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## Thrombocytopenia in Pregnancy

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### ABSTRACT

Thrombocytopenia, defined as a platelet count less than  $150 \times 10^9/L$ , is the second leading cause of hematologic disorders in pregnancy after anemia. Thrombocytopenia can result from a variety of physiologic or pathologic conditions, several of which may have a significant impact on both mother and fetus. This editorial briefly presents the specific causes of thrombocytopenia in pregnancy, their obstetrical implications and management.

**Key words:** Thrombocytopenia; Pregnancy

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### EDITORIAL

Thrombocytopenia, generally defined as a platelet count less than  $150 \times 10^9/L$  [1], is a common hematologic finding during pregnancy, occurring in 7 to 10 percent of all pregnant women<sup>[1]</sup>. Uncomplicated pregnancy is associated with 15 to 20 percent lower platelet count compared to non-pregnant state, decreasing as gestation progresses, most probably as a result from a combination of dilutional effects and pooling of platelets in the splenic and placental circulation<sup>[1,2]</sup>. In the majority of pregnant women, thrombocytopenia is mild and associated with fewer bleeding complications than non-pregnant women due to the procoagulant state induced by increased levels of fibrinogen, factor VII and von Willebrand factor, reduced protein S activity and suppressed fibrinolysis<sup>[3]</sup>.

Occasionally, thrombocytopenia during pregnancy and postpartum period may be a serious disorder with significant morbidity for the mother, the fetus and the neonate. Evaluation and management may be challenging because there are many potential pregnancy-specific and pregnancy-unrelated causes, although some of them may occur with increased frequency during gestation. For many etiologies there are no specific diagnostic tests. The differential diagnosis is impacted by the time on onset, the severity of thrombocytopenia, and the clinical finding<sup>[3,4]</sup>.

Pregnancy-associated conditions include: gestational thrombocytopenia (GT), preeclampsia with severe features, HELLP syndrome (hemolysis, elevated liver enzymes and low platelets), and acute fatty liver of pregnancy (AFLP), hereditary thrombotic thrombocytopenic purpura (TTP) and hereditary complement-mediated thrombotic microangiopathy (C-TMA), and disseminated intravascular coagulation (DIC). GT (also named incidental thrombocytopenia of pregnancy) is by far the most common cause, accounting for 75% of cases. It is a benign condition characterized by mild thrombocytopenia (platelet count  $\geq 100 \times 10^9/L$  occurs in 99% percent of women with GT) and the absence of other hematologic or clinical abnormalities. It typically occurs after the second trimester of pregnancy and resolves spontaneously shortly after delivery. GT is a diagnosis of exclusion and requires neither treatment nor special precautions for delivery as there is no risk to the neonate. Other listed conditions are all rare, associated with severe thrombocytopenia and acute systemic illness, and potentially life-threatening<sup>[3]</sup>.

The causes of non-pregnancy related thrombocytopenia that may present during pregnancy or as pre-existing conditions complicating pregnancy include: immune thrombocytopenia (ITP), Evans syndrome (ITP and autoimmune hemolytic anemia), hereditary

thrombocytopenia (type 2B von Willebrand disease, May Hegglin anomaly), infection (hepatitis C virus, hepatitis B virus, human immunodeficiency virus HIV, cytomegalovirus, Epstein-Barr virus), splenic sequestration (liver diseases, portal vein thrombosis, storage disease), systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), medications, nutritional deficiencies (vitamin B12, copper, folate), acquired TTP and Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS)<sup>[4,5]</sup>. The most frequent of these conditions is primary ITP, occurring in approximately 1 to 3 in 10.000 pregnancies (10-fold greater than in the general population). ITP is an autoimmune disorder caused by antiplatelet autoantibodies that accelerate destruction of circulating platelets (predominantly in the spleen) and interfere with platelet production. It may occur at any stage of the pregnancy, or the diagnosis is already established before pregnancy. The severity of thrombocytopenia is variable and may change during the pregnancy. The risk of bleeding is greater with platelet counts less than  $20 \times 10^9/L$  to  $30 \times 10^9/L$ . Antibodies can cross the placenta and cause fetal/neonatal thrombocytopenia. The correlation between maternal and neonatal platelet count is poor. Differentiating mild ITP from GP may be impossible (and unnecessary) in the absence of a previous history of ITP, as both entities are diagnoses of exclusion and neither requires treatment<sup>[3,6]</sup>.

**Diagnostic approach.** The evaluation of a pregnant woman with newly diagnosed thrombocytopenia includes careful history (course of the pregnancy, pre-pregnancy platelet count, use of drugs, infections, personal or family history of bleeding or autoimmune disorders), clinical presentation, and laboratory testing. The extent of testing for each pregnant woman should be individualized. The key initial assessment is a complete blood count with a peripheral blood smear. Basic tests include blood urea nitrogen, creatinine, spot urine protein to creatinine ratio, liver function tests (bilirubin, albumin, total protein, transferases, and alkaline phosphatase), and screening for coagulation abnormalities (prothrombin time, antithrombin, activated partial thromboplastin time, fibrinogen, D-dimers). Input from the treating obstetrician and hematologist is important to identify the need for additional testing. Antiphospholipid antibodies and lupus anticoagulant, antinuclear antibodies, viral screening (HIV, hepatitis B I C virus), *Helicobacter pylori* testing, thyroid function tests, quantitative immunoglobulin level measurement, direct antiglobulin test, VWD type IIB testing may be helpful. Testing for antiplatelet antibodies is neither sensitive nor specific in the diagnosis of ITP. Bone marrow examination is rarely indicated in pregnancy<sup>[3,5]</sup>.

**Principles of management.** The aim of the treatment is to maintain an adequate platelet count while minimizing the risk of maternal bleeding during pregnancy, delivery and postpartum period. Besides, the risk of neonatal thrombocytopenia and hemorrhage must be considered and appropriate precautions taken before birth. It is thus very important to understand various pathophysiological mechanisms leading to thrombocytopenia in pregnancy.

The risk of severe bleeding increases considerably with platelet count below  $50 \times 10^9/L$ . In the cases with active bleeding, platelet transfusions should be given immediately. In contrast, platelet transfusions are not indicated for women without bleeding, unless

delivery and/or invasive procedure is imminent. The platelet count threshold for vaginal delivery, cesarean delivery and neuraxial anesthesia is  $30 \times 10^9/L$ ,  $50 \times 10^9/L$  and  $80 \times 10^9/L$ , respectively. Forceps, vacuum-assisted delivery and fetal scalp sampling/electrodes should be avoided. In symptomatic patients with ITP, first-line therapies include intravenous gammaglobulin (IVIg) and oral corticosteroids. Platelet transfusion alone is not indicated because maternal antiplatelet antibodies result in rapid destruction of transfused platelets. Thrombocytopenia secondary to SLE or APS is generally less severe than that seen with ITP, and treatment strategy is similar to that in ITP. Thrombotic microangiopathies pose considerable therapeutic challenges. The mainstay of the treatment is delivery of the fetus. Prompt delivery is indicated for pregnancies  $\geq 34$  weeks of gestation, evidence of fetal distress, or severe maternal disease. TTP requires immediate treatment with plasma exchange, and anti-complement therapy is urgent treatment indicated in C-TMA. As most treatment recommendations for severe thrombocytopenia in pregnancy have been based on observational reports, the optimal care of the mother and safe delivery of the newborn needs to be established<sup>[3,4]</sup>.

Newborn testing is required in maternal ITP, neonatal thrombocytopenia in a previous pregnancy, and settings unrelated to maternal platelet count, as neonatal bleeding signs, congenital anomalies associated with thrombocytopenia and neonatal infections. When neonatal testing is performed, it should be done at delivery to determine the need for immediate therapy, typically by cord blood platelet count. Repeated testing and management depend on the degree of thrombocytopenia.

[ I ] An International Working Group established a platelet count less than  $100 \times 10^9/L$  as the threshold for diagnosis ((the Vicenza Consensus Conference; published in *Blood* in 2009, <https://doi.org/10.1182/blood-2008-07-162503>)

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