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PLATELETS AND THROMBOPOIESIS

Comment on Guillet et al, page 11

What to expect when an ITP patient is expecting

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In this issue of *Blood*, Guillet et al[1] prospectively studied the hematologic outcomes in pregnant patients with preexisting immune thrombocytopenia (ITP) and their nonpregnant matched controls.

"How will pregnancy affect my ITP?" As a practicing hematologist at the intersection of blood disorders and pregnancy, it is a common question asked by patients and driven by a combination of excitement and fear. People with chronic, stable ITP tend to gradually gain a sense of comfort when their condition has not required treatment for years; however, it is difficult for them to forget the worry and anxiety they felt with the initial diagnosis and during disease relapses leading to bleeding. These patients are concerned not only about the effect ITP has on their pregnancy outcomes, but about long-term implications that pregnancy can have in the prognosis of their ITP. As their treating hematologist, I share these concerns. The constant search for answers is typically met with even more questions. The art of my practice is carefully blending the best (available) evidence with patient expectations and preferences to allow for informed and shared decision-making. These are the times that I most regret taking the large randomized controlled trial data I learned for other conditions during medical training for granted!

Much of what is known about the outcomes of pregnant patients with ITP comes from retrospective studies which include individuals with a broad range of clinical characteristics. The reported risk of worsening ITP during pregnancy is approximately 30% and the risk of neonatal thrombocytopenia is of similar magnitude.[2-5] The heterogeneity in ITP duration, prior treatment, and platelet count at the time of pregnancy all pose challenges to the external validity of the studies. Additionally, although they provide a general framework to approach these patients clinically, prior studies do not address the question of whether a pregnancy (in a patient with known ITP) modifies the natural course of disease and changes their clinical outcomes.

In this study, the exposed cohort was matched by multiple characteristics including duration of ITP, status of their ITP at the time of pregnancy or study enrollment, and prior treatment (including rates of splenectomy in both groups). The non-exposed prospectively describes the natural history of ITP for nonpregnant females of reproductive age and provides us with the first reference cohort reported in the literature.

The authors focus on the primary end point of a worsening ITP event, defined as the combination of new bleeding, presence of severe thrombocytopenia, or initiation/modification of treatment (other than for delivery planning) during the study period. These outcomes are highly clinically relevant as they determine the time points at which patients require intervention to reduce risk of death or permanent disability. They show that pregnant patients, overall, do not differ from their nonpregnant counterparts in terms of worsening ITP around the time of gestation (including postpartum follow-up), supporting the notion that the biology of a patient's ITP is not significantly modified by pregnancy. Although the presence of recurrent severe thrombocytopenia and increased frequency of treatments was higher in the exposed cohort, this difference could be related to the closer monitoring of patients during pregnancy along with variability in the clinician's threshold to treat. However, bleeding events were not different.

The rates of pregnancy loss and preterm delivery in this study were not different from those of the general population. They also corroborate data from retrospective studies which indicate that 30% of patients required initiation or intensification of ITP treatment during pregnancy. Guillet et al found that 39% of the population studied received treatment before delivery. Treatment with corticosteroids and immunoglobulin in anticipation of delivery was successful in raising platelet counts which allowed for patients to have the option to receive neuraxial anesthesia. Beyond achieving adequate pain management, the ability to be awake for delivery is meaningful for patients and their families. This opportunity can be extended to most patients with appropriately timed treatment to optimize platelet counts before delivery.

Neonatal thrombocytopenia was present (as expected) in 27.2% of cases; it was associated with platelet counts less than $<50 \times 10^9$/L in the 3 months preceding birth and neonatal thrombocytopenia with a prior pregnancy. This study differed from prior reports that suggested prior splenectomy, but not

severe thrombocytopenia, is associated with neonatal thrombocytopenia. The discrepancies serve as a reminder of the large knowledge gap that remains in this often forgotten field.

In summary, yes, there are multiple shortcomings in this exposed/non-exposed cohort study. The population size is unsurprisingly small and there are other confounding factors such that may introduce bias. However, I choose to see the glass half full instead of half empty. Guillet et al help us take a small but firm step in our ability to better care for patients with less common disorders. Their investigation is especially meaningful as it includes a population that has been historically excluded from clinical research and deserves equitable access to safe and effective medical care.

Conflict-of-interest disclosure: Juliana Perez Botero declares no competing financial interests. ■

REFERENCES

1. Guillet S, Loustau V, Boutin E, et al. Immune thrombocytopenia and pregnancy: an exposed/nonexposed cohort study. *Blood*. 2023;141(1):11-21.
2. Loustau V, Debouverie O, Canoui-Poitrine F, et al. Effect of pregnancy on the course of immune thrombocytopenia: a retrospective study of 118 pregnancies in 82 women. *Br J Haematol*. 2014;166(6):929-935.
3. Fujita A, Sakai R, Matsuura S, et al. A retrospective analysis of obstetric patients with idiopathic thrombocytopenic purpura: a single center study. *Int J Hematol*. 2010;92(3):463-467.
4. Webert KE, Mittal R, Sigouin C, Heddle NM, Kelton JG. A retrospective 11-year analysis of obstetric patients with idiopathic thrombocytopenic purpura. *Blood*. 2003;102(13):4306-4311.
5. Won YW, Moon W, Yun YS, et al. Clinical aspects of pregnancy and delivery in patients with chronic idiopathic thrombocytopenic purpura (ITP). *Korean J Intern Med*. 2005;20(2):129-134.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Cheminant et al, page 60

To treat with curative intent or modify disease?

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In this issue of *Blood*, Cheminant et al report on the results of allogeneic hematopoietic stem cell transplantation (allo-HSCT) and conservative management for adults with inborn errors of immunity (IEI).[1]

Their study compared 79 adults (patients [cases]: age 15 years or older at transplantation) who received HSCT with 202 adults (controls) who were managed with other treatments for various combined immune disorders and who were selected from an IEI registry. Cases and controls were matched on birth decade; at last review, age older than that at transplantation; diagnosis of chronic granulomatous disease or combined immunodeficiency; and autoimmune or lymphoproliferative complications. They concluded that HSCT offers an advantage for disease-free survival despite the risk for death from the transplantation procedure.

The IEI include a heterogenous group of diseases caused by monogenic germ line mutations in more than 400 genes that regulate the immune system.[2] Patients' age at presentation varied. The more severe clinical phenotypes are present in childhood and are treated with HSCT or gene therapy. In contrast, IEIs that present later in life have a milder clinical phenotype and may not have a genetic diagnosis. Conservative management has been the accepted standard for treatment, especially for those without disease-related complications. The preference for disease-modifying treatments is influenced by a desire to avoid morbidity and mortality that is attributed directly to the transplantation procedure and that may outweigh the benefit of cure. Thus, when considering transplantation, it is prudent to consider an individual patient's risk from the transplantation per se and balance that with the risk of disease-related morbidities that can eventually lead to death. However, the clinical application of the above-mentioned approach presents unique challenges, the most important being patient selection and the timing of the intervention (transplantation). The availability of a donor who is suitably HLA-matched to a patient with minimal comorbidities at transplantation will ensure the best survival in children and adults.[3-5] In the context of inherited diseases when considering a relative as a potential donor, the workup must include screening for germ line mutations because only those without mutations are eligible to donate. Although HLA-matched unrelated donors are readily available for Whites, availability remains a challenge for non-Whites,[6] and published reports have shown HLA-mismatched donor transplantation increases the risk for graft failure and mortality.[3,4] With higher mortality risks for patients with 2 or more comorbidities[5] (a surrogate for disease severity), timing of referral to be considered for transplantation is critical to ensure a successful outcome.

Treatment choices are best studied prospectively to ensure comparable selection of patients and random assignment to treatments.[7] Such an approach is impractical in the context of studying rare diseases for the following reasons: lengthy accrual time, financial burden, patients' reluctance to be assigned very different treatments, and an inability to sustain the interest of patients and the scientific community for several years while awaiting the results of a lengthy trial. Thus, leveraging data that are available through a disease registry to identify suitable controls is an appealing strategy that was used by Cheminant et al. The authors duly acknowledge the observed differences between their cases and controls. Notably, those who underwent transplantation had a more severe clinical phenotype and more active complications at transplantation. The authors recognized the limitations of their approach and performed carefully controlled analyses, including validation of their observations through sensitivity analyses. Their findings will influence clinical decision-making for adults with IEIs.

Our challenge is to improve upon the rigor for conducting studies that use