2ND meeting of the European Research Consortium on ITP

NEW INSIGHTS INTO IMMUNE THROMBOCYTOPENIA

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ITP in Pregnancy: 2020 on

James B. Bussel MD

Professor Emeritus

Weill Cornell School of Medicine

Disclosures: consultant for Mara Bio, Recordati, Janssen, RallyBio, CSL Behring, Argenx, UCB

ITP in Pregnancy: What Would We Like to Know

- Pathophysiology of neonatal thrombocytopenia
- Longterm outcome of affected (and unaffected) neonates
- Does ITP worsen during pregnancy ?
- Treatment during pregnancy: beyond steroids and IVIG
  - TPO agents
  - Inhibitors of FcRn
- Is the risk of thrombosis elevated during pregnancy or after delivery ?
- PostPartum Hemorrhage: is it just the platelet count ?

Estimation of the Risk of Thrombocytopenia in the Offspring of Pregnant Women with Presumed Immune Thrombocytopenic Purpura

Journal: The *New England Journal of Medicine* **Year:** 1990
Authors: Samuels P, Bussel JB, Braitman LE, Tomaski A, Druzin ML, Mennuti MT, Cines DB.

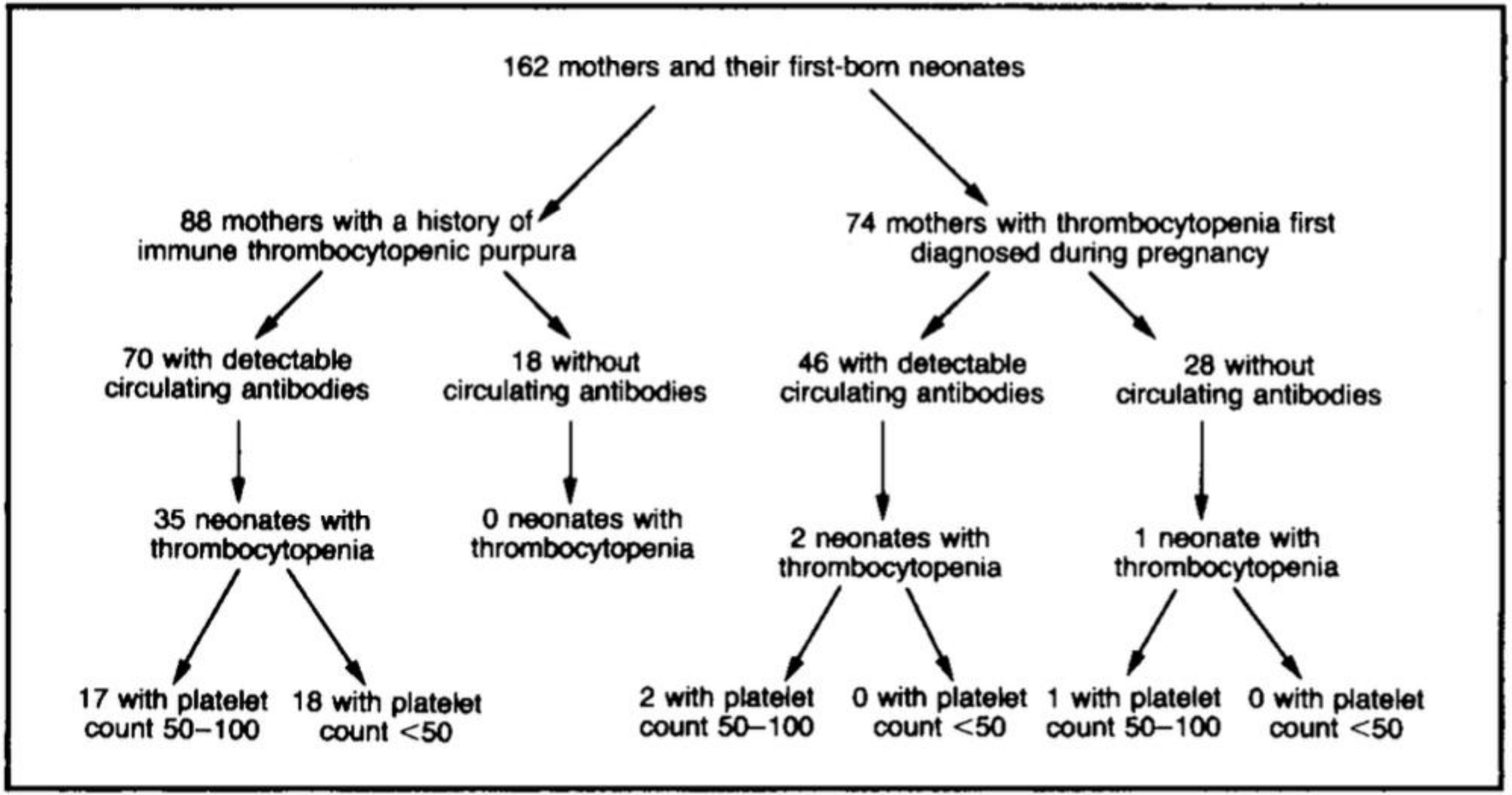


Figure 1. Identification of High-Risk and Low-Risk Neonates in the Study.
The relation between the neonatal platelet counts after the index pregnancy, the maternal history, and the results of indirect antiglobulin tests in all 162 patients are shown. Platelet counts indicated are $\times 10^{-9}$ per liter.

The NEW ENGLAND JOURNAL of MEDICINE

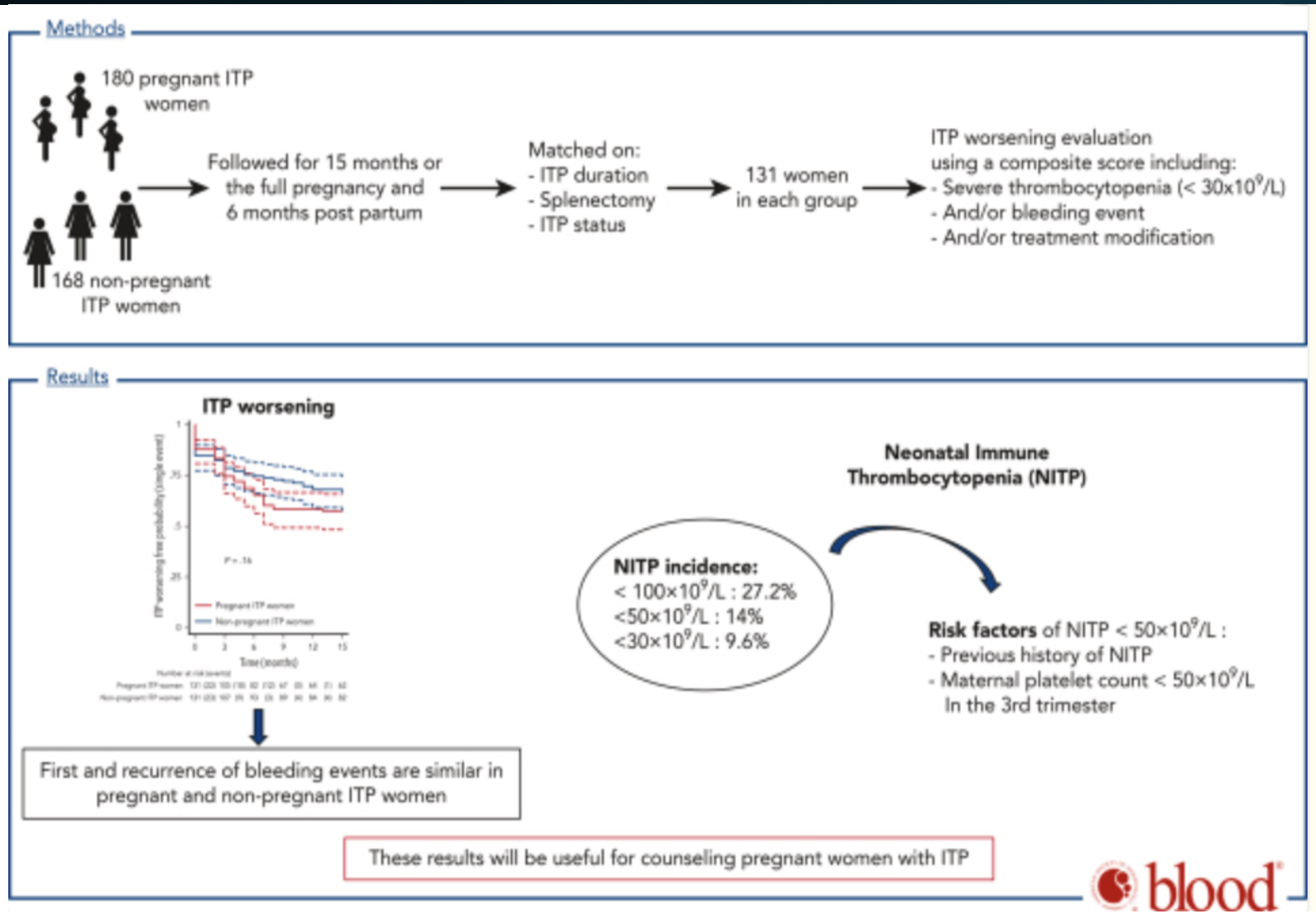
REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Management of Primary Immune Thrombocytopenia in Pregnancy

James B. Bussel, M.D., Ming Hou, M.D., Ph.D., and Douglas B. Cines, M.D.

Immune Thrombocytopenia and Pregnancy: An Exposed/Nonexposed Cohort Study- Guillet et al., 2023



Takeaways:

- Pregnant women with ITP does not increase risk of severe bleeding during pregnancy despite higher rates of platelet count reduction and treatment adjustments
- Nearly 85% showed return to ITP status after pregnancy
- NITP is associated with NITP history, severity of maternal ITP, and circulating anti-platelet antibodies

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Short- and Long-term Outcome of Neonates with Thrombocytopenia from Maternal Immune Thrombocytopenia- Sorin et. al., 2026

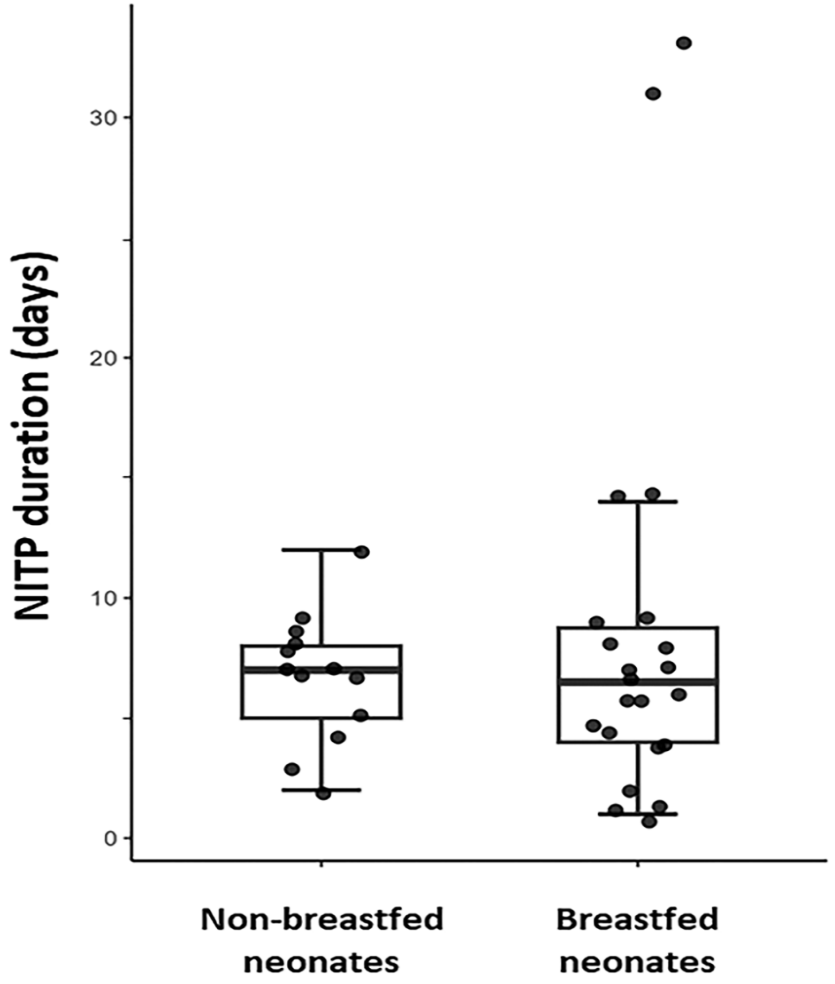

Figure 1 NIPT duration in breastfed and non-breastfed neonates. NITP was defined as mild with nadir neonate platelet count 50–100 × 10^9/L, moderate 30–49 × 10^9/L and severe <30 × 10^9/L.

Short- and Long-term Outcome of Neonates with Thrombocytopenia from Maternal Immune Thrombocytopenia- Sorin et. al., 2026

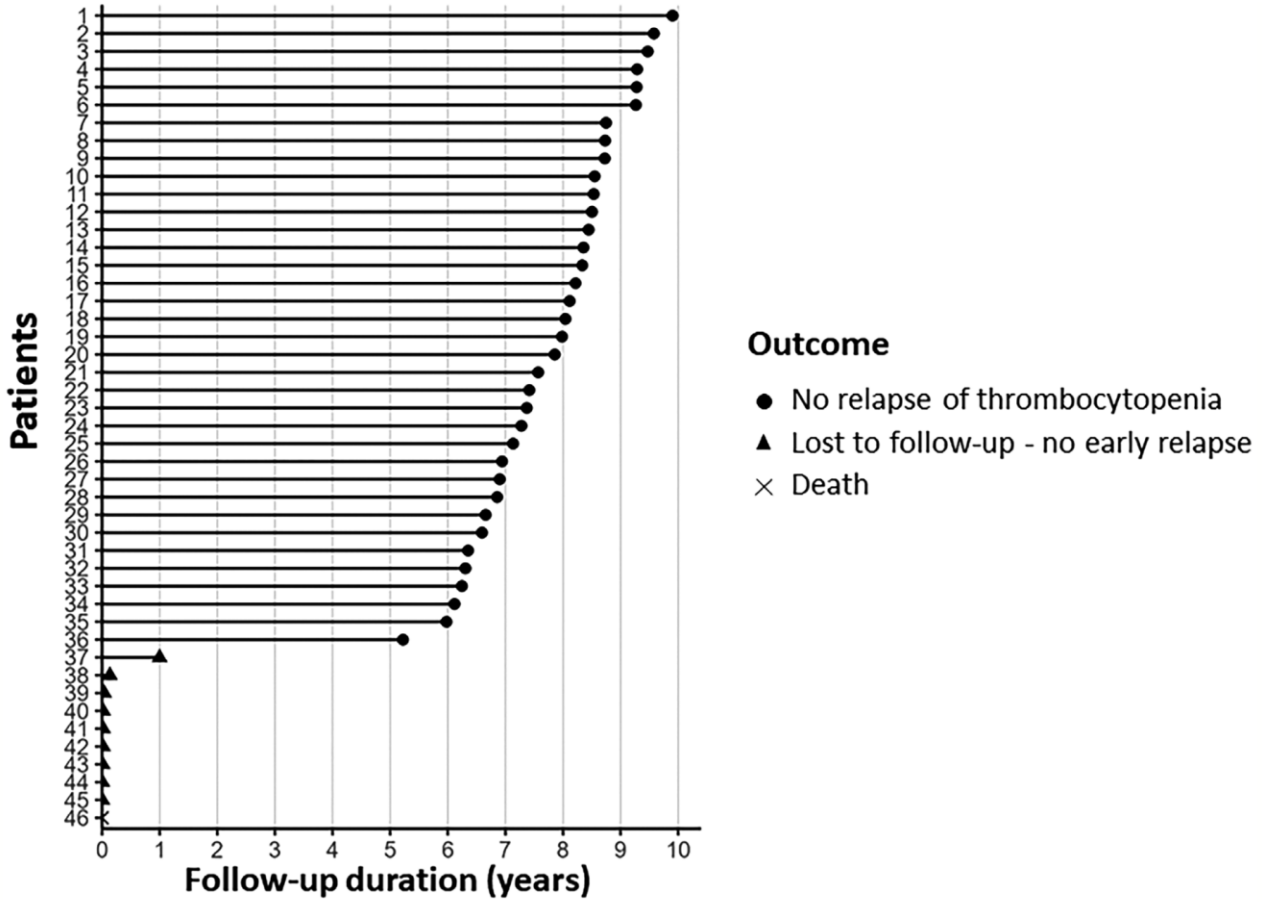

Figure 2: Long-term follow-up. Swim plot showing individual duration of follow-up for NITP, ordered from longest (top) to shortest (bottom) follow-up. Each horizontal line represents one patient. The symbol at the end of the line indicates the outcome at the end.

Weill Cornell Medicine

Increased Frequency of Autism by Previous Established Diagnosis and by Questionnaire Screening in Children with Fetal-Neonatal Alloimmune Thrombocytopenia (FNAIT) With and Without an Intracranial Hemorrhage (ICH)

Our hypothesis explaining increased risk of autism in FNAIT-affected children: Placental inflammation (based on five controlled studies showing placental inflammation) is induced by anti-HPA-1a antibodies binding to β3 (HPA-1a) expressed on syncytiotrophoblasts in the placenta, leading to inflammation and thus an increased occurrence of autism.

Could anti-GPIIIA antibodies in maternal ITP have the same effect ?

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  - Inhibitors of FcRn
- Is the risk of thrombosis elevated during pregnancy or after delivery ? MORE INFORMATION NEEDED
- PostPartum Hemorrhage: is it just the platelet count ? MORE INFORMATION NEEDED

- Almost all women with ITP have a decrease in the platelet count during gestation, and in many cases, therapy must be reinitiated or intensified, often, but not only, in preparation for delivery

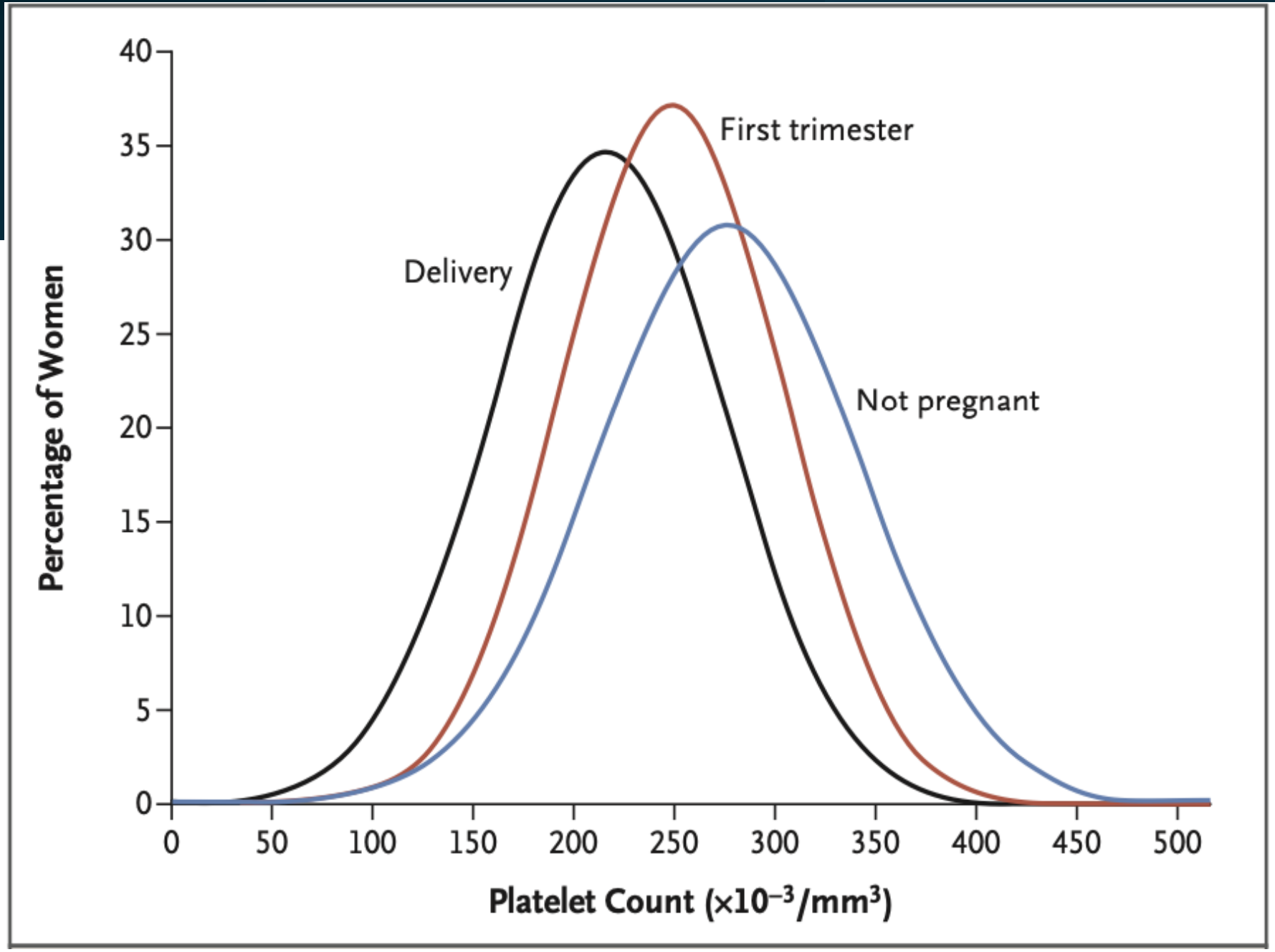


Figure 2. Platelet Counts during Pregnancy.

- ITP is the most common cause of thrombocytopenia in the 1st and 2nd trimesters and of maternal platelet counts < 80×10^3 per cubic millimeter throughout gestation in otherwise healthy women

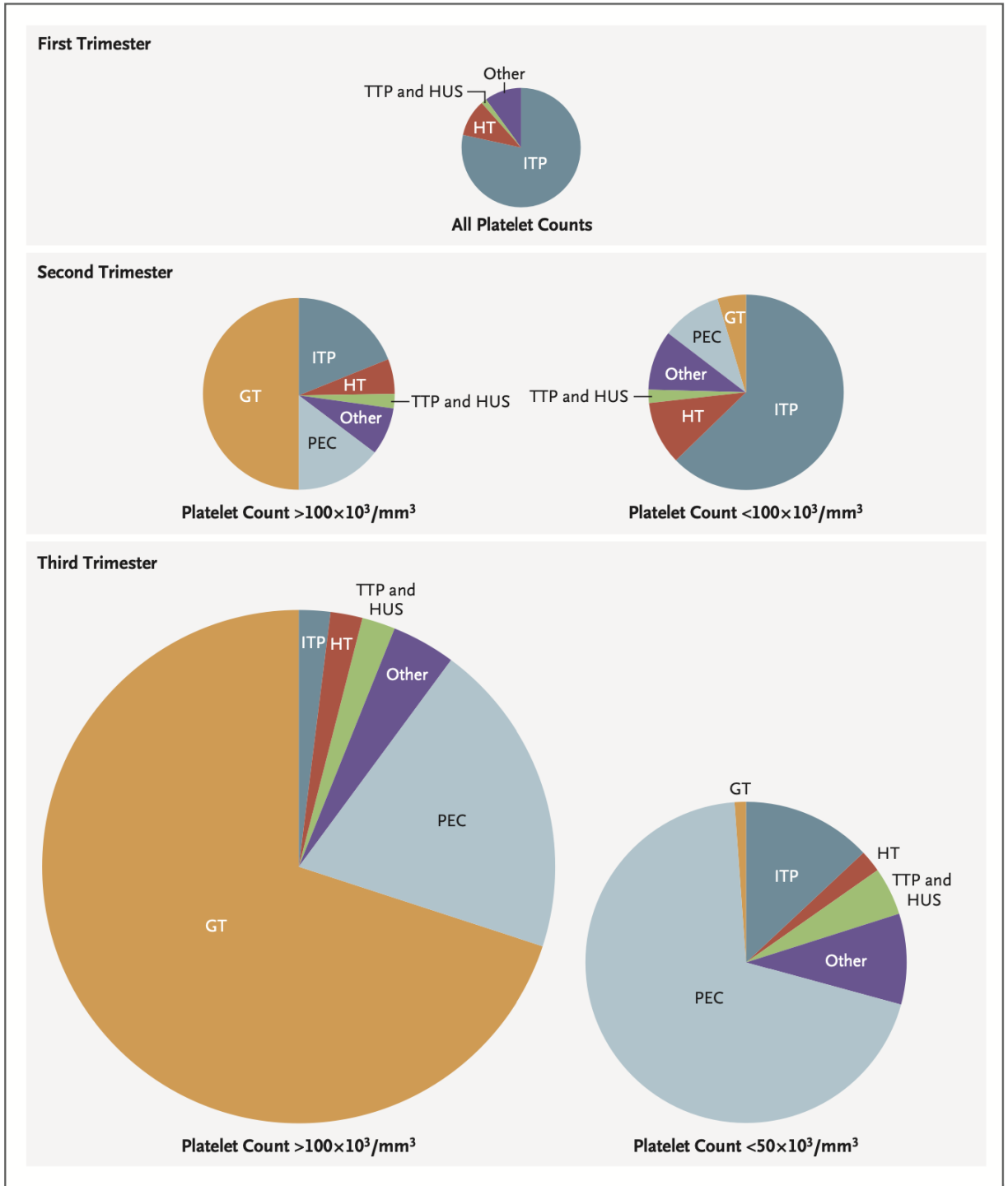


Figure 1. Estimated Prevalence of Causes of ITP in Pregnant Women According to the Trimester of Detection and Platelet Count

Immune Thrombocytopenia and Pregnancy: An Exposed/Nonexposed Cohort Study

Journal: *Blood*. **Year:** 2023 **Authors:** Stéphanie Guillet et al.

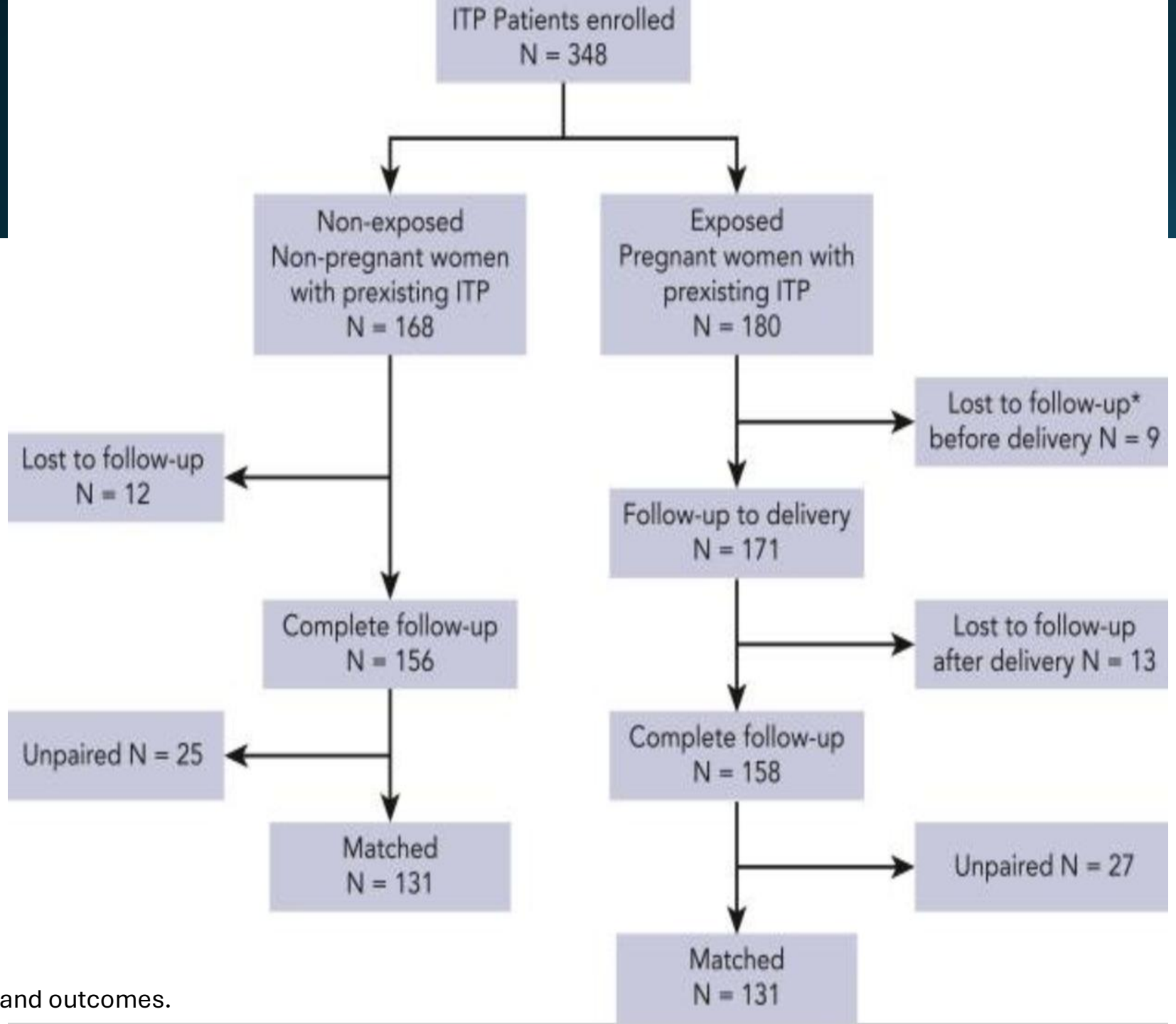
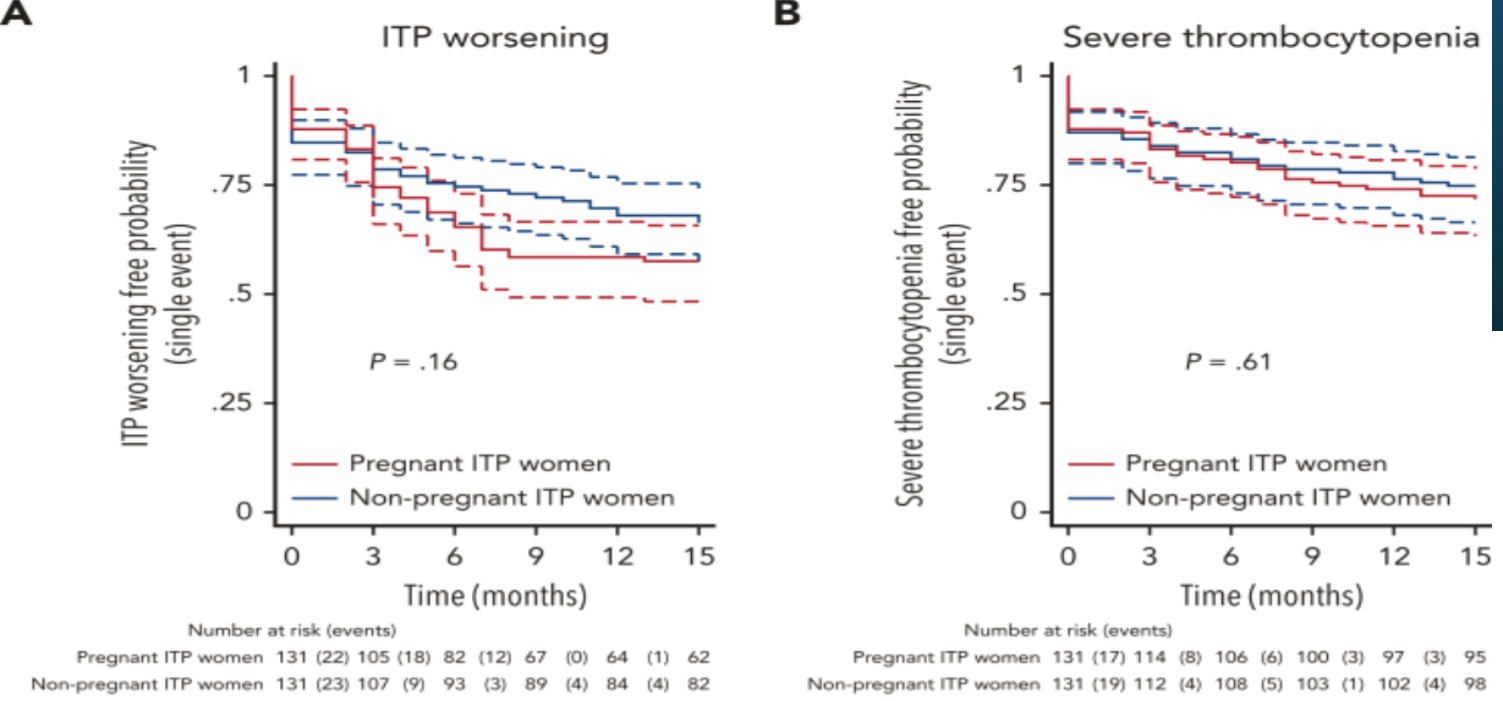
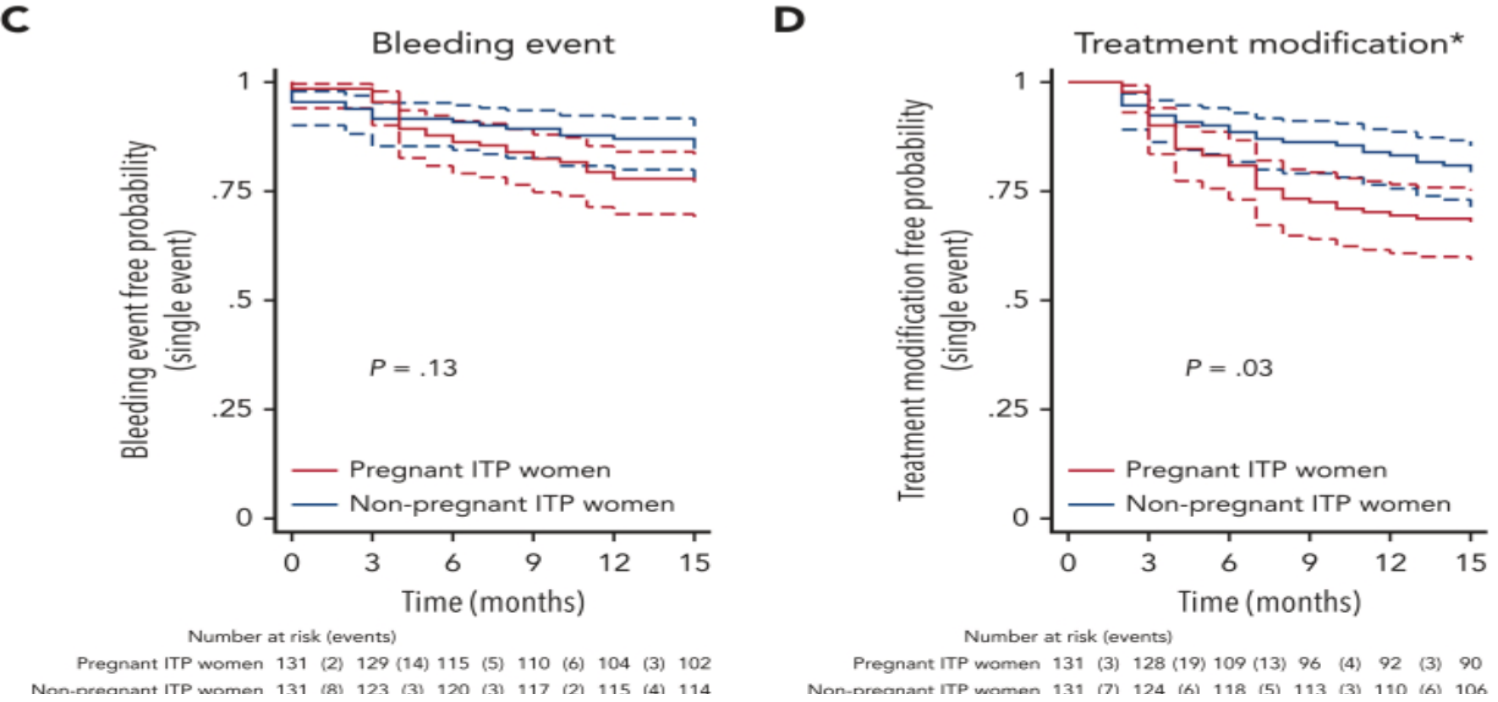


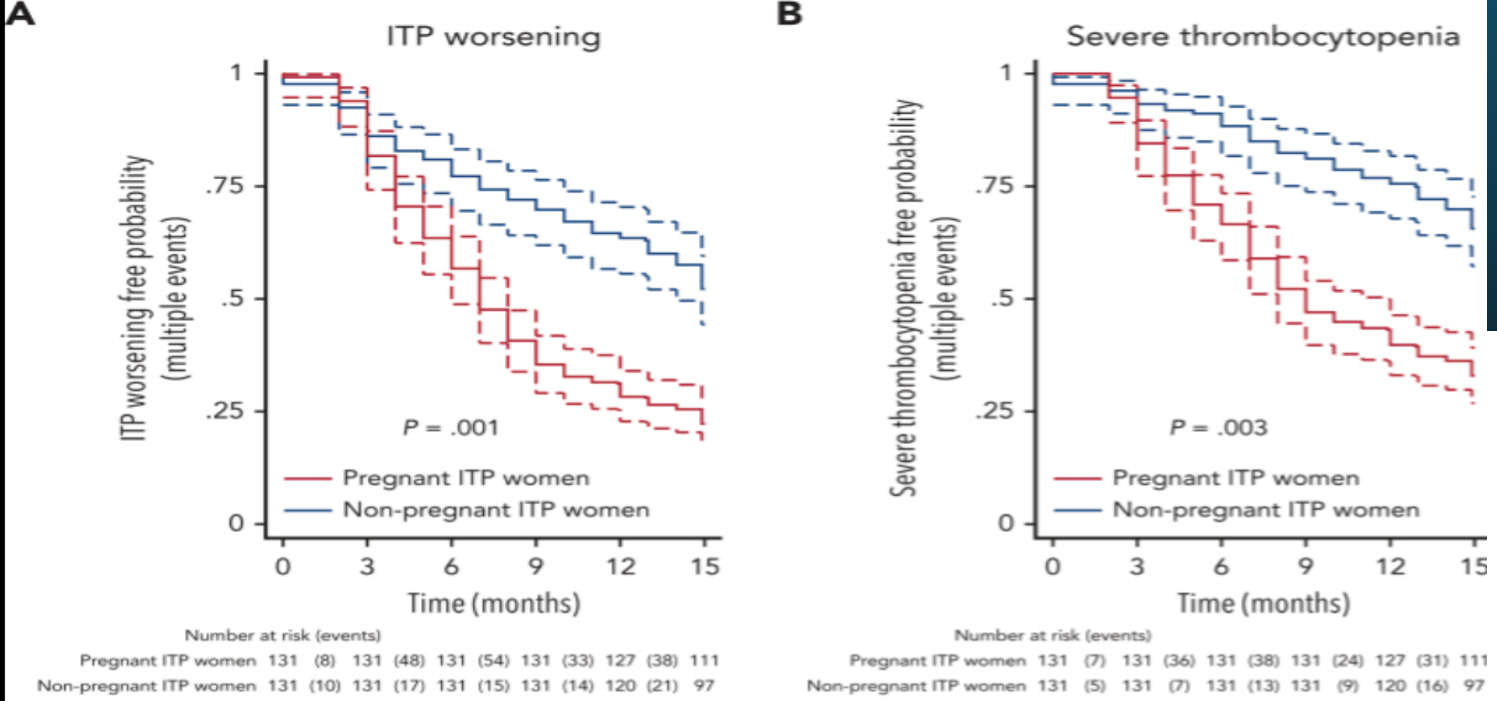
Figure 1. Enrollment and outcomes.

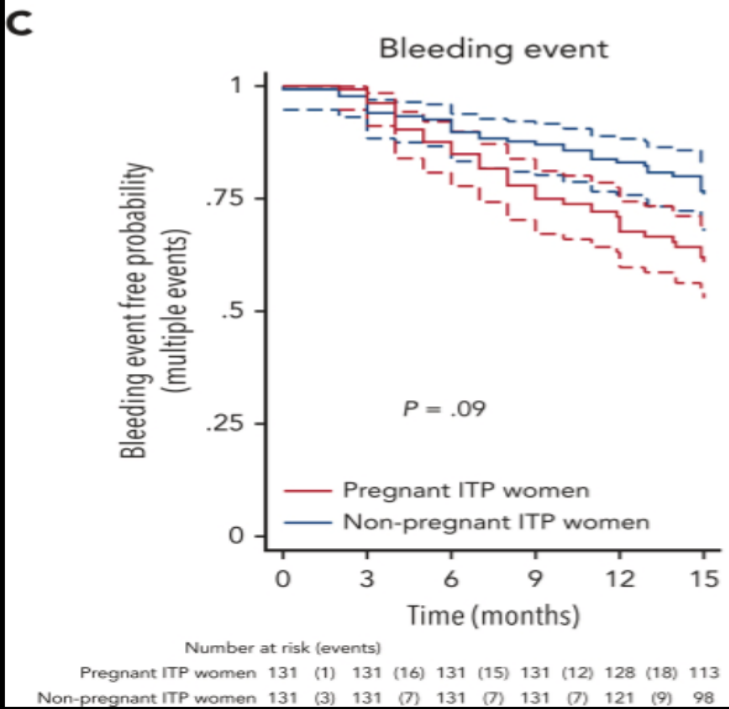


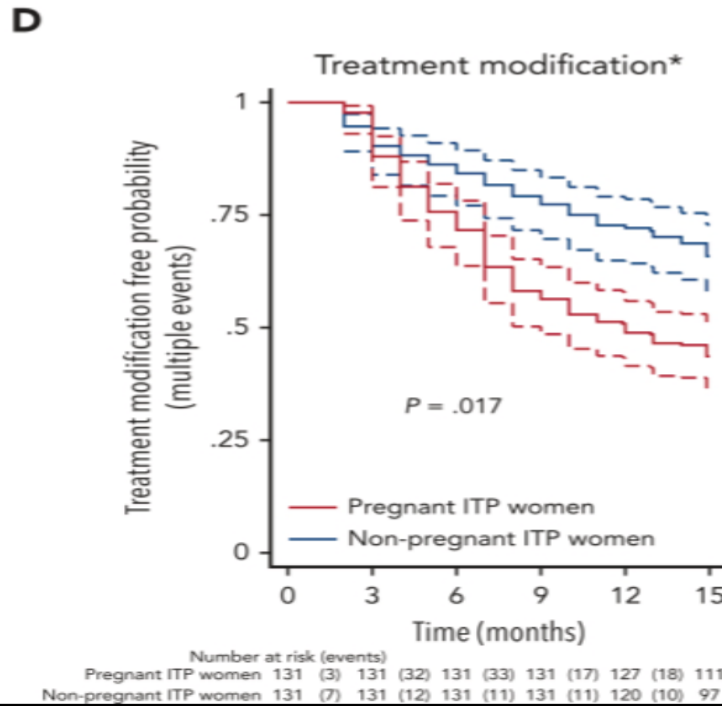


- No difference in incidence of severe thrombocytopenia (platelet count <30,000) or incidence of bleeding events
- ITP treatment modification was more frequent for pregnant than for nonpregnant women with ITP

Figure 2. Incidence of first ITP worsening during pregnancy among matched pregnant and nonpregnant women with ITP.







- ITP worsening based on recurrence of events more frequent in pregnant than in nonpregnant women with ITP, with more treatment modification and more severe thrombocytopenia.

- No difference in bleeding events

Figure 3. Incidence of recurrent ITP worsening during pregnancy among matched pregnant and nonpregnant women with ITP.

- What Platelet Count is Needed for Delivery ?

Sufficient platelet count for regional anesthesia

- An interdisciplinary taskforce was convened.
- Through a systematic review and modified Delphi process, the taskforce concluded that the risk of spinal epidural hematoma associated with a platelet count >/=70 x 10^9/L is likely to be very very low in obstetric patients with thrombocytopenia secondary to immune thrombocytopenia (ITP) (in the absence of other risk factors)
- 50,000 is the consensus threshold for delivery itself

Bauer ME, Arendt K, Beilin Y, Gernsheimer T, Perez Botero J, James AH, et al. Consensus Statement on Neuraxial Procedures in Obstetric Patients With Thrombocytopenia. *Anesth Analg.* 2021;132:1531-1544.

- Beyond Prednisone and IVIG, what treatments can we use ?

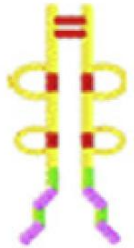
Michel et al Blood 2020: TPO in Pregnancy Collection of Anecdotal Cases

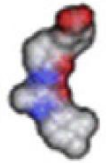
- 15 women with ITP in pregnancy
- 8 received eltrombopag and 7 received romiplostim
- Efficacy in all patients but anecdotal compendium
- 1 case of neonatal thrombocytosis
- No thromboembolic events

Treatment Of Immune Thrombocytopenia (ITP) During Pregnancy With Thrombopoietin Receptor Agonists (TPO-RA)

Population → **Outcomes** → **Conclusions**

45 pregnancies of women with ITP treated with:
Romiplostim n=22
Eltrombopag n=21
Both in the same pregnancy n=2
Median of three treatment lines failure prior to TPO-RA





- Platelet response rate- 86.7% (same for both)
- Favorable maternal safety profile: no thromboembolism
- Neonatal thrombocytopenia- one third of cases
- Neonatal thrombocytosis- 3 cases

TPO-RA use during pregnancy is associated with high response rates and appears safe for mother and fetus;
Breastfeeding ???

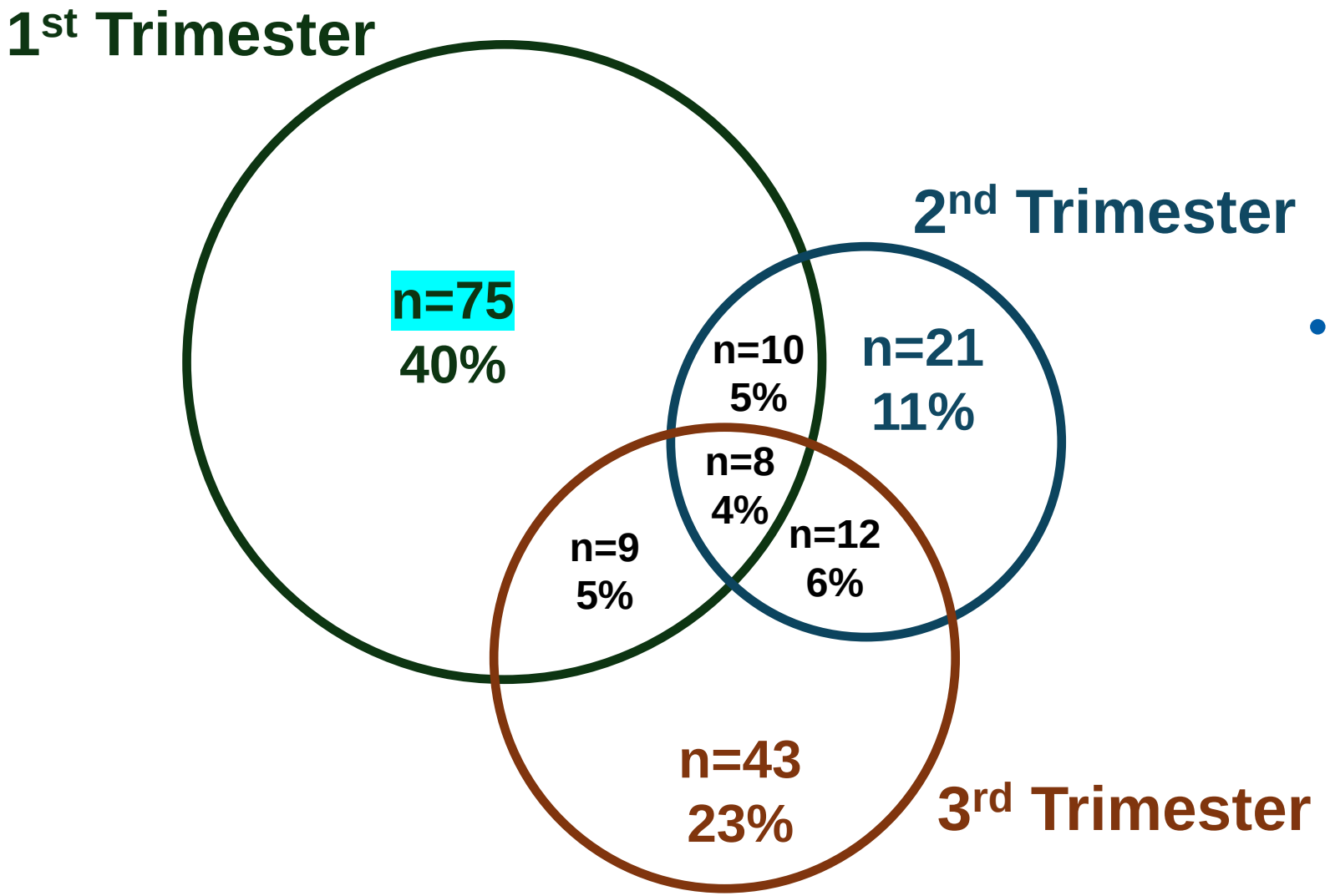
Surveillance Program of Romiplostim Use Connected to Pregnancy

James B. Bussel, MD,[1*] Nichola Cooper, MD,[2] Tatiana Lawrence, MD,[3] Marc Michel, MD,[4] Emilie Vander Haar, MD,[1] Kejia Wang,[3] Hossam Saad, MD[3]

[1]Weill Cornell Medicine, New York, NY, USA; [2]Hammersmith Hospital, London, UK;
[3]Amgen Inc., Thousand Oaks, CA, USA; [4]Henri Mondor University Hospital, Université Paris-Est Créteil, France

American Journal of Hematology, November 2022

Maternal Exposure to Romiplostim (N = 186)



- Prepartum exposure:
  - n=71 (38%)
  - longest duration of exposure ~5 years

Based on 186 known maternal exposures.

Congenital Anomalies

	Details
Inguinal hernia	• Age of mother: 31 • Exposure: 1st trimester for 21 days • Pregnancy outcome: hypertension; cesarean at 32 weeks • Birth outcome: 2400 g; hospitalized for thrombocytopenia;
Congenital cytomegalovirus infection	• Age of mother: 31 • Exposure: 2nd and 3rd trimesters • Pregnancy outcome: normal; labor induced at 37 weeks • Birth outcome: 1821 g; thrombocytopenia that resolved
Trisomy 8	• Age of mother: 33 • Exposure: 3rd trimester for 7 days • Pregnancy outcome: unknown • Birth outcome: infant died at 7 days of age

Literature

- Inguinal hernia: ~0.4% births
- Congenital cytomegalovirus infection: ~1 in 200 births
- Trisomy 8: 1 in 25,000–50,000 births

- There was 1 report of single umbilical artery with no data on pregnancy or birth outcomes

Infant Complications (Term and Preterm)

	N = 92[a]
Any complication	16 (13%)
Thrombocytopenia[b]	12 (13%)
Respiratory distress	2 (2%)
Congenital anomaly[c]	3 (3%)
Very low weight	1 (1%)
Umbilical cord around neck	1 (1%)
B cell suppression[d]	1 (1%)
Cystic fibrosis	1 (1%)
Other[e]	1 (1%)

Thrombocytopenia

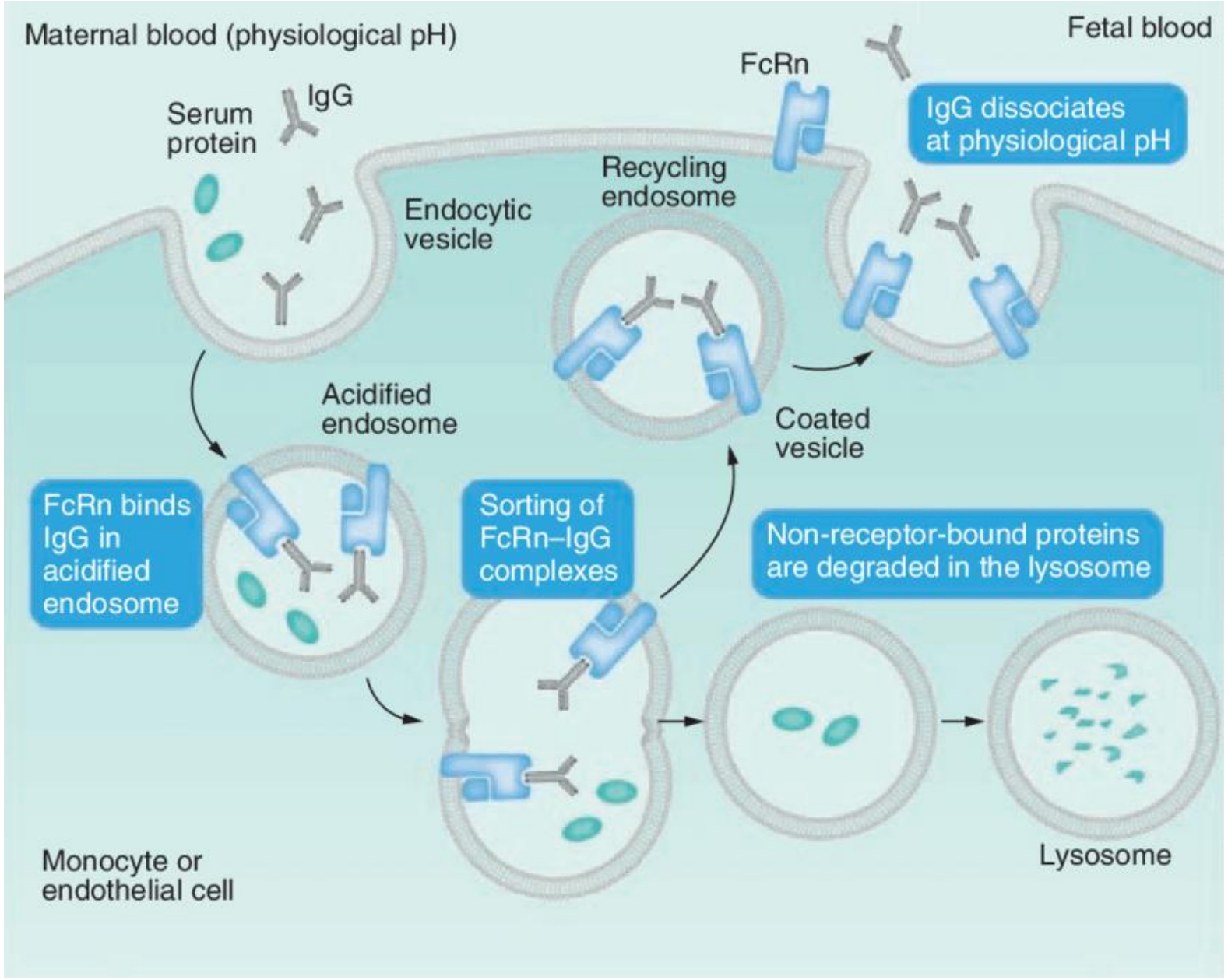
- 9 infants received immunoglobulins; 3 received platelet transfusions
- All infants were discharged home

Infants may have had more than one complication.
[a]Includes one case of twins. [b]8 abnormal pregnancy outcomes; 4 normal pregnancy outcomes. [c]1 inguinal hernia (abnormal pregnancy outcome); 1 cytomegalovirus infection (normal pregnancy outcome); 1 trisomy 8 (unknown pregnancy outcome; infant died at 7 days of age). [d]Secondary to rituximab; infant normal at 7 months of age. [e]Autism at 2 years of age.

Conclusions

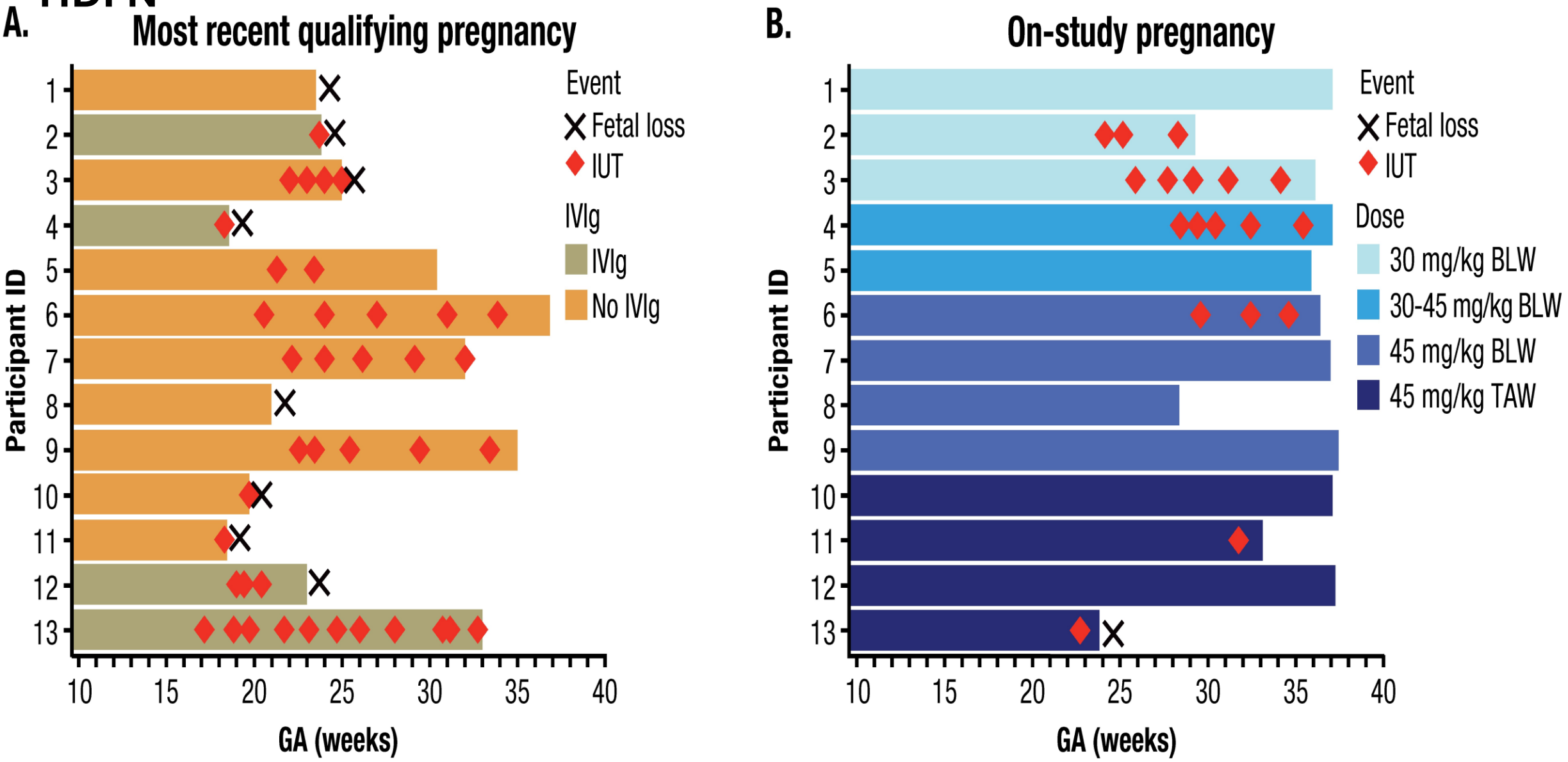
- A review of pregnancy cases in the PSP did not reveal any patterns suggestive of a specific safety concern for mothers, fetuses, and infants
- Approximately 65% of SAEs during pregnancy were due to underlying ITP
- A majority of abnormal births were from abnormal pregnancies; infant transient thrombocytopenia resolved at time of discharge
- Several published studies showed that the use of TpoRAs appears to be safe during pregnancy for the mother and fetus
- Romiplostim should be used during pregnancy if the potential benefit to the mother justifies the potential risk to the fetus

Blood 2023 Bussel et al



Malek, Antoine. Role of IgG antibodies in association with placental function and immunologic diseases in human pregnancy. Expert Rev. Clin. Immunol. 9(3) 235-249 (2013).

Phase 1 Study of Nipocalimab in Pregnancies with Early Onset Severe HDFN



Management of Primary Immune Thrombocytopenia in Pregnancy- Bussel et. al., 2023

First-line therapy

- No treatment of ITP in pregnancy has been approved by regulatory agencies
  - Prednisone at lowest effective dose
  - IVIG may be added, if inadequate hemostatic response to glucocorticoids or to prepare for delivery.

Second-line therapy

- No consensus on second-line treatment options,
- Rituximab in pregnancy has drawbacks:
  - slow response, compromises response to vaccinations, may increase the risk of neonatal hypogammaglobulinemia if administered in the third trimester.
- Splenectomy (rarely used) can be performed only early in the 2nd trimester
- Azathioprin has very slow response (used in renal transplantation in pregnancy)
- Cyclosporin has very limited ITP experience (used in IBD in pregnancy)

Newer second-line agents

- **TPO-receptor agonists ideally** for use in the 3rd trimester to prepare for delivery
- FcRn inhibitors-----no ITP in pregnancy data at this time (considerable ITP data with 3 agents)

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