Management of Idiopathic Thrombocytopenic Purpura in Pregnancy: Analysis of Maternal and Neonatal Outcomes

GEBELİKTE İDİOPATİK TROMBOSİTOPENİK PURPURA: MATERNAL VE NEONATAL SONUÇLARIN DEĞERLENDİRİLMESİ

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Abstract

Objective: To review the diagnosis, management and potential adverse outcomes of the pregnant women having idiopathic thrombocytopenic purpura.

Materıal and Methods: We retrospectively went through the medical records of seven women having idiopathic thrombocytopenic purpura during pregnancy. The diagnosis and clinical course, therapeutic modalities and maternal-neonatal outcomes were analysed.

Results: Seven pregnant cases meeting the diagnostic criteria of idiopathic thrombocytopenic purpura determined by American Society of Hematology were included. Four cases experienced premature rupture of membranes, premature labour, oligohydramnios and intrauterine fetal growth restriction respectively. One of the cases suffered from gingival bleeding and epistaxis, other three cases demonstrated mild cutaneous and mucous membrane purpura while the remaining ones appeared to be asymptomatic. Three cases required steroid therapy and platelet transfusions to raise the platelet count. Except vaginal lacerations in one case and uterine atonia in another, we did not observe any serious complication during labour. Of two neonates with low platelet count , only one needed therapy with IVIG, steroid and platelet transfusion. Fortunately no neonate had serious hemorrhagic diathesis.

Conclusion: Although pregnant women with idiopathic thrombocytopenic purpura should be closely monitorized due to potential maternal-neonatal hemorrhagic complications, a low incidence of bleeding diathesis with an uncomplicated pregnancy course and satisfying outcome is frequently observed. A multidisciplinary collaborative clinical approach seems to be required to manage those two subjects, the pregnant woman herself and the offspring.

Key Words: Idiopathic, thrombocytopenic, purpura, pregnancy

Özet

Amaç: İdiopatik trombositopenik purpuranın eşlik ettiği gebe kadınlarda tanı, klinik yönetim ve potansiyel olumsuz sonuçların gözden geçirilmesi.

Gereç ve Yöntemler: Gebelikte idiopatik trombositopenik purpuranın eşlik ettiği 7 olgunun tıbbi kayıtları retrospektif olarak gözden geçirildi. Tanı yöntemleri, klinik seyir, tedavi metodları ve maternal-neonatal sonuçlar değerlendirildi.

Bulgular: Amerikan Hematoloji Derneği'nin belirlediği kriterlere göre idiopatik trombositopenik purpura tanısı konulan 7 gebe kadın çalışmaya dahil edildi. Dört olguda sırası ile erken membran rüptürü, prematür doğum eylemi, oligohidramnios ve intrauterin fetal büyüme kısıtlılığı tespit edildi. Olgulardan 1'inde gingival kanama ve epistaksis, 3'ünde ciltte ve muköz membranlarda hafif derecede purpura bulguları gözlendi. Diğer olgular asemptomatik seyretti. Üç olguda platelet sayısını yükseltmek amacı ile steroid tedavisine ve platelet transfüzyonuna gereksinim duyuldu. Bir olguda meydana gelen vaginal laserasyonlar ve diğer 1 olguda gelişen uterin atoninin dışında doğum sürecinde ciddi bir komplikasyon ile karşılaşılmadı. Doğum sonrası platelet sayımı düşük tespit edilen 2 yenidoğandan sadece birinde IVIG, steroid ve platelet transfüzyonu ile tedavi gerekti. Yenidoğanların hiçbirinde ciddi kanama diatezi saptanmadı.

Sonuç: İdyopatik trombositopenik purpuranın eşlik ettiği gebe kadınlarda karşılaşılabilecek ciddi maternal-neonatal hemorajik komplikasyonlardan dolayı yakın monitorizasyon gerekmesine rağmen, bu olgularda gebelik süreci, sıklıkla son derece düşük oranda kanama diatezi ve tatmin edici klinik sonuçlarla komplikasyonsuz seyreder. Gebe kadının kendisi ve fetus olmak üzere 2 hastanın söz konusu olduğu bu olgularda multidisipliner kolloboratif klinik yaklaşımlara gereksinim duyulmaktadır.

Anahtar Kelimeler: İdyopatik, trombositopenik, purpura, gebelik

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Pregnancy may be complicated with thrombocytopenia in approximately 10% of obstetric patients due to a number of etiologic factors.[1] Low platelet count (<150 X 10^9/l) appears to be the most frequently identified coagulation abnormality in pregnancy secondary to a wide

variety of clinical situations ranging from benign disorders such as gestational thrombocytopenia to life-threatening conditions involving HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count).[2]

Idiopathic thrombocytopenic purpura (ITP, also known as primary immune thrombocytopenic purpura) is defined to be an isolated thrombocytopenia associated with no clinically apparent etiologic factor leading to low platelet count.[3-5] Immunologically mediated platelet destruction is determined to be the main pathophysiologic mechanism of ITP.[6] Antiplatelet antibodies of IgG type recognising the platelet membrane glycoproteins (platelet glycoproteins IIb, IIIa and I b/IX) are produced by the patient and consequently destruction of antibody-coated platelets by reticuloendothelial system (primarily by splenic sequestration) takes place exceeding the production of new platelets by bone marrow.[7] Furthermore those maternal autoantibodies of IgG class may cross the placenta and induce fetal or neonatal thrombocytopenia leading to potential risk of bleeding complications such as intracranial hemorrhage.[6,8] However those autoantiodies are recognised in only 80% of ITP cases.[9]

ITP seems to occur frequently in young females thus affecting the women of childbearing age.[10] It is diagnosed in 1 case of thrombocytopenia per 1000 pregnancies accounting for 5% of the subjects with pregnancy associated thrombocytopenia.[11] It is determined to be the most common cause of significant thrombocytopenia in the first trimester and is a diagnosis of exclusion since it does present no pathognomonic signs and symptoms.

Potential risk of maternal bleeding, requirement of different treatment modalities during gestation, controversies regarding the route of delivery and probable neonatal complications in the postpartum period make ITP a disease of concern during pregnancy. Pregnancy is accepted not to alter the clinical course of ITP in spite of some previous reports pointing out deterioting symptoms during pregnancy followed by improvement in the postpartum period.[12,13] A collaborative study with a multidisciplinary approach involving obstetricians, haemotologists, pediatricians and anaesthesists is mandatory for the optimal management of those obstetric cases with ITP.

We aimed to present our own clinical experience with seven pregnant women having ITP to review the diagnosis and management of this disorder in pregnancy and potential adverse outcomes of the women themselves and the neonates. We analysed retrospectively the medical records of those seven women with ITP for the diagnosis, clinical courses, treatment and both maternal and neonatal outcomes.

Material and Methods

We reviewed retrospectively the medical records of seven pregnant women fulfilling the diagnostic criteria of ITP given by the American Society of Hematology[14] who were administered to Kocaeli University, School of Medicine, Department of Obstetrics and Gynecology between 2004-2005 and managed in colloboration with Hematology Division at the same tertiary medical center.

Those cases who met the the inclusion criteria of pregnancy with a diagnosis of ITP were eligible for this study. Since ITP appears to be a diagnosis of exclusion due to presence of no pathognomonic signs, symptoms and laboratory investigation, the diagnosis is made to be based on 4 consistent features which accounted for the diagnostic criteria.[14] Those are defined to be persistent thrombocytopenia (platelet count <100 X 10^9/l) with or without peripheral megathrombocytes, normal or increased number of megakaryocytes detected by bone marrow aspiration, absense of splenomegaly and exclusion of systemic disorders or use of pharmacologic agents known as leading to thrombocytopenia. Gestational or incidental thrombocytopenia which is important for the differiantial diagnosis was excluded by the presense of persistent thrombocytopenia after delivery in ITP cases while low platelet count retuns to a normal level following delivery within 12 weeks in gestational thrombocytopenia cases.[8]

The subjects with a number of etiologic causes which may be associated with thrombocytopenia

such as pregnancy induced hypertension, disseminated intravascular coagulation, drug use, sepsis, autoimmune diseases such as Systemic Lupus Erythematosus (SLE), Thrombotic Thrombocytopenic Purpura (TTP), Hemolytic Uremic Syndrome (HUS) and hereditary forms of low platelet count were excluded.

Age, time of diagnosis, underlying medical conditions, administered medications, platelet counts determined before, during pregnancy and at delivery and clinical signs and symptoms of impaired hemostasis during pregnancy, therapies provided to increase the platelet counts during gestation or at birth, gestational age at delivery, delivery route, epidural anesthesia, estimated blood loss during delivery, transfusion of blood products, complications associated with delivery and the postpartum period were determined. Additionally neonatal platelet counts at birth and the following first week, neonatal complications and the treatments required were reviewed.

Complete blood count was repeated every 4 weeks until delivery. Platelet counts were determined in blood samples collected in tubes involving ethylenediaminetetraacetate (EDTA) using a Coulter MAXM (Coulter Scientific, Miami, Fla, USA) cell counter with an accompanying peripheral blood smear. Normal platelet count was determined as >150 X 10^9/l while it was found to be 100-150 X 10^9/l, 50-99 X 10^9/l and <50 X 10^9/l in mild, moderate and severe cases respectively.

Patients having platelet count higher than 50X10^9/l and presenting no bleeding did not require treatment immediately. Platelet transfusion was indicated if any bleeding occured or the platelet count was <50 X 10^9/l. Those subjects requiring therapy were administered oral Prednisone 1 mg/kg/day for 3-4 weeks until a normal platelet count was provided. Then steroids were reduced gradually within several weeks. Intravenous immunoglobulin (IVIG) was planned to be given at a dose of 0.4 g/kg/day for 5 consecutive days every 28 days for 2 cycles if indicated. Since all our patients that required medical therapy responded to either steroids or platelet transfusion, splenectomy was indicated in none of the cases. A patient was considered to present a complete response to therapy if the platelet count was increased to >150 X 10^9/l while a partial response if the count reached to ≥50-<150 X 10^9/l. No response was defined to be achieved when the count remained lower than 50 X 10^9/l.

Fetal blood sampling was not performed to detect the fetal platelet count in utero. Neonatal platelet count was determined by collecting cord blood sample at birth followed by platelet counts done by venipuncture on postnatal first, third, and fifth days. Neonatal thrombocytopenia was defined as a platelet count of less than 150 X 10^9/l.

Results

We reviewed the medical records of 7 pregnant women with ITP who were managed at Department of Obstetrics and Gynecology of Kocaeli University, School of Medicine in collaboration with Department of Hematology of the same medical center. Data concerning the mothers and neonates are demonstrated in Table 1.

The median age was found to be 27 ranging between 20-32. All cases were singleton pregnancies. Except 2 women who were giving birth to their second child, all the cases were primigravid. The gestational ages of those women at initial administration ranged between 16-40 weeks of gestation while median gestational age at delivery was 38 which appeared to be between 36-40 weeks.

One of the cases was complicated with premature rupture of membranes for 22 hours at 37th gestational week. Another subject was diagnosed of premature labour which ended with premature delivery unfortunately. Oligohydramnios and meconium-stained amniotic fluid were observed in one case. One of the subjects was found to have intrauterine fetal growth restriction, oligohyramnios and maternal anemia. We determined none of hypertensive disorder of pregnancy, placenta previa, placental ablation, postterm pregnancy, macrosomia and maternal mortality in our cases.

ITP was diagnosed during pregnancy in 5 of the subjects while 2 pregnant women were deter

Table 1. Data concerning the pregnant women with ITP and their neonates are demonstrated.

Case	Age (years)	Diagnosis of ITP	Gestational week at delivery	Symtoms and signs	Obstetric Complica-tion	Treatment	Delivery route	Birth weight (g)	Maternal compli-cations	Maternal platelet count (10^9/l)	Maternal platelet count at delivery (10^9/l)	Neonatal platelet count (10^9/l)	Neonatal therapy	Cord PH
1	27	32. week of gestation	40	None	Meconium stained amnios	None	Vaginal	3250	Vaginal lecerations	81	82	110	Observed due to mild dyspnea	7.310
2	32	40. week of gestation	40	None	None	None		3950	None	71	96	123	Hypoglyce-mia	7.300
3	26	36. week of gestation	38	Bruising	None	Steroid, thrombocyte solution	Vaginal	3150	None	30	50	50	Mild bruising	7.310
4	20	Chronic ITP (16)	39	Bruising	Premature rupture of membranes (22 hours)	Steroid, thrombocyte solution	Vaginal	2650	Uterine atonia	70	110	138	None	7.330
5	27	37. week of gestation	37	None	None	None	Vaginal	2850	None	95	95	124	None	7.335
6	28	Chronic ITP (26)	36	Bruising	Preterm labour and delivery	None	Abdominal (fetal distress)	2500	None	71	87	132	None	7.283
7	26	36. week of gestation	36	Epistaxis, gingival bleeding, bruising	Maternal anemia, intrauterine fetal growth restriction, oligohydramnios	Steroid, thrombocyte solution	Abdominal (fetal distress)	2000	none	11	45	21	Mild bruising, IVIG, thrombocyte solution, steroid	7.310

mined to have ITP before pregnancy (Those cases were diagnosed 2 years and 8 months before conception). The cases who were diagnosed during pregnancy were shown to have persistent thrombocytopenia for at least 3 months thereafter in order to differiantiate from incidental or gestational thrombocytopenia. Unfortunately we did not have the opportunity to detect IgG type antiplatelet antibodies which appear in some of ITP cases. Maternal platelet counts were found to be ranging between 11-95 X 10^9/l (median:71 X 10^9/l) at initial administration while appeared to be between 45-110 X 10^9/l (median:87 X 10^9/l) at delivery. Four cases did not require any therapy while 3 subjects needed steroid therapy to raise the platelet count. We achieved partial response in two cases and no response in the other one. Intravenous immunoglobulins and splenectomy were indicated in none of the cases while 3 patients needed platelet transfusions before delivery. We observed mild cutaneous and mucous membrane purpura in 4 cases while one subject complained of gingival bleeding and epistaxis and the remaining 3 cases had no symptoms of hemorrhagic diathesis. Significant bleeding signs and symptoms involving hematuria, gastrointestinal bleeding or deep tissue hemorrhage were fortunately detected in none of the cases.

Of 7 pregnant cases 5 women were were delivered vaginally while we performed cesarean section in two cases in which acute fetal distress was the indication of abdominal deliveries. Regional anesthesia was done in none of the cases due to potential bleeding complications.

Except vaginal lacerations in one case and postpartum hemorrhage due to inadequate uterine contraction in another case (managed by Oxytocin infusion) we did not determine complications in our cases such as vagina hematoma, wound hematoma etc. In both cases estimated blood loss was approximately 1000 cc. Maternal hospitalization time in the postpartum period ranged between 24-72 hours (median: 48 hours).

We had no neonatal mortality and no Apgar scores below 8. The cord pH values were determined to be between 7.28-7.33 (median: 7.310). Birth weights ranged between 2000-3950 g (median: 2850).

Neonatal platelet counts were determined immediately by cord blood analysis at birth and all of the neonates were followed for a week. Median

neonatal platelet count was found to be 123 X 10^9/l ranging between 21-138 X 10^9/l. Only two of the neonates had low platelet count (21 X 10^9/l – 50 X 10^9/l) at delivery. The one with higher platelets was found to have mild bruising and did not require any treatment while the other was managed with IVIG (750 mg/kg), 3 units of thrombocyte solutions (15 cc/kg) and steroid (2 mg/kg) administration. Fortunately, the latter one did not experience any serious hemorrhagic diathesis, presented only mild bruising clinically and was discharged on 13rd postpartum day with a platelet count of 217 X 10^9/l. One of the other neonates had hypoglycemia in the early postnatal period and another one was observed in the neonatal unit for 24 hours due to mild dyspnea and history of meconium stained amniotic fluid during labour. The others did not experience disorders due to hemostatic impairment or any other morbidity. None of the cases had antenatal cordocentesis or fetal scalp sampling in order to demonstrate fetal thrombocytopenia for the prediction of any neonatal complication.

Discussion

In spite of early case reports and clinical studies pointing out a high maternal-perinatal morbidity and mortality in pregnancies complicated with ITP,[14,15] recent experiences present more optimistic suggestions for the impact of ITP on pregnancy outcomes.[14,16,17] Therefore we reviewed our own pregnant cases with ITP that we managed in a period of 1.5 years in order to highlight the controversies about diagnosis, management, and maternal-perinatal complications in those cases.

ITP is an autoimmune disorder leading to IgG-mediated platelet destruction which is due to binding of autoantibodies directed against platelet antigens. Those antibodies in turn cross the placenta and potentially may lead to neonatal thrombocytopenia.[3] Therefore ITP in pregnancy is a disorder of two individuals; the pregnant woman and her fetus.

ITP occurs in approximately one case of low platelet count per 1000 pregnancies and accounts for 5% of subjects with pregnancy associated thrombocytopenia.[11]

Diagnosis of ITP in pregnancy is not always easy especially when it is discovered during pregnancy. It should be differiantiated from incidental thrombocytopenia which is a benign condition that disappears after delivery. The presense of antiplatelet antibodies is not enough for certain diagnosis. Then a thorough history excluding the other causes of low platelet count, stage of gestation at which thrombocytopenia is discovered first, severity and whether it continues after delivery are suggested to be the clinical points of utmost importance for the diagnosis of ITP. Absense of a prior platelet count and a count <100 X 10^9/l in the first trimester that declines progressively as the pregnancy continues seem to be consistent with ITP while mild thrombocytopenia in the second or third trimester, not associated with proteinuria or hypertension mostly points out incidental thrombocytopenia.[18] Review of our own cases demonstrated that only two of the subjects were previously known to be patients with ITP while five cases were diagnosed during pregnancy. None of the cases were assessed in the first trimester. The diagnosis was based on the criteria of American Society of Hematology involving the exclusion of the other causes of low platelet counts in pregnancy.[14] Additionally all the cases were shown to be thrombocytopenic for at least 12 weeks after delivery which provided the differiantial diagnosis with gestational thrombocytopenia. Unfortunately, we were not able to look for antiplatelet antibodies in those cases. Nevertheless the presense of those antibodies is not absolutely required for the definite diagnosis.

ITP appears to be an insidious disease with the symptoms such as easy bruising, petechia, epistaxis and gingival bleeding although some cases are asymptomatic. We observed mild symptoms such as bruising in our cases. Just a single case with a platelet count of 11 X 10^9/l at administration was determined to be suffering from gingival bleeding and epistaxis. Fortunately, none of our cases presented serious hemorrhagic symptoms and signs such as gastrointestinal hemorrhage, deep tissue bleeding or large wound hematomas.

The unpredictable course and potential complications of ITP during pregnancy such as adverse affects of steroid treatment, preeclampsia, eclampsia, HELLP syndrome, placental complications, maternal bleeding and fetal complications are additional stress factors.

Pregnancy does not seem to alter the clinical course of ITP while some studies suggest deterioation of symptoms during pregnancy and subsequent improvement after the delivery.[19] Our two cases previously known to have ITP did not complain of detoriation of the disease during pregnancy.

The therapeutic approach in a pregnant woman with ITP is similar to nonpregnant state except the third line therapeutic agents (Azathioprine, Cyclophosphamide, vinca alchaloids etc) due to their fetotoxic affects. Glucocorticoids, intravenous immunoglobulin (IVIG), AntiD, splenectomy are well-established therapeutic options for ITP.

Subjects with platelet counts >30 X 10^9/l and no bleeding signs or symptoms such as petechia or mucosal bleeding do no usually require immediate therapy. Platelet transfusion may be indicated in the presense of bleeding and low platelet count <30 X 10^9/l. However more agressive measures should be established to allow invasive procedures such as epidural anesthesia although some authors recommend to restrict those invasive interventions[20] or to provide sufficient hemostasis during delivery. Some studies point out suggestions about platelet counts to be raised over 100 X 10^9/l while others find platelet counts more than 50 X 10^9/l to be adequate in this manner.

Oral Prednisone (1-2 mg/kg/day) is usually recommended with gradual reduction of doses until the counts are stabilised at 75-100X10^9/l. Since the placental enzymes are determined to inactivate a major portion of the drug, Betamethasone or Dexamethasone may be preferred.[21]

Although the clinical response is transient and the treatment is expensive due to requirement of multiple doses, IVIG (2 mg/kg) may be an alternative therapeutic aproach.

Splenectomy may be indicated in refractory cases to medical therapy in order to reduce the platelet destruction through the spleen. It should be performed in the second trimester of pregnancy in order to prevent premature labour and technical difficulties due to a large gravid uterus.

In none of our cases splenectomy or IVIG administration was indicated while three subjects required steroid administration and transfusion of thrombocyte solution.

Bleeding complications during delivery are mostly associated with surgical incision and lacerations of the birth canal. Placenta previa or placental ablation seem to be no more frequently encountered in those women. Risk of postpartum bleeding due to insufficient uterine contraction is not increased since mechanical hemostasis instead of a significant contribution of platelets occurs after delivery. During delivery platelet counts must be maintained above 50 X 10^9/l, platelet transfusion is essential in the cases with lower counts. One of our cases experienced vaginal laceration which caused an estimated blood loss of 1000 cc. Another woman who delivered vaginally having insufficient uterine contraction (uterine atonia) in the early postpartum period required emergent treatment with high doses of Oxytocin. This complication seemed not to be associated with ITP in pregnancy since mechanical uterine contraction rather than platelet function is accepted to prevent early postpartum bleeding.

The major controversial issue regarding the pregnant women with ITP appears to be the delivery route. A number of previous case reports suggested abdominal delivery in those cases in order to prevent neonatal intracranial hemorrhage due to vaginal delivery. A literature review of 18 studies reported that 12% of the neonates presented severe thrombocytopenia and the rate of intracranial bleeding was only 1% suggesting no relation with the mode of delivery.[22] It is concluded that delivery route should be just based on obstetric indications.[12,20,23-25] Furthermore although some authors recommended to perform cordocentesis in order to determine the fetal platelet counts antenatally to plan abdominal delivery in the case of low platelet

counts (<50 X 10^9/l)[25], some others did not agree with those since the morbidity-mortality risk of this procedure is much higher than the risk of severe bleeding during delivery (2% versus 1%).[18,23,26,27] In our cases, we determined the route of delivery according to obstetric indications, fetal distress was the indication for cesarean section in our two cases who delivered abdominally. None of the cases had antenatal cordocentesis to determine the fetal platelet counts since we agree with the opinion that suggests this procedure as having much higher risk of bleeding.

As a consequence of transplacental transfer of maternal IgG antibodies, 10-20% of the neonates present platelet counts <50 X 10^9/l, 5% of the neonates may have platelet counts <20 X 10^9/l. Intracranial hemorrhage leading to mortality or morbidity such as neurological sequelae is the major fetal risk especially during the stress of vaginal delivery.[28] The severity of maternal thrombocytopenia or maternal IgG concentrations do not seem to predict the fetal platelet count at delivery.[18,20,27] Delivery of a thrombocytopenic sibling appears to be the most reliable predictor of fetal thrombocytopenia.[6] Some authors recommend antenatal detection of fetal platelet counts by fetal scalp sampling during labour or cordocentesis which may be further complicated by bleeding and fetal distress.[2,10,29,30] In our cases only two neonates demonstrated to have low platelet counts after delivery. The case with a platelet count of 50 X 10^9/l did not present any complication other than mild bruising and required no therapy since the platelet count was increased spontaneously through the follow up period. The neonate with a platelet count of 21 X 10^9/l needed to be treated with steroids, IVIG and thrombocyte solution. The subject was managed to be discharged with a platelet count of 217 X 10^9/l after a hospitalization of 13 days. Fortunately the case did not demonstrate any complication other than bruising.

In conclusion, we demonstrated that pregnant subjects with ITP require close monitorization due to potential maternal-neonatal bleeding complications and those may need intervention to raise platelet counts. However our current experiences and previous data in literature point out a low risk of hemostatic impairment in those cases, the pregnancy is usually uncomplicated and presents good outcome. A multidisciplinary colloborative approach is mandatory in such a disorder enrolling two patients, the pregnant woman herself and the fetus.

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