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Immune Thrombocytopenic Purpura in Pregnancy- A Prospective Observational Study in a Tertiary Care Centre

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Abstract:

Objectives: *Immune thrombocytopenic purpura (ITP) in pregnancy necessitates management of two patients, the mother and the newborn. Complications like maternal bleeding, fetal and neonatal thrombocytopenia demands appropriate and timely therapy. This prospective observational study was designed to explore and summarize the current approach to the investigation, diagnosis, management and outcome of ITP in pregnancy.*

Materials and Methods: *Women with ITP admitted in the Fetomaternal Medicine Department of Bangabandhu Sheikh Mujib Medical University (BSMMU) from 2009 -2017, were included in the study. Total number of high risk pregnancy during that period were 7704 among them 20 cases were pregnancy with Immune Thrombocytopenic Purpura (ITP). Patients were managed under joint supervision of the fetomaternal medicine specialist and the hematologist. Prednisolone was considered as a first line drug in management protocol. Platelet transfusion was considered if there were symptoms or count <20X10^9/L at any stage of pregnancy or <50 X10^9 / L in late pregnancy without symptoms. Platelet count of newborn was performed at birth and repeated on day four and count<150X10^9/L was considered as neonatal thrombocytopenia.*

Results: *Frequency of ITP among high risk patients was found 2.5/1000 live birth, most were preexisting (75%). Almost all cases (95%) were treated with prednisolone. Commonest clinical presentations were gum bleeding (70 %) and purpuric rashes (60%). Though during pregnancy, severe thrombocytopenia (<50 X10^9/L) was found in 7 patients (35%) but none was at the time of delivery, as drugs and/or platelet transfusion was considered to make delivery process safe. Platelet transfusion needed in 77.7% cases in a range of 1-75 units. Primary PPH noted in 3 cases (17%), increased bleeding during surgery in 5 patients (33%) and one patient needed ICU support. Neonatal thrombocytopenia noted in 5 cases (28%). Though 2 of the neonates needed NICU admission but none needed platelet transfusion and all the babies were discharged healthy.*

Conclusion: *This study documents that pregnancy with ITP need close monitoring, require agents to raise the platelet count and repeated platelet transfusion to maintain reasonable safe platelet count. There are chances of PPH, capillary oozing during surgery. However good outcome is possible for most women, fetus and neonates with appropriate and timely therapy.*

Key words: *ITP in pregnancy, Platelet transfusion, Neonatal Thrombocytopenia*

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Introduction:

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by immunologic destruction of otherwise normal platelets in response to an unknown stimulus leading to thrombocytopenia and manifested as bleeding tendency from different sites of the body.[1] The pathophysiology of ITP is actually a cross-talk between platelets and immune system. In ITP, auto reactive T helper cells (T_h cells), also known as $CD4^+$cells and B cells become activated and then proliferate escaping the regulatory T cells (Treg) surveillance which maintains self tolerance. B cells produce auto-antibodies against platelet surface antigens. As megakaryocytes share the same antigens, the autoantibodies easily bind to it and platelets are phagocytosed by splenic and hepatic macrophages. The activated T_h cells then induce B cells to continue producing platelet autoantibodies and thus maintain the pathogenic loop.[2,3] Recent studies showed deficiency of a glycoprotein hormone and platelet production inducer 'thrombopoitien' may contribute in pathogenesis .[4]

Diagnosis, evaluation and management of ITP during pregnancy and postpartum period may appear challenging. It occurs in one to two of every 1,000 pregnancies and accounts for 5% of cases of pregnancy-associated thrombocytopenia.[5] Despite its rarity compared to gestational thrombocytopenia, it is the most common cause of isolated thrombocytopenia in the first and early second trimesters. Diagnosis of ITP in pregnancy with asymptomatic thrombocytopenia occur by routine testing, or less commonly when presented with severe thrombocytopenia accompanied by bruising, bleeding, and petechiae. There is no accurate and definitive test for diagnosis. It is mostly by excluding other causes of thrombocytopenia as bone marrow studies or antiplatelet antibodies are not specific. [6] Regarding preexisting ITP, it may either worsen leading to maternal and fetal complications or remain quiescent during gestation.[7] Though pregnancy is not discouraged in pre-existing ITP, but close monitoring and additional therapy may be needed during pregnancy and after delivery due to the potential risk of maternal hemorrhage when the platelet count is low. As antibodies can cross the placenta leading to thrombocytopenia in the newborn, neonatal monitoring is necessary.[8]

Material and methods:

All booked or unbooked cases of ITP in pregnancy admitted in the Fetomaternal medicine Department of Bangabandhu Sheikh Mujib Medical University from 2009-2017 were included in the study. Gestational thrombocytopenia, thrombocytopenia due to systemic lupus erythematosis, lymphomas, leukemias, HELLP syndrome were excluded from the study. As followed in some studies, thrombocytopenia was categorized as mild with platelet count 100,000-150,000/ml, moderate with <50,000-99,000/ml, severe with 50,000/ml and very severe with count < 10,000/ml in this study.[9,10] Patients were managed under joint supervision of the Fetomaternal medicine specialist, hematologist and neonatologist. For booked cases, antenatal care (ANC) was planned as monthly in the first and second trimester, every 2 weeks after 28 weeks, weekly after 36 weeks and more frequently if needed. In prenatal period if count was $\leq 30 \times 10^9$/L or clinically relevant bleeding present, medical treatment was started with oral corticosteroid i.e. Prednisolone 1mg/kg/day for 21 days, then tapered to the lowest possible doses. In refractory cases other drugs like Azathioprine, Dapsone, and Romiplostim was considered. Prior to labor and delivery, aim was to keep platelet count $\geq 80 \times 10^9$/L to make regional anesthesia safe if needed. Platelet transfusion was considered in cases where there were features of haemmorhage or count $<20X10^9$/ L at any stage of pregnancy because of the risk of life-threatening haemorrhage or in late pregnancy when delivery was emergent and platelet count was <50 $X10^9$ / L as no time was in hand for correction with medical therapy. Mode of delivery was determined by obstetric indications. The third stage was actively managed. Neonatal passive immune thrombo-cytopenia was considered when platelet count was <150,000/ml. Each neonate was examined by a neonatologist at the time of birth. Platelet count was done within first 24 hours of delivery and if count was found $< 1.5X10^9$/L then platelet count was done daily until it begins to rise. Steroid was considered at a dose of 1mg/kg body weight / day if thrombocytopenia was detected. Platelet transfusion was considered if count became < 20,000/ cu mm of blood, or there was any bleeding manifestation.

Data entry of patient's information was done in a predesigned case record sheet made for the purpose. Data were cleaned and analyzed by using statistical software SPSS version-23. Results were statistically described in terms of range, mean, SD, frequencies and percentages.

Results:

Table-I

Year wise frequency of ITP cases among high risk patients (N= 20)

Year	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
High risk cases	833	895	915	1054	705	782	823	895	802	7704
ITP cases (%)	02(.24)	02(.22)	05(.54)	01(.9)	01(.14)	02(.25)	02(.24)	02(.22)	03(.37)	20(.25)

Frequency on average was 0.25% i.e. 2.5/1000 live birth/year

Table-II

Analysis of ITP cases (N=20). Presented as mean, range and percentage

Characteristics	Number(range/ percentage)
Maternal age in years : mean ±SD (range)	20.8 (18-33)
Para (range)	0-2
Type	
Preexisting (Before Pregnancy)	15 (75%)
Deteriorated during pregnancy	08(53%)
Diagnosed in Pregnancy	05 (25%)
Clinical presentation at diagnosis	
Gum bleeding	14(70%)
Purpuric Rashes	12(60%)
Petichae	07(35%)
Menorrhagia	05(25%)
Epistaxis	03(15%)
P/V bleeding	01(5%)
Mean Gestational age at admission in weeks (range)	36.1 (22-39)
Mean Gestational age at delivery in weeks (range)	37.1(24 -40)
Preterm birth	03 (15%)
Complications during pregnancy	
Haemorrhagic manifestations (Haemoptysis, Haematuria,	03 (15%)
PV bleeding)	04 (20%)
Severe thrombocytopenia(5-10X10^9)	02 (10%)
Severe anemia needed BT	
Treatment	
Prednisolone	19 (95%)
Azathioprine	07 (35%)
Dapsone	02
Romiplostim	
Spleenectomy (before pregnancy)	
Platelet Transfusion needed	
Unit (Percentage) Range (Mean)	15 (75%),1-75unit (12)

Mean maternal age was 20.8 years. Majority (75%) had Preexisting ITP.
Mean gestational age at admission and at delivery was 36 and 37 weeks respectively.
Prevalence of prematurity was 15%.Almost all received prednisolone (95%)for treatment.
Platelet transfusion needed in 75% cases.

Table-III

Platelet count/cu mm of blood at diagnosis, during pregnancy, at delivery, presented as number, range, (mean) and mode. Severity of thrombocytopenia is presented as Number (N) of patients (%)

	At Diagnosis	During Pregnancy	At delivery
Platelet count : range	5000-1.2L	5000-1.5L	20,000-2.5L
(Mean) Mode	(29650), 20000	(32700),5000	(1.05L),80000
Mild	01(5%)	02(10%)	08 (40%)
Moderate	03(15%)	02 (10%)	11 (55%)
Severe	11 (55%)	07 (35%)	01 (05%)
Very severe	05 (25%)	09 (45%)	Nil

Mean platelet count at the time of diagnosis, pregnancy and delivery were 29650, 32700, 1.05 L/ mm^3 respectively. Very severe thrombocytopenia i.e. platelet count <10,000 was nil at the time of delivery.

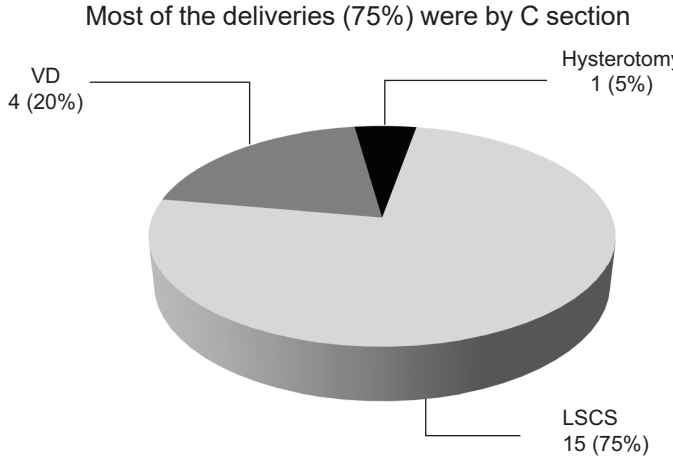

Fig.-1: *Mode of delivery N=20, (%)*

Table-IV

Outcome of the baby: N=20(%)

Live birth	19 (95%) %)
Preterm birth	03 (15%)
Birth weight in Kg, range (mean)Low birth weight	0.5 -4.3 (2.74 kg)04 (20%)
Good Apgar score	18
Neonatal admission (For neonatal jaundice)	02
Platelet Count at birth: N=19 (%)	
Normal	12 (63.2%)
Impaired	07 (36.8%)
Mild	04 (21%)
Moderate	02(10.5%)
Severe	01(5%)
Mean platelet count was 1.64×10^9/L, ranging 30,000 - 2.8X 10^9/L.	

Neonatal thrombocytopenia was noted in 36.8% cases

Discussion:

Mild thrombocytopenia is seen in up to 10% of pregnancies; ITP accounts for only 5% of cases of thrombocytopenia in pregnancy.[5] Available studies showed its incidence is 0.1- 1 case per 1000 pregnancies.[11,12,13] The data of this study of 9 years showed its frequency among high risk group of patients on average was 2.5/1000 live birth (Table 1). This slight

increase may be due to the fact that it was a referral center where high risk pregnancies were referred from all corners of the country. Mean age of the mothers in this study was 24.2 years. In a study on ITP in pregnancy for 10 years, the mean age of women was 28 (range: 18 - 41).[14] In a retrospective study median age was 29 years.[15] All these studies indicate most of the time mothers of ITP are very young. Type of ITP in pregnancy i.e. whether preexisting or diagnosed in pregnancy is found different in different studies. In this study most cases were preexisting ITP (75%). In a retrospective 11-year analysis, majority had preexisting ITP (69.7%)[15], in a study in Iran it was 33.3%[16], in another study of 4-year it was 44%.[10] Preexisting ITP may either worsen or remain quiescent during gestation. In this study 53% preexisting ITP deteriorated in terms of platelet count and complications (Table II). Diagnosis of ITP during pregnancy is challenging as it needs to be differentiated from Gestational thrombocytpania (GT). As a general rule if count is >70,000/mL, more likely GT but when fall < 50,000/mL it is more likely ITP.[17] In a study Lescale found that significantly higher proportion of patients with ITP had indirect IgG compared to patients with GT (85.9% versus 60.3%, *P* <0.001), but significant overlap existed, limiting its clinical value.[18] The bleeding in ITP is mucocutaneous in the form of petechiae, purpura, easy bruising, epistaxis, gingival bleeding, and menorrhagia.[19] In the present study commonest presenting symptoms were gum bleeding (70%) and purpuric rashes (60%) (Table II). These features are seen when count usually goes below < 20,000 /mm^3 and indicative of the risk of serious bleeding. In extreme cases, internal bleeding in vital organs specially intracerebral hemorrhage might even occur. Fortunately none of the patient of this study had such catastrophic bleeding indicating proper management following the well defined protocol. The clinical management of pregnancy-associated with ITP is a complex task, needs close monitoring by the obstetrician and hematologist. All the women of this study received prednisolone which like many other studies were considered as the first line therapy for women having counts < 30 x 10^9/L or having relevant bleeding. In ITP for simple thrombocytopenia, platelet transfusion is not indicated and not justified as antiplatelet antibodies induce rapid destruction of transfused platelets.[20] One random unit of platelets usually raise the platelet count in an adult by 5,000–8,000/cumm.[21] In ITP the rise is less pronounced due to destruction of donor platelets. This temporary measure is to be considered in severe thrombocytopenia raising the risk of life-threatening hemorrhage and also when delivery is emergent and adequate time is not in hand for correction by medical therapy. Though there is no prospective randomized trial but most experts consider 80,000/ml platelet count safe for delivery.[22,23,24] American Society of Hematology (ASH) recommends 50,000/ml safe for both vaginal delivery and cesarean section.[23] British Committee for Standards in Haematology. (BCSH) recommended 80,000/ml for caesarean section under epidural anesthesia.[24] In this study, 75% of the samples needed 1-75 unit (mean 9unit) platelet transfusion. This high rate of platelet transfusion was mostly for preparation of delivery with safe platelet count and in some for prevention of catastrophic bleeding from severe thrombocytopenia. In the study of Young-Woong Won et al, platelet transfusion needed in 48.4% cases and mean number transfusion was 9 units.[25] Controversies continued for long about the safest mode of delivery in ITP especially in regards of risk of feto-maternal haemmorhage. Though cesarean section was preferred in some studies for prevention of fetal intracranial hemorrhage, but available evidences do not support it. [26-30] This view was also supported in the present study, though mode of delivery was mostly by caesarean section (75%) for obstetric indications but vaginal delivery was possible in 20% cases without any complications. Rather increased capillary oozing and primary PPH was noted among few cases of C section group. In a retrospective analysis, Hussein & colleagues noted that vaginal deliveries in 36% and cesarean sections in 64% cases with good fetomaternal outcome.[10] In a retrospective study from 1988 to 2007, preterm delivery was found significantly and independently associated with ITP.[31] Preterm Birth was noted 23.3% in another study[32] In this study preterm delivery was noted in 15% of pregnancies. This view is not supported in a study of Iran, where there was no premature deliveries among ITP cases.[16] Among the samples of the present study one of the patients needed hysterotomy as she presented with several bouts of pervaginal bleeding with placenta praevia and had repeated episodes of severe thrombocytopenia.

There is 10% chance of neonatal thrombocytopenia

at the time of delivery due to destruction of antibody-sensitized platelets in fetal spleen.[33] This may lead to intracranial hemorrhage in <1% of the newborns with ITP.[33] In this study passive immune thrombocytopenia was noted among 36.8% of the newborn, amongst 1(5%) had severe thrombocytopenia but fortunately didn't need platelet transfusion as there was no bleeding manifestations and platelet count returned to normal spontaneously within 2-5 days.

Conclusion:

The frequency of ITP in pregnancy among high risk patients of 9 years was on average 2.5/1000 live birth and most were preexisting. Severe thrombocytopenia was found among 20% cases and 15% showed haemorrhagic manifestations. Almost all of the patients were treated with prednisolone .To prevent catastrophic bleeding and to make delivery safe 75% of the patients needed platelet transfusion for severe thrombocytopenia. Mean gestational age at admission and at delivery was 36 and 37 weeks respectively. Prevalence of prematurity was 15%. Regarding neonatal outcome, 36.8% neonates showed passive thrombocytopenia, amongst 1(5%) had severe thrombocytopenia but no platelet transfusion needed as with time the count improved.

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