Current insights into the study and management of preeclampsia

Maria Bari[1,2], G. Peltecu[1,2], Alina Veduta[1], Andra Atanasiu[1]

1. Spitalul Clinic de Obstetrică şi Ginecologie Filantropia, Bucharest (Romania)
2. UMF "Carol Davila", Bucharest (Romania)

Correspondence:
Dr. Maria Bari
e-mail: bari.maria@yahoo.com

Abstract

Preeclampsia represents a disorder which is responsible for an important procent of the maternal and perinatal morbidity and mortality in general, though it afects only 2% of the total pregnancies. In all cases of preeclampsia, only one quarter (0.5% of pregnacies) represents the severe forms or those with an early onset; these forms present in fact, a great influence on the morbidity and mortality rates. Currently, gestational hypertension has one of the most extensive research in obstetrics. Therefor, new data on preeclampsia is rapidly discovered. The recent insights into the pathogenesis of preeclampsia provide, not only theoretical basis, but also a practical use in order to prevent preeclampsia, by identifying some screening tools that would accurately assess each individual risk for preeclampsia. Early preventation of preeclampsia is of great importance, as it is recommended by National Institute for Clinical Excellence from Great Britain, one of the most reliable European medical forums. This recommendation from 2008 describes the assesment of each individual risk for hypertension disorders, during the first antenatal counselling, so that it can be developed some personalised antenatal care plan. The assesment of each individual risk for hypertension related-pregnancy, and finally, the eficient management of preeclampia can be achievd, only by the understanding of the physiopatology and etiolopathology of this complication. The aim of the present review is to describes the two important aspects: analysis of preeclampsia's mechanisms and means of prevention by evaluating each individual risk of hypertension-related pregnancy.
Keywords: *preeclampsia, disorder, mecanism, prevention, hypertension.*

Abbreviated words: *HLA= human leukocyte antigen; NK= natural killer; KIR= killer IgG-like receptor; Th= T helper; TNF= tumor necrosis factor; IL= interleukin; IFN= interferon; VEGF= vascular endothelial growth factor; PGF= placenta growth factor; sFlt-1= soluble fms-like tyrosine kinase-1; sEng= soluble endoglin; TGF= transforming growth factor; IUGR= intrauterine growth restriction; DNA= deoxyribonucleic acid; PAPP-A= pregnancy-associated plasma protein A; FMF= Fetal Medicine Foundation; ADAM12= a disintegrin and metalloprotease 12; PP-13= placenta protein-13; PTX-3= pentraxin-3.*

1. Etiology and pathogenesis of preeclampsia

The theories regarding the etiology and pathogenesis of preeclampsia include: the genetic predisposition, the immunological basis, the alteredd angiogenic balance, the placental hypoxia, the systemic release of placental necrotic material. These hypotheses partially merge, in fact they all play a contributor role into the pathophysiology of preeeclampsia[1,2].

The genetic predisposition theory is based on the well-known fact that family history is a high risk factor for preeclampsia[3]. It is well established that primigravid women with affected mother or sisters have a three - to thirty - fold higher risk of the disease than primigravid women with no such history[4,5]; some studies of preeclampsia in twins showed some consistent data, as well, but no absolute facts4. It is unlikely that preeclampsia presents one genetic pattern, although the polygenic pattern doesn't fit either.

The genetic linkage analysis has identified a few potentially significant loci at 2p12, 2p25, 9p136, but the results have not been replicated consistently in all populations. Furthermore, there are large studies that couldn't demonstrate any linkage present in preeclampsia[6,7].

The maternal contribution to development of preeclampsia can be partially explained by epigenetic control/fetal programming[8,9]. Moreover, if the female fetus is derived from a pregnancy with placental failure, it would have a higher risk for metabolic imbalance, endothelial dysfunction and even preeclampsia, during adult life[10]. Therefore, a study of sisters with preeclampsia, whose mother never had this disease, would be of great interest.

A feature of preeclampsia genetic determinism is the special type paternal contribution. A woman who becomes pregnant by a man whose previous partner had preeclampsia is at higher risk of developing the disorder although the pregnancy with the previous partner was normotensive. This fact is suggested by the involvement of a genetic incompatibility, rather than of an own-self genetic predisposition. Recent studies describe the preeclampsia development basis as the genetic incompatibility between both paternal and fetal haplotype human leukocyte antigen (HLA-C), natural killer (NK), and killer IgG-like receptor (KIR) antibodies (with immunomodulatory role) from the maternal decidua[12].

The extravillous trophoblast cells express the classical molecules (polymorphic) of histocompatibility class

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I, HLA-C, but only during the first trimester, in small amounts; it functions as a ligand-receptor for the maternal decidual NK, with great influence on their activity. A multitude of combinations are possible between the fetal HLA-C and the maternal KIR genotype.

Most interactions HLA-C/KIR are activating the cells decidual NK, except HLA-C2/ KIR-A, which constantly have inhibitive effects (HLA-G type). The interaction between the fetal haplotype HLA-C2 and the maternal KIR AA genotype has little effect on NK cell activation, during the early stages of placental development; it has been associated with a greatly increased risk of preeclampsia[10,12].

The immunological theory is based on the excessive maternal inflammatory response, suggesting that preeclampsia occurs more frequently in cases of reduced exposure of the mother to paternal antigens, prior to pregnancy. It's been established that increasing 'doses' of paternal antigens associates a high risk for preeclampsia: twin pregnancy, mola pregnancy, (diandric triploids). Consistent with this hypothesis is the observation that low tolerance of the maternal immune system towards the semiallogenic fetus, would be the cause of a more superficial trophoblastic invasion, leading to the onset of preeclampsia (maternal-paternal immune maladaptation).

Pregnancy itself has been described as a state of controlled mild inflammation situation at both local and systemic level; the local immunological response is of a unique type, allowing and supporting the trophoblast development. Preeclampsia is characterised by the absence of the particular feature of the maternal immune response at the endometrial/myometrial level which makes possible the trophoblast remodelling of spiral arteries, just like in normal pregnancies. Fetal cells seem to be in an impaired balance with the maternal cell, at the decidual level, unlike normal pregnancies, therefore the trophoblastic invasion is limited by a maternal extensive and maladapted immune response.

The immunological theory considers the excessive inflammatory systemic response as a main result of the low maternal tolerance towards the fetal antigens. The altered activation of T helper $(Th)_1/Th_2$ cells is thought to be the primary event of the local immune maladaption, causing the final systemic endothelial dysfunction. Specific Th_1 inflammatory cytokines are tumor necrosis factor (TNF)α, interleukin (IL_6), IL_{12} and interferon (IFN)-γ. Macrophages, both placental and systemic, and monocytes release high levels of TNF, IL_6 and IL_{12} in preeclampsia. IL_{12} stimulates NK cell production of IFN-γ and naive T lymphocytes; TNF enhances the monocyte production of IL_{12}, even more. Therefore, a positive feedback loop regarding the Th1 lymphocytes activation has been initiated, leading eventually to the full-blown clinical syndrome of preeclampsia. Although attractive, this hypothesis overlaps partially with the genetic determinism theory of preeclampsia, and remains to be fully validate.

The main counter argument (or the most important aspect that remains to be included in a certain pattern) is that there are certain cases of preeclampsia, with already altered maternal conditions, in which the pre-existing vascular dysfunction plays a crucial role[10,13]. However, in these cases, it seems that the systemic effects precede the locally placental changes (but it doesn't necessarily involve direct causal relationships between them).

2. Imbalance of angiogenesis and anti-angiogenesis factors

It is well acknowledged that in preeclampsia, the increased production of anti-angiogenesis factors disturb the balance of angiogenesis[14,15]. Nevertheless, it hasn't been entirely established whether this imbalance represents an epiphenomenon or the actual trigger for preeclampsia onset. The second assumption has solid basis, since angiogenesis factors are those directly involved into the vascular placental development (villositar level)[16-21]. Normally, vascular endothelial growth factor (VEGF) and its receptor VEGFR-2 are expressed intensely in early gestation period and decline towards term, whereas VEGFR-1/sVEGFR-1 and placenta growth factor (PGF) significantly increase in late gestation[60]. The anti-angiogenic factors, which probably control the activity of angiogenic factors, may naturally occur in normal pregnancies as well, soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng) are the best known and most studied ones[16-21]. sFlt-1 represents the soluble isoform of VEGFR-1, which naturally occurs by the alternative splicing of the messenger ribonucleic acid of the growth factor VEGF[15,17-20]. It has been demonstrated that the genes for Flt-1 are carried on chromosome 13, therefore trisomy 13 pregnancies are known to associate a higher risk of preeclampsia.

sEng is a coreceptor for transforming growth factor (TGF)-β[1,3]. A novel placenta-derived soluble form of Eng, referred to as sEng, is an anti-angiogenic protein that appears to be another important mediator of preeclampsia[15,17-20].

Preeclampsia early studies have suggested that the production of anti-angiogenic factors is significantly increased, inhibiting the effects of VEGF and PGF, leading to endothelial dysfunction. Unfortunately, recent studies of sFlt-1 serum measurements in normal pregnancies versus preeclamptic pregnancies have failed to establish whether sFlt-1 can be used as a prevention maker for preeclampsia[22].

Placental hypoxia plays a key role in preeclampsia. Hypoperfusion appears to be both a cause and a consequence of abnormal placental development and systemic dysfunction in preeclampsia[6]. A causal relationship between poor placental perfusion, abnormal placental development, and preeclampsia is supported by the following examples. Animal models have successfully reproduced at least some of the findings of preeclampsia, by the mechanically decrease of the uteroplacental blood flow. Preeclampsia is more common in women

who live at high altitudes due to the pre-placental hypoxia.

The placentation mechanisms are sensitive to oxygen concentration in the environment. Placental hypoxia which is physiological in the early stages of the pregnancy causes the stabilization of hypoxia-inducible factor 1α and increased concentrations of TGF-β_3, maintaining the extravillous trophoblast into a proliferative and noninvasive state (ensuring the presence of a sufficient population of trophoblast cells). The TGF-β_3 effect of limiting the trophoblastic invasion is consistent with the well-known anti-invasive and anti-proliferative role of TGF-β family[23,24].

Once the maternal placental circulation has been established at 10-12 weeks of pregnancy, the placental oxygen level increases and TGF-β_3 levels decrease, allowing the trophoblastic invasion of the spiral arteries to take place. It has been suggested that the persistence of placental hypoxia after 10-12 weeks of pregnancy, leads to immature trophoblast development (intermediate stage characterized by the expression of integrin α_5), abnormal remodelling of spiral arteries and onset of preeclampsia. Therefore, low oxygen levels in placenta, beyond the first trimester of pregnancy, triggers the switch of integrins, a characteristic of preeclampsia. Preeclamptic placentas remain positive for α_5, fail to express α_1 integrin, express fibronectin in excess and a large number of trophoblastic cells in proliferative intermediate stage; finally the extravillous trophoblast fails to adopt an endovascular phenotype. This mechanism is probably explained by the over-expression of TGF-β_3; its inhibition restores the invasive ability of the extravillous trophoblast[23,24].

The reason for which the placental oxygen level fails to elevate, or why does the oxygen response not occur, in prone to preeclampsia pregnancies, are yet to be established.

It can be speculated that there is some disorder involved in the endovascular development of extravillous cytotrophoblast layer, a delayed involution or lack of response to the 'signal' which, in normal pregnancies, triggers the disaggregation of the endovascular cytotrophoblastic plugs that develop in the lumen of spiral arteries, after 10 weeks of gestation.

3. The systemic release of placental necrotic material

A new concept, different form the maternal-fetal interface, suggests that the placenta is a barrier which is overcome in preeclampsia. In brief, the maternal-fetal interface dysfunction theory is based on the maternal - paternal incompatibility, emphasized by the low maternal immune tolerance to paternal antigens, which generates initially local reactions, with final systemic response and maternal endothelial damage. On the other hand, the second hypothesis, mentioned above, known as 'the vascular concept' describes the pre-existing vascular dysfunction/vasospasm at the spiral arteries level as the major cause for placental ischemia, reperfusion and systemic release of placental necrotic material with an inflammatory response (overcoming the placental barrier). This theory can not be valided in its original form; it is contradicted by the fact that placental ischemia alone with vasospasm can not explain the differences between maternal and fetal phenotype, i.e. preeclampsia, intrauterine growth restriction (IUGR) from placental insufficiency[10]. Huppertz has recently proposed[25] a more appealing form of this theory. In his proposed model, preeclampsia is the result of the syncytiotrophoblast dysfunction (the placenta), where as IUGR is the result of the extravillous cytotrophoblast dysfunction, sometimes these two disoders may coexist; if the trophoblastic injury occurs during the early stages of its development than it's more likely for the both sincitial and extravillios cell layers to be affected, leading to a coexistence of preeclampsia and IUGR in early-onset forms of placental disoder[25].

Systemic release of placental tissue in both normal and pathological pregnancy has been a well known fact for quite some time[25-27]. Holzgreve and his group have studied in details the presence of placental tissue, fetal cell, fetal/placental deoxyribonucleic acid (DNA) in the maternal bloodstream[28]. Syncytiotrophoblastic apoptosis leads to the release of large inert particle (syncytial knots) and amorphous placental material in the maternal circulation. This aspect is to be found significantly increased in preeclamptic pregnacies, in contrast to normal pregnacies.

Placental apoptosis is highly emphasized in preeclampsia. While circulating placental material, in normal pregnancy is the result of physiological apoptosis and it can be processed by macrophages at the first lung passage, the circulating placental material, in preeclampsia, is mainly obtained from a process of necrosis/aponecrosis; it presents a long half-life in the maternal bloodstream, causing important inflammatory reaction. Serum of patients with preeclampsia reduces trophoblast viability by increasing its sensitivity to Fas-mediated apoptosis[10,29]. Particles such as placental syncytial knots are found in the systemic circulation (post-pulmonary) in women with preeclampsia, but not in those with normal pregnancies[10,25]. In addition, it has been proved that placental hypoxia after 10 weeks of gestation (important candidate as *primo movens* in preeclampsia) can also affect the syncytiotrophoblastic function (not only the extravillios trophoblast), by increasing syncytiotrophoblastic barrier permeability[24]. Therefore, Huppertz's hypothesis is appealing.

Placental ischemia with reperfusion and systemic release of placental material, certainly play a major role into the pathophysiological mechanisms of preeclampsia, but it is unlikely, with little exception, that the vascular dysfunction is the primary event of preeclampsia onset. The immunological response dysfunction due to the maternal-fetal immune maladaptation or incompatibility, which is found at the maternal-fetal

interface, presents even a more solid basis, leading to increased apoptosis and trophoblast aponecrosis, a characteristic feature of preeclampsia.

Chaouat[30] claimed that the two theories (immunological and vascular) can not be easily separated, due to the fact that placental cytokines have multiple characteristics with great influence on intercellular communication, angiogenesis, regulation of vascular tone, inflammation and coagulation. This aspect is also suggested by recent research.

Most etiopathogenic theories mentioned above have one common pathophysiological result- abnormal remodeling of spiral arteries, in pregnacy. The directly involved mechanism is represented by the defective trophoblast invasion. The trophoblast invasion causes an excessive inflammatory reaction even in a normal pregnacy, but without the altered immunological response, present in preeclampsia, therefore the primary event that triggers this disoder seems to be the low maternal tolance to the allogenic fetus (genetic incompatibility in HLA-C system?)[10-14].

The final result of all pathophysiological mechanisms described above is represented by the endothelial dysfunction, which leads to the characteristic systemic signs and symptoms of preeclampsia.

Despite extensive research and numerous proposed theories, 'X Factor', which would represent the contrate prove of the direct link between placental defective development and maternal endothelial dysfunction, has not been identified yet. It's actually quite likely that there is more than one mechanism that causes endothelial dysfunction in preeclampsia.

Although 'X Factor', the cause of global endothelial dysfunction remains elusive and it is unlikely to ever identify it as a single entity, there are a number of biological, biochemical and functional parameters which present a different pattern in preeclampsia compared with normal pregnancies. Their profile in both cases, normal and pathological is already known.

The second relevant issue addressed in our review is the prediction of preeclampsia risk, using some of these factors as screening markers for preeclampsia.

4. Early screening for preeclampsia

The concept of screening involves identifying individuals at high risk for not apparent pathology in an unselected population. Screening test is based on the existence of one or more parameters easily measurable, which different values in affected individuals have compared to non-affected individuals.

All the above pathophysiological processes involve potential screening markers for preeclampsia. The study of preeclampsia pathophysiological mechanisms would be of great value if it finds some practical use; it can lead to the discovery of some screening markers, in order to define a method for prediction of preeclampsia (as a first step towards prevention and/or treatment of preeclampsia).

There have been identified several factors, which present significantly different biochemical serum levels in women who developed preeclampsia compared to women who didn't.

The most important are pregnancy-associated plasma protein A (PAPP-A), PGF and inhibin A. inhibin A measure-

Table 1 Potential biochemical markers for preeclampsia[18]

MARKER	First half of pregnancy	Second half of pregnacy	Clinic preeclampsia	Used combination
sFlt-11	-	↑	↑	sEng[2], PGF[3], VEGF[9], eco
sEng2	-	↑	↑	sFlt-1[1], PGF[3], eco
PGF[3]	↓	↓	↓	sFlt-1[1], sEng[2], eco
PP13[4]	↓	↑	↑	eco
PTX-3[5]	↑	↑	↑	
PAPP-A[6]	↓	↓	↓	eco
ADAM12[7]	↓	-	-	
P-selectin	↑	↑	↑	sFlt-1[1], activin A, adhesion molecules
Free-fetal DNA[8]	±	↑	↑	inhibin A
adrenomodulin	↑	↑	↑	

1sFlt-1= soluble fms-like tyrosine kinase 1; 2sEng= soluble endoglin; 3PGF= placenta growth factor; 4PP13= placenta protein-13; 5PTX-3= pentraxin-3; 6PAAPP-A= pregnancy-associated plasma protein A; 7ADAM12= a disintegrin and metalloprotease 12; 8DNA= deoxyribonucleic acid; 9VEGF= vascular endothelial growth factor

ment is not, however, included in the available pregnancy assessment protocols for the first trimester.

In the future, proteomics will certainly, prove to be the best method that can identify the high risk pregnacies for preeclampsia.

A list of potential biochemical markers of preeclampsia is presented in Table 1 (modified after Holzgreve[18]).

Uterine artery Doppler evaluation and placental volume assessment represent the ultrasound parameters that can be used in the screening process.

Despite the conservative attitude towards the routine assessment of uterine artery, it becomes evident that this test has a high sensitivity and an acceptable specificity for gestational hypertension[1,32]. Placental volume is more difficult to assess, from a technical point of view (unlikely to be of routine use) and placental volume distribution values is dependent of the uterine artery Doppler parameters and, especially, the values of PAPP-A.

PAPP-A is a highly glycosylated dimeric protein, the only-identified protease of insulin-like growth factor binding protein-4[18,33] which has been widely used as a biochemical screening marker of Down syndrome for a long time. Low levels of PAPP-A are associated with a number of pregnancy outcomings such as chromosomal abnormalities, fetal growth restriction as well as preeclampsia and stillbirth[34-38].

PAPP-A has a molecular mass of 400 kDa and is found in the serum of pregnant women, most often as a complex with a pro-form of major eosinophil basic protein, most likely an inhibitor of protease activity of PAPP-A[18].

There is considerable experience in the use of PAPP-A to predict chromosomal abnormalities at the end of the first trimester of pregnancy[39,40]. Thus it was observed that low levels of PAPP-A may indicate an increased risk of preeclampsia[37,38]. Low PAPP-A level has a high positive predictive value but a low negative predictive value in preeclampsia prediction (there are many women with normal levels of PAPP-A developing preeclampsia). However PAPP-A appears to be a useful marker in the risk assessment for gestational hypertension, at the end of the first trimester of pregnacy. As expected, PAPP-A is a specific marker for early preeclampsia[41].

PGF is a factor involved in placental angiogenesis. Placental hypoxia is associated with reduced levels of angiogenic factors (VEGF, PGF) and higher levels of anti-angiogenic factors (sFlt-1, Seng)[10]. Altered levels of VEGF, PGF, sFlt-1 and sEng seem to precede the clinical onset of preeclampsia and correlate with increased severity of disease[18].

Although the initial studies have showed that serum levels of sFlt-1 is significantly increasing before the clinical onset of preeclampsia[18,40], a more recent study on first trimester screening program conducted by Fetal Medicine Foundation (FMF) has failed to confirm sFlt-1 as a potential screening marker for preeclampsia. They showed that in early pregnancy, sFlt-1 levels are not significantly different in women with normal pregnancy compared with those who develop preeclampsia[22]. In fact, the study results are not inconsistent with the FMF previous studies regarding the fact that serum levels of VEGF are not detectable in pregnancy and sFlt-1 levels are significantly different in women with hypertension compared to the healthy ones, not in early pregnancy, but only after mid 2nd trimester[18].

PGF importance in preeclampsia prediction, however, is supported by data from both the CPEP study, Calcium for Preeclampsia Prevention[42] and the FMF. PGF is therefore a valuable candidate for a place in the future screening protocols for preeclampsia.

sFlt-1/PGF ratio has been considered to be a better marker for the risk of preeclampsia[18,33]. A high sFlt-1/PGF ratio (PGF level fell concurrently with the rise of sFlt-1) indicates an increased risk of preeclampsia. Unfortunatly, this aspect can be demonstrated only after 25 weeks of gestation[43].

Altered uterine artery Doppler velocimetry can be considered as the primary screening marker for preeclampsia, available at the moment.

Impaired blood flow through the uterine arteries has been observed in pregnancies prone to preeclampsia or fetal growth restriction, for a long time[44].

First systematic studies in this field have focused on the blood flow in the uterine arteries in the second trimester of pregnancy[45-48].

The FMF approach in order to develop an early screening test for preeclampsia has shown that the blood flow in the uterine arteries is significantly different in pregnancies prone to develop hypertension outcomings, even from the first trimester of pregnancy[40,41,49-52].

The boold flow parameters in uterine arteries have to be evaluated systematically, using the standardized technique described by Nicolaides[51] in order to be used as preeclampsia screening markers: measurement of uterine artery at paracervical area, using the smallest possible angle of insonation.

This method provides good reproductive and consistent results. Studies of uterine artery Doppler velocimetry for prediction of preeclampsia have reported that the objective method, using flow waveform ratios for assessing the uterine artery is superior to the subjective one.

5. Conclusions

Recent data suggest that it should be used the uterine artery pulsatility index with the lowest resistance to flow, in preeclampsia risk assesment (not the pulsatility index media for both uterine arteries).

There is enough evidence that the factors mentioned above, PAPP-A, PGF and uterine arteries pulsatility index, can be combined in an examination protocol at the end of the first trimester (along with risk assessment for chromosomal abnormalities) in order to identify a large percentage of preeclampsic pregnancies (especially in the early stages), with a relatively small false positive percentage. Next step would be to find an effective intervention management for subsets population identified as having high risk of developing hypertension in pregnancy. ■

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