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# 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 Kos [1]. 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 births [2]. 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 detected [2].

Why is the problem still significant? The PE incidence has grown by 25% in some of the developed Western world countries [5]. 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 simpliest 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 endothelic 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-

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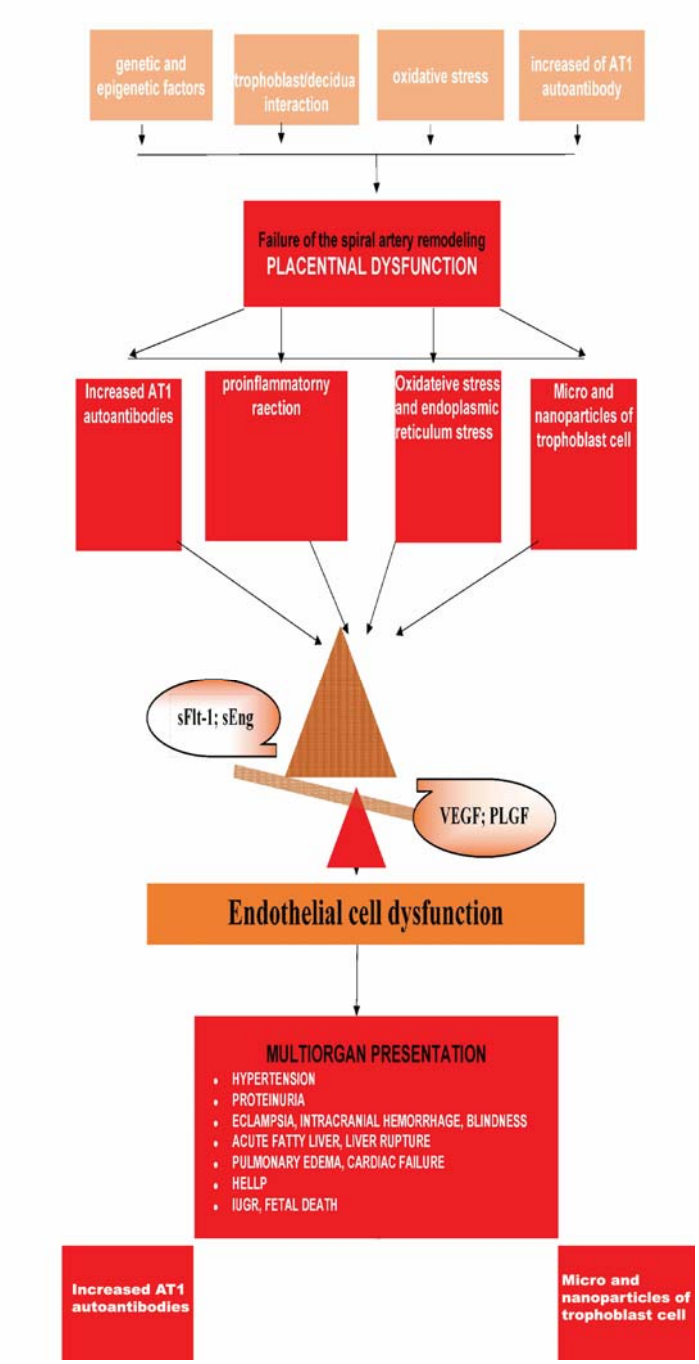


**Fig. 1 – The pathophysiology of preeclampsia.**
**sFlt-1 – the soluble fms-like tyrosine kinase 1; sEng – the soluble endoglin; PLGF – the placental growth factor; VEGF – the vascular endothelial growth factor; AT1 – the angiotensin receptors 1; IUGR – the intrauterine growth restriction; HELLP-hemolysis, 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 $m^2$ [12]. 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 gestation [13].

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) extravilloustrophoblast (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 1774 [14]. A century and a half ago, it was speculated that the spiral arteries undergo a change in their structure during pregnancy; in 1927 Otto Grosser [15] 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 layers [16]. 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 segment [17].

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 segment [20]. It is obvious that the spiral artery remodelling process is not a process taking place according to the all or nothing principle [16].

*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 proliferation [25]. 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 differentiation [26].

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 processes [27]. 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 response [30]. These two processes are mutually connected in a complex way and their balance plays a major role in the placental homeostasis [31].

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 complements [35]; 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 birth [39], PPROM [40] IUGR [41, 42] and pyelonephritis [43], 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 sEngwhich together with the proinflammatory cytokines lead to endothelial activation and vasospasm, i.e. to endothelial dysfunction [44]. 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 sEng [45]. 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 formof receptor belonging to the vascular endothelial growth factor (VEGF group) of the receptor (VEGFR-1). sFlt-1 is exprimated in an insoluble form (Flt-1) on endothelial cell membranesand 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-1receptors 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,

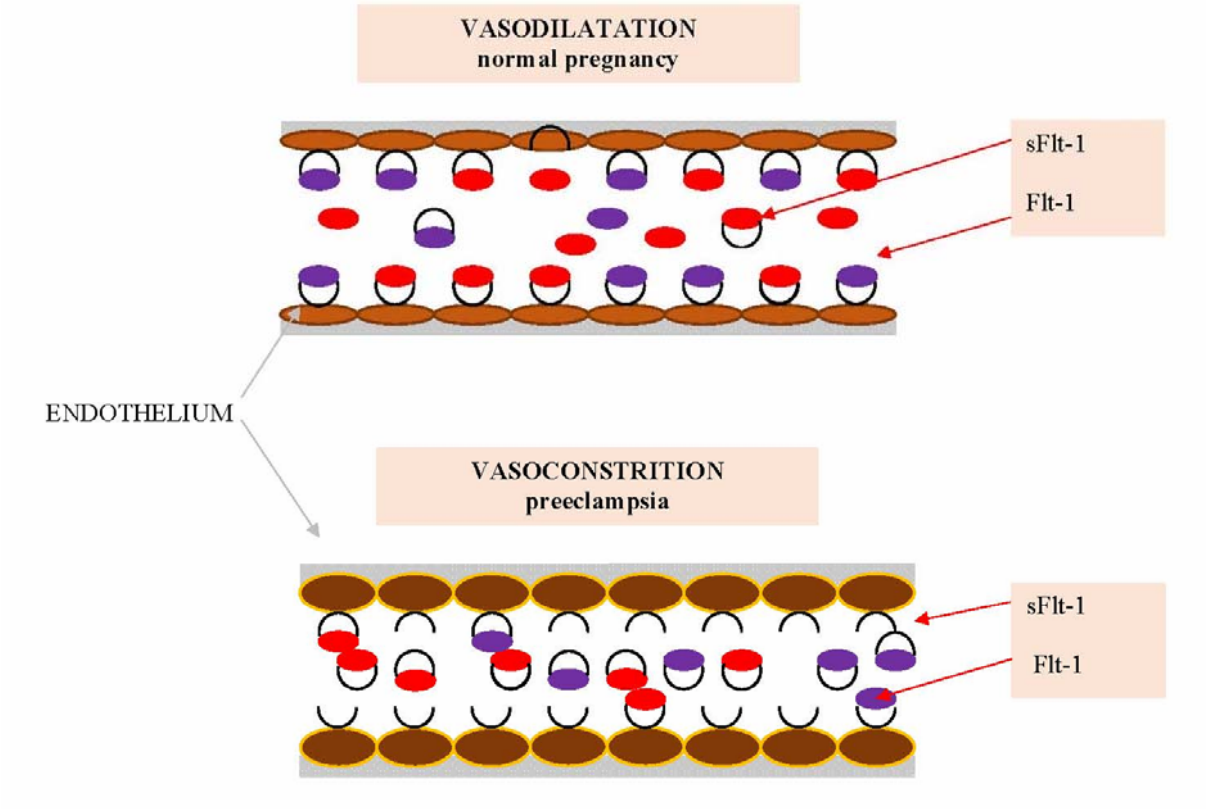


**Fig. 2 – The functioning of the placental growth factor and vascular endothelial growth factor. PLGF – placental growth factor; VEGF – vascular endothelial growth factor; sFlt-1 – soluble fms-like tyrosine kinase 1; Flt-1 – non soluble fms-like tyrosine kinase 1.**

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 ways [47]. 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 trimester [47]. Since in the first trimester there is the condition of lesser oxygenation, each hyperfusion and hyperoxigenation 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 markers [49–52]. simply and quickly define these markers and have been in commercial use since 2010 [49]. These markers have been incorporated into the German PE guide [58] 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 cells [59]. 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 restriction [60–63]. 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 apliphication effect of angiogenic factors [65].

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

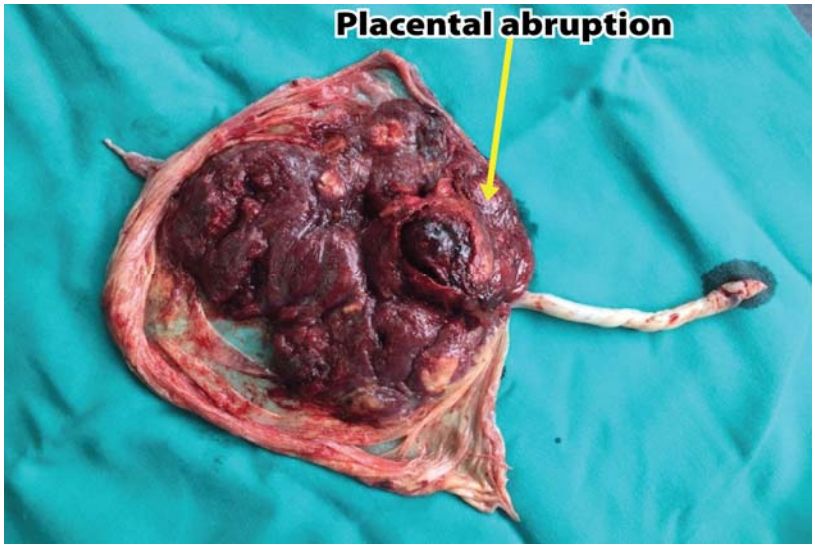


**Fig. 3 – Preeclamptic placenta**

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 to all questions but further potential clinical use of analysing (PLGF, sFlt-1, sEng) is yet to be expected [66].

*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 sEng [69]. Antibodies on AT1 receptors ead to the occurrence of hypertension through the activation of complements and through the stimulation of antiangiogenic factor production, sFlt-1 and sEng [70]. Lack of immunoassay for these specific AT1 receptors disturbs further understanding of their role and their possible application in clinical practice.

*Activation of trombocytes and thrombin*

Thrombocytopenia is one of the prognostically most unfavourable laboratory indicators in PE [71]. Thrombocytopenia sometimes precedes the occurrence of clinical signs of PE [71]. 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 B2 [72]. Vasoconstriction and thrombocytopenia in PE most probably occur as a result of reducing the prostacyclin synthesis [73]. The increase in vasoconstriction thromboxane A2 and reduction of vasodilation prostacyclin can be found in PE [74]. 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 cascade [75]. In literature there is a multitude of explanations for excessive creation of thrombin in PE [76]. 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 expression [78]. MiRNAs are included in the regulation of trophoblast proliferation, apoptosis, migration and invasion [79]. 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 outcome [82].

*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 associations [89]. 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-eclampsiais 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 PE [89].

Pre-eclampsia manifests itself as early and late PE; these forms are nowadays considered as various PE entities/subgroups [90]. 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 ≥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 ≥140/90 mm Hg, measured twice with a gap of 4 h (when one measures the blood pressure value ≥ 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 thrombocytesis less than 100.000/μL), kidney insufficiency (concentration of creatinine in serum above 97 μmol/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 3 [85].

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/μL), kidney insufficiency (concentration of creatinine in the serum above 97 μmol/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 ≥ 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 theTable 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 outcome [96]. One cannot but notice that proteinuria ≥ 5g /24, as was already mentioned, is no longer a criterion for diagnosing severe PE. Moreover, IUGR is no longer conside

**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 Obstehricians 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<br>- 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<br>- P/K ratio ≥ 0.3<br>- 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 | ≤ 100 x $10^6$/L |
| Renal insufficiency | serum creatinine > 97μmol/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 Hcalth and Clinical Exellence (NICE 2010) and the American College of Obstetricians and Gynecologists (ACOG 2002)**

| NICE (2010) | ACOG (2002) |
|---|---|
| Mild<br>systolic 140–149 mmHg and/or<br>diastolic 90–99 mmHg | Mild to mederate<br>systolic 140–159 mmHg and/or<br>diastolic 90–109 mmHg |
| Moderate<br>systolic 150–159 mmHg and/or<br>diastolic 100–109 mmHg | Severe<br>(any two if present) |
| Severe<br>systolic ≥ 160 mmHg and/or<br>diastolic ≥ 110mmHg | systolic ≥ 160 mmHg and/or<br>diastolic ≥ 110 mmHg<br>proteinuria ≥ 5gr/24 h or 3 +++<br>oliguria ≤ 500 mL/24 h<br>cerebral or visual symptoms<br>pulmonary edema or cyanosis<br>epigastric or upper quadrant pain<br>impaired liver function<br>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 | ≤ 100 x $10^6$/L |
| Progresisve renal insufficiency | serum creatinine > 97μmol/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 postpartum [97].

Gestational hypertension has been marked with elevated blood pressure ≥ 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 ≥ 140/90 mm Hg, is classified as chronic hypertension [98].

*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 gestation [98]. 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 wrong [99]. 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 ≤ $100 \times 10^6$/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 ≥ 97μmol/L; sudden occurrence of proteinuria or its major aggravation.

If the blood pressure is only elevated, ≤ 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 stated [89].

## 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.

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## R E F E R E N C E S

1. *Yapijakis C.* Hippocrates of Kos, the father of clinical medicine, and Asclepiades of Bithynia, the father of molecular medicine. Review. In Vivo 2009; 23(4): 507−14.
2. *Abalos E, Cuesta C, Carroli G, Qureshi Z, Widmer M, Vogel JP,* et al. WHO Multicountry Survey on Maternal and Newborn Health Research Network. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG 2014; 121(Suppl 1):14−24.
3. *Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D*, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. BJOG 2011; 118(Suppl1): 1−203.
4. *Lisonkova S, Joseph KS.* Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. Am J Obstet Gynecol 2013; 209(6): 544.e1−544.e12.
5. *Wallis AB, Saftlas AF, Hsia J, Atrash H*K. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987-2004. Am J Hypertens 2008; 21(5): 521−6.
6. *Word Health Organisation.* The world health report: Make every mother and child count. Geneva: WHO; 2005. Available from: http//www-who.int/whr/2005/whr2005_en.pdf
7. *Duley L.* Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. Br J Obstet Gynaecol 1992; 99(7): 547−53.
8. *Callaghan WM, Mackay AP, Berg CJ.* Identification of severe maternal morbidity during delivery hospitalizations, United States, 1991-2003. Am J Obstet Gynecol 2008; 199(2): 133.e1−8.
9. *Kuklin EV, Ayala C, Callaghan WM.* Hypertenesive disorders and severe obstetric morbidity in the United State. Obstet Gynecol 2009; 113(6): 1299−306.
10. *Bellamy L, Casas JP, Hingorani AD, Williams DJ.* Pre-eclampsia and risk of cardiovascular disease and cancer in later life: Systematic review and meta-analysis. BMJ 2007; 335(7627): 974.
11. *Armanini D, Sabbadin C, Donà G, Andrisani A, Ambrosini G, Bordin L.* Maternal and fetal outcomes in Preeclampsia: Interrelations between Insulin Resistance, Aldosterone, Metabolic Syndrome, and Polycystic Ovary Syndrome. J Clin Hypertens (Greenwich) 2015; 17(10): 783−5.

12. *Burton GJ, Jauniaux E.* Sonographic, stereological and Doppler flow velocimetric assessments of placental maturity. Br J Obstet Gynaecol 1995; 102(10): 818−25.
13. *Burton GJ, Charnock-Jones DS, Jauniaux E.* Regulation of vascular growth and function in the human placenta. Reproduction 2009; 138(6): 895−902.
14. *Hunter W.* Anatomia uteri humani gravidi tabulis illustrata. The Anatomy of the Human Gravid Uterus exhibited in Figures. Birmingham: John Baskerville, 1774.
15. *Grosser O.* Frühentwicklung, Eihautbildung und placentation des Menschen und der Säugetiere. München: J.F. Bergmann; 1927.
16. *Lyall F, Robson S, Bulmer J.* Spiral artery remodeling and trophoblast invasion in preeclampsia and fetal growth restriction. Hypertension 2013; 62(6): 1046−54.
17. *Pijnenborg R, Bland JM, Robertson WB, Brosens I.* Uteroplacental arterial changes related to interstitial trophoblast migration in early human pregnancy. Placenta 1983; 4(4): 397−413.
18. *Khong TY.* Placental vascular development and neonatal outcome. Semin Neonatol 2004; 9(4): 255−63.
19. *Romero R, Dey SK, Fisher SJ.* Preterm labor: One syndrome, many causes. Science 2014; 345(6198): 760−5.
20. *Brosens I, Pijnenborg R, Vercruysset L, Romero R.* The Great Obstetrical Syndromes are associated with disorders of deep placentation. Am J Obstet Gynecol 2011; 204(3): 193−201.
21. *Mistry HD, Wilson V, Ramsay MM, Symonds ME, Broughton Pipkin F.* Reduced selenium concentrations and glutathione peroxidase activity in preeclamptic pregnancies. Hypertension 2008; 52(5): 881−8.
22. *Poston L, Raijmakers MT.* Trophoblast oxidative stress, antioxidants and pregnancy outcome: A review. Placenta 2004; 25 Suppl A: S72−8.
23. *Zeeman GG, Dekker GA, van Geijn HP, Kraayenbrink AA.* Endothelial function in normal and pre-eclamptic pregnancy: a hypothesis. Eur J Obstet Gynecol Reprod Biol 1992; 43(2): 113−22.
24. Critchley H, MacLean A, Poston L, Walker JJ. Pre-eclampsia. London: RCOG Press; 2004.
25. *Duracková Z.* Some current insights into oxidative stress. Physiol Res 2010; 59(4): 459−69.
26. *Genbacev O, Zhou Y, Ludlow JW, Fisher SJ.* Regulation of human placental development by oxygen tension. Science 1997; 277(5332): 1669−72.
27. *Lee J, Giordano S, Zhang J.* Autophagy, mitochondria and oxidative stress: cross-talk and redox signaling. Biochem J 2012; 441(2): 523−40.
28. *Zhang K, Kaufman RJ.* From endoplasmic-reticulum stress to the inflammatory response. Nature 2008; 454(7203): 455−62.
29. *Burton GJ, Yung HW, Cindrova-Davies T, Charnock-Jones DS.* Placental endoplasmic reticulum stress and oxidative stress in the pathophysiology of unexplained intrauterine growth restriction and early onset preeclampsia. Placenta 2009; 30 Suppl A: S43−8.
30. *Redman CW, Sargent IL.* Microparticles and immunomodulation in pregnancy and pre-eclampsia. J Reprod Immunol 2007; 76(1−2): 61−7.
31. *Wu F, Tian FJ, Lin Y.* Oxidative Stress in Placenta: Health and Diseases. Biomed Res Int 2015; 2015: 293271.
32. *Vince GS, Starkey PM, Austgulen R, Kwiatkowski D, Redman CW.* Interleukin-6, tumour necrosis factor and soluble tumour necrosis factor receptors in women with pre-eclampsia. Br J Obstet Gynaecol 1995; 102(1): 20−5.
33. *Cackovic M, Buhimschi CS, Zhao G, Funai EF, Norwitz ER, Kuczynski E,*et al. Fractional excretion of tumor necrosis factor-alpha in women with severe preeclampsia. Obstet Gynecol 2008; 112(1): 93−100.
34. *Sunder-Plassmann G, Derfler K, Wagner L, Stockenhuber F, Endler M, Nowotny C, et al.*Increased serum activity of interleukin-2 in patients with pre-eclampsia. J Autoimmun 1989; 2(2): 203−5.
35. *Wang W, Irani RA, Zhang Y, Ramin SM, Blackwell SC, Tao L,* et al. Autoantibody-mediated complement C3a receptor activation contributes to the pathogenesis of preeclampsia. Hypertension 2012; 60(3): 712−21.
36. *Ahmad S, Ahmed A.* Elevated placental soluble vascular endothelial growth factor receptor-1 inhibits angiogenesis in preeclampsia. Circ Res 2004; 95(9): 884−91.
37. *Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF,* et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med 2004; 350(7): 672−83.
38. *Venkatesha S, Toporsian M, Lam C, Hanai J, Mammoto T, Kim YM,* et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. Nat Med 2006; 12(6): 642−9.
39. *Gervasi MT, Chaiworapongsa T, Naccasha N, Blackwell S, Yoon BH, Maymon E,* et al. Phenotypic and metabolic characteristics of maternal monocytes and granulocytes in preterm labor with intact membranes. Am J Obstet Gynecol 2001; 185(5): 1124−9.
40. *Gervasi MT, Chaiworapongsa T, Naccasha N, Pacora P, Berman S, Maymon E,* et al. Maternal intravascular inflammation in preterm premature rupture of membranes. J Matern Fetal Neonatal Med 2002; 11(3): 171−5.
41. *Sabatier F, Bretelle F, D'ercole C, Boubli L, Sampol J, Dignat-George F.* Neutrophil activation in preeclampsia and isolated intrauterine growth restriction. Am J Obstet Gynecol 2000; 183(6): 1558−63.
42. *Ogge G, Romero R, Chaiworapongsa T, Gervasi MT, Pacora P, Erez O,* et al. Leukocytes of pregnant women with small-for-gestational age neonates have a different phenotypic and metabolic activity from those of women with preeclampsia. J Matern Fetal Neonatal Med 2010; 23(6): 476−87.
43. *Naccasha N, Gervasi MT, Chaiworapongsa T, Berman S, Yoon BH, Maymon E,* et al. Phenotypic and metabolic characteristics of monocytes and granulocytes in normal pregnancy and maternal infection. Am J Obstet Gynecol 2001; 185(5): 1118−23.
44. *Borzychowski AM, Sargent IL, Redman CW.* Inflammation and preeclampsia. Semin Fetal Neonatal Med 2006; 11(5): 309−16.
45. *Ramma W, Buhimschi IA, Zhao G, Dulay AT, Nayeri UA, Buhimschi CS,* et al. The elevation in circulating anti-angiogenic factors is independent of markers of neutrophil activation in preeclampsia. Angiogenesis 2012; 15(3): 333−4.
46. *Shibuya M.* Vascular endotelial growth factor and its receptor system: Physiological functions in angiogenesis and pathological roles in various diseases. J Biochem 2013; 153(1): 13−9.
47. *Ahmed A, Dunk C, Ahmad S, Khaliq A.* Regulation of placental vascular endothelial growth factor (VEGF) and placenta growth factor (PlGF) and soluble Flt-1 by oxygen: A review. Placenta 2000; 21 Suppl A: S16−24.
48. *Forsythe JA, Jiang BH, Iyer NV, Agani F, Leung SW, Koos RD,* et al. Activation of vascular endothelial growth factor gene transcription by hypoxiainducible factor 1. Mol Cell Biol 1996; 16(9): 4604−13.
49. *Verlohren S, Galindo A, Schlembach D, Zeisler H, Herraiz I, Moertl MG,* et al. An automated method for the determination of the sFlt-1/PlGF ratio in the assessment of preeclampsia. Am J Obstet Gynecol 2010; 202(2): 161.e1−161.e11.
50. *Verlohren S, Herraiz I, Lapaire O, Schlembach D, Moertl M, Zeisler H,* et al. The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. Am J Obstet Gynecol 2012; 206(1): 58.e1−8.
51. *Verlohren S, Herraiz I, Lapaire O, Schlembach D, Zeisler H, Calda P,* et al. New gestational phase-specific cutoff values for the use of the soluble fms-like tyrosine kinase-1/placental growth factor ratio as a diagnostic test for preeclampsia. Hypertension 2014; 63(2): 346−52.
52. *Álvarez-Fernández I, Prieto B, Rodríguez V, Ruano Y, Escudero AI, Álvarez FV.* New biomarkers in diagnosis of early onset preeclampsia and imminent delivery prognosis. Clin Chem Lab Med 2014; 52(8): 1159−68.

53. *Pinheiro CC, Rayol P, Gozzani L, Reis LM, Zampieri G, Dias CB,* et al. The relationship of angiogenic factors to maternal and neonatal manifestations of early-onset and late-onset preeclampsia. Prenat Diagn 2014; 34(11): 1084−92.
54. *Chaiworapongsa T, Romero R, Savasan ZA, Kusanovic JP, Ogge G, Soto E,* et al. Maternal plasma concentrations of angiogenic/anti-angiogenic factors are of prognostic value in patients presenting to the obstetrical triage area with the suspicion of preeclampsia. J Matern Fetal Neonatal Med 2011; 24(10): 1187-207.
55. *Schaarschmidt W, Rana S, Stepan H.* The course of angiogenic factors in early- vs. late-onset preeclampsia and HELLP syndrome. J Perinat Med 2013; 41(5): 511−6.
56. *Chaiworapongsa T, Romero R, Korzeniewski SJ, Kusanovic JP, Soto E, Lam J,* et al. Maternal plasma concentrations of angiogenic/antiangiogenic factors in the third trimester of pregnancy to identify the patient at risk for stillbirth at or near term and severe late preeclampsia. Am J Obstet Gynecol 2013; 208(4): 287.e1−287.e15.
57. *Chaiworapongsa T, Romero R, Korzeniewski SJ, Cortez JM, Pappas A, Tarca AL,* et al. Plasma concentrations of angiogenic/anti-angiogenic factors have prognostic value in women presenting with suspected preeclampsia to the obstetrical triage area: a prospective study. J Matern Fetal Neonatal Med 2014; 27(2): 132−44.
58. German guideline. 2015. Available from: http://www.awmf.org/uploads/tx_szleitlinien/015-018l_S1_Diagnostik_Therapie_hypertensiver_Schwangerschaftserkrankungen_2014-01.pdf [accessed 2015 January].
59. *Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, Mclaughlin MK.* Preeclampsia: An endothelial cell disorder. Am J Obstet Gynecol 1989; 161(5): 1200−4.
60. *Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF*, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med 2004; 350(7): 672−83.
61. *Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S,* et al, Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 2003; 111(5): 649−58.
62. *Maharaj AS, Walshe TE, Saint-Geniez M, Venkatesha S, Maldonado AE, Himes NC,* et al. VEGF and TGF-beta are required for the maintenance of the choroid plexus and ependyma. J Exp Med 2008; 205(2): 491−501.
63. *Lu F, Longo M, Tamayo E, Maner W, Al-Hendy A, Anderson GD*, et al. The effect of over-expression of sflt-1 on blood pressure and the occurrence of other manifestations of preeclampsia in unrestrained conscious pregnant mice. Am J Obstet Gynecol 2007; 196(4): 396.e1−7; discussion 396.e7.
64. *Thadhani R, Kisner T, Hagmann H, Bossung V, Noack S, Schaarschmidt W*, et al. Pilot study of extracorporeal removal of soluble fms-like tyrosine kinase 1 in preeclampsia. Circulation 2011; 124(8): 940−50.
65. *Ramma W, Ahmed A.* Is inflammation the cause of pre-eclampsia?. Biochem Soc Trans 2011; 39(6): 1619−27.
66. *Herraiz I, Simón E, Gómez-Arriaga PI, Martínez-Moratalla JM, García-Burguillo A, López JE,* et al. Angiogenesis-Related Biomarkers (sFlt-1/PLGF) in the Prediction and Diagnosis of Placental Dysfunction: An Approach for Clinical Integration. Int J Mol Sci 2015; 16(8): 19009−26.
67. *Gant NF, Chand S, Whalley PJ, Macdonald PJ.* The nature of pressor responsiveness to angiotensin II in human pregnancy. Obstet Gynecol 1974; 43(6): 854.
68. *Dechend R, Luft FC, Lindheimer MD.*. Agonistic autoantibody-mediated disease. In: *Lindheimer MD, Roberts JM, Cunningham FG,* editors. Chesley's Hypertensive Disorders in Pregnancy. 3rd ed. San Diego: Elsevier; 2009. p. 287−96.
69. *Parrish MR, Murphy SR, Rutland S, Wallace K, Wenzel K, Wallukat G,* et al. The effect of immune factors, tumor necrosis factor-alpha, and agonistic autoantibodies to the angiotensin II type I receptor on soluble fms-like tyrosine-1 and soluble endoglin production in response to hypertension during pregnancy. Am J Hypertens 2010; 23(8): 911−6.
70. *Girardi G, Yarilin D, Thurman JM, Holers VM, Salmon JE.* Complement activation induces dysregulation of angiogenic factors and causes fetal rejection and growth restriction. J Exp Med 2006; 203(9): 2165−75.
71. *Romero R, Vizoso J, Emamian M, Duffy T, Riely C, Halford T,* et al. Clinical significance of liver dysfunction in pregnancy-induced hypertension. Am J Perinatol 1988; 5(2): 146−51.
72. *Kenny LC, Baker PN, Cunningham FG.* Platelets, coagulation, and the liver. In: *Lindheimer MD, Roberts JM, Cunningham GC,* editors. Chesley's hypertensive disorders in pregnancy. San Diego: Elsevier; 2009. p. 335–51.
73. *Romero R, Lockwood C, Oyarzun E, Hobbins JC.* Toxemia: new concepts in an old disease. SeminPerinatol 1988; 12(4): 302−23.
74. *Walsh SW.* Preeclampsia: an imbalance in placental prostacyclin and thromboxane production. Am J Obstet Gynecol 1985; 152(3): 335−40.
75. *Cadroy Y, Grandjean H, Pichon J, Desprats R, Berrebi A, Fournié A*, et al. Evaluation of six markers of haemostatic system in normal pregnancy and pregnancy complicated by hypertension or pre-eclampsia. Br J Obstet Gynaecol 1993; 100(5): 416−20.
76. *Chaiworapongsa T, Yoshimatsu J, Espinoza J, Kim YM, Berman S, Edwin S*, et al. Evidence of in vivo generation of thrombin in patients with small-for-gestational-age fetuses and pre-eclampsia. J Matern Fetal Neonatal Med 2002; 11(6): 362−7.
77. *Kobayashi T, Tokunaga N, Sugimura M, Kanayama N, Terao T.* Predictive values of coagulation/fibrinolysis parameters for the termination of pregnancy complicated by severe preeclampsia. Semin Thromb Hemost 2001; 27(2): 137−141.
78. *Ambros V.* The functions of animal microRNAs. Nature 2004; 431(7006): 350−5.
79. *Fu G, Brkic J, Hayder H, Peng C.* MicroRNAs in human placental development and pregnancy complications. Int J Mol Sci 2013; 14(3): 5519−44.
80. *Wang S, Olson AE.* AngiomiR-skey regulators of angiogenesis. Curr Opin Genet 2009; 19(3): 205−11.
81. *Wu F, Yang Z, Li G.* Role of specific microRNAs for endothelial function and angiogenesis. Biochem Biophys Res Commun 2009; 386(4): 549−53.
82. *Abdelhalim RM, Ramadan DI, Zeyada R, Nasr AS, Mandour IA.* Circulating Maternal Total Cell-Free DNA, Cell-Free Fetal DNA and Soluble Endoglin Levels in Preeclampsia: Predictors of Adverse Fetal Outcome?, A Cohort Study. Mol Diagn Ther 2016; 20(2): 135−49.
83. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000; 183(1): S1−S22.
84. *Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM.* The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society fort he Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 2001; 20(1): 9−14.
85. *ACOG Committee on Obstetric Practice.* ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 2002; 77(1): 67−75.
86. *Lowe SA, Brown MA, Dekker GA, Gatt S, McLintock CK, McMahon LP,* et al. Society of Obstetric Medicine of Australia and New Zealand. Guidelines for the management of hypertensive disorders of pregnancy 2008. Aust N Z J Obstet Gynaecol 2009; 49(3): 242−6.
87. *Turner JA.* Diagnosis and management of pre-eclampsia: An update. Int J Womens Health 2010; 2: 327−37.

88. National Collaborating Centre for Women's and Children's Health 2011. Commissioned by the National Institute for Health and Clinical Excellence. Available from: http://www.nice.org.uk/nicemedia/live/13098/50475/50475.pdf [accessed 2011 May 31].
89. *American College of Obstetricians and Gynecologists*. Task Force on Hypertension in Pregnancy . Hypertension in Pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013; 122(5): 1122−31.
90. *Sibai B, Dekker G, Kupferminc M*. Pre-eclampsia. Lancet 2005; 365(9461): 785−99.
91. *Lisonkova S, Sabr Y, Mayer C, Young C, Skoll A, Joseph KS*. Maternal morbidity associated with early-onset and late-onset preeclampsia. Obstet Gynecol 2014; 124(4): 771−81.
92. *von Dadelszen P, Magee LA, Roberts JM*. Subclassification of preeclampsia. Hypertens Pregnancy 2003; 22(2): 143−8.
93. *Thornton CE, Makris A, Ogle RF, Tooher JM, Hennessy A*. Role of proteinuria in defining pre-eclampsia: Clinical outcomes for women and babies. Clin Exp Pharmacol Physiol 2010; 37(4): 466−70.
94. *Homer CS, Brown MA, Mangos G, Davis GK*. Non-proteinuric pre-eclampsia: A novel risk indicator in women with gestational hypertension. J Hypertens 2008; 26(2): 295−302.
95. *National Collaborating Centre for Women's and Children's Health (UK)*. Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy. London: RCOG Press; 2010.
96. *von Dadelszen P, Payne B, Li J, Ansermino JM, Pipkin BF, Cote AM*, et al. Prediction of adverse maternal outcomes in preeclampsia: Development and valdation of the fullPIERS model. PIERS Study Group. Lancet 2011; 377(9761): 219−27.
97. *Ditisheim A, Boulvain M, Irion O, Pechère-Bertschi A*. Atypical presentation of preeclampsia. Rev Med Suisse 2015; 11(485): 1655−8. (French)
98. *Seely EW, Ecker J*. Clinical practice. Chronic hypertension in pregnancy. N Engl J Med 2011; 365(5): 439−46.
99. *Fisher KA, Luger A, Spargo BH, Lindheimer MD*. Hypertension in pregnancy: clinical- pathological correlations and remote prognosis. Medicine (Baltimore) 1981; 60(4): 267.

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