Perspective

Thrombocytopenia in Pregnancy; A Pakistani Perspective

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Abstract: Thrombocytopenia in pregnancy is mostly taken as platelets less than normal lower limit. The normal limit of platelets in pregnancy is 106-120x10^9/l [1]. Thromocytopenia is the second important cause of haematologic disorders in pregnancy, first being anemia [1-3].Gestational thrombocytopenia is responsible for approximately 75% of all cases of thrombocytopenia seen mostly in pregnancy. Another important aspect is hypertension in pregnancy. It can result in thrombocytopenia as well. These disorders constitute about 20% and immune thrombocytopenia accounts for about 4% [4, 5]. Other causes of thrombocytopenia are quite uncommon in pregnancy.

The aim of this review is to highlight different aspects of thrombocytopenia seen commonly in pregnancy, their impact on decisions made by physicians and obstetricians as well as causes of thrombocytopenia encountered in pregnant females in Pakistan and challenges faced by obstetricians and haematologists.

Keywords: Thrombocytopenia, Gestational thrombocytopenia, Pregnancy, Preeclampsia, Immune thrombocytopenia, Alloimmune thrombocytopenia.

INTRODUCTION

Thrombocytopenia is an important finding encountered during pregnancy .Anemia is the commonest one and most prevalent [1]. Thrombocytopenia is diagnosed in approximately 5-6% of pregnancies [6, 7].

Thrombocytopenia in pregnancy is classified as mild, moderate and severe. In mild cases platelet counts are less than 150x10^9/l but more than 100x10^9/l. In moderate it is more than 50x10^9/l but less than 100x10^9/l. Severe cases have less than 50x10^9/l count [8, 9]. Increased platelet "turn over" or dilutional effect of increased blood volume during pregnancy may be responsible for thrombocytopenia [10-13].

In one study it was found that the main etiological factors of thrombocytopenia among cases with platelet count < 150000/µl were gestational thrombocytopenia (59.3%), preeclampsia (10.0%) and HELLP syndrome (12.0%), immune thrombocytopenia (11.0%). Lower limit of platelet count during otherwise normal pregnancy is considered to be 106-120x10^9/l [1, 14].

Thrombocytopenia was found to be associated with higher rates of placental abruption, preterm deliveries, intrauterine growth restriction and stillbirth [14].

In Pakistan, prior studies show that most frequently reported etiology of low platelets in pregnancy is benign gestational one, which is seen in about 6% of the cases and constitute approximately 70-75% of all other causes .The platelet count is about 10% less than normal and this is mostly noticed on full blood counts done in the final trimester and usually becomes normal within 6 weeks after delivery. Immune mediated thrombocytopenia is documented in about 0.03% of pregnancies [3].

PROCOGULANT EFFECT OF NORMAL PREGNANCY

Bleeding manifestation in pregnant females with thrombocytopenia are less commonly seen due to procoagulant effect of normal pregnancy. This effect is seen because of increased level of factor VIII, decreased protein S and raised Von Willebrand factor levels [15]. This is a beneficial effect which prevent severe and life threatening bleeding in first two trimesters [15].

CAUSES OF THROMBOCYTOPENIA IN PREGNANCY [16-18]

Causes which are specific to pregnancy:

1. Gestational thrombocytopenia.
2. Preeclampsia/eclampsia.
3. Acute fatty liver of pregnancy.
4. HELLP syndrome.

Causes not specific to pregnancy:

1. Drug induced.
2. Immune thrombocytopenia.
3. Congenital(BERNARD-SOULIER,IIB VWD).
4. Viral or bacterial infections.
5. Malaria, Leishmania.
6. Antiphospholipid syndrome.
7. Splenomegaly.
8. Megaloblastic anemia.

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GESTATIONAL THROMBOCYTOPENIA, MECHANISM AND TREATMENT

The underlying main mechanism responsible for gestational thrombocytopenia is dilutional effects of expanded volume and accelerated breakdown of platelets as they passes through placenta and mainly through its trophoblastic surface [1,19, 20]. In twin pregnancy platelet counts are found to be lower in comparison with single pregnancy, which may be due to greater increase in thrombin [4].

Platelet count noted gestational thrombocytopenia rarely goes below $70x10^9$/l. No treatment advised except for close monitoring of platelet count. Spontaneous recovery mostly occurs after delivery [4, 21, 22].

In a study a total 71 (1.9%) pregnant females had thrombocytopenia. Thrombocytopenia was divided into four groups depending on the platelet count, i.e. those with platelets below 20,000/µl, between 20-50,000/µl, between 50-100,000/µl and more than 100,000/µl. Patients having chronic liver disease and drug induced thrombocytopenia were excluded from that study. Thrombocytopenia was mostly labelled as gestational thrombocytopenia and was present in 24 (33.8%) patients. According to most other studies approximately 70% of pregnant females with thrombocytopenia have gestational thrombocytopenia [23].

PRECELAMPSIA AND ECLAMPSIA

Thrombocytopenia seen with hypertensive disorders (preeclampsia, eclampsia) is important cause of morbidity and mortality in pregnancy. Platelet count usually remains above 20,000/µl [23-25].

HELLP syndrome complicates about 20% cases of preeclampsia. This condition may be seen without proteinuria and hypertension and become difficult to diagnose.70% cases of HELLP are seen antepartum but 30% are seen postpartum complicating the whole picture [25, 26].

The pathophysiology of this syndrome is same as preeclampsia. Endothelial damage with release of tissue factor can cause coagulation activation [23].

In another study HELLP was reported in 26.7% of thrombocytopenic patients in pregnancy. In the same study, HELLP syndrome was associated with high maternal and fetal morbidity as well as mortality which may be due to placental abruption, preterm deliveries, APGAR scores lower than normal, intrauterine growth retardation and maternal deaths. In mothers severe postpartum hemorrhage was observed in those diagnosed as having HELLP syndrome and coagulopathy was associated with dead fetus. An association with thrombotic thrombocytopenic purpura is also noted [27-29].

In a study done in Peshawar, Pakistan which included pregnant females with hypertension related pregnancy disorders, significantly low platelet count were noted in preeclamptic females. It has been observed that thrombocytopenia in pregnant females with eclampsia is more prevalent than in control females i.e. 13.6% in eclampsia and 1.1% in the control women [23, 30].

FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy is a rare finding but can be a severe condition complicating pregnancy. Clinical manifestations include abdominal pain. Gastrointestinal symptoms maybe present including nausea and anorexia. Laboratory changes include markedly deranged liver functions, hypoglycemia and in some cases hyperuricemia. Renal impairment is reported in some cases but blood pressure remains normal. Thrombocytopenia in acute fatty liver of pregnancy may be severe [31-33].

Effective treatment for preeclampsia or eclampsia is delivery. Dexamethasone 10 mg every 12 hours antepartum and postpartum is usually recommended until platelet count is in safe range [34]. If thrombocytopenia and renal dysfunction worsen, plasmapheresis may be used. Platelet count normalizes by day 4 postpartum [35].

The pathophysiology of thrombocytopenia in preeclampsia is endothelial injury which causes in microvasculature. Schistocytes on the peripheral film with increased bilirubin alongwith markedly raised LDH are hallmark of this disorder [36].

THROMBOTIC THROMBOCYTOPENIC PURPURA AND HEMOLYTIC UREMIC SYNDROME

Pregnant females who has developed TTP in previous pregnancies are at higher risk of relapse [37]. These women have a higher mortality. Recurrence rate is 92 % in those with congenital TTP. Pregnant females with any such history should be closely monitored [37, 38]. Serial blood counts and ADAMTS13 levels needed [23].

Indeed, postpartum TTP are rarer than antepartum TTP and usually occur after late delivery in the 3rd trimester and a mean postpartum 4th day (0-42 days) [36]. Timely and vigorous plasm exchange is advised [23].

In a study by the author of this review in 2008, which was done on patients with thrombotic thrombocytopenic purpura, in which 4 females were diagnosed as having TTP in third trimester of pregnancy and after delivery, two of them had intrauterine death of the foetus. All of these patients received plasma infusion as well as plasma exchange and immunosuppression. Two of them survived [27]. This indicates dismal survival of these patients.

IMMUNE THROMBOCYTOPENIA

Steroids in low doses can be used to treat pregnant females with immune thrombocytopenia but can cause increase in infection rate [21]. IVIg can also be used during pregnancy. Pregnancy does not cause increase in bleeding manifestations, but risk of bleeding increases as platelet falls below 20,000/µl [21, 22]. For normal vaginal delivery 50,000/µl count is appropriate [21].

There are reports of successful and harmless use of azathioprine,ciclosporin and anti D during pregnancy. These are placed in category C and D keeping in mind the reports of affected foetal growth in some studies [29].

In a study reported from Pakistan which included 30 patients with ITP during pregnancy, there were very few bleeding symptoms reported i.e approximately 23%. The most commonly used treatment was platelet transfusions and corticosteroids [25].

AUTOIMMUNE DISORDERS DURING PREGNANCY

Many autoimmune disorders can complicate pregnancy and can result in thrombocytopenia. The underlying cause of thrombocytopenia in these cases may be secondary immune thrombocytopenia or thrombotic microangiopathy. Cases of antiphospholipid syndrome can result in thrombocytopenia as well as thrombotic tendency during pregnancy [39, 40].

Antiphospholipid syndrome is reported frequently as a syndrome associated with thrombosis and thrombocytopenia during pregnancy. Thrombocytopenia with platelet count less than 50000/µl requires use of corticosteroids to prevent bleeding [40]. Aspirin in low doses and low molecular weight heparin is needed to prevent foetal loss [40].

In a study done in UK revealed diagnosis of SLE in 10/100,000 Pakistani national women living in UK [6].

Survival of Pakistani SLE patients is found to be significantly lower in comparison to that of the Caucasian studies reported in last ten years. Lupus nephritis is not only responsible for organ damage but is also a major factor for survival. Infection is considered as the commonest cause of death. Involvement of renal system and infections are important risk factors responsible for rising mortality [24].

All women with autoimmune disorders should take aspirin in low dose i.e 75 mg and it should be preferably started from 12 weeks. If there is increased risk of venous thromboembolism low molecular weight heparin is needed in prophylactic dose as according to RCOG guidelines [41].

CONSIDERATIONS FOR BABY

Antibodies which are responsible for immune mediated thrombocytopenia are mostly IgG and these can cross the placenta [4].

According to a review only 1% of neonates born to thrombocytopenic mothers had thrombocytopenia. This is not significantly different from 2.0% neonates with thrombocytopenia born to non-thrombocytopenic mothers [41].

Neonatal thrombocytopenia can be expected more likely if a previous child of that mother was born with thrombocytopenia.

In a study from Pakistan regarding bleeding manifestations in mother, antepartum bleeding was seen in 16.0% cases, postpartum hemorrhage was noted in 41.3% and unfortunate maternal mortality was in 8.0% of the patients [25].

77.0% of neonates were delivered at term whereas 22.9% were delivered preterm.14 (16%) cases of IUD and 6 (6.9%) of IUGR were present, remaining all were healthy alive. Neonatal outcome in term of mean Apgar score at 5 minutes was 7 [25].

More recently the management of immune thrombocytopenia is revolutionized by the use of thrombopoietin receptor analogues [30]. Many pregnant females may require these newer agents like thrombopoietin receptor agonists, mycophenylate or even Rituximab due to refactoriness to first line modalities, but these can result in unknown problems in the fetus. Changed criteria for preeclampsia, increasing confidence in diagnosing microangiopathic hemolytic anemia in pregnancy as well as evidence in favour of use of anticomplement treatment of atypical haemolytic uremic syndrome during pregnancy are changing patient care quickly [21].

Regarding alloimmune thrombocytopenia, development of recombinant human placental antibody will be a potential breakthrough which will block binding of maternal HPA-1a antibodies to fetal platelets [41].

RARE CAUSES OF THROMBOCYTOPENIA IN PREGNANCY

These may include congenital platelet disorders like Bernard-Soulier syndrome and constitutional anemias like Fanconi anemia [41].

Management of pregnancies with severe thrombocytopenia is still a challenge in Pakistan with main group of patients of previously known immune thrombocytopenia [42]. Collaborative efforts of hematologists and obstetricians can result in improving outcome in mother and newborn. Newer agents are being increasingly used in chronic cases, although no case reports of their successful use are published to date.

CONFLICT OF INTEREST

Declared none.

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