

**NEW ASPECTS OF PATHOGENESIS, SCREENING AND PREVENTION OF
PREECLAMPSIA****Dr. Dilufar Khodjaeva***

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ABSTRACT

Complications of preeclampsia (PE) - the cause of 30% of maternal deaths and severe morbidity. To date, the pathogenesis of this terrible complication of gestation has not been fully studied, prevention issues are debated. The latest foreign studies from the PubMed, Medline and ISI Web of Knowledge databases on this issue summarize several aspects of PE pathogenesis: endoplasmic reticulum stress, apoptosis, endothelial cell activation, inflammatory response, microthrombosis and thrombotic microangiopathy (TMA), allogeneic incompatibility. Strategies for determining individual risk, screening and preventing PE are also considered.

KEYWORDS: Preeclampsia, hypertensive disorders, pathogenesis, complications of gestation, thrombotic microangiopathy, risk of preeclampsia, prevention of preeclampsia.

INTRODUCTION

Pathological conditions during pregnancy, characterized by increased blood pressure (BP), complicate approximately 10% of all births in the United States of America and are the main cause of maternal and perinatal morbidity and mortality. About 1/3 of all maternal deaths associated with pregnancy occurred due to complications caused by preeclampsia (PE) - 1.5 per 100 thousand live births. About 40% of these deaths are due to the development of cerebrovascular complications.^[1] Hypertensive disorders - one of the most common conditions during pregnancy; they are associated with increased risk of PE, placental abruption, fetal/newborn and/or mothers' death, early termination of pregnancy and low birth weight.^[2] Early PE increases the risk of fetal death [relative risk (RR) - 5.8; it is associated with significantly increased RR of perinatal mortality and high neonatal mortality (RR 16.4)]. The RR of perinatal and neonatal mortality for late PE is 2.0.^[3] During 3 months after birth, approximately 39% of patients with PE have arterial hypertension (AH), and about 20% have proteinuria; in addition, proteinuria persists for 1-15 years after delivery at 10-15%.^[4] In women with a history of PE, the incidence of chronic hypertension is 15.8 times higher, along with an increased risk of developing type 2 diabetes mellitus in the future.^[5] In addition, women who have developed severe PE, are at high risk for the development of renal failure. PE is also considered a major risk factor for cardiomyopathy after birth. Patients with PE in history are at high risk of death for more than 20 years after delivery.^[6] Presumably, this situation is due to systemic

oxidative damage suffered by the body. PE is defined as hypertension during pregnancy with significant proteinuria or dysfunction of target organs that occur after 20 weeks of gestation in women who have previously had normal blood pressure. PE complicates the course of about 2-7% of pregnancies^[7] and is an important factor influencing mortality and the development of severe complications in the perinatal period. PE often arises de novo, however, in the presence of AH, a preexisting pregnancy, there is a significant likelihood of developing a combined PE. Hypertension diagnosed during pregnancy can be one of four separate pathological processes: chronic hypertension, hypertension in pregnant women, PE, chronic hypertension in combination with PE,^[8] which requires a differentiated approach for the best effect of therapy and reducing the risk of adverse outcomes. Is pregnancy pre-existing hypertension or PE complicated? Knowing the answer to this question is important for determining the intensity of monitoring the health status of the mother and fetus and assessing the need for urgent treatment of increasing hypertension. Despite significant efforts to improve understanding of the pathogenesis and prevent the development of PE, significant progress in reducing maternal and perinatal morbidity has not yet been achieved. There is no complete clarity regarding the triggering mechanisms of PE, perhaps this factor is the infectious process. Since acute infections significantly increase the concentration of proinflammatory cytokines in the blood and trigger endothelial reactions, the systemic response to the infection may be of some importance for the pathogenesis of the development of

PE. There is evidence of an increased risk of PE in the presence of urinary tract infections, periodontal disease, chlamydial pneumonia or bacterial vaginosis at any time during pregnancy.^[9]

Most pregnant women are young healthy women, but in rare cases, pregnancy may be complicated by severe thrombocytopenic syndromes. In particular, pregnant women with thrombocytopenia may develop the following syndromes: HELLP syndrome (Hemolysis, Elevated Liver enzymes and Low Platelets), fatty hepatitis of pregnant women and some forms of thrombotic microangiopathy (TMA),^[10] which are classified as serious complications that largely predict for the life and health of women. TMA is a group of heterogeneous disorders characterized by disseminated thrombosis of arterioles and capillaries, which leads to thrombocytopenia and disorders in target organs.^[11] Today, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), microangiopathic hemolytic anemia (MAHA), MAHA provoked by pregnancy, and MAHA triggered by transplantation are distinguished from TMA. Acquired TTP forms are found in approximately 95% of all cases. Usually, the disease is associated with antibodies of the IgG class to ADAMTS13 and, as a rule, affects women, with a peak incidence of new cases in the third to fourth decade of life.^[12] Signs and symptoms of TMA develop in 1:25 000–1: 100 000 pregnant women. TMA may develop a second time, complicating systemic disorders that have previously occurred (against the background of severe PE) or against the background of severe comorbidities. These include malignant hypertension, HELLP syndrome, infectious and autoimmune diseases (eg, antiphospholipid syndrome), malignant neoplasms and sepsis with disseminated intravascular coagulation, as well as drug therapy.^[13]

HELLP syndrome is often found in comparison with other causes of TMA associated with pregnancy, sometimes they are practically indistinguishable from HELLP syndrome since their clinical signs partially overlap.

According to a French registry containing information for 42 cases of pregnancy-related TTP, 23 patients with autoantibodies to ADAMTS13 TTP were diagnosed as acquired, while 19 patients had no autoantibodies and a diagnosis of hereditary TTP was found.^[14]

Classic TTP, with an ADAMTS13 level of <5%, can develop at any gestational age. The main sign confirming the diagnosis of TMA is a pronounced decrease in the activity of ADAMTS13 (<10%) in the blood plasma.^[15]

The frequency of new cases of TTP in pregnancy is theoretically estimated at 1:25 000, which is much higher than the same indicator for the general population. Apparently, atypical clinical manifestations are characteristic of TTP developing in the second trimester

at the 20–22nd week of pregnancy. Apparently, pregnancy provokes TTP, and during subsequent pregnancies, a relapse may develop, while, according to some studies, the frequency of relapses can reach 20%.^[16] The cause of thrombocytopenia during pregnancy can also be fatty hepatitis in pregnant women, which often develops in late pregnancy or in the postpartum period and is associated with PE in 50% of cases. In patients with congenital TTP, the recurrence rate during pregnancy is very high, so preventive therapy is needed as soon as possible. Sometimes an urgent delivery is the only effective treatment for TMA in pregnancy.

Under the conditions of operative diagnosis and effective therapeutic intervention, maternal survival over the past 20 years has increased from 79% to almost 100%.^[9] However, the outcome for the mother during the first episode of TTP, which developed during pregnancy, is unfavorable in comparison with those who have developed the disease again. According to the French registry (42 cases of TTP associated with pregnancy), the maternal survival rate was 88%, 3 patients developed neurological disorders or progressive renal failure, and 2 patients were fatal. The outcome for the fetus was unfavorable (antenatal fetal death in 70%), which was probably due to the frequency of TTP debut earlier than the 28th gestation week.^[17] The UK registry data on pregnancy outcomes in 12 patients with acquired TTP showed that none of the women with TTP, who first developed during pregnancy, had a disease that was fatal, but in 4 cases the fetus occurred death of the fetus and in 1 case – abortion.^[9] Severe complications of pregnancy, including fetal loss syndrome, PE, HELLP syndrome and TMA, have significant social and economic consequences that have a negative impact not only on women and their immediate environment but also on the health system as a whole.^[18] In an effort to prevent recurrent complications of pregnancy, doctors often prescribe anticoagulants, such as heparin and aspirin, but the question of whether this kind of intervention is always helpful remains open.

Etiology and Pathogenesis

Physiological gestational changes in local microcirculation

Trophoblast cells are differentiated first and provide the possibility of embryo implantation. It is they who are ultimately responsible for transporting oxygen to the fetus, feeding the fetus and removing its waste products. At week 10, trophoblast invasion leads to apoptosis of the muscle layer of the spiral arteries, resulting in the formation of a vascular bed with reduced intravascular pressure. Despite the known exact mechanism of muscle layer remodeling, it is currently believed that trophoblast cells interact with a special type of lymphocytes called uterine (decidual) natural killers (uNK).

Pregnancy is also characterized by certain physical and physiological changes that contribute to the development

of the tendency to hypercoagulation. Stagnation of blood in the pelvic veins caused by a pregnant uterus leads to a decrease in blood flow velocity in the lower extremities. Meanwhile, in addition to a number of physical factors during pregnancy, physiological and hormonal changes in the placenta themselves are the key to the pathogenesis of its many undesirable outcomes. The placenta is a highly vascularized organ consisting of low-resistant vessels, therefore, it is very reasonable to conclude that thrombosis in the placental vascular network can lead to functional insufficiency of the placenta, reduced fetal growth rates, and other undesirable gestational complications. During pregnancy, an increase in VII, VIII and X blood coagulation factors, an increase in von Willebrand factor levels and fibrinogen concentrations, as well as a decrease in protein S activity and acquired resistance to activated protein C with a constant level of antithrombin III are observed.^[19] The placental circulation is shifted toward procoagulant status, which seems to counterbalance the risk of bleeding during implantation due to the fact that maternal blood flows through the intervillous space. Trophoblasts lining the spiral arteries of the uterus and eventually spreading to the placenta have a reduced ability to Lyse fibrin compared to other endothelial cells. This is believed to be associated with high levels of plasminogen activator inhibitors (PAI-1 and PAI-2), which form the structure of fibrin in the placental area and inhibit the action of tissue plasminogen activator anticoagulant.

Trophoblasts also secrete large amounts of tissue factor and phosphatidylserine, declining their equilibrium further and further toward increased coagulation potential. Microparticles - extracellular vesicles that spread during cellular signaling and apoptosis, are also involved in the development of thrombotic complications during pregnancy.^[20] However, as in every biological model, within the placental environment, there are compensatory mechanisms for creating a counterweight to the prothrombotic status, which include annexin V, which is crucial for preventing intervillous thrombosis, tissue factor inhibitors (TFPI-1 and TFPI-2), thrombomodulin, and prostacyclin.^[21]

Pathophysiology of preeclampsia

Stress of the endoplasmic reticulum can be caused by many stimuli, and the exact cause of PE is still unknown. However, there is a high probability of damage due to ischemia and reperfusion, taking into account the associated pathology of the spiral arteries. Early development of PE is associated with a lack of conversion of the spiral arteries of the endometrium due to insufficient trophoblast invasion. The conversion normally extends from contact with the placenta to the inner third of the myometrium, it is associated with the loss of smooth muscles and the elastic layer of the vessel walls. The portion of the arteries directly below the endometrium / myometrium border is a specialized segment with a high contractile ability, which is believed

to prevent excessive blood loss during menstruation. Scientists have suggested^[22] that in the event of PE development, the preservation of this segment causes a predisposition to spontaneous vasoconstriction and damage due to ischemia and reperfusion. The steps that occur in vivo are currently unknown, but various options are possible. Ischemia episodes can lead to a decrease in intracellular glucose concentrations, which potentially limits normal glycosylation in the endoplasmic reticulum, activating the response of unstructured proteins. Alternatively, ischemia will reduce the intracellular levels of adenosine triphosphate (ATP), disrupting the function of the glucose-regulated family of proteins GRP (Glucose-regulated protein) and, possibly, even Ca^{2+} -dependent ATPase of ion pumps in the membrane of the endoplasmic reticulum. Ischemia can also have a direct effect on the release of Ca^{2+} from the endoplasmic reticulum, changing the redox balance within the cell and affecting the thiol calcium channel protein groups. The loss of Ca^{2+} in the lumen of the endoplasmic reticulum will exacerbate the situation by disrupting the protein structuring mechanism and activating Ca^{2+} -dependent signal transduction pathways in the cytosol, which ultimately can lead to the opening of the mitochondrial transition pore membrane and the subsequent formation of active oxygen forms. The stress of the endoplasmic reticulum is chronic, probably since the end of the first trimester, since the development of the maternal circulation.^[20] Dilation of endoplasmic reticulum cisterns in syncytiotrophoblasts, indicating a violation of the endoplasmic reticulum homeostasis, has been described in PE. Thus, in 2011, researchers obtained the first molecular data on the activation of the response of unstructured proteins in the placenta in cases of stunted growth of the fetus during normotension and associated with early development of PE.^[11] In both sets of placentas, phosphorylation of the eukaryotic initiation factor 2 α was observed - Eukaryotic Initiation Factor (eIF2 α), which was absent in the placenta from healthy pregnant women. The degree of phosphorylation of eIF2 α was higher in cases of delayed growth of the fetus and PE, suggesting a higher level of stimulation of the endoplasmic reticulum. Immunohistochemical analysis showed that these phenomena were localized mainly in syncytiotrophoblasts and the endothelial cells of the fetal capillaries.^[13] The effects of endoplasmic reticulum stress on the function of the placenta are diverse; they have just begun to be studied. Inhibition of protein synthesis as a result of eIF2 α phosphorylation has a number of consequences for the development of the placenta, since it involves a number of protein kinases (Akt) and other regulatory proteins. Akt plays a central role in cell proliferation, and the loss of their activity is likely to have a serious adverse effect on the development of the placenta. Reduced Akt levels were observed in JEG-3 cells after exposure to hypoxia, reoxygenation, and glucose deficiency. Turning off Akt1 in the experiment (in mice) resulted in delayed growth of the placenta and fetus, confirming the relationship between Akt phosphorylation levels and the mass of the

placenta.^[2] Cyclin D1 is another protein that is seriously affected by the response of unstructured proteins; it was reported about its significant shortage in the cents during fetal growth retardation, including in combination with PE. Although no direct evidence has been obtained that changes in Akt and cyclin D1 play a causal role, they correspond to a smaller placental phenotype observed with fetal growth retardation, and more so with fetal growth retardation in combination with PE.^[2,8] Syncytiotrophoblasts also synthesize a wide range of growth factors, such as vascular endothelium growth factor and members of the family of insulin-like growth factors, which can act auto or paracrine. Reduced synthesis or loss of function due to improper structuring of proteins, apparently, can have an adverse effect on the development of the placenta. The placenta is an endocrine organ that secretes peptides and steroid hormones, which in turn have a multifaceted effect on the physiology and metabolism of the mother.

Despite the wide recognition that the activation of maternal endothelial cells represents the second stage of PE syndrome, there are no morphological studies that would be performed on the endothelial cells of the peripheral vessels of women with PE. Thus, it is currently not possible to determine whether endoplasmic reticulum stress occurs in endothelial cells and whether this can contribute to an increase in TNF α levels. There are reports describing the dilatation of the endoplasmic reticulum in the endothelial cells of umbilical vessels, indicating a loss of homeostasis of the endoplasmic reticulum.^[23] If the same pathology is noted in endothelial cells in PE, it is possible that the stress of the endoplasmic reticulum is not limited to the placenta in vascular complications of gestation. The factors released during damage to endotheliocytes cause damage to the endothelium and its dysfunction in the distal regions of the spiral arteries, which explains the occurrence of systemic effects observed in severe PE. Some of these factors belong to the class of anti-angiogenic proteins, which include FMS-like tyrosine kinase-1 (sFLT-1, soluble FMS-like tyrosine kinase). sFLT-1 binds vascular endothelial growth factor (VEGF), inhibiting VEGF signaling, resulting in hypertension, proteinuria, and glomerular endotheliosis. Endoglin is another anti-angiogenic protein identified as a PE agent possibly involved in the pathogenesis of PE. This glycoprotein, located on the cell surface, is a β -receptor coreceptor of a transforming growth factor that interacts with sFLT-1, as a result of which PE can develop. Elevated levels of endoglin were observed in women who subsequently developed PE.^[24] A reduced number of cytotrophoblasts or their absence, caused either by an inflammatory process or by exposure to mononuclear (MNC) cells, can also be a cause of impaired remodeling of the spiral arteries, which results in a pathological condition characterized by intense blood flow and increased pressure in the vessels. Therefore, the myometrium of pregnant women with PE remains susceptible to the effects of endogenous and exogenous adrenergic

stimuli.^[13] The “intense blood flow / high blood pressure” condition that exists in spiral arteries with incomplete gestational rearrangement leads to hemodynamic stress of the endothelium. In addition, the emerging placenta is under threat of ischemia-reperfusion injury due to spontaneous vasoconstriction of the maternal arteries. These injuries lead to the rapid formation of reactive oxygen radicals, which, in turn, contributes to further traumatization of the endothelium and microthrombus formation.^[3,5]

Risk Factors

Well-known factors, the presence of which gives the basis to refer the patient to a high risk group for the development of PE: PE in history, age over 40 years, chronic autoimmune diseases, family history of PE, diabetes mellitus type 1, multiple pregnancy, lack of childbirth in history, obesity, preexisting hypertension and kidney disease. The most important factor is the presence of PE in history: the risk of developing PE during subsequent pregnancy increases by 7.6 times.^[3] When a child is pregnant, the developmental risk of developing PE is 3.0, and during a triple pregnancy, it increases even more.^[6] Despite efforts to identify risk factors that lead to the occurrence of PE, at least 2/3 of cases of PE develop in nulliparous people in the absence of other significant risk factors. Most women whose pregnancy is complicated by PE are primiparous (73.1%) over the age of 34 (37.2%), with overweight/obesity (44.7%).^[5] Stress (45.5%), the presence of PE in family history (17.2%), anxiety associated with childbirth (16.2%), and lack of sleep (10.1%) were the most common estimated trigger factors for PE in 34, 6% of respondents.^[1] The relationship between the use of ART and hypertensive complications of gestation has been established. This relationship can be explained by a number of differences between pregnancies with natural fertilization and pregnancies after ART: effects on the endometrium due to controlled stimulation of the ovaries, differences in the implantation process due to the fact that the formation of trophoblast in ART is in vitro, but not in vivo. The use of DOs in ART programs is a risk factor for the development of PE compared to IVF cycles with their own oocytes with a weighted odds ratio (OR) calculated using a random effects model (heterogeneity between studies). There is no unambiguous opinion on whether the transfer of embryos obtained in ART programs with TO, is a risk factor for the development of PE is not yet. However, recipients of ART programs with DO are pregnant women of late reproductive age, usually with inadequate ovarian function and many other factors independently associated with PE. A meta-analysis of 11 studies performed by A. Blazquez, D. Garcia et al. (2016), showed that the prevalence of PE in pregnancy with the use of TO was 17.2% [95% confidence interval (CI) - 9–29%], whereas in pregnancy after ART with autologous oocytes, this indicator was 5.7% (95% CI - 0–13%) (χ^2 - 246.5; $p < 0.001$). 10 of the 11 studies included in the meta-analysis reported an increased risk of developing

PE during pregnancy with a TO compared to that with a pregnancy with its own oocyte. The weighted OR value was 2.9. The meta-analysis procedure showed that multiple pregnancies (score = 0.08; $p = 0.19$) and patient's age (score = -2.29; $p = 0.13$) did not significantly contribute to the effect of DO on the development of PE. However, the obtained values of p demonstrate that there is a tendency to achieve a level of significance for the relationship between age and the effect of DO on the development of PE.^[11]

Screening Procedure

For population-based screening for PE, it is recommended to use the most reliable clinical markers of PE, determined antenatally. Since no single analysis can accurately predict PE in clinical practice, interest has emerged in studying multifactor models, including available clinical and laboratory prognostic factors. These models for calculating the risk of PE are based on the separation of factors into particularly significant and secondary.^[16] Patients are shown counseling by specialized specialists (therapist, cardiologist, urologist, endocrinologist, etc.) in the presence of one significant factor or ≥ 2 secondary risk factors. Half of the women from those who subsequently may develop PE can be identified using this model.^[10]

The risk markers of PE available in the II and III trimester include:

- Indicators of perfusion of the placenta, vascular resistance, and morphology (average maternal blood pressure in the II trimester, daily monitoring of mean blood pressure, Doppler);
- Maternal cardiac output and systemic vascular resistance;
- Placental endocrinological indicators (plasma-associated A protein associated with pregnancy, α -fetoprotein, free β -subunit human chorionic gonadotropin, inhibin A);
- Maternal renal function (serum uric acid or microalbuminuria);
- Maternal endothelial function and interaction of endothelium and platelets (platelet count, antiphospholipid antibodies or homocysteine);
- Oxidative stress (serum lipids);
- Circulating angiogenic factors;
- Dopplerography of uterine arteries in the first trimester may be a useful indicator, but it requires additional evaluation in actual practice.^[19] Many clinically available biomarkers were evaluated, but none of the above diagnostic and clinical methods reached an ideal sensitivity of $\geq 90\%$ for predicting PE. Only dopplerometry of the uterine arteries in the period of 20–24 weeks has a sensitivity of $> 60\%$ for the detection of PE, subject to a number of restrictions at the time of the examination:
- Pregnant woman is at increased risk of developing PE;
- Research is carried out in the II trimester;
- To predict severe and early PE.

In women with abnormal dopplerometry of the uterine arteries, more careful observation should be considered to identify PE and the risk of other adverse outcomes. In a low-risk population, this method is not effective for predicting PE.^[13]

Routine screening for thrombophilia in the presence of PE in the history is not recommended, except for women who meet the clinical criteria of antiphospholipid syndrome.^[8]

Prevention

An effective method involving the complete prevention of PE has not been developed until recently. Perhaps this can be explained by the fact that the formation of the pathogenetic links of the disease occurs over the course of weeks until the patient begins to manifest symptoms.^[2] Therefore, prophylactic measures should be carried out until 16 weeks, when gestational reconstruction of the spiral arteries of the uterus occurs. Such early interventions have the greatest potential to reduce the risk of developing early PE. The list of recommendations for the prevention of PE has a number of nuances depending on the risk category.^[3]

Dose adjustment of aspirin based on platelet function tests can improve its efficacy in the prevention of PE in women at higher risk. Low-molecular-weight heparins (LMWH) in prophylactic doses are associated with minimal risk for the mother and theoretically for the fetus since they do not penetrate the placental barrier. Severe allergic reactions are rare (1.2%), and no heparin-induced thrombocytopenia was detected. The prophylactic use of LMWH was rarely associated with ante- (0.42%) and intrapartum hemorrhage (0.92%), as well as with a hematoma of a wound after a cesarean section or vaginal delivery (0.65%). Admission of LMWH can be stopped at 34–36 weeks to avoid intra- and postnatal risk. The independent role of concomitant use of aspirin requires clarification.^[7]

CONCLUSION

Hypertensive complications of gestation largely determine maternal and perinatal morbidity and mortality. PE develops after the 20th week of pregnancy and is permitted after delivery; diagnosed in the presence of hypertension, proteinuria, or objective and subjective symptoms of target organ damage. It is important for clinicians to assess properly long-term maternal morbidity since PE is highly correlated with a lifelong risk of developing chronic hypertension and renal failure. Despite the fact that specific series of events leading to the development of PE are not fully known yet, several new pathogenetic mechanisms have been established. Stress of the endoplasmic reticulum is one of the components of the group of the total cellular response to stress. There are complex interactions between it and oxidative stress, and it is likely that with many complications both of these conditions will occur simultaneously. The intense secretory activity of

syncytiotrophoblasts makes them vulnerable to the stress of the endoplasmic reticulum, which is confirmed by the results of molecular and morphological studies. There are numerous consequences for the development and function of the placenta, including a decrease in cell proliferation and activation of proinflammatory pathways with the participation of the mother's immune system.

Infectious diseases, certain drugs, activation of the complement system and neutrophils, as well as the release of human neutrophil proteins, extracellular DNA, histones, etc., can trigger the development of an acute episode of TMA / TTP. The scope of our knowledge about TMA has significantly expanded, despite the rarity of these diseases, but not all possible trigger factors of acute TTP are clear. Recent advances in ADAMTS13 research allow us to confidence level to distinguish TTP from other TMA. Despite a number of advances in the diagnosis and treatment of TMA, mortality, exacerbations, and relapses remain a serious problem. In this regard, a deeper understanding of potential triggers, the selection of biomarkers to predict long-term results of treatment or relapse, as well as the development of new additional and more effective means of therapy are urgently needed. Despite the emergence of new diagnostic methods, treatment options and the continuation of research, the outcomes of some forms of TMA are not up to par, which indicates the need for further development.

REFERENCES

- Momot A.P., Kudinova I.Y., Belozerov D.E. Physiological pregnancy - the model of absent thrombosis. *Tromboz, Gemostaz i Reologia [Thrombosis, hemostasis and rheology]*, 2016; 67(3): 297–8.
- Blazquez A., Garcia D., Rodriguez A., Vassen R., et al. Is oocyte donation a risk factor for preeclampsia? A systematic review and metaanalysis. *J Assist Reprod Genet*, 2016; 33: 855–63.
- Dhariwal N.K., Lynde G.C. Update in the management of patients with preeclampsia. *Anesthesiol Clin*, 2017; 35: 95–106.
- Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. *BMJ*, 2003; 327: 955–60.
- Hutton JD, James DK, Stirrat GM, Douglas KA, Redman CW. Management of severe pre-eclampsia and eclampsia by UK consultants. *Br J Obstet Gynecol*, 1992; 99: 554–6.
- Ounsted MK, Moar VA, Good FJ, Redman CW. Hypertension during pregnancy with and without specific treatment; the development of the children at the age of four years. *Br J Obstet Gynaecol*, 1980; 87: 19–24.
- El-Qarmalawi AM, Morsy AH, al-Fadly A, Obeid A, Hashem M. Labetalol vs. methyldopa in the treatment of pregnancy-induced hypertension. *Int J Gynaecol Obstet*, 1995; 49: 125–30.
- Narayan B., Nelson-Piercy C. Medical problems in pregnancy. *Clin Med*, 2016; 16(6): s110–6.
- Ford J.B., Schemann K., Patterson J.A., Morris J., et al. Triggers for preeclampsia onset: a case-crossover study. *Pediatr Perinatal Epidemiol*, 2016; 30: 555–62.
- Leaf R.K., Connors J.M. The role of anticoagulants in the prevention of pregnancy complications. *Clin Appl Thromb Hemost*, 2015; 1–8.
- Saha M., McDaniel J.K., Zheng X.L. Thrombotic thrombocytopenic purpura: pathogenesis, diagnosis, and potential novel therapeutics. *J Thromb Haemost*, 2017 Jun 29.
- Burton G. J., Yung H. Endoplasmic reticulum stress in the pathogenesis of early-onset pre-eclampsia. *Pregnancy Hypertens*, 2011; 1: 72–8.
- Savignano Ch., Rinaldi C., De Angelis V. Pregnancy-associated thrombotic thrombocytopenic purpura: Practical issues for patient management. *Transfus Apher Sci*, 2015; 53(3): 262–8.
- Martin JN Jr, Rinehart BK, May WL, Magann EF, Terrone DA, Blake PG. The spectrum of severe pre-eclampsia: comparative analysis by HELLP (hemolysis, elevated liver enzyme levels, and low platelet count) syndrome classification. *Am J Obstet Gynecol*, 1999; 180: 1373–84.
- Redman CW, Bonnar J, Beilin L. Early platelet consumption in pre-eclampsia. *Br Med J*, 1978; i(6111): 467–9.
- Sharma SK, Philip J, Whitten CW, Padakandla UB, Landers DF. Assessment of changes in coagulation in parturients with pre-eclampsia using thromboelastography. *Anesthesiology*, 1999; 90: 385–90.
- Walker JJ, Cameron AD, Bjornsson S, Singer CR, Fraser C. Can platelet volume predict progressive hypertensive disease in pregnancy? *Am J Obstet Gynecol*, 1989; 161: 676–9.
- von Dadelszen P, Magee LA, Devarakonda RM, Hamilton T, Ainsworth LM, Yin R, et al. The prediction of adverse maternal outcomes in pre-eclampsia. *J Obstet Gynaecol Can*, 2004; 26: 871–9.
- Rychel V, Williams KP. Correlation of platelet count changes with liver cell destruction in HELLP syndrome. *Hypertens Pregnancy*, 2003; 22: 57–62.
- Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ*, 2005; 330: 565.
- Royal College of Obstetricians and Gynaecologists. The Use of Electronic Fetal Monitoring. Evidence-Based Clinical Guideline No. 8. London: RCOG Press, 2001.
- The FIGO Textbook of Pregnancy Hypertension. An evidence-based guide to monitoring, prevention, and management/eds L.A. Magee, P. von Dadelszen, W. Stones, M. Mathai. The Global Library of Women's Medicine, 2016; 456.
- Shatzel J.J., Taylor J.A. Syndromes of Thrombotic Microangiopathy. *Med Clin North Am*, 2017; 101(2): 395–415.

24. Weinstein L. Syndrome of hemolysis, elevated liver enzymes, and low platelet count: a severe consequence of hypertension in pregnancy. *Am J Obstet Gynecol*, 1982; 142: 159–67.
25. Galan HL, Ferrazzi E, Hobbins JC. Intrauterine growth restriction (IUGR): biometric and Doppler assessment. *Prenat Diagn*, 2002; 22: 331–7.