucosal and/or cutaneous bleeding) and 12.7% of patients experienced postpartum hemorrhage. The majority of patients received epidural anesthesia and were delivered vaginally [9].

2.2. Management

Since there is only one reported randomized clinical trial in this patient population, most of the data on the management of ITP in pregnant women is based on observational studies [18]. The management of ITP during the first and second trimesters is identical to that of non-pregnant individuals (Table 1). Pregnant women with a platelet count less than 30×10^9/l, bleeding, or a planned procedure should receive either corticosteroids and/or IVIg as first line treatment [12]. Both corticosteroids and IVIg are considered to be safe in pregnancy although corticosteroids may increase the risk of gestational diabetes mellitus and hypertension [19–21]. The suggested starting dose of prednisone or prednisolone is 10 mg daily with the dose adjusted to maintain the platelet count greater than 30×10^9/l. The dose of prednisone or prednisolone used is rarely more than 30 mg daily [17]. IVIg (1 g/kg as a single dose or divided into two doses) may be given alone or in combination with steroids [17]. Monitoring the effect and duration of platelet response to IVIg may be useful in determining its expected effect during delivery.

There is limited data to guide the management of ITP refractory to corticosteroids and IVIg in pregnancy. Successful use of anti-D in pregnancy was demonstrated in a small prospective study [22]. However, its use is relatively contraindicated in pregnancy due to risk of acute hemolysis and anemia. If anti-D is administered during pregnancy, the neonate should be monitored for jaundice, anemia, and a positive direct Coombs test since the antibody may cross the placenta [17]. The successful use of thrombopoietin receptor agonist romiplostim has been described in several case reports of pregnant patients with primary and secondary ITP but its safety in pregnancy is not well-established [23–25].

A study of 153 pregnancies in women who received the chimeric anti-CD20 monoclonal antibody rituximab for lymphoma, immune cytopenias, and other autoimmune diseases was performed to assess the safety of rituximab in pregnancy. However, it is difficult to determine the effect of rituximab on pregnancy outcomes in this study due to the severity of maternal disease and the concomitant use of potentially teratogenic agents. The pregnancy outcomes of four patients with ITP who received antepartum rituximab included: one neonate born at 35 weeks with lymphopenia, one neonate born 36 weeks with absent B cells, one neonate born at 38 weeks with no complications noted, and one neonate born at 39 weeks with neonatal thrombocytopenia with cerebral hemorrhage. Two additional patients with ITP received antepartum rituximab; one while the pregnancy was ongoing at the time of study publication and one live birth with no additional details provided [26].

The use of cytotoxic agents, such as cyclophosphamide and vinca alkaloids, is not recommended in pregnant patients due their assumed risk of teratogenicity [12]. However, favorable pregnancy outcomes have been reported with their use in the second and third trimesters in the patients with malignancies [27]. Experience with thiopurines in pregnancy is primarily in patients with inflammatory bowel disease but has not been reported in pregnant patients with ITP [28].

Open or laparoscopic splenectomy may be considered during the second trimester or with cesarean section in refractory patients [29,30]. Splenectomy during the first trimester is associated with increased risk of spontaneous abortion and is technically difficult in the third trimester due to gravid uterus.

Severe thrombocytopenia (platelet count $< 20 \times 10^9$/l) is associated with an increased risk of intracranial hemorrhage [31]. Thus, it is also important to aggressively manage common complications of pregnancy, such as emesis and constipation, which may increase intracranial pressure and place thrombocytopenic patients at increased risk of intracranial hemorrhage.

2.3. Delivery

Because of concerns for severe neonatal thrombocytopenia and hemorrhage, cesarean section was historically recommended for all women with ITP. However, given the low risk of neonatal hemorrhage in more recent studies, it is now recommended that the mode of delivery should be based on obstetric indications [12]. In the most recently published series of patients with ITP in pregnancy, 75% of women had vaginal deliveries. Of the 25% of women who underwent cesarean