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Thrombocytopenia in pregnancy – pathogenesis and diagnostic approach

Małopłytkowość u kobiet ciężarnych – patogeneza i różnicowanie

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Summary

Thrombocytopenia (TP) affects 7-10% of pregnant women. It occurs 4 times more frequently in pregnancy than in the non-pregnant women population. Women with thrombocytopenia in pregnancy are a heterogeneous and poorly known group.

There are several possible causes of thrombocytopenia in pregnancy. The most common are: gestational thrombocytopenia (GE) (60-75%), preeclampsia (PE) and HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome associated TP (21%), and idiopathic immune thrombocytopenia (ITP) (3-10%). Although thrombocytopenia diagnosed in pregnancy in most cases has a mild course, it has also been reported to be associated with a higher rate of preterm birth and premature detachment of the placenta. Some cases of severe thrombocytopenia with systemic involvement are associated with high risk of serious perinatal complications and require early diagnosis, careful clinical monitoring and medical treatment.

The differential diagnosis and proper assessment of clinical risk of TP during pregnancy may be of great concern. The article discusses these issues, focusing on pathophysiology of TP in pregnancy.

Keywords: thrombocytopenia in pregnancy • immunological thrombocytopenia • gestational thrombocytopenia • preeclampsia • HELLP • TTP

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Homeostasis of the body changes during pregnancy. The changes involve both the concentration of plasma coagulation factors and the blood cellular components, including platelets. Thrombocytopenia is defined as a platelet count of less than 150 10 G/l. It is classified as mild (100-150 G/l), moderate (50-100 G/l) or severe (less than 50 G/l) TP. Usually, only a platelet count less than 100 G/l is considered to be clinically significant [4, 19, 31,32]. Thrombocytopenia occurs in 7-10% of the population of pregnant women but in hypertensives in up to 23%. They are diagnosed with TP four times more often than non-pregnant women [2, 4, 14, 29, 30]. Women diagnosed with thrombocytopenia during pregnancy are a heterogeneous group. Efficient differentiation of the causes and clinical risk assessment of thrombocytopenia diagnosed during pregnancy are sometimes difficult and may require cooperation between medical professionals of different specialties.

CAUSES AND CLASSIFICATION

There are several potential causes of thrombocytopenia in pregnancy. Some of them are characteristic only for pregnancy and pathophysiologically related to it: gestational thrombocytopenia (GE), thrombocytopenia which is a component of pre-eclampsia (PE, pre-eclampsia) and HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), acute fatty liver of pregnancy (AFLP). Other TPs are diagnosed independently in people of childbearing age, and some diagnoses are made in women during pregnancy: idiopathic immune thrombocytopenia (ITP), thrombocytopenia associated with congenital thrombocytopathy, as well as infectious, drug-induced, deficiency or associated with a proliferative bone marrow disease TP. Some TPs may occur more frequently in pregnancy because of the pregnancy conditions conducive to their development: disseminated intravascular coagulation (DIC), thrombotic thrombo-

cytopenic purpura (TTP), hemolytic uremic syndrome (HUS) [2, 29, 31]. The causes of thrombocytopenia in pregnancy are summarized in Table 1.

The most common causes of a decreased number of platelets in pregnancy are: GE (60-75%), PE and HELLP (21%) as well as ITP (3-10%) [6,19,30,32,43]. The proportion remains similar when we focus only on clinically relevant moderate to severe thrombocytopenia [32].

Most TPs diagnosed during pregnancy are characterized by a mild course and good outcome for mother and fetus. From the 10% of pregnant women affected by TP, in 8% the platelet count varies between 100 and 150 G/l [4, 30, 31, 32]. Moderate to severe thrombocytopenia is often secondary and may indicate a higher severity of the underlying disease, affecting perinatal complications. In newborns of mothers with moderate and severe thrombocytopenia a higher incidence of lower 5-minute Apgar score, intrauterine fetal growth restriction (IUGR) and stillbirths was observed. These cases did not involve GE or ITP, but they coexisted with DIC, PE, HELLP syndrome, familial TTP, antiphospholipid syndrome or myeloproliferative disease in pregnancy [32,40]. These disease states are associated with high risk and require early diagnosis, careful clinical monitoring and medical treatment.

Although women with more severe thrombocytopenia are able to carry the pregnancy to term, there is difficulty in ensuring adequate hemostasis during labor, which can be manifested by massive bleeding. At birth the placenta is separated in fast blood flow through maternal vessels, limited due to uterine contractions, and smooth, spontaneous coagulation in the maternal vessels. This process requires efficient mechanisms of hemostasis, in which platelets play an important role [2,32,41]. It has been observed that, compared with pre-

Table 1. Causes of thrombocytopenia in pregnancy

TPs pathophysiologically associated with pregnancy	TPs pathophysiologically not associated with pregnancy	
	More common in pregnancy and during labor	Occurring in pregnant as often as in non-pregnant patients
Gestational thrombocytopenia (GE)	TTP	ITP
Pre-eclamptic TP (PE)	DIC	spurious TP
HELLP TP	HUS	congenital TP
Acute Fatty Liver of Pregnancy TP (AFLP)		TP associated with bone marrow proliferative disease
		Infectious TP (EBV, HCV, CMV, HIV, H. Pylori).
		drug-induced TP
		deficiency TP/vit.B12

HELLP – Hemolysis Elevated Liver enzymes Low Platelets; AFLP – Acute Fatty Liver of Pregnancy; PE – PreEclampsia; DIC – Disseminated Intravascular Coagulation; CMV – Cytomegalovirus; EBV – EpsteinBarr Virus; HCV – Hepatitis C Virus; HIV – Human Immunodeficiency Virus; HUS – Hemolytic-Uraemic Syndrome; TTP – Thrombocytic Thrombocytopenic Purpura



gnant women with normal platelet counts, pregnant women with thrombocytopenia are older and thrombocytopenia is associated with a higher rate of preterm birth and premature detachment of the placenta [32].

GESTATIONAL AND IMMUNE THROMBOCYTOPENIA – GE AND ITP

Platelet count during pregnancy is reduced by approximately 10% compared to pre-pregnancy values. It is the most prominent in the third trimester of pregnancy [4]. The platelet count can also be slightly lower in multiple pregnancies [6,18]. For most women, these values still fall within the reference range, and in some mild thrombocytopenia occurs [39].

GE

GE – the leading cause of thrombocytopenia in pregnant women – statistically is not associated with a significant burden for the mother and fetus [32,39]. It is a diagnosis of exclusion. It is believed that it causes only mild thrombocytopenia, which manifests itself in the second half of pregnancy. Observations of pregnant women with moderate and severe thrombocytopenia indicate that in these groups, GE is also the most recognized cause of a decreased platelet count [32]. There have been isolated reports of severe GE and complications in the form of massive perinatal hemorrhage, or atypical symptoms of gestational thrombocytopenia in the form of subretinal hemorrhage [23,25,41]. Therefore the patient diagnosed with GE should be carefully monitored and regularly inspected.

The etiology of GE is not clear. This is explained by the dilution of blood during pregnancy as well as by increased activation and peripheral platelet consumption, which are constantly in contact with the imperfect, easily damaged surface of the trophoblast [13,29]. The formation of GE may be affected by increased immunological mechanisms in pregnancy. Evidence suggestive of immune-dependent platelet destruction in GE may be its transient and reversible nature as well as the presence of antibodies bound to the platelets in titers similar to those in women with idiopathic immune thrombocytopenia (ITP) [22].

In the differential diagnosis of GE, ITP primarily should be taken into account. Differentiating between the two is difficult. Some believe that more severe platelet disorders are the result of the immune process in ITP [18,22,26,29]. A platelet count value below which gestational thrombocytopenia must be ruled out when looking for its cause has not been specified. ASH (American Society of Hematology) guidelines and the BCSH (British Committee for Standards in Haematology) proposed the following values, respectively: 70 G/L and 80 G/L. Below these values GE diagnosis is less likely [5,11,37]. Maternal platelet count in GE usually returns to normal values within 1-6 weeks after birth [29]. Persistent thrombocytopenia after this time also leads to

a search for other reasons; the time of onset and the platelet count before and after pregnancy help to distinguish GE from mild ITP [31]. To the differentiation between GE and ITP, the determination of the number of reticulated platelets in the second trimester may be helpful; its percentage grows at a higher peripheral immune platelet consumption [38]. As there are many similarities, we may suspect that GE may be a mild, less expressed form of ITP. Table 2 lists the characteristics of GE.

Table 2. Characteristics of gestational thrombocytopenia (GE) [18,19,20,21,22]

Characteristics of GE
No specific diagnostic test - the diagnosis is made by excluding other causes;
Usually mild thrombocytopenia, platelet counts above 70 G/L;
Usually no bleeding in the mother;
No thrombocytopenia in history taken before pregnancy;
Usually occurs in the middle of the second trimester or in the third trimester of pregnancy;
Is not associated with a reduced platelets count in the newborn;
Relieves spontaneously after birth (in 1-2 months);
May recur in subsequent pregnancies.

ITP in pregnancy

ITP is a moderate thrombocytopenia. In observational studies the median platelet count in pregnant women with ITP was 77 G/L. ITP is not generally considered to be an important cause of perinatal bleeding, but in some patients it is severe and poses a serious risk of bleeding complications [26,29,35,43]. The incidence of ITP is estimated at 1-10/10 000 pregnancies [20]. Although it occurs more rarely than gestational thrombocytopenia, it is the most common cause of thrombocytopenia observed in the first and the beginning of the second trimester of pregnancy [37].

In the majority of patients, asymptomatic thrombocytopenia is detected in tests. In more severe cases the diagnosis is preceded by the occurrence of petechiae, a tendency to cutaneous mucosal bleeding and easy bruising. The diagnosis of ITP, similarly to GE, is a diagnosis of exclusion. Moreover, the detection of antiplatelet antibodies is not a differentiator between GE and ITP, as in many women with GE high concentrations of serum IgG antiplatelet agents can be found [3,9,22]. One of the important elements that differentiate GE and ITP is a medical history taken before conception. The presence of thrombocytopenia before pregnancy or its severity (<50 G/L) makes the diagnosis of ITP more likely. In the absence of data on the platelet count before pregnancy, significant thrombocytopenia emerging early in the first trimester with a tendency to deepen during pregnancy suggests the diagnosis of ITP, and mild thrombocytopenia developing at the end of the second or in the third

trimester, not associated with proteinuria or hypertension, will lead to the diagnosis of GE [37].

ITP is caused by antiplatelet autoantibodies, but the exact manner of its formation has not been fully elucidated. In immune thrombocytopenia, auto-antibodies are directed against antigens of the platelet surface, such as fibrinogen receptor, glycoprotein Ib/IX and IIb/IIIa, Ia/IIa, V and IV. Presence of autoantibodies on the surface of platelets leads to their increased uptake within the reticuloendothelial system of the spleen. In the ITP classical model, the antibody-coated platelets are destroyed by macrophages as well as by complement-dependent and cytotoxic T-cell-mediated lysis. It is assumed that platelet turnover is increased in ITP and thrombocytopenia occurs when the process balance moves toward destruction, while the production of new platelets becomes less efficient [20,37]. Recent studies indicate that several mechanisms are involved in the pathogenesis of ITP: decreased platelet counts may be due to changes in the number of individual T cell subtypes, especially the loss of regulatory T cells, and a shift towards T-pro-inflammatory responses [27]. In experimental studies it has been observed that in addition to the direct mechanism of platelet destruction, some of the antiplatelet antibodies (GP Ib/IX Ab in patients with quinine-induced thrombocytopenia) act directly on megakaryocytes, inducing their apoptosis, hindering differentiation and maturation and impairing the production of new platelets [33]. The genetic polymorphism in promoter regions of genes encoding pro-inflammatory interleukins IL-1 and IL-2 and others may be involved in the pathogenesis of ITP. Patients with chronic ITP have a significantly higher incidence of polymorphic variant allele 2 in IL-1-RN and the variant allele G in IL-2-330 than in the healthy population. These variants were independently associated with chronic ITP in adults [34]. A reduced concentration of IL-27 in serum and decreased mRNA expression of IL-27 in patients with the active form of ITP have been observed, which may indicate the involvement of interleukin in the pathophysiological disease process [24]. It is suggested that, in this process, an important role is played by CD72 coreceptor present on B cells, whose deficit is associated with autoimmunity in animal models. The ligand for CD72 is a CD100 glycoprotein present on T cells, B cells and antigen-presenting cells. Patients with an active form of ITP had significantly lower mRNA expression of the CD72 coreceptor than the ITP patients in remission, and in healthy adults [44]. The importance of the mechanisms for the course of ITP in pregnancy and whether similar mechanisms occur in GE are not known yet. There are also data on the effects of hormones (testosterone, estrogens, dopamine and its synthetic derivatives) on ADP-mediated platelet activation, and on the expression of P2Y12 receptors on megakaryocytes (G protein-coupled receptor involved in ADP-dependent platelet aggregation) [1,21]. The answer to whether hormonal receptor modulation of platelet function in GE and ITP can be expected, and whether it can be affected pharmacologically, requires appropriate research.

THROMBOCYTOPENIA ACCOMPANYING LIFE-THREATENING OBSTETRIC DISORDERS

Pre-eclampsia and HELLP syndrome related TP

Pre-eclampsia and eclampsia are a significant cause of maternal and neonatal morbidity and mortality [42]. This is the most common medical problem complicating pregnancy – it affects 3-14% of pregnancies and may be accompanied by thrombocytopenia [37].

PE is usually manifested in the third trimester of pregnancy, and affects pregnant women below 20 or above 30 years of age [37]. HELLP syndrome is considered to be a PE complication. It occurs in 0.5-0.9% of all pregnancies and in 10-20% of pregnancies with severe PE. The diagnosis is based on the triad of symptoms: microangiopathic hemolytic anemia (MAHA), abnormal liver enzyme function, and thrombocytopenia with the platelet (PLT) count below 100 G/L. High levels of low-density lipoprotein (LDH) and bilirubin are helpful in the diagnosis. HELLP syndrome is associated with significantly higher maternal and neonatal mortality than PE. It is associated with: increased rate of caesarean section, the risk of damage to the kidneys and liver in the mother, convulsions, detachment of the placenta, DIC, the need for transfusion of blood products, prolonged hospitalization and death [42].

The mechanism leading to the formation of thrombocytopenia in PE patients is not fully understood. The normal or increased number of megakaryocytes suggests compensation of increased peripheral PLT loss (consumptive thrombocytopenia). Similarly, the pathogenesis of PE and accompanying phenomena is not entirely clear, but we know that it is caused by factors associated with the placenta and vascular endothelial activation [13,16]. It is thought that the disorder occurs at the implantation of the placenta, when the trophoblast adheres to the endometrium, causing maternal uterine vascular remodeling [13,26]. The researchers observed, among other things, abnormal expression of intercellular adhesion particles, vascular endothelial growth factor (VEGF), its receptor in trophoblasts, and plasmatic soluble major histocompatibility complex (MHC) class I chain-related molecule [15,37,42]. In studies on PE and HELLP, increased concentrations of anti-angiogenic proteins such as soluble Fms-like tyrosine kinase 1 (sFlt1), soluble endoglin (sEng, soluble endoglin), which is a receptor for TGF-beta (tumor growth factor-beta) on endothelial cells, and a decrease in the concentrations of pro-angiogenic factors such as placental growth factor (PlGF), were observed in pregnant women during clinically active disease [42]. Some observations show the usefulness of sFlt1 and sEng in the differential diagnosis of preeclampsia (high sensitivity and specificity). Patients with non-HELLP thrombocytopenia had a profile of angiogenic factors similar to normotensive patients, while patients with HELLP had concentrations of sFlt1 and sEng significantly exceeding the 90th



percentile, and PlGF concentrations lowered. Markers of angiogenesis are helpful in differentiating thrombocytopenia conditions which may be accompanied by symptoms that are components of pre-eclampsia (e.g. ITP/GT with associated hypertension) from PE and HELLP syndrome [42]. This is important because these conditions require extremely different management: while the isolated TPs have a generally benign course and are treated conservatively, in HELLP it is crucial to quickly terminate pregnancy. However, the data on this subject are contradictory. In contrast, in spite of reports of experimental research on the role of sEng in the pathophysiology of HELLP (directly responsible for the development of HELLP syndrome in rats), in another study the usefulness of its determination in the differentiation between HELLP and PE in humans was limited [16].

It is known that the generalized intravascular inflammatory activity is enhanced in PE, which is clinically manifested by hypertension and proteinuria. HELLP as a serious complication of PE is characterized by platelet thrombi in the microcirculation. There is a theory that the essential role is played in these pathologies by a sudden vascular endothelial activation cascade that leads to the release of von Willebrand factor (VWF) multimers, which bind to platelets, causing aggregation. In HELLP patients, it is observed that the concentration of ADAMTS-13 (a plasma metalloproteinase decomposing active VWF multimers) is moderately lowered as in thrombotic thrombocytopenic purpura (TTP). It has been observed that the concentration of active VWF was increased in patients with HELLP, compared to both healthy women and those with PE, while the concentration of ADAMTS-13 was reduced to a similar extent in HELLP and PE [17]. This creates the potential to differentiate among patients with PE those developing HELLP and requiring special care. Significantly increased active VWF in plasma of women with HELLP strongly correlates with the ratio VWF propeptide/VWF – regarded as an indicator of acute endothelial cell activation. Therefore, there is a hypothesis that sudden acute activation of endothelial cells resulting in the release of a large number of active VWF multimers in a short time exceeds available blood metalloproteinase ADAMTS-13 [17]. This explains the formation of thrombotic microangiopathy in HELLP occurring according to a similar principle as in TTP. Consumptive thrombocytopenia, hemolytic anemia and liver function damage are caused by the formation of platelet thrombi in the microcirculation. The possibility of pharmacological blocking of the reaction between VWF and glycoprotein Ib/a might create the opportunity for effective therapeutic intervention.

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) IN PREGNANCY

Thrombotic thrombocytopenic purpura (TTP) is a rare (3.7-6 per million/year) and life-threatening disorder that should be taken into consideration in differentiation of thrombocytopenia diagnosed during pregnancy [7]. TTP occurs 10 times more often in women than in

men. It is believed that pregnancy may be a causative factor in as many as 5-25% of TTP cases, both congenital late-onset and acute idiopathic TTP [12].

Full-blown TTP is characterized by thrombotic microangiopathy associated with hemolytic anemia, coagulopathy, consumptive thrombocytopenia, hypertension, gastrointestinal symptoms (nausea, vomiting, abdominal pain), impaired kidney function, neurological symptoms (seizures, confusion) and fever [7]. In untreated TTP, thrombosis occurs in the placenta, leading to fetal growth restriction, intrauterine death and secondarily PE in the mother [10,36]. The above symptoms appearing during pregnancy in various configurations are not very specific and may also occur in PE, HELLP and HUS (hemolytic-uremic syndrome); therefore it should always be taken into account [7, 36]. Differentiation poses many difficulties and has a great importance for further treatment and prognosis. The conditions to be considered in the diagnosis of thrombocytopenia associated with hemolytic anemia during pregnancy are shown in Table 3. Before initiating treatment, determination of the concentration of ADAMTS-13 and anti-ADAMTS-13 antibodies may be helpful. In HELLP syndrome and eclampsia, concentration of ADAMTS-13 is indeed reduced, but no anti-ADAMTS-13 antibodies can be found [12,36]. In thrombotic microangiopathy associated with pregnancy, combined care of the obstetrician, anesthesiologist, hematologist, and neonatologist is required. The diagnosis of gestational TTP becomes even more difficult if symptoms appear after birth. There are reports of massive delayed postpartum hemorrhage caused by TTP associated with pregnancy [7]. According to the British

Table 3. Causes to be included in the differential diagnosis of thrombocytopenia associated with hemolytic anemia in pregnancy [39,40]

Differential diagnosis of thrombocytopenia associated with hemolytic anemia in pregnancy:
Autoimmune haemolysis of immune thrombocytopenia (Evans syndrome)
DIC
Thrombocytopenia associated with pregnancy: HELLP, AFLP, eclampsia, PE;
Effects of drugs
Malignant hypertension
Infections (CMV, HHV, adenoviruses) (meningococcus, pneumococcus) (fungi)
Autoimmune diseases (SLE), vasculitis
HUS (some authors regard TTP and HUS in pregnancy as the same disease)
Proliferative diseases
Antiphospholipid syndrome

HELLP- Hemolysis Elevated Liver enzymes Low Platelets; AFLP – Acute Fatty Liver of Pregnancy; DIC – Disseminated Intravascular Coagulation; PE – PreEclampsia; CMV – CytoMegalovirus; HHV - Human Herpes Virus; SLE – Systemic Lupus Erythematosus; HUS – Hemolytic-Uraemic Syndrome; TTP – Thrombotic Thrombocytopenic Purpura

guidelines, for each patient during pregnancy or after childbirth in whom microangiopathy cannot be fully explained by HELLP or PE (diagnosis is not certain), the diagnosis of TTP and urgent plasmapheresis should be considered. Termination of pregnancy is considered to be the procedure of choice, but in the case of TTP it does not always guarantee a cure [10, 28, 36]. As an additional test in certain high-risk cases, some researchers recommend performing thromboelastography besides platelet count and coagulation tests [8].

CONCLUSION

Although thrombocytopenia diagnosed in pregnancy in most cases has a mild course and good outcome, the

more rarely observed deep thrombocytopenia with systemic involvement determines the severity of the patient's general condition and may significantly affect perinatal complications. It usually involves a specific group of patients with the diagnosis of DIC, HELLP and TTP. The differential diagnosis and proper assessment of clinical risk of TP during pregnancy are difficult and require cooperation between medical professionals of different specialties, but they are of great concern for further treatment and prognosis. The better understanding of pathophysiology of these conditions brings hope for future therapeutic strategies.

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