

Trombocitopenia immune (ITP) in gravidanza

Dott.ssa Simona Raso MD, PhD

**U.O.C Malattie Rare e degli Organi Emopoietici
A.O. Ospedali Riuniti Villa Sofia-Cervello, Palermo**



Disclosures of SIMONA RASO

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen						X	
SOBI						X	
Alexion						X	



Thrombocytopenia in pregnancy

- Thrombocytopenia (PLT <below $150 \times 10^9/L$) is one of the most frequently encountered haematological findings in obstetric practice.
- Thrombocytopenia occurs in approximately in 7%-11% of all pregnancies
- It is most common in the third trimester and the differential diagnosis of thrombocytopenia is challenging.
- Multiple syndromes have overlapping laboratory and clinical features and most lack a confirmatory test.
- Thrombocytopenia of any etiology potentially increases the risk of obstetric bleeding and is a common cause of maternal morbidity and mortality worldwide.

Table 1. Causes and relative incidence of thrombocytopenia in pregnancy

Pregnancy-specific
Isolated thrombocytopenia
Gestational thrombocytopenia (70%-80%)
Thrombocytopenia associated with systemic disorders
Preeclampsia (15%-20%)
HELLP syndrome (< 1%)
Acute fatty liver of pregnancy (< 1%)
Not pregnancy-specific
Isolated thrombocytopenia
Primary immune thrombocytopenia–ITP (1%-4%)
Secondary ITP (< 1%)*
Drug-induced thrombocytopenia (< 1%)
Type IIb VWD (< 1%)
Congenital (< 1%)
Thrombocytopenia associated with systemic disorders
TTP/HUS (< 1%)
SLE (< 1%)
Antiphospholipid antibody syndrome (< 1%)
Viral infections (< 1%)
Bone marrow disorders (< 1%)
Nutritional deficiency (< 1%)
Splenic sequestration (liver diseases, portal vein thrombosis, storage disease, etc; < 1%)

*Secondary ITP includes isolated thrombocytopenia secondary to some infections (HIV, HCV, *H. pylori*) and to other autoimmune disorders, such as SLE.

Cines DB et al. Blood. (2017)



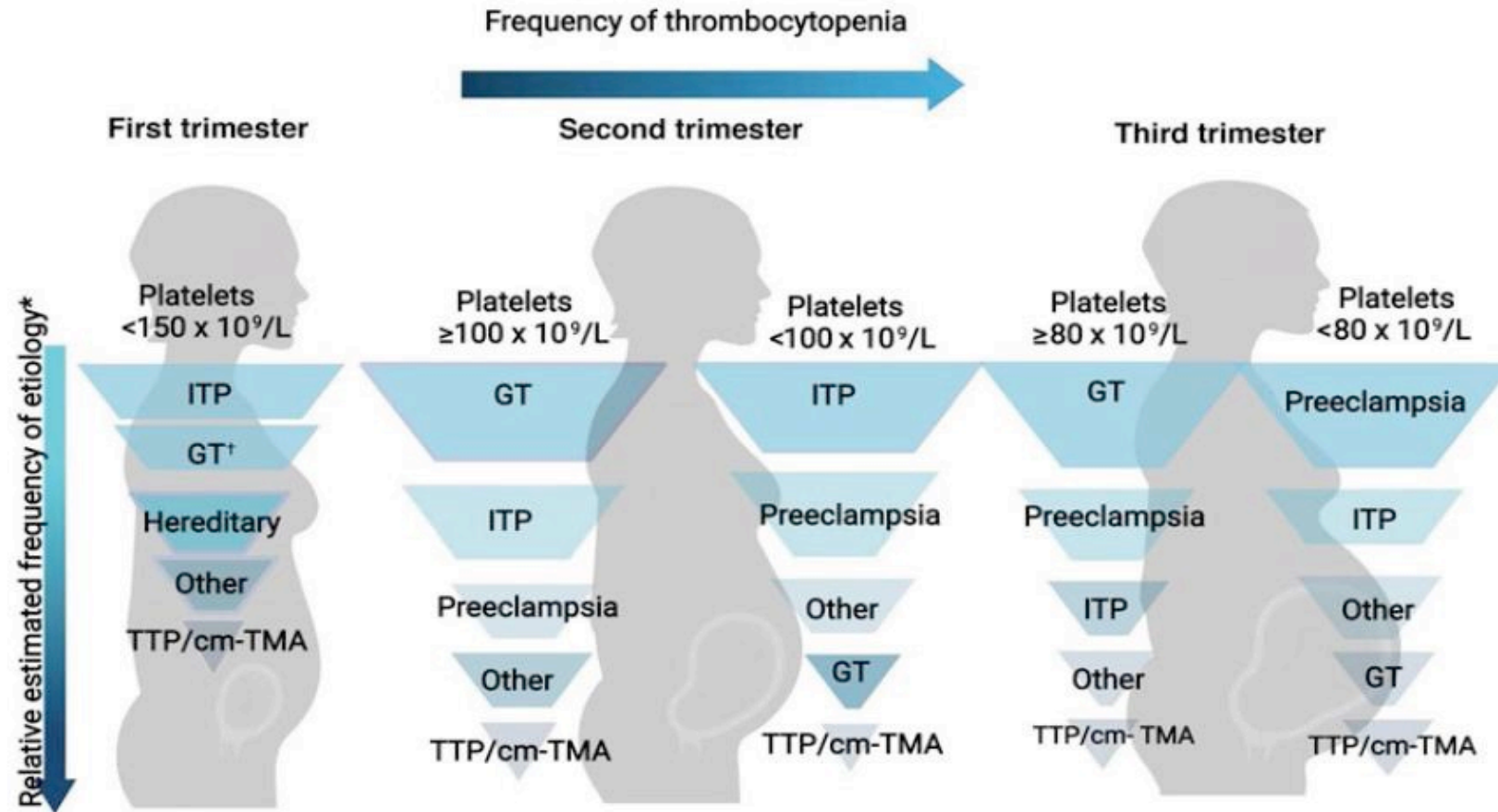
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Causes of thrombocytopenia in pregnancy by trimester of presentation and severity



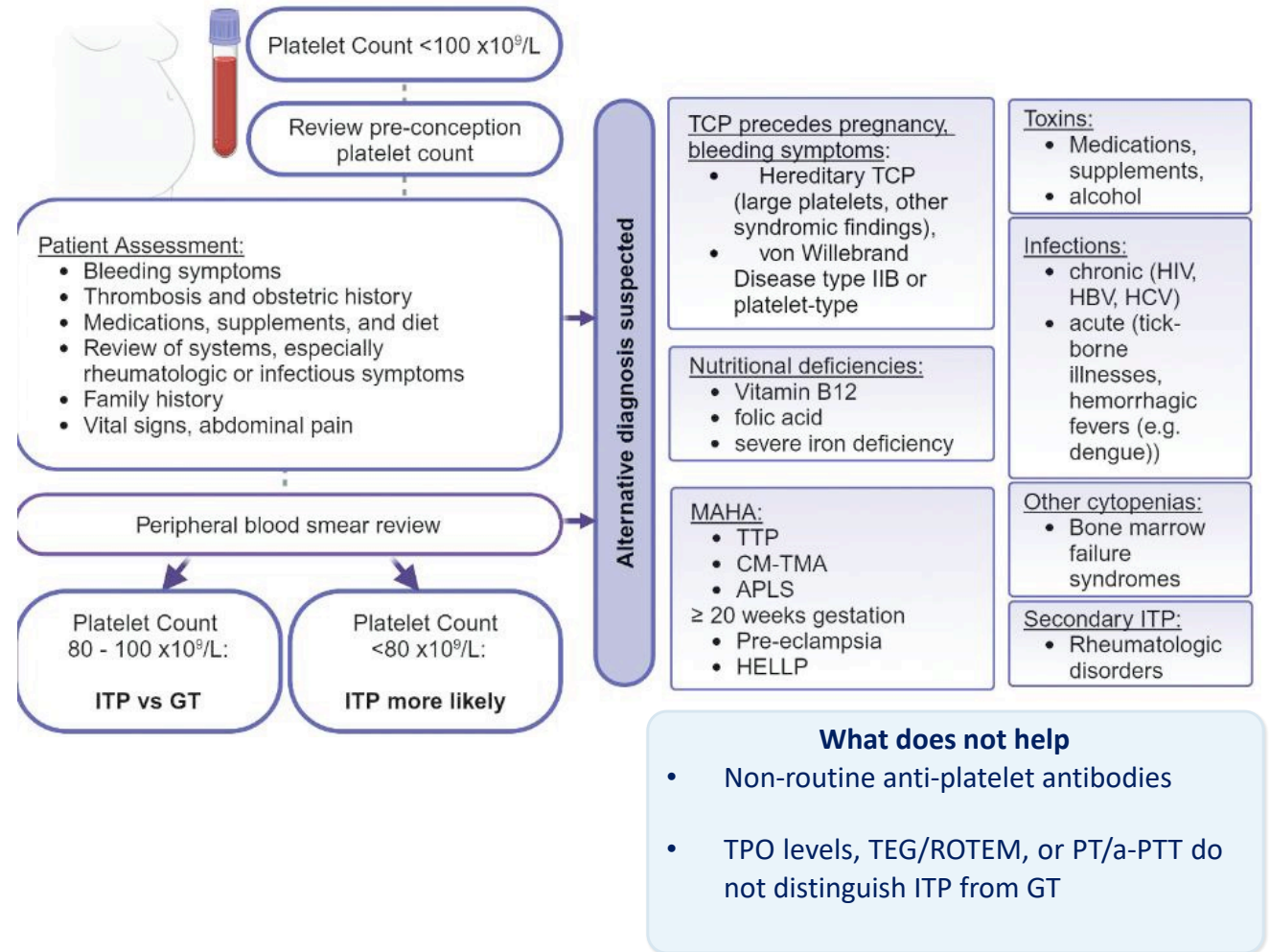
Beltrami-Moreira M, Sharma A, Bussel JB. Immune thrombocytopenia and pregnancy: challenges and opportunities in diagnosis and management. Expert Rev Hematol. 2024 Sep;17(9):595-607.



Diagnostic approach to thrombocytopenia in pregnancy

Clues to the diagnosis of ITP are

- 1) The occurrence of severe thrombocytopenia ($<20 \times 10^9/L$) at any time during pregnancy;
- 2) The occurrence of thrombocytopenia early in the pregnancy or outside of pregnancy;
- 3) Variability in the PLT count over time with or without treatment.
- 4) Evidence of PLT count improvement after treatment with high-dose corticosteroids or high-dose intravenous immunoglobulin (IVIG)



Trombocytopenia immune (ITP) in pregnancy

- ITP is defined as a platelet count below $100 \times 10^9/L$ in the absence of another cause
- ITP occurs in approximately 1:1.000-1:10.000 pregnancies
- The disease accounts for 1 to 4% of the cases of pregnancy associated thrombocytopenia
- Most common cause of a $PLT < 50 \times 10^9/L$ detected in the 1st and 2nd trimesters
- Estimated incidence of maternal bleeding symptoms an incidence of 18.1% and most episodes were mild (ecchymosis, petechiae, and dripping nose bleeds with moderate blood loss)
- **Major concerns:**
 - 1) Post-partum hemorrhage (PPH)
 - 2) Discussion regarding the mode of delivery/neuroaxial anesthesia
 - 3) Neonatal immune thrombocytopenia (NIPT)

Beltrami-Moreira M, Sharma A, Bussel JB. Immune thrombocytopenia and pregnancy: challenges and opportunities in diagnosis and management. Expert Rev Hematol. 2024 Sep;17(9):595-607.



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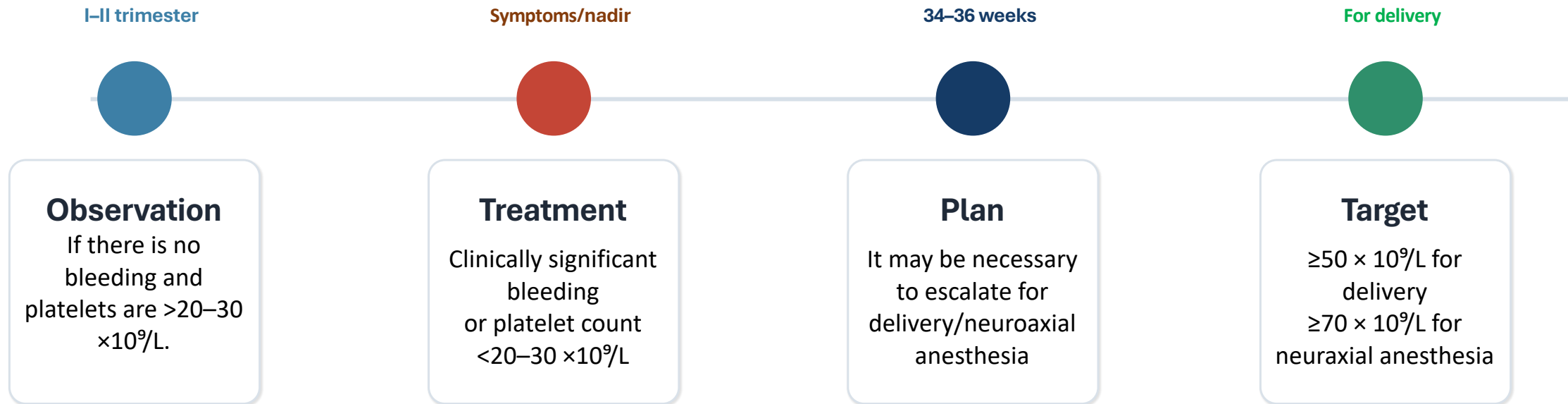
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Timing and goals of treatment change throughout pregnancy

One-third of mothers with ITP need treatment for thrombocytopenia prior to labor and delivery



Clinical practice: the decision is not “platelet-count only.”

The same value may warrant observation at 18 weeks, but active treatment at 37 weeks.

PPH Incidence: What the Evidence Shows

- In the general population, platelet counts $<50 \times 10^9/L$ at labor admission are associated with an increased risk for severe PPH, irrespective of thrombocytopenia etiology.
- PPH incidence varies due to changing definitions of PPH but has been reported at rates between 2 and 6% in all comers.
- In patients with ITP, the risk of PPH may be higher, but the reported risk is variable
- 2022: meta-analysis of small observational and not controlled studies described an event rate of severe PPH between 0 and 20%
- 2023: in a French cohort of women with ITP, PPH occurred in 10% of women, but with only 2 patients receiving red blood cell transfusions and median PLT at delivery 64 (IQR 12–218) $\times 10^9/L$.
- 2024: in retrospective US national study based on National Inpatient Sample (NIS) database postpartum bleeding rates were higher in 215 patients with ITP (10.2% vs. 4.4%; $p < 0.001$).

Gonzalez-Porras JR et al. Bleeding complications associated with pregnancy with primary immune thrombocytopenia: a meta-analysis. Open: Companion J Thromb Haemostasis. 2022;6(3):e230–e230. ; Guillet S et al. Immune thrombocytopenia and pregnancy: an exposed/nonexposed cohort study. Blood. 2023;141 (1):11–21.

Delivery modality

Mode of Delivery

Surgical delivery should be determined by **obstetric indication alone** — the presence of ITP is not itself an indication for caesarean section.

Multidisciplinary Planning

A coordinated MDT approach — involving obstetrics, haematology, and anaesthesia — should be used to schedule delivery, enabling timely optimisation of platelet counts and reducing haemorrhagic risk.

Neuraxial Anaesthesia

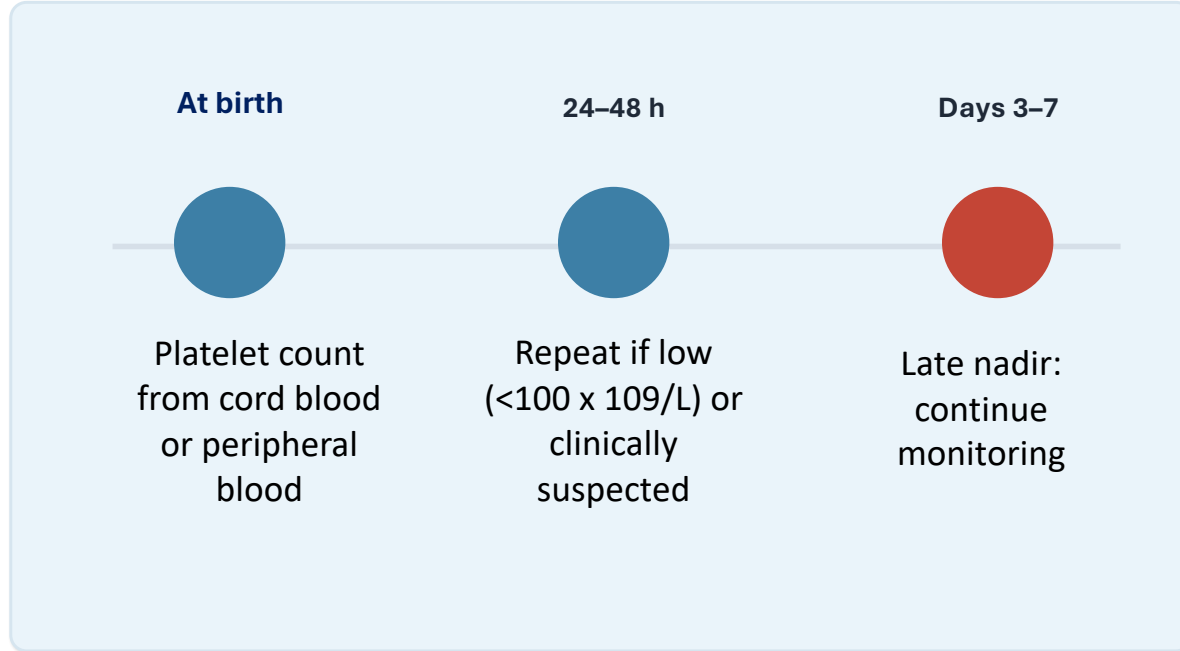
Scheduled delivery increases the likelihood of achieving platelet thresholds compatible with neuraxial anaesthesia, improving patient choice and perioperative safety.



Society for Obstetric Anesthesia and Perinatology issued a consensus statement in 2021 concluding that risk of spinal epidural hematoma is very low when the PLT is greater than **70 ×10⁹/L** in obstetric patients with ITP in the absence of other risk factors

Neonatal immune thrombocytopenia (NITP)

The platelet count at birth is not sufficient: the nadir may occur after a few days.



Key Interpretive Caution

Reported ICH rates are confounded by three factors: the rarity of the event, inclusion of Grade 1 cases, and evidence that ICH may occur *prior to* labour and delivery, not as a consequence of it.

- NITP may occur with incidences ranging from 8 to 37.5% depending on the definition of thrombocytopenia.
- The incidence PLT nadir $<50 \times 10^9/L$ ranges from 9 to 15%
- Overall neonatal outcomes in the context of maternal ITP remain favourable.
- Neonatal intracranial haemorrhage (ICH) is rare ($<1\%$). Historical figures are inflated by inclusion of Grade 1 ICH — clinically irrelevant and present in normal term newborns
- ICH is most frequently reported when neonatal PLT $<10 \times 10^9/L$
- There is no evidence that delivery by caesarean section reduces the rate of neonatal ICH in this population



Predictors of thrombocytopenia in newborns

- **Correlations between neonatal platelet counts in the first and second siblings at birth (P = 0.015) and at nadir (P = 0.035)**
WebertK et al. Blood 2003

- **Maternal treatment for ITP such as splenectomy did not correlate with a risk of neonatal thrombocytopenia.**
 - **The presence of an older sibling with neonatal thrombocytopenia is a reliable risk factor for neonatal thrombocytopenia in subsequent pregnancies.**
- HakisugaK et al, Blood Research 2014

- **Previous history of neonatal thrombocytopenia: OR 5.55 [CI 1.72-17.89], p: 0.004**
 - **Maternal plt count < 50 x 10⁹/L within 3 months before delivery: OR 4.07 [CI 1.41-11.73] p:0.009**
- GuilletS et al, Blood 2023*



Immune thrombocytopenia and pregnancy: an exposed/nonexposed cohort study

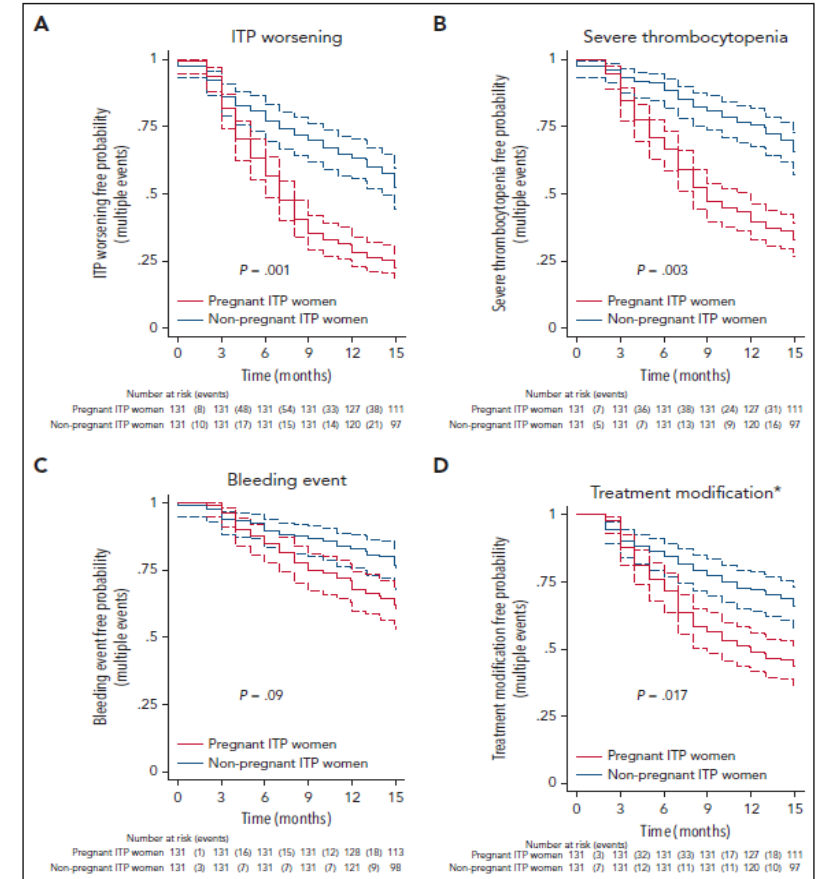
- 131 pregnant women with ITP were matched to 131 non pregnant women with ITP by history of splenectomy, ITP status (no response, response, complete response), and duration
- The primary outcome was the first occurrence of ITP worsening defined by a composite end point including bleeding events and/or severe thrombocytopenia (<30x10⁹/L) and/or ITP treatment modification.
- Analyzed occurrence of multiple events of ITP worsening and each criterion of the composite end point
- Groups were followed for 15 months
- Studied also incidence of NITP and risk factors

Guillet S, Ebbo et al. Immune thrombocytopenia and pregnancy: an exposed/nonexposed cohort study. Blood. 2023 Jan 5;141(1):11-21.



Pregnancy and ITP outcomes

- The first occurrence of ITP worsening did not differ between pregnant and nonpregnant women with ITP (53.4 per 100 person-years [95% confidence interval {CI}, 40.8-69.9] vs 37.1 [95% CI, 27.5-50.0]);
- Recurrence of severe bleeding events was not different between groups (P = .4).
- Pregnant women with ITP were more likely to have recurrence of severe thrombocytopenia and treatment modification (HR, 2.71 [95% CI, 1.41-5.23], P = .003; HR, 2.01 [95% CI, 1.14-3.57], P = .017, respectively).



Guillet S, Ebbo et al. Immune thrombocytopenia and pregnancy: an exposed/nonexposed cohort study. Blood. 2023 Jan 5;141(1):11-21.



Immune thrombocytopenia therapies in pregnancy

Table 1. Immune thrombocytopenia therapies in pregnancy.

First-line agents		
Steroids	prednisone	Preferred agent. It does not cross the placental. Initial dose may be lower than in non-pregnant individuals (0.25-0.5 mg/kg)
	dexamethasone	To be avoided. It can cross the placenta and limited evidence suggests possible fetal harm
Intravenous Immunoglobulin		Similar efficacy to prednisone as single agent, but with faster response, often to a higher platelet level. Often used in combination with steroids to increase response rates and duration of response. High cost.
Second-line agents		
Rituximab		Extensive experience in other auto-immune conditions. It can cross the placenta but neonatal outcomes are usually good. Best in anticipation of pregnancy.
Azathioprine		Use is acceptable so it may be continued, however very slow to achieve platelet count improvement and rarely initiated during pregnancy
Thrombopoietin receptor agonists	romiplostim	Most clinical safety experience reported. No major fetal harm noted. It appears effective in refractory cases, however there are no comparative studies assessing potential harm. Not recommended for routine use.
	eltrombopag	Some clinical experience (20-30 cases). No major fetal harm noted. It appears effective in refractory cases, however there are no comparative studies assessing potential harm. Not recommended for routine use.
	avatrombopag	No experience reported pre-clinical evidence of fetal harm: use not recommended
Agents contraindicated or not favored		
Cyclophosphamide		Decreased fertility and teratogenic
Danazol		Decreased fertility and teratogenic
Mycophenolate mofetil		Teratogenic
Vinca alkaloids		Teratogenic
Cyclosporin A		<u>Used in organ transplant setting but safer options are available in ITP</u>
Fostamatinib		Pre-clinical evidence of fetal harm: use not recommended



Choice of therapies in pregnancy

Table 1. Therapeutic options and considerations for treatment of ITP during pregnancy and lactation

Treatment	Dosing	Response rates (%)	Time to response	Maternal considerations	Fetal considerations	Lactation considerations
FIRST LINE						
Prednisone	20–60 mg/d	40–70	3–14 days	HTN, diabetes, premature delivery, insomnia, mood lability, fluid overload	Hypoglycemia, prematurity, risk for cleft palate when exposed in first trimester	Low risk
IVIg	0.4 g/kg up to 5 days or 1 g/kg for 1–2 days	40–80	1–3 days	Headache, fluid overload, HTN, aseptic meningitis, myalgias, hemolysis	Hemolysis	Low risk
SECOND LINE (Minimal data available. No uniform recommendations exist regarding optimal agent.)						
Not recommended in pregnancy, but use described						
Romiplostim	1–10 µg/kg/wk	70–80	7–14 days	Headache, myalgia	Thrombocytosis	Limited data, thus not advised. Detected in breast milk. ^{56,57}
Eltrombopag	2.5–7.5 mg/d	70–80	7–14 days	Elevated LFTs, headache	Thrombocytosis	Limited data, thus not advised
Cyclosporine	3–5 mg/kg of body weight/d	Insufficient data on ITP in pregnancy to calculate	4–12 weeks	Renal injury, HTN, tremor	IUGR	Present in breast milk. Monitor for neonate infection
Rituximab	375 mg/m ² weekly × 4	40–60	1–8 weeks	Infusion reaction, hypogammaglobulinemia, infection, curtailed vaccine response	Hypogammaglobulinemia, reduced B cells	Minimal concentrations, low risk
Azathioprine	50–75 mg/d	Insufficient data on ITP in pregnancy to calculate	8–16 weeks	Transaminitis, neutropenia, infection	Case reports of use in renal transplant recipients with congenital anomalies, heme toxicity, and IUGR	Neonate neutropenia has been reported. Avoidance or neonate CBC monitoring advised
Generally contraindicated in pregnancy, but use described						
Dapsone	100 mg/d	40–50	7–14 days	Hemolysis	Anemia, prematurity	Hemolytic anemia reported (check G6PD level and monitor CBC)
RhD immune globulin	50 µg/kg of body weight	70	4–5 days	*Limit use to nonsplenectomized patients. Hemolysis, renal failure, infusion reaction	Anemia, jaundice	Low risk
Splenectomy	Optimal timing is early second trimester or before pregnancy	50–80	1–60 days	Bleeding, infection, thrombosis risk, preterm labor	Prematurity	Minimal risk
CONTRAINDICATED IN PREGNANCY						
Vinc alkaloids Cyclophosphamide Mycophenolate mofetil Danazol Fostatinib						

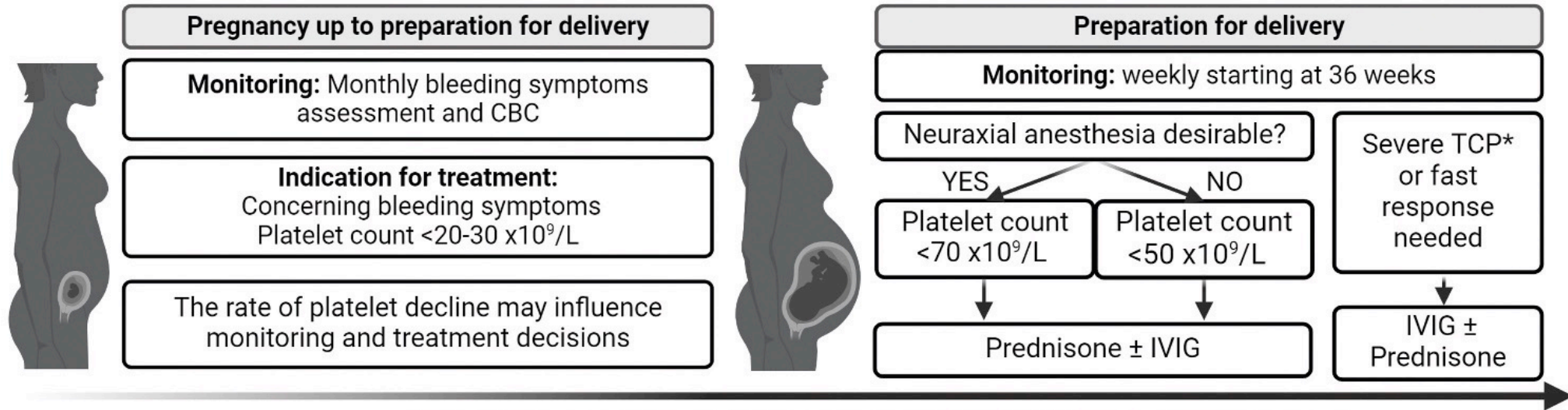
G6PD, glucose-6-phosphate dehydrogenase; HTN, hypertension; IUGR, intrauterine growth retardation; LFTs, liver function tests.

The choice of first or second-line therapy for ITP in pregnancy should be guided:

- 1) Urgency of treatment
- 2) Expected time to response
- 3) Patient-specific risk factors
- 4) Proximity to delivery



General approach to the management of ITP in pregnancy



	1 st trimester	2 nd trimester	3 rd trimester
1st line			
Prednisone	✓	✓	✓
IVIg	✓	✓	✓
Rituximab	May be considered**		
Refractory			
Splenectomy	✗	✓	✗
Other***	✓	✓	✓
TPO-RA			May be considered**

Beltrami-Moreira M, Sharma A, Bussel JB. Immune thrombocytopenia and pregnancy: challenges and opportunities in diagnosis and management. Expert Rev Hematol. 2024 Sep;17(9):595-607



TPO receptor agonists (TPO-RAs)

TPO-RAs, including romiplostim, eltrombopag, and avatrombopag

Each of these drugs is expected to cross the placenta thus, they have the potential to affect the fetus

- 1) romiplostim via FcRn binding
- 2) eltrombopag and avatrombopag as small molecules

Romiplostim and **avatrombopag** carry FDA label language indicating potential fetal harm following in utero exposure. No specific label information exists for **eltrombopag** in this context.

In preclinical animal studies, fetal toxicity occurred only with very high doses of TPO-RAs that exceeded therapeutic doses in humans





Romiplostim use in pregnant women with immune thrombocytopenia

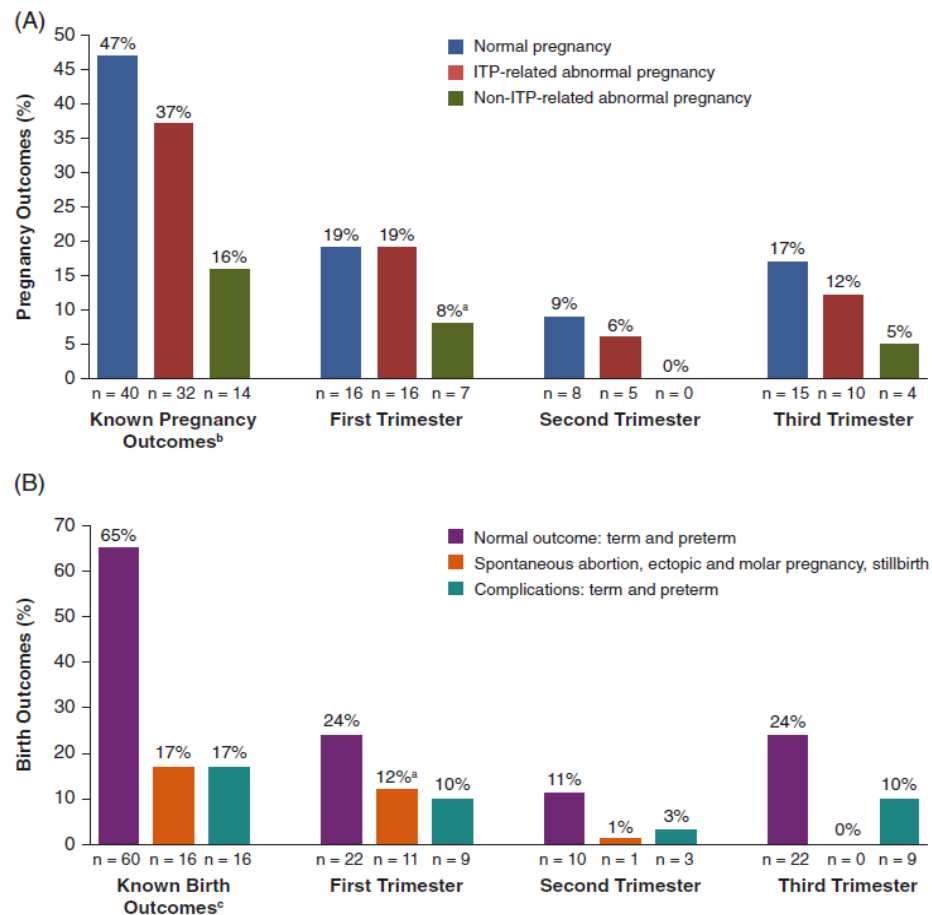
Known mother outcome: 86/186

The Pregnancy Surveillance Program collected patient information from 2017–2020 for 186 pregnant women exposed to romiplostim from 20 days before pregnancy to the end of pregnancy.

Timing of exposure was available in 128 women.

Intrapartum exposure was known for the first, second, and third trimesters for 74 (40%), 22 (12%), and 44 (24%) mothers, respectively, with 15 mothers exposed during >1 trimester.

First trimester exposure was most common, reflecting the point at which many mothers first became aware of their pregnancy.



Know birth outcome: n= 92

Bussel JB, Cooper N et al. Romiplostim use in pregnant women with immune thrombocytopenia. Am J Hematol. 2023 Jan;98(1):31-40.

Pregnancy and birth outcomes

The AEs reported in this dataset are in line with those reported in the published literature for the general pregnant population.

TABLE 1 Pregnancy outcomes

	n (%) (N = 86)
Normal	40 (47)
Abnormal (≥1 SAE)	46 (53)
Hematologic	30 (35)
Thrombocytopenia	24 (28)
Venous thrombosis	2 (2)
Thrombocytosis	1 (1)
DVT	1 (1)
Vaginal bleeding	1 (1)
Postpartum clots	1 (1)
Obstetrics/gynecology	17 (20)
Spontaneous miscarriage	11 (13)
Ectopic pregnancy (medical termination)	3 (3)
Cesarean section	3 (3)
Molar pregnancy (medical termination)	1 (1)
Stillbirth	1 (1)
Uterine leiomyoma	1 (1)
Vaginal bleeding	1 (1)
Covering placenta	1 (1)
Uterine atony	1 (1)

Cardiovascular	7 (8)
Hypertension	2 (2)
Preeclampsia	5 (6)
Infection	7 (8)
UTI	3 (3)
Viral infection	4 (5)
Death	2 (2)
Pre-existing AML with aortic aneurysm rupture	1 (1)
Venous thrombosis	1 (1)
Hepatobiliary	2 (2)
Cholestasis	1 (1)
Increased liver enzymes	1 (1)
Endocrine	1 (1)
Gestational diabetes	2 (2)
Hyperthyroidism	1 (1)

Note: Mothers may have had more than one event.
Abbreviations: AML, acute myelogenous leukemia; DVT, deep vein thrombosis; SAE, serious adverse event; UTI, urinary tract infection.

TABLE 2 Birth outcomes

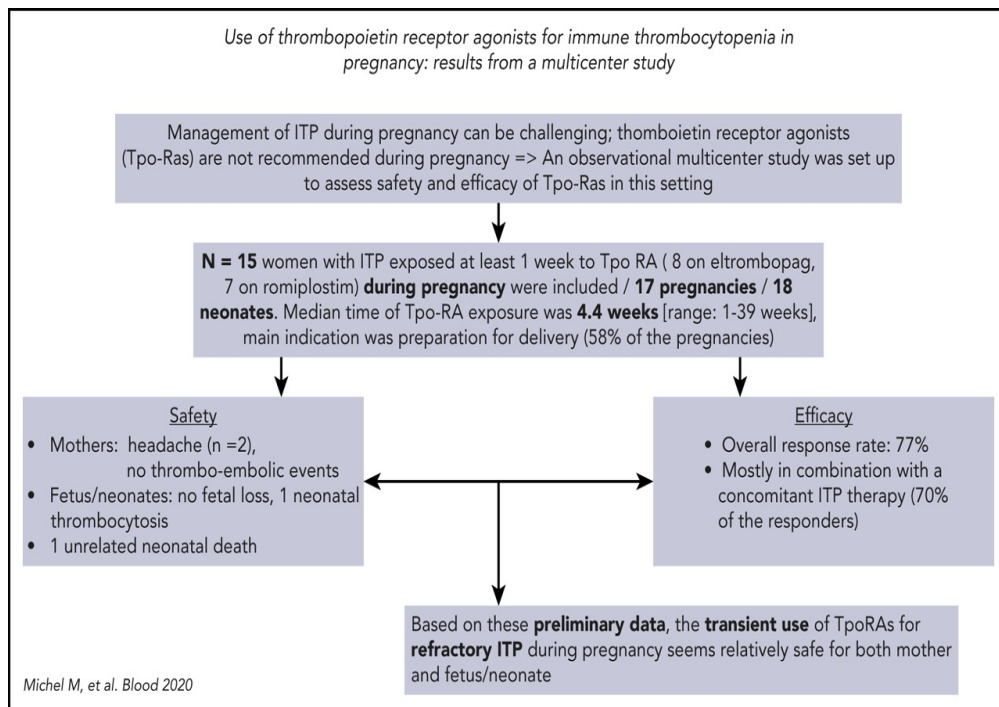
	n (%) (N = 92 ^a)
Normal	60 (65)
Term	54 (59)
Preterm	6 (7)
Abnormal	32 (34)
Spontaneous miscarriage	11 (12)
Complications, term	10 (11)
Complications, preterm	6 (7)
Ectopic pregnancy (medical termination)	3 (3)
Molar pregnancy (medical termination)	1 (1)
Stillbirth	1 (1)

12/16 thrombocytopenia



Use of thrombopoietin receptor agonists for immune thrombocytopenia in pregnancy: results from a multicenter study

Marc Michel,¹ Marco Ruggeri,² Tomas Jose Gonzalez-Lopez,³ Salam Alkindi,⁴ Stéphane Cheze,⁵ Waleed Ghanima,^{6,7} Tor Henrik Anderson Tvedt,⁸ Mikael Ebbo,⁹ Louis Terriou,¹⁰ James B. Bussel,¹¹ and Bertrand Godeau¹



Treatment of immune thrombocytopenia during pregnancy with thrombopoietin receptor agonists

Amihai Rottenstreich^{1,2,3,4} | James B. Bussel⁵

Comprehensive review examines the safety and efficacy of TPO-RA in 45 pregnancies of women with ITP

- romiplostim n = 22; eltrombopag n = 21; both in the same pregnancy n = 2.
- Failure of the median of 3 treatment lines during pregnancy prior to TPO-RA.
- A platelet response ($>30 \times 10^9 /L$) was seen in 86.7% (including a CR $>100 \times 10^9 /L$ in 66.7%) and was similar between eltrombopag and romiplostim (87.0% and 83.3%, $p = 0.99$).
- The maternal safety profile was favourable, with no thromboembolic events encountered.
- Neonatal thrombocytopenia was noted in one third of cases, with one case of ICH grade 3, and neonatal thrombocytosis was observed in three cases.
- No other neonatal adverse events attributable to TPO-RAs were seen

Marc Michel. Use of thrombopoietin receptor agonists for immune thrombocytopenia in pregnancy: results from a multicenter study, Blood, 2020,



RETROSPECTIVE ITP-NETITALIAN STUDY

11

Patient and treatment Characteristics

33

Women enrolled

14 pregnancies (1 twin), 15 newborns

Median age (yrs)

Range 22–46 years at delivery

3

Prior therapy lines

Median (range 0–6); includes 5 splenectomies

12

Median disease duration

Years in chronic ITP patients (range 1–41)

ITP Classification

3 de novo ITP diagnoses made during pregnancy; **11 pregnancies** in patients with pre-existing chronic ITP. All patients were steroid-refractory prior to TPO-RA initiation.

TPO-RA Regimens

Romiplostim

10 patients · Median 6 mcg/kg/week

Eltrombopag

4 patients · Median 25 mg/day

Median treatment duration before delivery: **31 days** (range 5–350). Combined therapies included steroids (7), steroids + IVIG (2), IVIG alone (2), and steroids + ciclosporin-A (1).

THROMBOPOIETIN-R AGONISTS EFFICACY AND SAFETY IN PREGNANT ITP PATIENTS AND THEIR NEWBORNS: A MULTICENTER RETROSPECTIVE ITP-NETITALIAN STUDY

Response rate and maternal outcomes

Outcomes	
TPO-RA therapy ORR – n (%)	16 (100)
- CR (all)	11 (69)
CR with romiplostim	6
CR with eltrombopag	5
- PR (all)	5 (31)
PR with romiplostim	4
PR with eltrombopag	1
Median plt count @delivery (range) x 10 ⁹ /L	112 (58-250)
Cesarean section – n (%)	5 (31)
VTE prophylaxis with LMWH after delivery	4 (25%)

Maternal and neonatal adverse events

Outcomes	
Peripartum bleeding - n (%)	1 (6) [WHO 2]
Thombosis during TPO-RA treatment - n (%)	0 (0)
Bleeding during TPO-RA treatment – n (%)	0 (0)
Other adverse events during TPO-RA treatment – n (%)	0 (0)
Thrombocytopenia in newborns – n (%)	10 (62,5)
Bleeding in newborns – n (%)	1 (6) [WHO 1]
Treatment of thrombocytopenia in newborns (n = 10)	
- IVIG alone – n (%)	3 (30)
- Platelet transfusion + IVIG – n (%)	7 (70)
- Breastfeded neonates (out of 12 known) – n (%)	6 (50)

M.Carpenedo, G. Carli, A. Patriarca, M. Napolitano, M. Bellini, A. Condorelli, F. Mendicino, V. Sammartano, F. Zaja. Abstract EHA -SIE 2024



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Breastfeeding and counseling in ITP women

- ITP is not a contraindication to breastfeeding, however, whether breastfeeding worsens or perpetuates neonatal thrombocytopenia has been a topic of contention
- Antiplatelet antibodies have been identified in the breast milk of pregnant people with ITP, and infrequent occurrences of persistent neonatal thrombocytopenia have been described.
- Rituximab exposure during lactation has not been associated with neonatal B-cell depletion.
- Romiplostim exposure during lactation has resulted in low levels of romiplostim in breast milk, and neonatal thrombocytosis has been reported sometimes persisting even after breastfeeding is stopped.
- Discuss teratogenic risk and contraception with all women with Immune thrombocytopenia of reproductive age
- Recommend effective contraception during treatment with TPO-RAs (e.g., Eltrombopag, Romiplostim)
- If pregnancy is desired → ensure shared informed decision-making before any off-label TPO-RA use

Marc Michel. Use of thrombopoietin receptor agonists for immune thrombocytopenia in pregnancy: results from a multicenter study, Blood, 2020,



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Take home messages

- In a pregnant patient with thrombocytopenia, the correct sequence is: rule out obstetric/haematologic emergencies → assess the likelihood of ITP → assess risk of bleeding -> plan treatment VS vigilance
- Newborn risk is low but present and could be related to severity of thrombocytopenia within 3 months before delivery
- First-line management of ITP in pregnancy remains unchanged: corticosteroids and IVIG are still the standard of care.
- TPO-RAs show good efficacy in refractory ITP, but exposure data remain limited and do not support routine use.
- New evidence confirms a rapid expansion of therapeutic options but a persistent pregnancy-specific evidence gap.
- Clinical management should remain based on established therapies, individualized risk stratification, and multidisciplinary decision-making, reserving novel agents for highly selected refractory cases.

