



A new pathophysiological concept and new classification of pre-eclampsia

Novi koncept patofiziologije i nova klasifikacija preeklampsije

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Key words:
pre-eclampsia; diagnosis; classification.

Ključne reči:
preeklampsija; dijagnoza; klasifikacija.

Introduction

The first description of eclampsia (E) was given by Hippocrates, a father of modern medicine (460-377 BC), a son of Heraclides from the island of Kos¹. After more than two millennia since the first descriptions, the syndrome of pre-eclampsia/eclampsia (PE/E) has remained a multi-system disorder of unknown etiology. The diagnosis is based on a clinical picture and laboratory analysis; an efficient prevention and screening are missing, the therapy is symptomatic, while giving birth still remains the only causal therapy.

Hypertensive disease in pregnancy (HDP) implies various clinical entities with hypertension being the common one. Thirty-one epidemiological studies have been published in the period from 1979 to 2013 with the incidence of PE on the global level in five different regions of the World Health Organisation and in 29 countries amounting to 2.16%, while the incidence of E amounts to 0.28%². In Europe, more than 90% of deaths of mothers caused by PE/E could have been avoided^{3,4}. Pregnant women having PE/E have a greater incidence of induced births, C-sections and preterm births². In women with E, an exponential risk growth for death or high threat to the life of the pregnant woman, fetal death, neonatal death, perinatal death and reception to the neonatal intensive care unit has been detected².

Why is the problem still significant? The PE incidence has grown by 25% in some of the developed Western world countries⁵. Another major reason is the estimate that every year 50,000–60,000 women in the world die from PE and its complications^{6,7}. For each of these deaths one must add 50–100 pregnant women whose life is threatened due to PE/E^{8,9}.

PE represents a major reason of iatrogenic prematurity while the last but not the least important reason is that PE has been recognised as a serious risk factor for the appearance of cardiovascular and metabolic diseases in the later life of the woman and her new-born^{10,11}.

The etiology and pathophysiology of pre-eclampsia

How can we define in the simplest way the pathophysiological PE mechanism today? Pre-eclampsia is a disease of the placenta from which both the mother and a fetus suffer. This definition fulfils the criterion of simplicity, but unfortunately it is not scientifically sufficient, i.e. why, how, when? Much is known today and if we were to explain PE in the shortest possible way, nowadays we can summarise: various genetic and epigenetic factors have an influence on an inappropriate spiral artery remodelling process, i.e. bad placentation, which as a consequence has a bad placenta perfusion and the appearance of oxidation placenta stress, which stimulates the synthesis of different humoral mediators leading to endothelial dysfunction of different organs and organic systems of the pregnant woman and the fetus, presenting itself as a multi-system disease, which PE today definitely is (Figure 1).

The basic problem in studying the aetiology and pathophysiology of pre-eclampsia is the non-existence of the uniform HDP criteria even though in the past decades there have been several attempts to introduce the unique criteria by different international associations studying HDP. Another aggravating circumstance is the issue whether PE is one or several diseases. Just like HELLP (haemolysis, low thrombo-

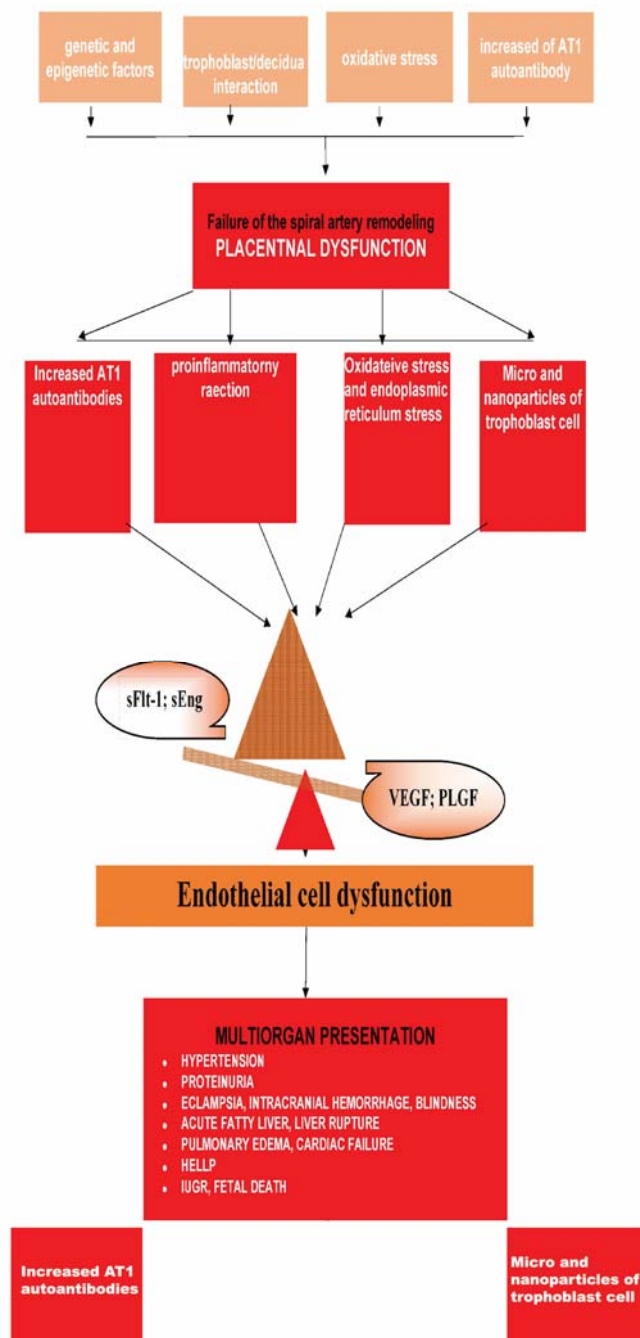


Fig. 1 – The pathophysiology of preeclampsia.

sFlt-1 – the soluble fms-like tyrosine kinase 1; sEng – the soluble endoglin; PLGF – the placental growth factor; VEGF – the vascular endothelial growth factor; AT1 – the angiotensin receptors 1; IUGR – the intrauterine growth restriction; HELLP-hemolysis, elevated liver enzymes, low platelet count.

cytes and increased liver enzymes) separated itself as a special entity, the early and late PE can already be considered separate entities. Basically, the new classification primarily leans on the new understanding of PE pathophysiology and extensive epidemiological studies.

Spiral artery remodeling

The human placenta is a temporary organ, one of the most vascular organs, which is made of a tissue that is 98%

of fetal, i.e. trophoblast origin; only approximately 2% are of decidua, uterine, mother's origin. The length of the capillary system of the placenta at the end of the pregnancy amounts to approximately 550 km and its surface is approximately 12 m²¹². The capillary surface of the placenta is essential for the growth and development of the fetus. The vasculogenesis starts 3 weeks after conception, so as for the fetoplacental circulation to be established, around 8 weeks of gestation¹³.

An appropriate development of trophoblasts on one side and the adjustment of blood vessels of the uterus on the

other, are conditions for a normal human pregnancy development. The trophoblast is a tissue originating from a fertilised egg cell, carrying the genetic embryo constellation. There are three types of trophoblasts: 1) syncytiotrophoblast (STB), 2) cytotrophoblast (CTB), 3) extravillous trophoblast (EVT). EVT proliferates from the so-called chorionic villi in charge for the stabilisation and fixation of the placenta, as opposed to the freely floating chorionic villi submerged in intervillous space providing spiral arteries with blood. EVT has the features of the invasive tissue which will spread into the uterus stroma. The goal of the EVT invasion is that in the uterus stroma it reaches the spiral arteries.

The first description of spiral arteries was given by the Hunter brothers, William (1718–1783) and John (1728–1793) Hunter, in their masterpiece “Anatomy of the Human Gravid Uterus” published far back in 1774¹⁴. A century and a half ago, it was speculated that the spiral arteries undergo a change in their structure during pregnancy; in 1927 Otto Grosser¹⁵ for the first time came up with the idea that these new cells, remodelling the spiral artery wall, are aretrophoblast cells. Nevertheless, it was scientifically proven that the “new cells” in the spiral artery walls are trophoblasts only with the introduction of cytokeratin immunohistochemical tests, which have finally confirmed the trophoblast origin of endovascular and intramural cells in the spiral artery wall. The process of trophoblast invasion, to which the spiral arteries are subjected, implies a loss of endothelial cells of the spiral arteries, loss of elastic lamina as well as a loss in the muscular layer, which is replaced by fibrinoid layers¹⁶. The wall of the changed arteries becomes thinner, softer and has a large capacity for passive dilatation, while the lumen of spiral arteries becomes expanded after trophoblast invasion so that the blood stream is larger. At the same time, the remodelled endothelium of spiral arteries becomes insensitive to the vasoconstrictors. The remodelling takes place in decidua but also in the myometrial segment, on average in approximately 100 spiral arteries of a placenta.

The sense of adequate remodelling of spiral arteries is to transform the placenta into a large capacity and low pressure organ and for the spiral arteries primarily to become insensitive to regulatory mechanisms of mother's blood pressure. The spiral artery remodelling process takes place on two occasions (the “two wave invasion” theory). The first wave of the EVT invasion (from the so-called anchoring chorionic villi) takes place only in the deciduas of the spiral arteries from 8–10 weeks of gestation. The second wave of EVT invasion happens between 16 and 18 weeks of gestation. The EVT invasion in this second wave takes place in the deeper myometrial spiral artery segment¹⁷.

The EVT invasion process into the spiral artery wall, beside two invasion waves, takes place also from two directions: 1) interstitial and 2) endovascular. Thus, it can be said that the spiral artery wall is exposed to the trophoblast EVT invasion both from “outside” and from the “inside”, i.e. interstitially and endovascularly.

It remains an open question as to why the inadequate spiral artery remodelling process through trophoblast invasion in certain cases leads to the manifestation of the clinical

picture of PE, while sometimes it is an intrauterine fetal growth restriction (IUGR), and sometimes an early birth (PTP)^{18,19}. It can nowadays be said that the most important obstetric entities: PE, PTP, placental abruption, preterm premature rupture of fetal membranes (PPROM) and late miscarriages are results of “deep placentation disorders”, i.e. inadequate remodelling of spiral arteries in the deep myometrial segment²⁰. It is obvious that the spiral artery remodelling process is not a process taking place according to the all or nothing principle¹⁶.

Oxidative stress

Placental insufficiency results in oxidative stress (OS). Pre-eclampsia is characterised by an excessive production of free radicals and/or non-existence of a satisfactory antioxidative capacity^{21–24}. Oxidative stress can be simply defined as a misbalance in the production of oxidants (free radicals and reactive metabolites) and their elimination, i.e. the protective mechanism of the antioxidative system. The oxidants include the reactive forms of oxygen (ROS) and the reactive forms of nitrogen (RNS). ROS and RNS promptly react with lipids, proteins and DNA cell molecules, thus manifesting harmful effects. The mitochondria are one of the most important sources of ROS in trophoblast cells but they are also the most important place of their action. It is conventional wisdom that the oxidative stress is always harmful. Oxidative stress plays a very complex and significant role in the signal modulation processes, emphasises the synthesis of antioxidant enzymes and impacts the reparation processes, inflammation, apoptosis and cell proliferation²⁵. In the first trimester, the embryo develops in a low oxygen environment as opposed to the second trimester when there is a significantly larger exchange in oxygen on the level of the placenta in order to meet the needs of the growing fetus. It is precisely this low oxygenation that is significant for the proliferation of trophoblasts in the first trimester. The experiments of Genbačev et al.²⁶ have shown that the low oxygenation of trophoblasts in the first trimester has an impact on the good proliferation of trophoblasts but not on its invasivity and differentiation²⁶.

OS have and impact on autophagy and apoptosis, the two key interrelated processes. Autophagy is a protective while apoptosis is a destructive process at the level of the placenta. Autophagy has recently become one of the most interesting and most studied processes²⁷. It is considered that autophagy is a self-regulating, catabolic process with the aim to remove the undesirable proteins, damaged organelles and their harmful products. According to the most recent understanding, autophagy represents the most important protection of trophoblast cells in the conditions of OS. Contrary to the conditions of OS, apoptosis is activated in a complex way which has as a consequence a programmed cell death of trophoblast cells and inadequate remodelling of spiral arteries. Lately, the importance of the endoplasmic reticulum (ER) stress which occurs as a result of ischemia of intervillous space due to inadequate remodelling of spiral arteries is emphasised. The ER stress, as a consequence, has an inadequate

posttranslational protein modification and their insufficient “folding”²⁸. There is a problem of the so-called unfolded protein response or UPR)²⁹. UPR further leads to the end of trophoblast cell proliferation and if UPR is present, it leads to apoptosis. The trophoblast apoptosis has as a consequence the release of micro and nanoparticles in the maternal circulation, which possess the ability of stimulating a proinflammatory response³⁰. These two processes are mutually connected in a complex way and their balance plays a major role in the placental homeostasis³¹.

Oxidative stress triggers also other humoral processes: proinflammatory response and release of cytokines: tumour necrotising factor (TNF)-alpha, interleukins (IL-6), (IL-2)³²⁻³⁴, activation of complements³⁵; stimulation of the synthesis of antiangiogenic factors: soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), reducing the production of placental growth factor (PLGF)³⁶⁻³⁸.

Since the intravascular inflammation, beside in PE, can also be found in other obstetric syndromes such as preterm birth³⁹, PPROM⁴⁰ IUGR^{41,42} and pyelonephritis⁴³, without hypertension and proteinuria, so that the conclusion imposes itself that the very inflammation exists in pre-eclampsia, but that it is not sufficient to cause the disease symptoms. Nowadays, the prevalent opinion is that the placental hypoxia leads to the release of antiangiogenic factors sFlt-1 and sEng which together with the proinflammatory cytokines lead to endothelial activation and vasospasm, i.e. to endothelial dysfunction⁴⁴. It has been shown lately that the increased

maternal systemic proinflammatory response in PE does not correlate with the level of antiangiogenic sFlt-1 and sEng⁴⁵. It is not known what the interaction between the inflammatory and the angiogenic system is, however, the possibility that the inflammatory system stimulates the angiogenic system and vice versa is not excluded.

Angiogenic factors

Since Maynard and associates in 2003 published that excessive placenta production of sFlt-1 represents a major factor in the PE pathophysiology, the literature is considering different major functions of these important biomarkers. sFlt-1 is a soluble form of receptor belonging to the vascular endothelial growth factor (VEGF group) of the receptor (VEGFR-1). sFlt-1 is expressed in an insoluble form (Flt-1) on endothelial cell membranes and placenta (mostly on syncytiotrophoblast cells) (Figure 2). VEGF has an important function in the development of endothelium, its proliferation, vascular permeability and fenestration of endothelial cells. VEGF realises its function by connecting to insoluble Flt-1 receptors on the endothelium. If the soluble form of Flt-1 receptors is in increased concentration, VEGF will tie to them and in this way its connection on the receptors on the endothelium will fail. In this way, also the positive impact of VEGF on the endothelial cells will fail, too. Placental growth factor (PLGF) is also a member of the VEGF family with a strong proangiogenic, positive action on endothelial cells,

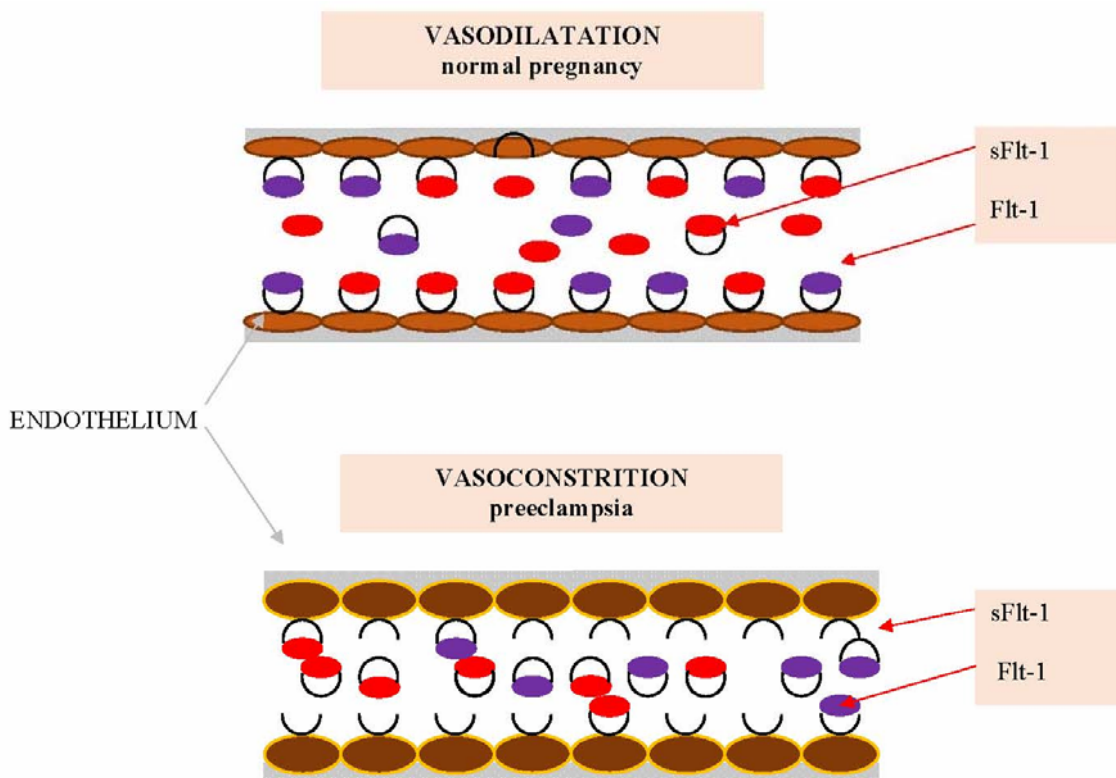


Fig. 2 – The functioning of the placental growth factor and vascular endothelial growth factor. PLGF – placental growth factor; VEGF – vascular endothelial growth factor; sFlt-1 – soluble fms-like tyrosine kinase 1; Flt-1 – non soluble fms-like tyrosine kinase 1.

which realise its function also through the same receptors as VEGF but in a somewhat modified way.⁴⁶ In the same way sFlt-1 is connected to the PLGF molecules, reduces its concentration and, thus, its positive effect on endothelial cells is missed.

Primarily, light is shed on the major role of angiogenic factors in explaining the PE pathophysiology. In the past five years in the literature there has been a significant number of papers discussing the role of angiogenic factors in predicting PE, differential diagnosis and HDP classification; recently, the possible clinical use of the sFlt-1/PLGF ratio in the prediction of unfavourable perinatal PE complicated pregnancy outcome is of major importance.

In PE, the concentration of antiangiogenic factors is growing (sFlt-1 and sEng), while the concentration of proangiogenic factors PLGF and VEGF is decreasing. PLGF and VEGF have a positive effect on the endothelium in pregnancy but in different time periods and in different ways⁴⁷. VEGF has a major role in the branching of angiogenesis, it stimulates endothelial proliferation and migration in the first trimester of pregnancy, while PLGF helps the so-called angiogenesis without the branching of angiogenesis (non-branching angiogenesis) in the second and third pregnancy trimester⁴⁷. Since in the first trimester there is the condition of lesser oxygenation, each hyperfusion and hyperoxygenation may block the VEGF level and lead to early PLGF pick which has as a consequence inadequate blood vessel branching of trophoblast villi and may lead to the pregnancy's development being stopped (Figure 3)^{47,48}.

sFlt-1/PLGF ratio has better diagnostic performances than the analysis of individual sFlt-1 or PLGF markers⁴⁹⁻⁵².

simply and quickly define these markers and have been in commercial use since 2010⁴⁹. These markers have been incorporated into the German PE guide⁵⁸ and formally there are no official recommendations, so that this test has not yet entered the official clinical protocols.

Roberts et al.⁵⁹ stated, back in 1989, long before realising the role of angiogenic factors, the theory on PE as a disease of endothelial cells⁵⁹. Back then, there was no sufficient explanation on which "toxin" in the mother's blood leads to the disease of the endothelium. The concept of endothelial dysfunction is a valid dogma even today.

Out of the large number of biomarkers, PE, sFlt-1, and sEng represent the most important biomarkers leading to endothelial dysfunction. Experimental studies on animals have shown that the elevated level of the circulating sFlt-1 may lead to presentation of all the characteristics of human PE: hypertension, proteinuria, brain oedema, haematological disorders and fetal development restriction⁶⁰⁻⁶³. Thadhani et al.⁶⁴ associates have shown that by removing sFlt-1 through apheresis from the pregnant woman's plasma, one mitigates the clinical manifestations of PE.

Nowadays, it is considered that the PE mechanism is a complicated and complex one; therefore, one has suggested a hypothesis of a combined excessive inflammatory response and disbalance of angiogenic factors. It is assumed that the inflammatory mediators act locally through autocrine or paracrine mechanisms leading to the aplification effect of angiogenic factors⁶⁵.

Nevertheless, the antiangiogenic status of the mother does not always have PE as a consequence. The reasons for such a re-

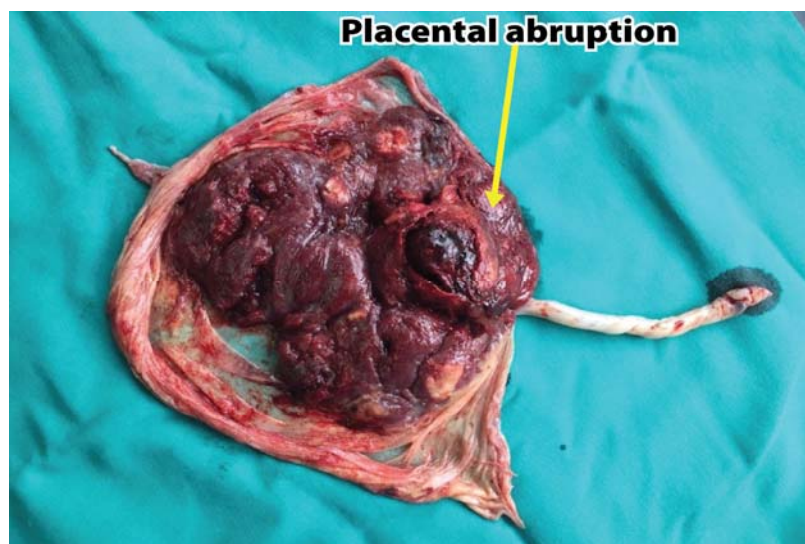


Fig. 3 – Preeclamptic placenta

This relationship represents one of the most important, new, laboratory tests pointing to the need of an urgent birth in pregnant women with PE and predicts an unfavourable outcome of the pregnancy complicated through PE^{50,53-57}. The application of sFlt-1/PLGF relationship in practice has been made possible by the introduction of automatic tests which

response are not clear, however, it is assumed that it is necessary to cross the individual threshold of disbalance of pro- and antiangiogenic factors. It is necessary to realise a sufficiently large production of antiangiogenic factors; their prolonged action is necessary but also the constitutional sensitivity of the maternal endothelium on the action of antiangiogenic factors. There is no

response to all questions but further potential clinical use of analysing (PLGF, sFlt-1, sEng) is yet to be expected⁶⁶.

Antibodies on angiotensin II receptors (AT)

As opposed to a normal pregnancy which is characterised by reduced sensitivity of endothelium on angiotensin II, in pregnant women with PE, due to genetic factors, immunomodulation, and external factors, there is an excessive sensitivity on angiotensin II^{67, 68}. This sensitivity can be detected even before 24 weeks of gestation. It was established that some pregnant women with PE create autoantibodies on type one angiotensin II receptors (AT1). Antibodies on AT1 receptors injected to pregnant rats lead to hypertension, proteinuria, and increased levels in sFlt-1 and sEng⁶⁹. Antibodies on AT1 receptors lead to the occurrence of hypertension through the activation of complements and through the stimulation of antiangiogenic factor production, sFlt-1 and sEng⁷⁰. Lack of immunoassay for these specific AT1 receptors disturbs further understanding of their role and their possible application in clinical practice.

Activation of thrombocytes and thrombin

Thrombocytopenia is one of the prognostically most unfavourable laboratory indicators in PE⁷¹. Thrombocytopenia sometimes precedes the occurrence of clinical signs of PE⁷¹. It is considered that a reduced number of thrombocytes occur as a result of different factors: increase in the size of the thrombocytes, shorter life of the thrombocytes, increase in the thrombocyte factor 4 or due to increased production of thrombocyte thromboxane B2⁷². Vasoconstriction and thrombocytopenia in PE most probably occur as a result of reducing the prostacyclin synthesis⁷³. The increase in vasoconstriction thromboxane A2 and reduction of vasodilation prostacyclin can be found in PE⁷⁴. The activation of thrombocytes can lead to the creation of thrombi in the microcirculation of different organs and placenta.

One of the major characteristics of PE is the activation of coagulation cascade⁷⁵. In literature there is a multitude of explanations for excessive creation of thrombin in PE⁷⁶. The following is listed as a reason: endothelial dysfunction, activation of thrombocytes, monocyte chemotaxis, lymphocyte proliferation and neutrophil activation but also an increased synthesis of tissue coagulation factors that are released under the influence of proinflammatory cytokines. The thrombin leads to a creation of fibrin deposits in different organs in PE. Excessive creation of thrombin may range from subclinical to the occurrence of disseminated intravascular coagulation as one of the most serious PE complications. The excessive creation of thrombin can be monitored in laboratory by defining the concentration of thrombin-antithrombin (TAT) complex or by defining antithrombin III^{76, 77}.

Pre-eclampsia genetics

The hereditary factor has been for a long time recognised as the starting important event in the occurrence of PE.

It is still unknown in which way the inheritance takes place and which genes are responsible. Molecular research has the capacity to provide indications of the basic causes of PE which are not available through other research methods. Such a strategy has been made possible by the expansive development and merging of molecular biology and information technologies. Two approaches are used for the purpose: testing the gene polymorphism in the candidate, while the other approach implies integrational systemic study of the entire human genome. The literature presents a large number of polymorphisms of different candidates' genes.

MicroRNAs (MiRNAs) are non-coding RNA segments of a size of 21–25 nucleotide bases, for which it is considered that they post-translationally regulated the gene expression⁷⁸. MiRNAs are included in the regulation of trophoblast proliferation, apoptosis, migration and invasion⁷⁹. MiRNAs are significant also in the regulation of angiogenesis^{80, 81}.

The plasma concentration of free DNA (cfDNA) fragments, as well as free fragments of fetal DNA (cffDNA) have their place in screening, detection, but also in the prediction of an unfavourable perinatal PE outcome⁸².

Classification of hypertension diseases in pregnancy

The HDP classification has a major importance for the study of all of the aspects of hypertension disease in pregnancy. In the literature there is a large number of different HDP classifications, both on the part of national and on the part of various international associations^{83–88}. The confusion significantly slows down the basic research in PE etiology and pathophysiology and also impacts the recommendations and prevention protocols as well as the treatment of the hypertension disease in pregnancy. Since 2013, after a guide was published by the American College of Obstetricians and Gynaecologists (ACOG) workgroup, there has been a tendency of wider implementation of new diagnostic criteria into national guides also of other countries and associations⁸⁹. This classification basically and primarily leans on the new understanding of PE pathophysiology and also to extensive epidemiological studies. The ACOG HDP classification has the tendency to be simple, precise and easy for clinical application. According to this classification, HDP can be divided into four basic groups: 1) Pre-eclampsia/eclampsia; 2) Chronic hypertension; 3) Chronic hypertension with superimposed pre-eclampsia; 4) Gestational hypertension.

Pre-eclampsia/eclampsia diagnosis

Pre-eclampsia is a specific form of hypertension in pregnancy having a multi-system presentation. It can be said that the PE syndrome, which is primarily characterised by the appearance of hypertension after 20 gestation weeks in previously normotensive women that mostly comes together with proteinuria but may also be associated with most varied other symptoms and signs.

Hypertension and proteinuria have earlier been two basic, classic criteria for making the PE diagnosis. Beside the

above two classic PE criteria, some expecting mothers, beside hypertension, also have multi-system symptoms or signs which even without the presence of proteinuria point to a severe form of PE⁸⁹.

Pre-eclampsia manifests itself as early and late PE; these forms are nowadays considered as various PE entities/subgroups⁹⁰. Early PE manifests itself before 34 gestation weeks, while late PE manifests itself after 34 gestation weeks^{4,91,92}. The maternal and fetal morbidity and mortality are far more frequent in the subgroup of early PE, before 34 gestation weeks^{4,91}. The basic differences between early and late PE are presented in the Table 1.

The most important in the new classification of PE is that proteinuria is no longer the basic and necessary criterion for diagnosing PE with elevated blood pressure $\geq 140/90$ mmHg^{93,94}. Proteinuria ≥ 5 g and IUGR are no longer the criteria for diagnosing severe PE. Another important fact is the introduction of the indicators of multi-system endothelial dysfunction as equal criteria for diagnosing PE.

According to the new ACOG classification, PE is defined as elevated systolic blood pressure of 140 mm Hg or diastolic blood pressure of 90 mm Hg or more, or both the systolic and the diastolic blood pressure are above $\geq 140/90$ mm Hg, measured twice with a gap of 4 h (when one measures the blood pressure value $\geq 160/110$ mm Hg, the next measurement can follow immediately, in just a few minutes, for the purpose of introducing antihypertensive therapy) with proteinuria in 24 h-urine ≥ 300 mg or protein/creatinine ratio ≥ 0.3 or in absence of quantitative methods one can use the read proteins in urine on a test tape 1+. In absence of proteinuria, in order to diagnose PE it is necessary that, beside hypertension, there is at least one of the following criteria: thrombocytopenia (number of thrombocytes less than 100.000/ μ L), kidney insufficiency (concentration of creatinine in serum above 97 μ mol/L), decreased liver function (enzyme activity AST and ALT twice higher than the upper

limit of the referential interval), appearance of lung oedema or appearance of cerebral, i.e. visual symptoms (Table 2)⁸⁹.

Diagnosing severe pre-eclampsia

Several different approaches have earlier been used by different associations in order to evaluate the severity of pre-eclampsia. According to the English The National Institute for Health and Clinical Excellence (NICE)⁹⁵ the severity of PE is evaluated only by basing it on blood pressure, while ACOG in 2002 estimated the severity of PE by basing it on blood pressure, but also on other indicators as presented in the Table 3⁸⁵.

According to the new ACOG classification of 2013, the use of the term moderate PE is not recommended but rather "PE without severe PE characteristics", while severe PE is one in which, according to ACOG, beside the basic criterion of elevated systolic blood pressure 140–160 mm Hg and/or diastolic blood pressure 90–110 mmHg also fulfils one of the following criteria: thrombocytopenia (a number of thrombocytes is lower than 100,000/ μ L), kidney insufficiency (concentration of creatinine in the serum above 97 μ mol/L), liver insufficiency (enzyme activity AST and ALT twice higher than the upper limit of the referential interval), appearance of the lung oedema or appearance of cerebral, i.e. visual symptoms. Severe pre-eclampsia is also elevated blood pressure $\geq 160/110$ combined with proteinuria or some of the other criteria of severe PE as presented in the Table 4.

Severe PE increases the morbidity and mortality of the mother and fetus and the characteristics of severe PE stated in the Table 4, when developed in the clinical picture, represent prognostically unfavourable, major factors, which make severe PE a serious disease, with a larger risk for an unfavourable outcome⁹⁶. One cannot but notice that proteinuria ≥ 5 g /24, as was already mentioned, is no longer a criterion for diagnosing severe PE. Moreover, IUGR is no longer considered

Table 1

Basic differences between early and late preeclampsia

Early onset preeclampsia (≤ 34 weeks of gestation)	Late onset preeclampsia (≥ 34 weeks of gestation)
A fetal diseases that is typically associated with placental dysfunction	Maternal disorder due to underlying maternal constitutional factors
Reduction in placental volume (Figure 3)	Normal placental volume
IUGR	Normal fetal growth
Abnormal uterine and umbilical artery Doppler measurement	Normal uterine and umbilical artery Doppler evaluation
Adverse maternal and fetal outcomes	Favorable maternal and neonatal outcomes
Low birth weight	Normal birth weight

IUGR – intrauterine growth restriction.

Table 2

American College of Obstetricians and Gynecologists (ACOG 2013) diagnostic criteria for preeclampsia

Blood pressure	- systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg on two occasions at least 4 h apart after 20 weeks of gestation in a woman with a previously normal blood pressure - systolic ≥ 160 mmHg or diastolic ≥ 110 mmHg, confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy
Proteinuria	- ≥ 300 mg per 24 h or - P/K ratio ≥ 0.3 - dipstick 1+ (used only if other quantitative methods not available)
Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following	
Thrombocytopeni	$\leq 100 \times 10^6/L$
Renal insufficiency	serum creatinine $> 97 \mu\text{mol/L}$, or a doubling of serum creatinine concentration in the absence of the renal disease
Impaired liver function	elevated blood concentrations of liver transaminases to twice normal concentration
Pulmonary edema	
Cerebral or visual symptoms	

Table 3

Severity classification of preeclampsia by the National Institute for Health and Clinical Excellence (NICE 2010) and the American College of Obstetricians and Gynecologists (ACOG 2002)

NICE (2010)	ACOG (2002)
Mild systolic 140–149 mmHg and/or diastolic 90–99 mmHg	Mild to moderate systolic 140–159 mmHg and/or diastolic 90–109 mmHg
Moderate systolic 150–159 mmHg and/or diastolic 100–109 mmHg	Severe (any two if present)
Severe systolic ≥ 160 mmHg and/or diastolic ≥ 110 mmHg	systolic ≥ 160 mmHg and/or diastolic ≥ 110 mmHg proteinuria $\geq 5\text{gr}/24\text{ h}$ or 3 +++ oliguria $\leq 500\text{ mL}/24\text{ h}$ cerebral or visual symptoms pulmonary edema or cyanosis epigastric or upper quadrant pain impaired liver function thrombocytopenia

NICE – The National Institute for Health and Clinical Excellence; ACOG – The American College of Obstetricians and Gynecologists.

Table 4

The American College of Obstetricians and Gynecologists (ACOG 2013) Severe characteristics of preeclampsia

Severe characteristics of preeclampsia (any of these characteristics)	
Blood pressure	systolic ≥ 160 mmHg or diastolic ≥ 110 mmHg on two occasions at least 4 h apart while the patient is on bed rest (unless antihypertensive therapy is initiated before this time)
Thrombocytopenia	$\leq 100 \times 10^6/L$
Progressive renal insufficiency	serum creatinine $> 97 \mu\text{mol/L}$, or a doubling of serum creatinine concentration in the absence of the renal disease
Liver insufficiency	elevated blood concentrations of liver transaminases to twice normal concentration or severe epigastric or upper quadrant pain
Pulmonary edema	
New-onset cerebral or visual disturbances	

ACOG – The American College of Obstetricians and Gynecologists; AST – aspartate aminotransferase; ALT – alanine aminotransferase.

red a criterion for severe PE because for IUGR there are special clinical guides.

Since it has become clear that PE is a multi-system disease due to endothelial dysfunction, it no longer surprises that there is a series of the so-called atypical forms of pre-eclampsia. This group of atypical PE includes pre-eclampsia without proteinuria, normotensive PE, PE before 20 gestation weeks but also PE manifested postpartum⁹⁷.

Gestational hypertension has been marked with elevated blood pressure $\geq 140/90$ mm Hg, without proteinuria, in pregnant women after 20 weeks of gestation, which used to be normotensive.

Eclampsia is the occurrence of tonic-clonic convulsive seizures in pregnant women with PE during pregnancy, during birth or immediately after birth.

Hypertension before conception or hypertension diagnosed in the first half of the pregnancy, before 20 ng $\geq 140/90$ mm Hg, is classified as chronic hypertension⁹⁸.

Superimposed pre-eclampsia diagnosis

In 17–25% pregnant women with chronic hypertension, a superimposed PE will also develop. In 50% of these pregnant women, PE will develop before 34 weeks of gestation⁹⁸. Pregnant women with superimposed PE have a worse forecast than those having only PE or only chronic hypertension. Establishing the diagnosis of superimposed PE is very often debatable and wrong⁹⁹. According to the ACOG work group, the diagnosis of superimposed PE is certainly possible in the following situations: sudden worsening of hypertension or the need to increase the therapy, while the regulation used to be good with smaller dosage of medicines; increased liver enzymes; decrease in the number of thrombocytes $\leq 100 \times 10^6/L$; pain in the upper right quadrant or occurrence of severe headache; pulmonic congestion or lung oedema; renal insufficiency measured by the increase of serum creatinine

$\geq 97\mu\text{mol/L}$; sudden occurrence of proteinuria or its major aggravation.

If the blood pressure is only elevated, $\leq 160/110$ mm Hg and if there is proteinuria, the superimposed PE can be marked as superimposed PE without the characteristics of severe PE. It is recommended to take care about the patient according to the PE protocol without any characteristics of severe pre-eclampsia. However, if beside chronic hypertension, there are manifestations of systemic damage, i.e. symptoms of severe PE (Table 4), the superimposed PE should be marked as the superimposed PE with characteristics of severe PE and should be taken care of according to the protocol for severe PE. From the classification aspect, both these forms are marked as superimposed PE; however, they will not be treated in the same way, as already stated⁸⁹.

Conclusion

Pre-eclampsia remains one of the most important obstetric entities. In the last decade, there has been a major progress in shedding light on the pathophysiology of pre-eclampsia. As a result of this knowledge, there has been a new approach to the classification of the hypertensive disease in pregnancy. Wider application of the recommended criteria by the American College of Obstetricians and Gynaecologists may assist in further studying of the aetiology and pathophysiology of pre-eclampsia but it must primarily enable the introduction of unique therapy protocols, as well as the prediction and prevention of pre-eclampsia.

Acknowledgements

This study was partially supported by the grant No 175036 from the Serbian Ministry of Education, Science and Technological Development.

R E F E R E N C E S

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Received on April 21, 2016.

Accepted on May 19, 2016.

Online First October, 2016.