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MULTIPLE AUTOIMMUNE DISEASES DIAGNOSED IN PREGNANCY: A CASE REPORT AND REVIEW OF MANAGEMENT

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Abstract

Multiple autoimmune diseases is association of immunological disorders. It represent the best example of polyautoimmunity.

Vitiligo, characterized by destruction of melanocytes, causes a patchy depigmentation of the skin. It has been hypothesized to have an autoimmune pathogenesis.

The autoimmune nature of most thyroid disease is important in the course of the illness during pregnancy and fetal consequences because of the association of thyroid antibodies with particular obstetric outcomes and the effect of pregnancy onantibody titers.

Immune (idiopathic) thrombocytopenic purpura (ITP) is an uncommon, but important cause of thrombocytopenia in pregnancy. It is a diagnosis of exclusion, and management should be based on a multidisciplinary care approach. ITP is characterized by moderate-to-severe thrombocytopenia commonly diagnosed in the first or early second trimester of pregnancy. The severity of thrombocytopenia has adverse implications on both maternal and fetal well-being.

Gestational diabetes mellitus (GDM) is characterized by carbohydrate intolerance of variable severity, with onset or first recognition during pregnancy. Some GDM patients manifest evidence for autoimmunity towards beta cells (insulin autoantibodies and anti-islet cell antibodies); however, the prevalence of such autoimmunity has been reported to be extremely low (<10%).

This paper is based on a case of ITP with generalized vitiligo with GDM with hypothyroidism in an ANC patient seen and managed in our institution and aims to discuss the various causes of thrombocytopenia and its implications in pregnancy as well as management of multiple autoimmune disesases in pregnancy based on current evidence and guidelines.

Introduction

We report a case of ITP diagnosed in pregnancy. The patient was a 39-year-old G2A1 who was admitted at 34 weeks gestation in view of GDM with hypothyroidism with deranged BSL. Collaboration between the obstetrician, endocrinologist and hematologist in our case was important to provide a smooth antenatal journey to ensure good maternal and fetal outcomes.

Case Report

Our patient had no past medical history, was known case of generalized vitiligo, diagnosed as hypothyroid at 12 weeks gestation and GDM at 25 weeks gestation and was started on treatment (thyroxin, insulin, metformin) and her antenatal follow-up was uneventful prior to the admission. On admission a platelet count was performed, and the value was 50×10^9/L. Peripheral blood film showed thrombocytopenia, but other blood cell types were normal. Her blood pressure was normal and there was no evidence of proteinuria. Her baseline liver function, renal function, coagulation screening and uric acid levels were within normal limits. Screening tests for infectious diseases such as

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hepatitis B, HIV, malaria and dengue were all negative. Autoimmune markers such as antinuclear antibody and anticardiolipin antibodies were also negative.

Her platelet counts were monitored on alternate days but was found to decrease. In view of the acute presentation and with no other obvious causes of thrombocytopenia, a working diagnosis of ITP was made, and she was started on oral prednisolone. Her blood sugar values were within normal limits. At 36 weeks her platelet count became 32 × 10^9/L despite on treatment. Antenatal corticosteroids were given in view of the risk of preterm labor. An ultrasound scan showed a normal growing fetus in a cephalic presentation with no placenta previa or retroplacental clots with normal Doppler studies and an estimated fetal weight of 2.4 kg. In view of increasing resistance to conventional ITP treatment and good fetal weight, plan for delivery was discussed at 36 weeks with the patient and her hematologist after weighing the risks and benefits of having a premature baby versus worsening thrombocytopenia that could potentially cause maternal morbidity and fetal thrombocytopenia due to transfer of antiplatelet antibodies transplacentally. As there was difficulty to time delivery with optimal platelet levels, induction of labor was deemed unsuitable and decision was made to deliver the baby by elective cesarean section at 36+0 weeks with platelet cover. Her platelet count was 32 × 10^9/L preoperatively. Risk of postpartum hemorrhage and possible need for medical treatment, uterine compression sutures and cesarean hysterectomy were discussed with the patient.

The cesarean section was uneventful, intraoperatively 8 pint platelets were transfused . She was otherwise well postoperatively. Her BSL profile was done on day 3 and was started on Metformin, stitches were removed on day 7 and the wound was healthy.

Thrombocytopenia is common and occurs in about 10% of all pregnancies. As ITP is a diagnosis of exclusion, it is therefore prudent to consider all causes of thrombocytopenia before making a diagnosis of ITP, as management is different depending on the cause.

ITP occurs in 0.1-0.2% of all pregnancies and is responsible for 5% of all cases of thrombocytopenia diagnosed in pregnancy. We will go through a brief overview of the common causes of thrombocytopenia before dwelling on the management of ITP in pregnancy.

Gestational thrombocytopenia is the most common cause, and it accounts for 65-80% of cases. Most importantly, patients remain asymptomatic, and the platelet counts are usually more than 70 × 10^9/L, with about two-thirds being 130 - 150 × 10^9/L. Gestational thrombocytopenia is not associated with fetal thrombocytopenia, and it spontaneously resolves after delivery.

Preeclampsia has to be considered in a patient with thrombocytopenia in the third trimester associated with raised blood pressure (≥ 140/90 mm Hg) and significant proteinuria > 0.3 g/day. The triad of microangiopathic hemolytic anemia, abnormal liver function (AST ≥ 70 IU/L), and thrombocytopenia with a platelet count less than 100 × 10^9/L constitutes the diagnosis of hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome. Other markers include an elevated LDH ≥ 600 IU/L and raised bilirubin levels ≥ 17.1 µmol/L. Both conditions require medical stabilization followed by delivery.

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are a continuum, and both are manifestations of a similar mechanism of microvascular platelet aggregation and are rare conditions.TTP is characterized by a pentad of microangiopathic hemolytic anemia, thrombocytopenia, neurological abnormalities, fever and renal dysfunction, and can occur in any trimester. HUS is predominated by renal abnormalities rather than neurological abnormalities and occurs most commonly in the postpartum period (> 90%). The manifestations of TTP and HUS may be confused with preeclampsia or HELLP syndrome, but hypertension is not common in TTP and HUS, and there is no coagulopathy.
Autoimmune conditions such as systemic lupus erythematosus (SLE) and antiphospholipid antibody syndrome may first appear or increase in severity during pregnancy and thrombocytopenia occurs in 10-30% of cases. It is important to note that about 25% of SLE patients have antiphospholipid antibodies which are associated with fetal

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loss and the need for anticoagulation. Positive screening for autoimmune antibodies in association with condition-specific signs and symptoms help define the definite cause.

Other causes of thrombocytopenia in pregnancy include: 1) disseminated intravascular coagulation; 2) acute fatty liver of pregnancy; 3) viral infections such as HIV and hepatitis C-induced thrombocytopenia; 4) drug causes, such as heparin-induced thrombocytopenia or cocaine which has been associated with a syndrome resembling HELLP; and 5) primary bone marrow disorder, usually associated with other blood cell dyscrasias. A bone marrow examination will be necessary to make a diagnosis of the type of bone marrow disorder.

In our case, all the common causes had been excluded by performing initial blood investigations and in the context of the history, physical findings and early presentation, a diagnosis of ITP was made and appropriate treatment rendered.

GDM is carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy. The incidence of GDM is 0.15–15%. It has been

demonstrated that GDM occurs as a result of a combination of insulin resistance and decreased insulin secretion. Autoimmune GDM is a concrete subgroup of women depicting humoral autoimmune markers against pancreatic cells in association with glucose intolerance at pregnancy. Islet cell autoantibodies include AA to islet cell cytoplasm (ICAs); to native insulin (IAAs); to glutamic acid decarboxylase (GAD65A); and to two tyrosine phosphatases (insulinoma associated antigens IA-2A and IA-2βA). ICAs are transferred by the placenta, but their passage has not been associated with fetal/neonatal morbidity. The prevalence of IAA was higher in the group of ICA positive women with GDM than in the ICA negative group. There is a strong association between HLA DR3/DR4 and islet autoimmunity of women with GDM. After delivery, the autoimmune process directed against beta cells may follow different pathways: (1) the restoration of normal glucose tolerance when pregnancy is over; (2) the appearance of DM-1 shortly after pregnancy; and (3) slow deterioration of the insulin secretory capacity due to the continuous progression of autoimmune destruction of the residual population of beta cells, resulting in a long subclinical period (LADA). Women with autoimmune GDM must be regarded as a high-risk group for the development of DM-1 in any of its clinical forms. These women are candidates for immunomodulatory interventions to prevent diabetes after pregnancy.

Vitiligo is a multifactorial disorder. Vitiligo, with an estimated prevalence ranging from 0.5% to 1%, is characterized by progressive de-pigmentation of the skin and mucous membranes due to autoimmune destruction of epidermal melanocytes and/or their auto-destruction due to toxic melanin biosynthesis metabolites. The two most common comorbid autoimmune diseases were thyroid disease (12.3%) and alopecia areata (3.8%). National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) have discovered a connection between a specific gene and the inflammatory skin condition vitiligo, as well as a possible host of autoimmune diseases. According to NIAMS vitiligo is "very highly associated" with a number of other autoimmune diseases, mostly thyroid disease, but also pernicious anemia, rheumatoid arthritis, psoriasis, lupus, Addison's disease, and adult-onset autoimmune diabetes. In addition to the involvement of humoral immune mechanisms in the pathogenesis of vitiligo, strong evidence indicates involvement of cellular immunity in vitiligo. The distribution of the lesions is usually symmetrical, although sometimes it is unilateral and has dermatomal arrangement.

Pregnancy is associated with significant but reversible changes in maternal thyroid physiology. There are two main types of thyroid antibodies: those that are directed towards cytoplasmic antigens (thyroid peroxidase (TPOAb) and \thyroglobulin (TgAb) antibodies) and those directed to the TSH receptor (TSHRAb).Pregnancy is associated with a decrease in antibody titers due to trophoblast secretion of immunosuppressant factors resulting in clinical improvement and the ability to discontinue medication in many patients. Conversely, antibody titers will increase postpartum and the development of postpartum thyroiditis. In women who continue to have high titers during pregnancy, passive placental transfer can lead to fetal thyroid disorders after mid-gestation. Hypothyroidism complicates between 1 and 3 per 1000 pregnancies and may be defined by inadequate thyroid hormone production

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despite pituitary gland stimulation (primary) or insufficient stimulation of the thyroid by the pituitary hypothalamus (central hypothyroidism). Women may enter pregnancy with either known hypothyroidism or could be diagnosed during pregnancy. In the developed world, autoimmune destruction of the thyroid gland (Hashimoto'sthyroiditis) is the most common cause of hypothyroidism. Globally, however, iodine deficiency is the leading cause of hypothyroidism. High-risk women who should be screened prior to pregnancy include those with a personal history of thyroid disease (hyper- or hypothyroidism, postpartum thyroiditis), a strong family history, known autoimmune disease, presence of a goiter, previous therapeutic neck irradiation, and those taking medications known to cause thyroid disturbance.

The management of ITP in pregnancy requires close collaboration between the obstetrician, hematologist, anesthetist and neonatologist. Upon diagnosis, the severity of thrombocytopenia should be ascertained, and platelet counts should be increased and stabilized to a safe level in pregnancy, especially during delivery and provision of epidural anesthesia. Patients will require close monitoring, with routine blood pressure and weight measurements, urine dipstick for protein and serial platelet counts at every visit. Treatment should be instituted, if platelets fall to an unsafe low level or if the patient is symptomatic for bleeding. The American Society of Hematology suggests a safe platelet count of at least 50×10^9/L for both vaginal delivery and cesarean section. Platelets less than 10×10^9/L or platelets $10 - 30 \times 10^9$/L in the second/third trimester or symptomatic bleeding are indications for treatment . The British Committee for Standards in Hematology suggests a safe platelet count of at least 50×10^9/L and 80×10^9/L for vaginal delivery and cesarean section respectively. A minimum platelet count of 80×10^9/L is considered safe for epidural analgesia. Platelets less than 20×10^9/L in any trimester is an indication for treatment under the BCSH guidelines.

The standard treatment for ITP is corticosteroids, with a starting dose of 1 mg/kg/day (weight based on pre-pregnancy weight), after which the dose should be titrated to the lowest effective dose to achieve remission. If rapid rise of the platelet count is necessary, then IV immunoglobulin would be the treatment of choice. IV immunoglobulin is less likely to cause adverse side effects. However, the use of IV immunoglobulin is limited by its high cost and transient response. For patients who do not respond to single therapy, a combination of corticosteroids and IV immunoglobulin may be considered. IV steroids such as pulse dexamethasone and methylprednisolone may be used in lieu of oral steroids in such cases.

The use of other medical treatments has also been tested. These treatments are still controversial due to lack of safety data and true efficacy. If these agents are to be used, it has been recommended not to use them in the first trimester when organogenesis occurs. Examples of such treatments include as follows. 1) IV anti-D has been used in women in their second and third trimesters. One study reported that six out of eight women had successful responses, with no maternal or fetal effects and no evidence of fetal hydrops. 2) Immunomodulating drugs such as azathioprine have been shown to work and found to be safe in pregnant women with renal transplants. Cytotoxic drugs such as cyclophosphamide cannot be used due to its teratogenic potential. 3) Monoclonal antibodies such as rituximab have been used to treat B-cell lymphoma and recently found to be able to treat ITP. 4) Use of thrombopoietic agents such as eltrombopag or romiplostim have been studied, but there is still little experience in their use in pregnancy. For cases refractory to conventional treatment or if treatment toxicities are unacceptable, splenectomy can be performed in the second trimester when fetal and anesthetic risks are minimal.

With regards to peripartum management in patients with ITP, the risk of maternal hemorrhage is minimized by ensuring minimum platelet counts required for vaginal delivery, cesarean section and epidural analgesia as stipulated by the ASH or BCSH guidelines are met. The transplacental passage of maternal antiplatelet antibodies in pregnancy can cause fetal thrombocytopenia, and the most feared consequence of this is fetal intracranial hemorrhage during vaginal delivery. The risk of intracranial hemorrhage in the offspring of patients with ITP is very low (< 1%). Various studies have also shown no correlation between maternal ITP status, platelet counts and the development of intracranial hemorrhage. Evidence so far has suggested that the most reliable predictor of fetal thrombocytopenia is a prior history of thrombocytopenia in an older sibling at delivery.

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There is no association between the mode of delivery and the risk of intracranial hemorrhage. As evidence has suggested poor correlation between maternal ITP and development of intracranial hemorrhage, it is recommended that cesarean section be performed for obstetric indications only.

The newborn should be assessed for thrombocytopenia with serial platelet counts for 1 week postpartum, as well as assess for intracranial hemorrhage. Brain imaging should be performed if neonatal platelet count is below 50×10^9/L. ASH has recommended that infants with platelet counts below 20×10^9/L or symptomatic for bleeding receive IV immunoglobulin

The first therapeutic step recommended in GDM is the individualization of medical nutrition therapy (MNT)depending on maternal weight and height. The daily energy intake recommended for women with ideal weight in the normal range is 30 kcal/kg of the ideal weight; for obese women 20–25 kcal/kg of the ideal weight,and for underweight women is 40 kcal/kg of the ideal weight.

Vitiligo is not associated with adverse pregnancy outcomes. Accordingly, patients with vitiligo should not be managed differently from the general obstetric population.

The goal of therapy in pregnant women with hypothyroidism is to return thyroid hormone levels to within the reference range. Levothyroxine sodium is the treatment of choice. Women who are newly diagnosed during pregnancy should be initiated on 1.0–2.0 microgram/kg/day or approximately 100 microgram of levothyroxine daily. Thyroid stimulating hormones should then be measured in 6 weeks and levothyroxine doses adjusted in 25 or 50 microgram increments. Once normalized, a TSH should be checkedevery 6–8 weeks throughout pregnancy to insure adequate replacement. Maternal TSH receptor-blocking antibodies can cross the placenta and also cause fetal thyroid dysfunction. However, the more common thyroid antibodies to thyroid peroxidase and thyroglobulin have little or no effecton fetal thyroid function even though they readily cross the placenta in the third trimester. Obstetric complications include increased risk of stillbirth, preterm delivery,pre-eclampsia and placental abruption.

After delivery, levothyroxine therapy should be returnedto the prepregnant dose and the TSH should be checked in6–8 weeks. Breastfeeding is not contraindicated in women treated for hypothyroidism. Levothyroxine is excreted into breast milk but levels are too low to alter thyroid function in the infant or to interfere with neonatal thyroid screening programs.

Conclusion

Multiple autoimmune disorders occur with increased frequency in patients with a previous history of another autoimmune disease.

The underlying mechanisms for these disorders are not yet understood. Familial or genetic, infectious, immunologic and psychological factors have been implicated in its development.

Environmental triggers in a genetically susceptible individual are believed to cause disorders of immune regulation

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