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RESEARCH ARTICLE

Isolated thrombocytopenia in pregnancy: A monocentric retrospective study of 63 pregnancies in 59 women

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Abstract

Thrombocytopenia during pregnancy is often thought to be associated with severe bleeding manifestations. Three are the main disorders associated with this condition: gestational thrombocytopenia (GT), immune thrombocytopenia (ITP), and inherited thrombocytopenias (ITs). Reaching the correct diagnosis of this condition has relevant therapeutic and outcome implications. We performed a retrospective, observational, monocentric study enrolling 59 consecutive women with isolated thrombocytopenia, attended to our referral center in the last 3 years. Together with personal and family history, platelet (PLT) count trend and mean platelet volume (MPV) in pregnancy are helpful for the diagnosis, with the highest PLT count in GT and lowest in ITs, with different timing of count decrease. MPV is significantly increased in both ITs and ITP. Misdiagnosis with ITP was responsible for unnecessary and unsuccessful therapy in some GT or ITs pregnant women, determining relevant side effects. Excluding inherited platelet function disorders (IPFDs), the bleeding risk for mother with thrombocytopenia and their newborns is similar to the general population. Vaginal delivery is associated with a lower risk of bleeding than cesarean section and therefore is preferable whenever obstetrical–gynecological conditions permit.

KEYWORDS
bleeding disorders, platelets, pregnancy, thrombocytopenia

1 | INTRODUCTION

Partum-related hemorrhage is the leading cause of morbidity and mortality among pregnant women. Even though mean platelet (PLT) count decreases from the first trimester during pregnancy in all women [1], thrombocytopenia, defined as PLT count $<150 \times 10^9$/L, addresses at least 5%–10% of all pregnancies [2, 3]. Three conditions are associated with isolated thrombocytopenia in pregnancy: gestational thrombocytopenia (GT), immune thrombocytopenia (ITP), and inherited thrombocytopenias (ITs) [2–4]. Although in the majority of cases thrombocytopenia represents a benign condition, it is fundamental not only establishing the bleeding risk but especially making a

diagnosis of certainty. This is challenging and important, since it has therapeutic and outcome implications, both for the mother and the fetus/newborn.

Since we are focusing only on isolated thrombocytopenia, we will not consider all the secondary thrombocytopenias associated with the most common obstetrical conditions such as preeclampsia, hemolysis, elevated liver enzymes and low PLTs syndrome, and acute fatty liver of pregnancy.

GT is responsible for the 75% of pregnancy-related thrombocytopenias. PLT count usually decreases progressively and thrombocytopenia occurs late in pregnancy [2, 3]. Thrombocytopenia is usually mild or moderate so that therapy is not required. PLT count returns to normal values spontaneously within 4–8 weeks after delivery. Neonatal outcomes are excellent, and newborns do not develop thrombocytopenia. If PLTs are less than 70×10^9/L, an overlapping ITP should be suspected [2–4].

ITP represents only 3% of isolated thrombocytopenias in pregnancy but is the main cause of low PLT count during the early stages of gestation [2]. ITP guidelines suggest starting therapy only in case of bleedings, severe thrombocytopenia (PLT $<30 \times 10^9$/L) or to prepare women for a safe delivery from 36 weeks of gestation onward. Oral corticosteroid or intravenous immunoglobulin (IVIG) is the first-line treatment. Rituximab and thrombopoietin receptor agonists (TPO-RAs) are not recommended as their effect in pregnancy is unknown. Splenectomy can be done safely via a laparoscopic approach in the second and third trimester, but its use is confined to nonresponder women. Immunosuppressive drugs (i.e., azathioprine and cyclosporine) should be used carefully and only in selected patients. PLT transfusions are useless unless the patient is bleeding [2–5]. Up to 30% of the newborns may develop transient thrombocytopenia, probably due to passive transfer of maternal anti-PLTs antibodies, and the incidence of intracerebral hemorrhage is not well known [6]. In order to prevent hemorrhagic complications, operative vaginal deliveries, such as forceps or vacuum-assisted vaginal delivery, should be avoided [2–4].

Finally, ITs are rare disorders, pre-existing pregnancy, but often discovered during the gestation. Of note, some ITs are not only associated with low PLT count but also with impaired PLT function, thus contributing to increase the bleeding risk [5, 6]. The delivery-associated bleeding risk correlates with the genetic defect responsible for IT, the presence of bleeding at previous surgery, and with a World Health Organization (WHO) bleeding scale of 3 or more. Regarding autosomal dominant disorder, or in case of double heterozygosis, we have also to take into account that the fetus could be affected too with the same IT and could have a theoretical risk of bleeding [2, 7, 8].

Unfortunately, only few studies have investigated how to deal with isolated thrombocytopenia in pregnancy.

Given these premises, we decided to perform a retrospective, monocentric study aimed at collecting and analyzing pregnancy features and outcomes in a series of women with isolated thrombocytopenia, attended to our referral center in the last 3 years.

2 | PATIENTS AND METHODS

2.1 | Patients

This is a single center, retrospective, observational study conducted at our outpatient clinic at the IRCCS Policlinico San Matteo Foundation of Pavia (Italy) between 2018 and 2021. We analyzed data from 63 consecutive pregnancies, related to 59 women with isolated thrombocytopenia for all causes or without a diagnosis of certainty, sent to our center for a diagnostic assessment or therapy advice.

We divided thrombocytopenia diagnoses into three categories: constitutional forms (comprising diagnosed and presumed inherited forms) and acquired forms, further subdivided into ITP and GT.

We evaluated all thrombocytopenic pregnant women, both referred to our attention by gynecologist colleagues, regardless of the degree of thrombocytopenia, and the thrombocytopenic patients already followed by our outpatient clinic.

We analyzed clinical, laboratory, and, where indicated, genetic data (see Supporting Information).

Regarding laboratory data, we considered complete blood count (CBC) during the first visit and at the end of pregnancy; PLT count at the time of diagnosis and out of pregnancy, during the three trimesters of pregnancy, at delivery and postpartum. We also evaluated blood smear and routine coagulation parameters. Whenever possible and when indicated, we performed cytofluorometry and in vitro study of PLT function for phenotypic characterization of ITs, as previously described [9].

Data on hemorrhagic manifestations and PLT of the newborn at delivery were collected, whenever available.

2.2 | Classification of bleeding

Spontaneous bleeding before pregnancy was measured using the WHO bleeding scale (see Supporting Information) [10]. For bleeding at delivery, the following definitions were adopted: "excessive bleeding requiring blood transfusion" (EBBT), based on transfusion of erythrocytes and/or PLTs during or after delivery to stop bleeding (prophylactic PLT transfusions in preparation for delivery were excluded), and "all excessive bleeding" (AEB), which includes EBBT subjects and subjects who did not receive blood products but whose bleeding was considered abnormal by the attending physician. Any type of bleeding in the newborns was considered abnormal.

This study was performed in accordance with the Declaration of Helsinki and approved by the institutional review board of the IRCCS Policlinico San Matteo Foundation of Pavia.

2.3 | Statistical analysis

Continuous variables were described using summary statistics (mean, standard deviation, and range). Comparisons among different groups

of patients were visualized using boxplots, showing median, interquartile range (IQR) and possible outliers falling beyond the box boundaries ±1.5 × IQR. Analysis of variance (ANOVA) was used to test the significance of the difference among groups. ANOVA for repeated measures was used to test the difference of variables measured on the same subjects several times.

Comparison of variable values within groups at two different time points was performed using *t*-test for paired data.

In order to show any statistically significant difference among the three groups of patients (GT, ITP, and ITs) concerning continuous measures, we performed the ANOVA and, in case of significant *F*-test, we performed a post hoc *t*-test among pairs of groups, applying the Bonferroni correction, thus considering the significance for $p < 0.017$ (i.e., 0.05/3).

All statistics were performed using the package Rstudio [11].

3 | RESULTS

About half of the pregnancies were classified as ITs (50.8%), a quarter as GT (25.4%), and the remaining quarter as ITP (23.8%). In the context of ITs, six cases of monoallelic Bernard–Soulier syndrome, one case of *ETV6*-related thrombocytopenia, and one case of *MYH9*-related disease were included. This distribution does not correspond to the one expected in pregnant women population. This could be explained by the fact that our hospital is a reference center for inherited PLT disorders, but we can also speculate about frequent misdiagnosis of isolated thrombocytopenias.

Patients' demographics, laboratory evidence on PLTs count and volume outside and during pregnancy, and bleeding at delivery are reported in Table 1, for both the sample as a whole and according to the three diagnostic categories.

The first finding of a reduced PLT count occurred in most cases (84.2%) before pregnancy, resulting in 70% of cases diagnosed with definite thrombocytopenia before pregnancy.

The first clinical evaluation occurred at 25 ± 9 weeks of gestation (range 9–39). Delivery occurred at week 38 ± 1.86 (range 32–41). Detailed information is available for 49 deliveries. Among them, 67.3% was performed vaginally, while cesarean section was performed in the remaining 32.7% of cases. In detail, we observed seven cesarean section for gynecological issues (i.e., breech presentation of the fetus, placenta previa marginalis, intrauterine growth restriction, premature rupture of membranes, and arrest at first or second stage), eight for thrombocytopenia, and one for both reasons.

More specifically, among ITs, vaginal deliveries were almost double compared to cesarean sections (15 vs. 7). The proportion was even higher in GT, where 12 vaginal deliveries and only one cesarean section were reported. On the contrary, six vaginal deliveries and eight cesarean sections emerged in the ITP group.

Blood losses at delivery were on average equal to 429 ± 253 mL (range 100–1200). Regarding bleeding manifestations at delivery, we did not observe any EBBT (only five patients underwent prophylactic transfusion for low PLT count), while there were two cases of AEB, respectively, one affected with ITP and the other with GT. At the time of delivery, all of them had a PLT count above 80×10^9/L and the hemorrhagic complications were related to obstetric–gynecological issues (i.e., tearing and episiotomy). Our data did not show any case of antepartum hemorrhage. Bleeding was then classified according to the type of diagnosis and by combining the type of diagnosis and the type of delivery, with evidence of increasingly higher average losses in the case of cesarean section (Table 1).

Regarding therapy, 12 women were treated with systemic steroids: nine cases of ITP, two cases of GT, and one case of ITs. Among patients requiring therapy, five cases of refractory ITP emerged which also required second-line therapy with IVIG with a good laboratory and clinical response, while only one case of ITP directly received this treatment for prophylactic purposes.

Our analyses (Figure 1) showed that GT cases had the highest PLT count that never dropped below 70×10^9/L; ITs had the lowest count with less difference between each trimester. GT and ITP have a similar slope (slightly higher in ITP) of the PLT count decrease curve between the first and second trimester, but between the second and third trimester for ITP this slope is lower. The observed difference in PLT count over time was statistically significant for GT and IT patients. On the contrary, ITP data, whose average values show a peak in the first semester, are affected by a high standard deviation, and there were not any statistically significant difference among trimesters.

None of the patients with a PLT count at delivery $>120 \times 10^9$/L underwent specific therapy, only one of them underwent prophylactic IVIG infusion because the previous pregnancy was complicated by neonatal ITP.

According to current guidelines, all the 12 women who received epidural anesthesia had a PLT count $>80 \times 10^9$/L (min value 85×10^9/L, max value 186×10^9/L, mean 112×10^9/L, and median 98–100×10^9/L).

Regarding PLT sizes (Figure 2), PLT macrocytosis is less in GT compared to the other categories of thrombocytopenia considered; in ITP and ITs, a wider IQR is observed. An increase of the mean platelet volume (MPV) for all three different types of thrombocytopenias was reported between the beginning and the end of pregnancy, with generally higher values in the case of constitutional diagnosis.

Collected data show an expected increase in MPV in the three categories of thrombocytopenia between the beginning and the end of pregnancy, with generally higher values in the group of IT, which is also the only one where the MPV increase is statistically significant ($p = 0.03$).

One of the aims of our work was to study the extent of blood loss during childbirth in relation to the diagnosis and type of delivery, whether natural or by cesarean section. As shown in Figure 3A, blood loss is very similar among the different types of disease, while higher blood loss is reported for cesarean section with respect to natural delivery (Figure 3B, $p = 0.05$ when considering the cesarean sections motivated by thrombocytopenia). More precisely, this difference is mainly due to values observed in ITP, where the statistical significance was higher ($p = 0.03$, average loss 283 ± 183 mL for vaginal deliveries, 571 ± 287 mL for cesarean sections).

TABLE 1 Mean, standard deviation, and range of demographic and clinical data of the cohort of patients.

	All (63 pregnancies)	1. Inherited (32)	2. Gestational (16)	3. ITP (15)	Analysis of variance, *F*-test and *t*-test*
Age at pregnancy (years)	31.7 ± 4.9 (22.7–40.0)	31.7 ± 5.2 (22.7–40.0)	32.6 ± 4.6 (23.5–39.5)	30.8 ± 5.2 (23.6–39.7)	ns
Platelet count ($\times 10^9$/L)					
Before pregnancy (mean)	120 ± 41 (10–201)	106 ± 31 (10–150)	160 ± 26 (115–195)	113 ± 56 (20–201)	$p = 0.0002$ 1 versus 2 $p < 0.0001$
First trimester	130 ± 41 (50–252)	113 ± 31 (50–171)	158 ± 29 (107–191)	136 ± 55 (64–252)	$p = 0.003$ 1 versus 2 $p = 0.0001$
Second trimester	105 ± 32 (34–175)	93 ± 24 (34–137)	128 ± 25 (82–175)	102 ± 42 (40–171)	$p = 0.001$ 1 versus 2 $p = 0001$
Third trimester	101 ± 42 (18–255)	89 ± 21 (36–134)	120 ± 40 (85–255)	101 ± 69 (18–214)	$p = 0.059$ 1 versus 2 $p = 0.009$
Postpartum	114 ± 48 (42–219)	106 ± 41 (42–202)	131 ± 44 (79–219)	113 ± 60 (42–219)	ns
MPV (fL)					
Beginning of pregnancy	10.8 ± 1.9 (7.1–18.1)	11.3 ± 2.3 (7.1–18.1)	10.2 ± 1.3 (8–12.8)	10.4 ± 1.3 (8–12.9)	ns
End of pregnancy	11.3 ± 2.0 (8.2–16.6)	11.9 ± 2.1 (8.8–16.6)	10.9 ± 2.1 (8.2–16.6)	10.6 ± 1.5 (8.6–12.8)	ns
Blood losses (mL)					
All deliveries	429 ± 253 (100–1200)	434 ± 204 (100–800)	428 ± 315 (200–1200)	421 ± 275 (100–1000)	ns
Vaginal delivery	401 ± 257 (100–1200)	423 ± 199 (100–700)	433 ± 342 (200–1200)	283 ± 183 (100–500)	ns
Cesarean section	487.5 ± 253 (200–1000)	457 ± 230 (200–800)	400 (only one case)	525 ± 296 (200–1000)	ns

Abbreviations: ITP, immune thrombocytopenia; MPV, mean platelet volume; ns, not significant; PLT, platelet.
*Statistical significance for post-hoc comparison between pairs of groups considered the Bonferroni correction, only significant differences are shown.

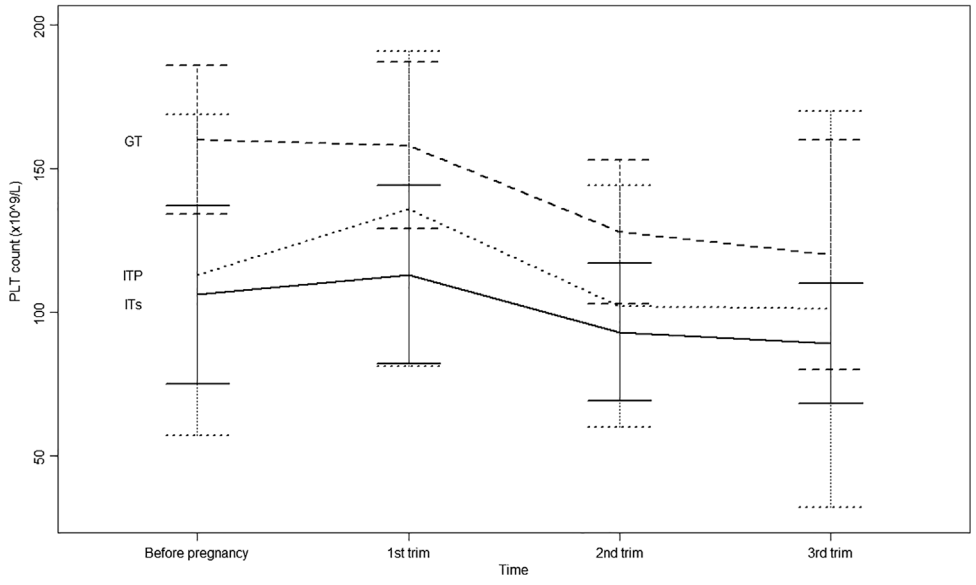

FIGURE 1 Platelet (PLT) count trend for each type of thrombocytopenia. Average PLT counts before pregnancy and in the various trimesters for each diagnosis: in gestational thrombocytopenia (GT; upper dashed line) PLT count is always normal before pregnancy and never dropped below 70×10^9/L; inherited thrombocytopenias (ITs; continuous line) had the lowest PLT count with less difference between each trimester (present also before pregnancy, as expected). In immune thrombocytopenia (ITP) patients (dotted line), the initial increase in PLT count during the first trimester is not spontaneous, but due to steroid and intravenous immunoglobulin (IVIG) therapy. The difference in PLT count between the beginning and the end of pregnancy is statistically significant for ITs and GT patients; however, this difference cannot be verified in ITP patients since they underwent therapy in order not to have a dangerous fall in PLT count.

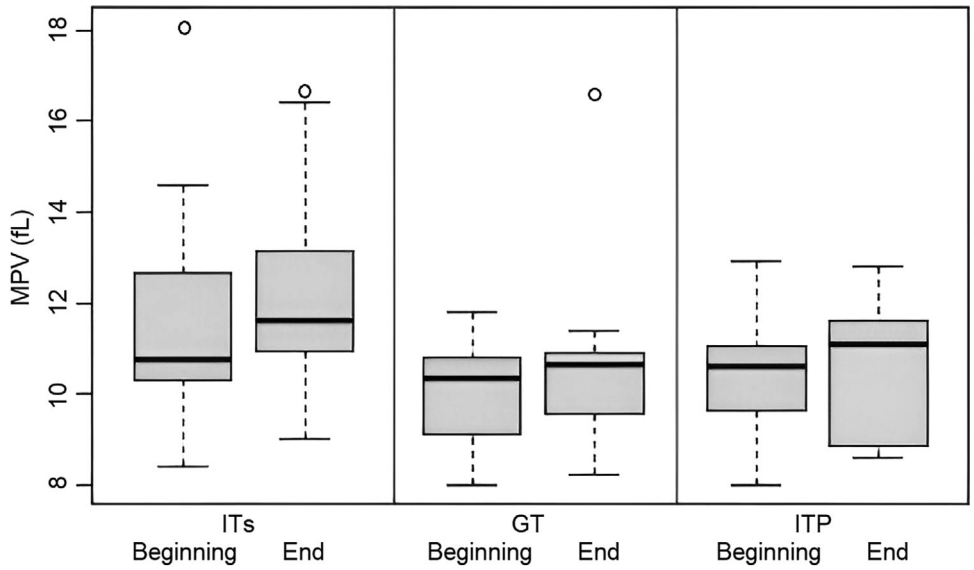

FIGURE 2 Mean platelet volume (MPV) values depending on diagnosis and time (beginning and end of pregnancy). The figure shows a general increase in MPV for each diagnosis during the gestation period. Inherited thrombocytopenias (ITs) women reported the highest MPV values, while there were no substantial differences between gestational thrombocytopenia (GT) and immune thrombocytopenia (ITP) patients even if GT is characterized by the smallest platelet size as expected.

The relationship between blood loss and PLT count shows a tendency to a negative correlation, but without reaching a statistical significance. It can be noticed that, for PLT count greater than 120×10^9/L, as expected, blood loss never gets over 500 mL.

4 | DISCUSSION

To our knowledge, this is the first single-center study to report a significant number of thrombocytopenic pregnant women, excluding inherited platelet function disorders (IPFDs), with a multidisciplinary clinical characterization thanks to collaboration with Gynecology Operating Unit.

We monitored PLT count every 4 weeks during the first two trimesters; we increased the frequency to every 1 week during the third trimester, or for any clinically significant bleeding or decline in PLT count. Our study proved a decrease of PLT count during pregnancy for all types of thrombocytopenia.

PLT count of GT patients never falls below 70×10^9/L. In ITP, the drop in PLT count is higher than in other categories, but in the last trimester there is not the expected deflection. This bias may be explained by the use of steroid therapy in cases of severe thrombocytopenia in order to prepare the patient for delivery.

Our results also show the diagnostic importance of MPV, together with family and personal history, phenotypic characterization, and PLT count trends.

In GT, PLT macrocytosis is minimal, as thrombocytopenia is likely to be caused by plasma hemodilution and not by altered bone marrow function nor increased peripheral destruction in respect to ITP. In IT, the presence of significant increase in PLT size can be explained by the underlying genetic mutations, which most often affect megakaryopoiesis and PLT formation. In ITP, the MPV at the beginning of pregnancy is within the normal range; as the gestational period advances, the immune disorder worsens with more and more PLT destroyed peripherally. By a compensatory mechanism, megakaryopoiesis is potentiated leading to the release of immature PLTs with increased MPV. Differential diagnosis between ITP and GT is usually evident on the basis of PLT count but may be more uncertain for intermediate PLT values ($60–90 \times 10^9$/L): in these cases, the PLT count trend over time [12], MPV and mean PLT diameter evaluated on peripheral blood smear, will be the main distinguishing features. The resolution of thrombocytopenia after the delivery does not help us to distinguish between the two forms, because both can go into complete remission; for sure, if PLT count does not normalize after delivery, GT can be excluded [6, 13].

Collaterally, our analyses confirmed a frequent observation in our clinical experience that is the importance to question a diagnosis, which is not of certainty, especially if it has been made in other centers, in order to ensure adequate treatment and follow-up. In fact, we have encountered cases of thrombocytopenic pregnant women treated with steroid therapy in previous pregnancies, who nevertheless, when subjected to our investigations, were found having an IT. In these cases, steroid therapy is not only unsuccessful, but it can also give side effects such as insomnia, weight gain, and metasteroid diabetes.

ITP during pregnancy usually needs treatment when PLT count is below $20–30 \times 10^9$/L, in case of bleedings, or in preparation to the delivery, whether a cesarean section or an epidural anesthesia is required [6]. According to international guidelines, a safe epidural anesthesia needs a PLT count $>70 \times 10^9$/L and cesarean section needs a PLT count $>50 \times 10^9$/L [14]. The first-line therapy consists in systemic corticosteroids and eventually IVIG [6, 13]. Azathioprine and cyclosporine are considered safe in pregnancy (due to the established

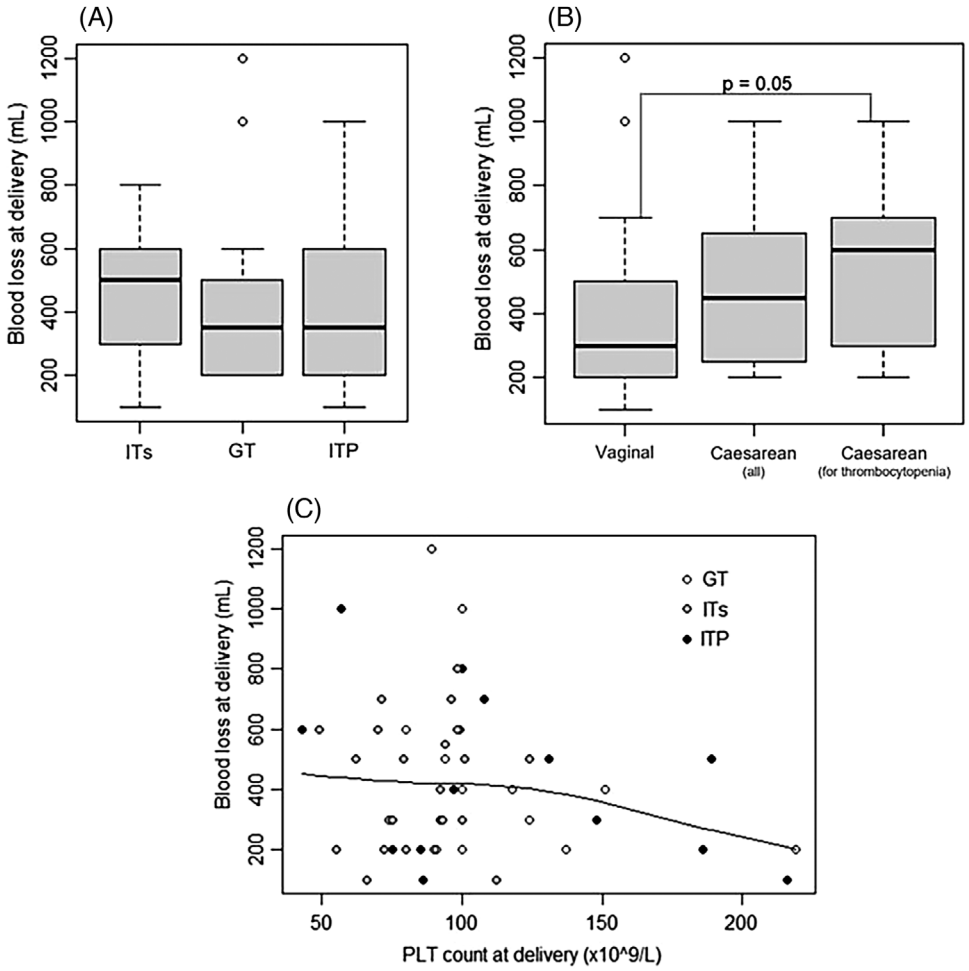

FIGURE 3 Blood loss regarding the diagnosis and the type of delivery. (A) blood loss by type of diagnosis: blood loss is very similar among immune thrombocytopenia (ITP), gestational thrombocytopenia (GT), and inherited thrombocytopenias (ITs), with no significant differences between the three groups; (B) blood loss by type of delivery: cesarean section is characterized by higher blood loss with respect to natural delivery; (C) correlation between blood loss and platelet count at delivery: the relationship between blood loss and platelet (PLT) count shows a tendency to a negative correlation, but without reaching a statistical significance. Of note, there are patients who showed a normal PLT count during the delivery: they were all ITP patient, who underwent therapy for increasing PLT count.

experience in the use of these drugs in pregnant women undergoing immunosuppressive therapy for previous transplantation or severe immunological diseases) [15–17] and may be used as second-line therapy. Splenectomy may be performed early in the second trimester. If possible, rituximab should also be avoided during pregnancy because of the slow effect, the reduced immune, vaccine response, and the risk of the newborn developing hypogammaglobulinemia if administered in the third trimester [13].

Management of women with ITP during pregnancy with poor response to corticosteroids and IVIG or with important side effects is challenging. TPO-RAs, approved for ITP, are not recommended during pregnancy, because they are likely to cross the placenta, and their safety is not established. This use is labeled as category C by the US Food and Drug Administration (FDA), but in Italy it is still avoided. Current evidence on the use of TPO-RAs in pregnant women with ITP is therefore limited, even though case reports and reviews show that the use of TPO-RAs is relatively safe [13, 18–21].

ITs in pregnancies do not require any pharmacological treatment, however, in case of bleeding manifestations or severe thrombocytopenia (PLT <20–30 × 10^9/L), the only therapeutic possible intervention is PLT transfusion [22].

In our study, we performed a thorough phenotypic characterization, which allowed us to accurately compare many patients. This shows us how important it is for these types of patients to be referred to a high specialized center, for the achievement of a more precise diagnosis and a better management. There should be no lack of close cooperation between anesthesiologist, gynecologist, and internist/hematologist for the management and treatment of individual patients.

Finally, excluding the IPFD forms [8], we have shown that there is no risk of major bleeding for mother and newborn, which seems to be comparable to that of the general population. The only data that really correlate with the risk of bleeding are PLT count, so it is important to monitor it and treat it correctly if necessary. Of note, for PLT count greater than 120 × 10^9/L, as expected, blood loss never gets over 500 mL.

As already demonstrated for IPFDs [8], vaginal delivery is safer in hemostatic terms than cesarean section, and therefore it is preferable whenever obstetrical and gynecological conditions are permissive.

In our experience and from our data, although limited, we confirm the contraindication to the use of operative vaginal deliveries, such as with forceps or ventouse, because some infants were thrombocytopenic and needed treatment with IVIG; however, after 1 month PLT count restored.

In conclusion, thrombocytopenia is a frequent finding during pregnancy; diagnosis can be challenging but must be reached as soon as possible in order to personalize treatment and define the bleeding risk for both the mother and the fetus/newborn.

PLT count trend and PLT macrocytosis, together with personal and family history, are very helpful in the diagnostic process.

Remembering that the type of delivery must be determined by obstetrical reasons, from the hematological point of view, natural delivery is always to be preferred to cesarean section. The clinical success of this study inevitably derives from collaboration and communication between the various specialists.

AUTHOR CONTRIBUTIONS

All the authors significantly participated in the drafting of the manuscript or critical revision of the manuscript for important intellectual content and provided approval of the final submitted version. Individual contributions are as follows: Federica Melazzini, Giulia Freddi, and Federico Vai designed and coordinated the study, interpreted data, and wrote the manuscript. Enea Parimbelli and Silvana Quaglini performed the statistical analysis. All the other authors followed up patients, locally collected data, and reviewed the paper for final approval. Federica Melazzini, Giulia Freddi, and Silvana Quaglini reviewed the paper and made final critical revisions for important intellectual contents.

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CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data supporting this study are available at IRCCS Policlinico Foundation Platelet Physiopathology Laboratory, Pavia, Italy, on request from the corresponding author.

ETHICS STATEMENT

Ethics committee approval on the third of July 2019 (protocol number: 20190062729).

PATIENT CONSENT STATEMENT

Each patient enrolled gave the written informed consent.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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