

**ORIGINAL ARTICLE** 



# Maternal and Fetal Outcomes of Pregnancy in Patients with Immune Thrombocytopenia

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#### Abstract

**Introduction** Immune thrombocytopenia (ITP) complicates 1–2 cases/10,000 pregnancies in India. Management of these patients is a challenge as it is associated with potential risks of maternal bleeding episodes and neonatal alloimmune thrombocytopenia (NAITP).

**Objective** To study the maternal and fetal/neonatal outcome of pregnancy in Indian patients with ITP and identify the risk factors for NAITP.

**Materials and Methods** In this retrospective study, all ITP patients with pregnancy who were diagnosed and treated at our center over 8 years (August 2010– August 2018) were evaluated for their hematological, obstetrical, and fetal outcomes.

**Results** Twenty-nine pregnancies in 27 ITP patients were studied. The mean interval between the diagnosis of ITP and each pregnancy was  $29 \pm 14.9$  months. The mean baseline platelet count was  $0.18 \pm 0.05 \times 10^{9}$ /L. Twenty-seven (93.1%) cases were treated with oral prednisolone. Twenty deliveries (69.0%) were vaginal and 9 (31.0%) deliveries were by cesarean section. There were no major bleeding episodes during pregnancy or delivery.

The mean neonatal platelet count was  $1.23 \pm 0.58 \times 10^{9}$ /L at birth. NAITP was seen in 3 (3.5%) neonates. No bleeds or intracranial hemorrhages were observed. Only maternal platelet count < 50 X 10<sup>9</sup>/L at delivery showed a statistical correlation with NAITP (p = 0.022). There was no positive correlation between NAITP and the duration of maternal ITP, the timing of ITP onset, or type of treatment.

**Conclusion** Successful outcome of pregnancies in ITP patients is possible, and the risk of maternal bleeding and NAITP is low.

Keywords Pregnancy · Fetus · Immune thrombocytopenia · Corticosteroids

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# Introduction

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by low platelet counts (< 150 X  $10^9/L$ ) and mucocutaneous bleeding. It is relatively common among women of the reproductive age and is the most frequent cause of thrombocytopenia during pregnancy after gestational thrombocytopenia [1, 2]. The incidence of ITP in pregnant women in India is approximately 1–2 cases for every 10,000 pregnancy and it accounts for 4–5% of all pregnancy-associated thrombocytopenia [3, 4]. Thrombocytopenia in ITP occurs due to the presence of anti-platelet auto-antibodies (IgG antibodies) against platelet membrane glycoproteins. The IgG-coated platelets are cleared from the circulation by the reticuloendothelial system, mainly the spleen producing thrombocytopenia [2].

Management of pregnant women with ITP is a challenge, and it requires a different approach compared to non-pregnant women with ITP. There is an inherent risk to life due to serious bleeding episodes both to the mother and in-utero fetus during the antenatal period. Also, there are potential adverse effects of drugs used for the treatment of thrombocytopenia on the course of pregnancy, the developing fetus, and the newborn. The most feared complication of ITP in pregnancy is "fetal or neonatal alloimmune thrombocytopenia (NAITP)" and intracranial hemorrhage (ICH) [5]. The trans-placental transfer of IgG platelet-specific autoantibodies can induce the development of neonatal thrombocytopenia and increases the risk of NAITP. It is seen in 10-15% of cases of ITP with pregnancy, and the incidence of ICH due to NAITP is less than 1% [2, 6]. Several studies have examined the outcome of pregnancy in women with ITP and have tried to identify maternal risk factors that can act as predictors of NAITP. These studies have observed that most of the pregnancies were uneventful [7-9].

There are very few studies on the outcome of pregnancy in Indian women with ITP [7, 10]. We conducted this study to evaluate the outcome of pregnancy in our ITP patients and identify the maternal risk factors which influence the occurrence of neonatal thrombocytopenia and associated risk of bleeding.

## **Methods and Materials**

#### **Study Population**

In this retrospective study, all pregnant women diagnosed with acute ITP before or during pregnancy and those with chronic ITP at our center from August 2010 to August 2018 were evaluated for their hematological, obstetric, and fetal outcome.

The diagnosis of ITP was based on standard diagnostic criteria (i) thrombocytopenia < 100 X  $10^{9}$ /L, (ii) normal peripheral blood smear and bone marrow examination, (iii) exclusion of other known causes of thrombocytopenia during pregnancy, including gestational thrombocytopenia, preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), and sepsis. Acute ITP was defined as ITP of less than 6 months duration and if the duration of ITP was more than 6 months it was defined as chronic ITP (3).

Platelet counts were performed on venous blood samples collected in vacutainers containing EDTA anticoagulant in 9:1 ratio using an automated cell counter. Thrombocytopenia was defined as platelet count <  $100 \times 10^9$ /L and was confirmed by manual microscopic count and examination of the peripheral blood film to exclude the possibility of platelet clumping.

Normal platelet count was defined as counts > 150  $\times 10^{9}$ /L, mild thrombocytopenia as 100–150  $\times 10^{9}$ /L, moderate thrombocytopenia as 50–99  $\times 10^{9}$ /L, and severe thrombocytopenia as < 50  $\times 10^{9}$ /L.

#### **Antenatal and Fetal care**

All the pregnant women were under the care of a team consisting of hematologists, obstetricians, and neonatologists. The antenatal check-up and platelet count evaluation were done every month in the first two trimesters and then every 2 weeks till 36 weeks and weekly thereafter till delivery. During each visit, the patients were evaluated for hematological, maternal, and fetal well-being.

During pregnancy, women with (i) platelet count < 30 X  $10^{9}$ /L in the first and second trimester; (ii) platelet count < 50  $X 10^{9}$ /L.in the last trimester, and (iii) those with significant bleeding manifestations were treated to raise their platelet counts. Patients in the first two trimesters who were asymptomatic and had platelet count between 30-50 X 10<sup>9</sup>/L received no treatment and were kept under close hematological observation. Corticosteroids were the first line of treatment in all the patients. Oral prednisolone was given in the dose of 1 mg/kg/d for 3 weeks, followed by gradual dose reduction to the lowest maintenance dose at which the platelet count remained > 50 X  $10^{9}$ /L. Patients who showed no response to oral steroids and in whom the platelet counts remained below  $< 30 \times 10^9$ /L or when there was a contraindication to steroid therapy, intravenous immunoglobulin (IVIG; 1.0 g/kg/d for 2 days), followed by a monthly maintenance dose (IVIG 0.4 g/kg/d, single dose) was used. The potential adverse effects of oral steroid and IVIG on the mother and fetus were explained to the patients and family members before starting the therapy.

The mode of delivery was decided in each case based on obstetric indication only. The platelet count was maintained at  $\geq$  50 X 10<sup>9</sup>/L for vaginal delivery and  $\geq$  80 X 10<sup>9</sup>/L for cesarean section under epidural anesthesia as per the recommended guidelines (1-3). In patients planned for a vaginal delivery if the platelet count was  $< 50 \text{ X } 10^9$ /L, single donor platelets (SDPs) were transfused to raise the platelet count to  $\geq$  50 X 10<sup>9</sup>/L before delivery. In patients planned for cesarean delivery, if the platelet count was  $< 80 \text{ X} 10^9/\text{L}$ then IVIG (1.0 g/kg/d) and SDP were used either alone or in combination to raise the platelet counts to  $\geq 80 \text{ X } 10^{9}/\text{L}$ . All the patients planned for vaginal delivery were allowed to go into spontaneous labor. Induction of labor was done only for obstetric reasons. The course, progress of labor, and fetal well-being were monitored carefully. The third stage of labor was managed actively. The patients were kept under close observation following delivery for any occurrence of post-partum hemorrhage.

The newborns were managed by the neonatologists. A cord-blood platelet count was performed at birth in all the new-borns (same technique as in the mother), followed by measurement of platelet count by venepuncture on days 1, 3, and 5. IVIG were infused (0.4 g/kg/d for 2 d) when the platelet count was < 50 X  $10^9$ /L.

We evaluated the following outcomes in this study:

- 1 Duration of ITP.
- 2 Types of treatment.
- 3 Maternal platelet counts during pregnancy and at the time of delivery.
- 4 Maternal complications during antenatal, delivery, and the post-partum period.
- A fetal and neonatal composite outcome of the following adverse events: stillbirth, preterm birth before 34 weeks of gestation, low birth weight babies (birth weight < 2.5 kg).</li>
- 6 Neonatal platelet counts at birth.
- 7 Neonatal intracranial hemorrhage diagnosed before hospital discharge (neonatal well-being and outcome).

Informed consent was obtained in each case. No new tests or interventions were performed during the study and treatment was as per the recommended guidelines. The study was performed with approval the Sanjay Gandhi Postgradiate Institute of Medical Sciences research board and ethics committee.

## **Statistical Analysis**

Baseline characteristics of the study population were summarized using descriptive statistical methods. Either the Student t-test or Wilcoxon rank-sum test was used for the comparisons of continuous variables, as appropriate. Data management and statistical analysis were performed using SPSS version 20.0 was used (SPSS Inc., Chicago, IL, USA). A 2-sided significance level of 0.05 was used, without adjustment for multiple comparisons.

#### Results

We diagnosed and managed a total of 29 pregnancies in 27 females with ITP over 8 years from August 2010 to August 2018. Twenty-three (85.2%) patients had acute ITP and the remaining 4 (14.8%) cases had chronic ITP. Twelve 44.4%) patients were primigravida and the remaining 15 (55.6%) cases were multigravida. Two patients had two pregnancies each during the study period. Four patients (14.8%) had positive anti-nuclear antibodies (ANA) on serological testing before pregnancy, but did not fulfill the criteria for

systemic lupus erythematosus. Patients with chronic ITP were previously treated with oral steroids and azathioprine. Two patients had also received eltrombopag and one case had undergone splenectomy. Four patients had associated hypothyroidism and were on thyroxin replacement therapy (Table 1).

#### **Antenatal and Obstetric Outcome**

The mean maternal age at the time of pregnancy diagnosis was  $36.9 \pm 3.3$  (range: 20–37) years. The mean interval between the date of diagnosis of ITP and each pregnancy was 29 + 14.9 (range: 1–120) months.

The mean baseline platelet count at diagnosis of pregnancy was  $0.18 \pm 0.05 \text{ X} 10^{9}/\text{L}$ . Twenty-seven (91.3%) pregnancies were treated with oral prednisolone during the antenatal period. Two patients showed an initial transient response to oral steroids and had to be treated with IVIG to maintain the platelet counts above the defined safe limits (> 50 X  $10^{9}$ /L). The mean maternal platelet count during the first and second trimester was  $0.45 \pm 0.43 \times 10^{9}$ /L and  $0.63 \pm 0.34 \times 10^{9}$ /L, respectively. In the last trimester, the average platelet count was  $0.78 \pm 0.56 \times 10^9$ /L. Maternal complications were seen 5 (17.2%) pregnancies. One patient developed pregnancy-induced hypertension with preeclampsia. (secondary to steroids therapy). Three patients developed steroid-induced diabetes. No serious systemic bleeding episodes or mucocutaneous bleeds were documented during the antenatal period. Only one (3.4%) patient developed retro-orbital hemorrhage during the pregnancy and it was managed successfully with platelet transfusions (Table 2).

Twenty deliveries (68.9%) were vaginal, and 9 (31.1%) deliveries were by cesarean section. There were no twin

Table 1 Clinical and laboratory profile of patients with pregnancy

Parameter	Observation
Type of ITP	
Acute ITP: n (%)	23 (85.2%)
Chronic ITP: n (%)	04 (14.8%)
Age (years): mean (range)	36.9±3.3 (20–37)
Parity	
Primigravida: n (%)	12 (44.4%)
Multigravida: n (%)	15 (55.6%)
Interval between diagnosis of ITP and preg- nancy (months)	29±14.9 (1–120)
Platelet count at diagnosis of pregnancy (X 10 <sup>9</sup> /L)	$0.18 \pm 0.05 \ (0.08 - 35)$
ANA/dsDNA positivity: n (%)	4 (14.8%)
Hypothyroidism; n (%)	4 (14.8%)

ITP immune thrombocytopenic purpura; ANA Anti-nuclear antibodies

 Table 2
 Clinical and hematological profile of ITP patients during the antenatal period

Parameter	Mean (Range)/N (%)
Platelet count in T1(X $10^{9}$ /L) mean ± SD	$0.45 \pm 0.43$
Platelet count in T2(X $10^{9}/L$ ) mean $\pm$ SD	$0.63 \pm 0.34$
Platelet count in T3 (X $10^9/L$ ) mean $\pm$ SD	$0.78 \pm 0.56$
Platelet count prior to delivery (X $10^{9}/L$ ) mean $\pm$ SD	$0.58 \pm 0.32$
Complications during pregnancy	
Steroid-induced diabetes: n (%)	3 (10.3%)
Pre-eclampsia	1 (3.4%)
Bleeding	1 (3.4%)
Therapy during pregnancy	
Steroids	27 (82.8%)
IVIG	2 (17.2%)

IVIG intravenous immunoglobulin; T trimester

 Table 3 Obstetric and fetal outcome in pregnant women with ITP

Type of delivery: n (%)	
Vaginal: n (%)	20 (68.9%)
Cesarean section: n (%)	9 (31.1%)
Treatment prior to delivery	
IVIG: n (%)	3 (10.4%)
SDP: n (%)	9 (31.0%)
Fetal sex	Males $=$ 23, females $=$ 6
Gestation (weeks)mean $\pm$ SD	36.9±1.9 (33–42)
Birth weight (grams)mean $\pm$ SD	$2473 \pm 406 (2272 - 3450)$
Complications	
NAITP	3
ICH	Nil
Fetal platelet count (X 10 <sup>9</sup> /L)	$1.23 \pm 0.58 \ (0.32 - 2.58)$

*IVIG* intravenous immunoglobulin; *SDP* Single donor platelet; *NAITP* neonatal alloimmune thrombocytopenia; *ICH* intracranial hemorrhage

pregnancy, preterm deliveries, or stillbirths (Table 3). The mean platelet count at the time of delivery was  $0.58 \pm 0.32$  X  $10^9$ /L. Three (33.3%) of the 9 cases who underwent cesarean section had platelet count < 50 X  $10^9$ /L before delivery and were treated with IVIG therapy, followed by SDP infusion to raise the platelet counts to  $\geq 80$  X  $10^9$ /L. In six (30%) of the 20 cases who had a vaginal delivery, the platelet counts were < 50 X  $10^9$ /L and they received SDP infusion alone just before delivery to raise their platelet counts above 50 X  $10^9$ /L. No post-partum hemorrhage or excessive post-operative bleed was documented in any case.

#### **Fetal Outcome**

The mean gestational age at birth was  $36.9 \pm 1.9$  (range: 33-42) week. The mean birth weight was  $2473 \pm 406$  g, and 12 neonates (41.3%) were low birth weight (birth weight < 2.5 kg). No intrauterine growth retardation (IUGR) or congenital defects like oral clefts were observed. The mean neonatal platelet count at birth was  $1.23 \pm 0.58 \times 10^{9}$ /L. Neonatal alloimmune thrombocytopenia (NAITP) was seen in 3 (10.3%) neonates. The platelet counts were below 100 X  $10^{9}$ /L in all the 3 neonates and it was < 50 X  $10^{9}$ /L in 1 (3.5%) neonate and was treated with IVIG. Cranial ultrasound was performed in all the newborns and none of them had ICH or any other serious bleeds. None of the newborns required platelet transfusions for thrombocytopenia. Mothers of neonates with NAITP had platelet counts less than 50 X  $10^{9}$ /L.

We investigated the influence of various maternal parameters on the platelet count of the current infant using Fisher's exact test. There was no positive correlation between NAITP and the duration of maternal ITP. There was no positive correlation between NAITP and the following parameters; splenectomy before pregnancy, the timing of diagnosis of ITP, treatments to raise the platelet count during pregnancy, or just before delivery, a progressive decline of maternal platelet count during pregnancy and mode of delivery. Maternal platelet less than 50 X 10<sup>9</sup>/L count at delivery showed a statistical trend for an association with NAITP (p = 0.022). We also did not find any difference in maternal or neonatal outcomes in the different treatment groups (p = 0.56 and 0.68, respectively).

#### Discussion

ITP is the second most common cause of thrombocytopenia in pregnancy after gestational thrombocytopenia and affects 1-2 cases per 10,000 pregnancies in our country.[4]. ITP has to be differentiated from gestational thrombocytopenia in women with pregnancy. The latter usually develops in the late second or third trimester of pregnancy and the platelet counts rarely fall below 70 X 10<sup>9</sup>/L. ITP on the other hand is a diagnosis of exclusion. In the presence of a previous history of thrombocytopenia, an underlying autoimmune condition, and platelet count  $< 50 \times 10^{9}$ /L, ITP is the most probable cause of thrombocytopenia [1, 2]. Management of pregnancy in ITP patients is a challenge because of the potential risk of serious bleeds in the mother and fetus during the antenatal period and delivery and in the neonates due to NAITP. Secondly, the drugs used to treat thrombocytopenia during pregnancy have adverse effects on the mother, the course of pregnancy, and fetal development. A multidisciplinary approach has to be adopted to manage the mother and fetus with the help of a hematologist, an obstetrician, and a neonatologist.

The data from several studies have shown that the incidence of bleeding episodes in ITP patients with pregnancy has varied from 8 to 30%, [7, 10, 11]. In a study of 43 pregnancies in 37 women with ITP, it was observed that less than 8% of cases had bleeding manifestations during the antenatal period [12]. Weber et al. studied 119 pregnancies in 92 women with ITP over 11 years and observed that 21.5% of them had moderate to severe bleeding episodes during their pregnancies [11]. In contrast, Suri et al. studied 16 cases of ITP with pregnancy and found that none of them had any fetal or maternal morbidity [8]. In our study, the bleeding episode was seen only in one case (3.4%), and it was secondary to the development of pre-eclampsia in the patient.

Studies have shown that approximately 31% to 40% of women with ITP require treatment to raise their platelet counts during pregnancy [6, 11, 12]. The therapeutic options are similar to those in non-pregnant women with ITP [1, 13]. Corticosteroids are the first-line treatment of choice. Prednisolone is the preferred corticosteroid and is given in a dose of 1 mg/kg/day for a duration of 3 to 4 weeks. Once the target safe platelet count is reached the dose is gradually reduced to the lowest effective dose to maintain platelet counts at a safe level. The use of corticosteroids during pregnancy is associated with adverse effects such as weight gain, gestational diabetes, accelerated bone loss, hypertension, and possibly abruptio placentae, and premature labor [5, 6]. Infants born to mothers treated with corticosteroids have shown an increased incidence of increased body weight, fetal deaths, and congenital anomalies like oral clefts [6]. Antenatal corticosteroids do not affect the neonatal platelet counts and therefore should not be given to near term mothers with the sole aim to prevent NAITP [14]. IVIG 1 g/kg/d in a single or two divided doses is used when patients fail to respond to corticosteroids or if there is life-threatening bleeding or a rapid rise in the platelet counts is desired. IVIG is safe for the fetus, but it is an expensive therapeutic option [1, 2, 13]. The efficacy of corticosteroids and IVIG in pregnant women with ITP is similar to that in the non-pregnant women with ITP. In a study by Sun et al. corticosteroids were compared with IVIG for the treatment of ITP in pregnancy. Treatment was not required in 137 pregnancies (58%). Of the remaining 98 pregnancies in 91 women, 47 (48%) were treated with IVIG, and 51 (52%) were treated with corticosteroids as the initial intervention. There was no difference in maternal platelet counts at the time of delivery, but the maternal outcome was better in the corticosteroid group. There was no significant difference in the fetal composite outcome between the IVIG and corticosteroid groups [15]. Experience with anti-RhD therapy in pregnant women is limited and is not recommended as firstline therapy because of the potential risk of acute hemolysis in the mother and the fetus [16]. Patients who fail to respond to either steroids or IVIG can be treated with oral azathioprine as its use in pregnancy is safe. Immune impairment may be seen in some infants with the use of azathioprine [17]. In our study, the mean platelet count at presentation was  $0.18 \pm 0.05 \times 10^{9}$ /L and all the cases required treatment. Twenty-seven (82.8%) pregnancies were treated with prednisolone. In two (17.8%) pregnancies, there was an inadequate response to prednisolone and the patients developed gestational diabetes. These two patients were treated with intravenous immunoglobulin (IVIG). We did not find any difference in maternal or neonatal outcomes in the different treatment groups (p = 0.56 & 0.68, respectively).

The mode of delivery in ITP patients should be based on obstetric indications only. Earlier the management of labor and delivery in pregnant women with ITP was based on the belief that vaginal delivery is associated with increased risk of ICH in the newborn secondary to vaginal birth trauma and therefore cesarean delivery should be preferred. Studies have now shown that uncomplicated vaginal delivery is equally safe as cesarean section and is not associated with increased risk of ICH in the newborn [8, 9, 15]. Vaginal delivery can be safely done with a platelet count of  $\geq 50 \times 10^9$ /L and it should be raised to >  $80 \times 10^9$ /L if a cesarean section is considered [1, 13, 18]. Procedures such as forceps and vacuum extraction should be avoided as it is associated with increased risk of hemorrhage [19]. In our study, the mean platelet count at delivery was  $0.58 \pm 0.32 \times 10^9$ /L. The majority of our cases (68.9%) had a vaginal delivery, and 31.1% were by cesarean section. No post-partum hemorrhage or excessive post-operative bleed were documented.

Post-delivery, the newborn's platelet count often declines during the first week and it needs close monitoring. Severe neonatal thrombocytopenia and ICH have been reported in the range of 4.6%–29.9% and 0%–3.7%, respectively [10, 11, 20]. In a meta-analysis of 288 infants born to mothers with ITP, it was observed that 10.1% of all neonates had platelet counts  $< 50 \times 10^{9}$ /L at birth and in 4.2% the platelet count was  $< 20 \times 10^{9}$ /L, but no cases of ICH were observed [21]. A review of several studies on the outcome of pregnancy in ITP patients has shown no correlation between the maternal platelet counts at delivery and the occurrence of NAITP [2]. Valat et.al. observed NAITP in 25% of infants born to ITP patients and severe thrombocytopenia was observed in 12.5% of the cases. They found a significant association between the neonatal platelet count at birth and the nadir maternal platelet count during pregnancy [22]. Loustau et al. conducted a retrospective study of 118 pregnancies in 82 women with ITP and found that the rate of NAITP in their study was 8.3%. The risk of NAITP was higher for women who had undergone splenectomy [23] Although the risk of ICH is small cranial ultrasound should be performed in all the newborns to detect occult ICH as it is associated with high morbidity and mortality. Computerized tomography (CT) scan and magnetic resonance imaging (MRI) should be performed to confirm the site and size of the bleed [1]. Sun et al. performed a cranial ultrasound on 25 neonates born to mothers with a history of ITP, but not on any treatment and they found that 2 [8%] neonates had ICH with NAITP [15]. Thus, emphasizing the need for measurement of cord platelet count at the time of delivery and cranial ultrasonography in all neonates. Measurement of fetal platelet counts by cordocentesis and fetal scalp blood sampling is no longer recommended as it is associated with a complication rate of 1 to 2% [24, 25]. IVIG is the treatment of choice for those newborns that have severe thrombocytopenia or bleeding like ICH [26].

Our data showed a lower incidence (3.5%) of NAITP and none of the newborns had ICH. The maternal platelet count < 50 X 10<sup>9</sup>/L showed a statistical trend for an association with NAITP (p=0.022). There was no positive correlation between NAITP and the duration of maternal ITP. Also there was no positive correlation between NAITP and the following parameters; splenectomy before pregnancy, the timing of diagnosis of ITP, treatments to raise the platelet count during pregnancy or just before delivery, a progressive decline of maternal platelet count during pregnancy and mode of delivery. There was also no association between NAITP and the history of chronic ITP in our study.

Our study had some limitations and potential biases, mainly because it was a retrospective study. Our hospital is tertiary care referral hospital and referral bias cannot be excluded. The size of the present study is small, and a larger study is required to validate our findings.

#### Conclusion

Management of pregnancy in ITP patients is a challenge. With treatment good hematological, obstetric, and neonatal support these women can successfully become mothers. Steroids are a cheap and effective way of maintaining adequate platelet counts in pregnancy and have a successful outcome with low maternal and neonatal morbidity even in a low-resource developing country like ours.

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#### **Compliance with Ethical Standards.**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical Approval** This was a retrospective study carried out on pregnant women with ITP attending the hematology department of the institute's hospital. No new tests or investigations were performed on the patients. The treatment was as per the recommended guidelines. The study was performed with the approval of Sanjay Gandhi Postgraduate Institute of Medical Sciences research board and ethics committee.

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