

# Etiopathology of preeclampsia

MATEUSZ MADEJCZYK, GRZEGORZ KRUSZYŃSKI, GRZEGORZ H. BRĘBOROWICZ

## Abstract

Roberts, Hubel, Redman and coworkers introduced the concept that it could be helpful to consider preeclampsia as a two stage disorder. Several placentally derived factors were suggested as possible linker between placental changes and general disease, including cytokines, antiangiogenic factors, syncytiotrophoblast microparticles (STBM) and formed blood products activated in the intervillous space. Oxidative stress is an attractive component as part of the linkage. Evidence for the involvement of early placentation is largely the abnormal release of placental proteins as early as the first trimester of pregnancy. Many authors supports the concept that the placental abnormality associated with preeclampsia occurs prior to completion of the remodeling of the vessels supplying the placental site. Oxidative stress is one proposed linker, as are SBTM and antiangiogenic factors. It has also been shown that preeclampsia is associated with increased apoptosis within the syncytiotrophoblast layer (increased shedding of apoptotic material into the maternal blood stream), while the interstitial extravillous trophoblast shows a reduced rate of apoptosis within the uterine wall.

**Key words:** preeclampsia, the two stage model

The Working Group's clinical classification schema has four categories: chronic hypertension, preeclampsia-eclampsia, preeclampsia superimposed upon chronic hypertension, and transient hypertension [1, 2].

The diagnosis of preeclampsia is determined by the de novo appearance of hypertension and proteinuria after mid pregnancy (but can rarely occur earlier with trophoblastic diseases such as hydatid mole). Proteinuria was defined as the urinary excretion  $\geq 0.3$  g in 24-hour collection. The working group gave tentative approval to qualitative testing, noting that a 24-hour measurement  $\geq 0.3$  g "usually correlated with 30 mg/dl, (1+dipstick) or greater in a random urine determination with no evidence of urinary tract infection". They stressed, however, that because there were discrepancies between the two approaches they strongly recommended diagnosis be based on a 24-hour collection [2].

## Metabolic syndrom

The clustering of metabolic and physiological abnormalities was first described in 1923 by Eskil Kylin as a syndrom consisting of hypertension, hyperglycemia, obesity, and hyperuricemia [3, 6]. Gerald Reaven, in his 1988 Bantign Lecture, described "syndrome X" as the clustering, more often than predicted by chance, of resistance to insulin-stimulated glucose uptake, hyperinsulinemia, hyperglycemia, elevated very low-density lipoprotein (VLDL) triglycemia, reduced high-density lipoprotein (HDL) cholesterol and hypertension. In 1998,

the World Health Organisation Task Force on Diabetes identified insulin resistance as the dominant cause of the metabolic syndrome [6, 22, 23]. The majority of epidemiological studies have used National Cholesterol Education Program (NCEP) criteria, defining metabolic syndrome as the presence of three or more of the following five risk factors: abdominal obesity, high triglycerides, low HDL cholesterol, hypertension, and elevated fasting glucose. The more recent International Diabetes Federation definition requires central obesity plus any two of the other four 2004 NCEP factors [24, 25].

## Metabolic syndrome: a cause of placental dysfunction?

Pre-pregnancy obesity is linked to a host of perinatal problems related to adverse outcome (gestational diabetes, cesarean delivery, infant macrosomia). The risk of perinatal death more than doubles with maternal obesity. Analysis of the National Hospital Discharge Survey of almost 25% in the rate of preeclampsia during the 18-year period ending in 2004. Much of this rise might reflect the growing "epidemic" of obesity [23-25].

A strong relationship exists between pre-pregnancy obesity and preeclampsia. Obesity and overweight contribute to both preterm preeclampsia and severe preeclampsia, a finding with potentially profound public health implications. Stone et al. compared 70 women with severe preeclampsia to more than 18000 normotensive con-

trols, all without history of pre-pregnancy hypertension, and observed that severe obesity and a history of preeclampsia were the only outstanding risk factors for development of severe preeclampsia. Women with abnormally low BMI in the first trimester are significantly less likely to develop preeclampsia or gestational hypertension than women with normal BMI [22]. The result of a large, prospective population based study showed that weight gain during the inter-pregnancy interval is strongly associated with risk of major maternal and perinatal complications, including preeclampsia, independent of whether women are overweight or lean [24].

Most women with preeclampsia are of normal weight but as a group these same women gain significantly more weight over subsequent decades postpartum than women who did not experience preeclampsia, suggesting that preeclampsia unmasks a latent predisposition to obesity. Gestational insulin resistance is accentuated in women with preeclampsia and this difference can be demonstrated in pregnant women weeks before clinically evident preeclampsia, and in postpartum women years after a preeclamptic pregnancy. This suggests that insulin resistance is an important underlying risk factor for preeclampsia, as it is for cardiovascular disease [25].

By analogy to the relationship of cardiovascular disease or type 2 diabetes to obesity and insulin resistance, it is unlikely that insulin resistance is the only metabolic change in obesity responsible for the increased risk of preeclampsia. Both lean and obese individuals who are insulin resistant are at increased risk for cardiovascular disease and type 2 diabetes. In obese and lean individuals with equivalent insulin resistance, however, type 2 diabetes still develops more frequently in the obese, indicating that the effect of obesity to increase morbidity is due to more than insulin resistance [24, 25].

An important advance in obesity research came with the understanding that obesity is characterized by chronic low-grade inflammation contributes to the development of insulin resistance, dislipidemia, oxidative stress, and cardiovascular problems associated with obesity. Obesity is associated with both local adipose inflammation and systemic inflammation. Obese individuals on average manifest increased plasma concentrations of several inflammatory markers and signaling cytokines, including IL-6, TNF- $\alpha$ , and C-reactive protein. Peripheral blood mononuclear cells from obese patients are in a pro-inflammatory state [16-18].

The dyslipidemia that occurs with preeclampsia closely resemble the dyslipidemia of metabolic syndrome and in many ways, it represents an accentuation of

normal pregnancy changes. Heightened gestational insulin resistance, abnormally increased concentrations of TNF- $\alpha$ , and increased human placental lactogen are thought to contribute to this dyslipidemia [19, 20].

Preeclampsia is not the only abnormal placentation-related pregnancy disorder associated with an increased risk for the development of cardiovascular disease later in life. Women with a history of recurrent spontaneous abortions are reportedly at increased risk of cerebrovascular disease later in life. Irgens et al. studied a very large cohort of women who delivered preterm (before 37 weeks) and whose pregnancies were not complicated by preeclampsia. Such women, who were then on average 13 years post the index pregnancy, had a 3-fold increased risk of cardiovascular death compared to matched women who delivered at term, the results shows to be independent of lifestyle or socioeconomic factors [22].

Preexisting metabolic syndrome or endothelial dysfunction may contribute to both placentation defects and later to cardiovascular disease. This hypothesis is consistent with pre-pregnancy, pregnancy and postpartum data. High cholesterol or triglycerides at less than or equal to 15 weeks' gestation were associated with a 2.8 fold and 2.0 fold increased risk for preterm birth. Both pre-pregnancy and early gestational dyslipidemia is associated with increased risk of preeclampsia. The CHAMPS (Cardiovascular Health After Maternal Placental Syndromes) population-based retrospective cohort study is also consistent with the hypothesis that pre-existing metabolic syndrome and endothelial dysfunction may contribute to both poor placentation and later cardiovascular disease. This study found a two-fold increased risk of premature vascular disease in women who had had a pregnancy affected by maternal placental syndromes, the latter defined as having had either preeclampsia, gestational hypertension, placental abruption, or placental infarction [19, 25].

A lesion sometimes found in the uteroplacental spiral arteries in preeclampsia or IUGR has been termed "acute atherosclerosis" because of the presence of foam cells and lipid inclusions resembling the atherosclerotic lesions of vascular disease. Higher concentrations of total cholesterol, phospholipids, and lipid peroxides have been observed in placenta decidua basalis, the area that contains the spiral arteries, from women with preeclampsia [1, 25].

Potential evidence for metabolic syndrome as a main reason of poor placentation is that women with pregnancies complicated by IUGR but without preeclampsia, who have spiral arteries lesions similar to pre-

eclampsia, do not generally develop hypertriglyceridemia and as a group tend to have lower total cholesterol and LDL cholesterol concentration than healthy pregnant controls. The aggregate data imply that it should be possible for women who are overweight or obese to meaningfully lower their risk of preeclampsia by achievable reductions in body weight before pregnancy [29, 32].

Preeclampsia, traditionally characterised by hypertension and proteinuria in previously normotensive pregnant women, remains one of the leading causes of maternal and fetal mortality in the developed world, and may have an incidence as high as 10% in certain population groups. The effects of this disorder are more systemic than historically assumed and involves gross damage of the maternal endothelium as well as over activation of the maternal immune system. Further pathological changes may involve the maternal brain, kidney and liver [1].

Roberts, Hubel, Redman and coworkers introduced the concept, that it could be helpful to consider preeclampsia as a two stage disorder. The first stage was reduced placental perfusion that led to the maternal syndrome. The reduced perfusion, appeared as secondary to failed remodeling of the maternal vessels supplying the intervillous space, was not sufficient to caused. It was possible to identify evidence of reduced placental perfusion in women who had growth restricted babies unassociated with maternal signs of preeclampsia [1, 2, 19, 20]. Furthermore, in one third of pregnancies complicated by preterm birth there was pathological evidence of failed placental vascular remodeling. This led to the concept that maternal constitutional factors, genetic, behavioural and environmental, modified by the physiological changes of pregnancy were necessary to interact with reduced placental perfusion to lead to the maternal abnormalities of preeclampsia. Many of these factors leading to the maternal syndrome were risk factors for cardiovascular disease in later life. The other important component of the model was the linkage between reduced perfusion and the maternal syndrome [1, 2].

Several placentally derived factors were suggested, including cytokines, antiangiogenic factors [5], syncytiotrophoblast microparticles (STBM) [7] and formed blood products activated in the intervillous space [4]. Oxidative stress was an attractive component as part of the linkage [3]. Reactive oxygen species could be generated by the reduced perfusion of the placenta with consequent activation of monocytes and neutrophils [3] passing through the intervillous space. Oxidative stress would also stimulate release of cytokines, antiangiogenic factors, micro-

particles and other potential linkers, many of whose systemic effects would also be mediated by oxidative stress. Although still a useful model, some modifications are appropriate based upon current knowledge. First, it is now being proposed that abnormal placentation is occurring before the stage of remodeling of the vessels supplying the intervillous space [3]. Evidence for the involvement of early placentation is largely the abnormal release of placental proteins as early as the first trimester of pregnancy.

### **The beginning of placental abnormalities**

Huppertz supports the concept that the placental abnormality associated with preeclampsia occurs prior to completion of the remodeling of the vessels supplying the placental site [4, 7]. He claims that the initial changes that lead to the clinical manifestations of preeclampsia, occur long before 12-20 weeks of gestation when the deep invasion of trophoblast with remodeling of the placental bed vessels is thought to occur. He proposes that trophoblast differentiation may be abnormal as early as the first trimester when these markers are measured. Thus, he suggests abnormalities of either the differentiation of the morula to trophoblast or later differentiation of trophoblast to cytotrophoblast and syncytiotrophoblast [9, 21]. Although somewhat circumstantial, the presence of these early markers clearly suggests, that there are important differences in placentation prior to deep trophoblast invasion with vascular remodeling. Huppertz proposes that the early changes, when present, would typically lead to the most severe placental dysfunction resulting in intrauterine growth restriction (IUGR) with preeclampsia. He suggests, that the concept that stage 1 of preeclampsia begins at the time of vascular remodeling should thus be modified given that abnormalities of placentation appear to occur prior to this time. However, there is evidence of trophoblast invasion of spiral arteries as early as 6-8 weeks gestation that is disordered in preeclampsia [4, 7]. It is also possible that the placental aberrations in early pregnancy suggested as important by Huppertz may be the root cause of both abnormal implantation/placentation and the abnormal placental bed vascular remodeling occurring in later pregnancy [4, 7, 8].

### **Preeclampsia is a two stage-disease**

Preeclampsia evolves two stages, pre-clinical and clinical. Each stage involves the maternal immune system in different ways. In the first stage there is an im-

portant element localized to the placental bed where placentation is typically inhibited in Stage 1 preeclampsia. In the second stage a diffuse systemic response predominates. These stages are associated with different patterns of maternal exposure to fetal tissues and potentially different consequences of immune maladaptation [19].

Maternal-fetal immune interfaces and maternal and maternal recognition of fetal (paternal) antigens.

Maternal exposure to feto-placental tissues varies with gestational age. Trophoblast are the relevant placental cells. This interfaces can be named as 1 and 2. Interface 1 is between maternal immune cells and invasive, extravillous trophoblast in the deciduas. It dominates during the first half of pregnancy when placentation is established and the placental bed is infiltrated with invasive cytotrophoblast. Interface 2 is anatomically distinct from the first, and comprises syncytiotrophoblast, which is the surface layer of chorionic villi. It is contact with maternal blood-borne immune cells. The interface becomes active when the intervillous circulation (weeks 8-10) is established and expands with growth of the placenta to become the dominant interface towards the end of pregnancy. If it promoted immune responses they would be systemic not local [19-21].

Maternal-placental immune responses will depend on what major histocompatibility (MHC) antigens are expressed by trophoblast and these are uniquely different from those of most somatic cells. The decidual (extravillous) trophoblast at Interface 1 does not express the strong polymorphic HLA-A, HLA-B (MHC type 1a) or HLA-D (MHC type 2) antigens, the principal stimulators of T-cell-dependent graft-rejection responses. HLA-G is not expressed in normal tissues other than the placenta and is confined to extravillous trophoblast. It is expressed in some malignancies where it may contribute to escape from immune surveillance; it is generally agreed that it confers a degree of immune privilege on trophoblast. A soluble form of HLA-G is also released and is detectable in blood [21, 22, 26].

At Interface 2, the syncytiotrophoblast is HLA-negative and immunologically neutral. The key point is that paternal alloantigens are only expressed at Interface 1 which is most active in the first half of pregnancy. This is the time that placentation may develop abnormally causing the later development of preeclampsia and fetal growth restriction. Hence Interface 1 needs to be considered in relation to Stage 1 preeclampsia, and immune events that affect placentation could explain its apparent partner specificity [26, 29].

Stage 2 preeclampsia appears to originate from the syncytial surface (Interface 2) of the placenta. The condition is characterized by an exaggerated maternal systemic inflammatory response involving the systemic inflammatory network including maternal endothelium. Hence, the markers of systemic inflammation that are altered in normal pregnancy are more severely affected in preeclampsia. The inflammatory changes may cause decompensation giving one or other of well-know crises of the condition. The important change in immune reactivity in preeclampsia is a loss of the specific Type 2 bias of normal pregnancy with increased production of INF- $\gamma$  and IL-2. This is associated with increases in a range of cytokines, chemokines, adipokines, angiogenic and antiangiogenic factors, which all reflect an inflammatory response. Other immunoregulatory factors are also affected. Circulating adipokines with cytokine activity, either pro-inflammatory or anti-inflammatory activates, are also increased in preeclampsia [26, 29].

### **The role of HLA and NK cells in etiopathology of preeclampsia**

The invasive cytotrophoblast which infiltrates organism of the mother is equipped by very special combination of HLAs antigens, especially HLA-G, -E and -C. In invasive decidua there is trophoblast which communicates with maternal lymphocytes. There are not classical T lymphocytes, belonging to HLAs, but there are typical for endometrium NK cells. Those cells express receptors which are recognized HLAs antigens of the cytotrophoblast.

Thus it is possible to say that NK cells are responsible for immune recognition of cytotrophoblast cells [8].

The NK cells receptors – KIRs – (killer immunoglobulin-like receptors) detect polymorphic HLA-C and HLA-G. The combination of KIRs decide about the stimulation or suppression of cytokin production which allows or not pregnancy to continue. The crucial part in this mechanism belongs to HLA-G antigens [8].

### **The linker in the Two Stage Model**

It is very interesting, what is the implicit common linker in the Two Stage Model for the two stages. Oxidative stress is one proposed linker, as are SBTM and antiangiogenic factors [11]. However, it is important that no such factor has ever been shown to be present in all cases of preeclampsia. Endothelial dysfunction seems consistent as a common convergence point for early

pathophysiological changes of preeclampsia [3, 6]. First, it suggests that not all cases of preeclampsia will be avoided by the same preventive strategy (certainly consistent with the results of large clinical trials). Second, it implies that, as with the carbohydrate intolerance of diabetes mellitus, there are different subtypes of preeclampsia [3].

### **Oxidative stress as a Mediator of Endothelial cell Dysfunction**

Oxidative stress is an imbalance between pro-oxidant and antioxidant forces resulting in an overall oxidant insult. In preeclampsia, oxidative stress has been postulated to lead to altered endothelial cell function. Indeed, the pro-oxidant environment of endothelial cells is extensive, as these cells are constantly exposed to extracellular factors in the circulation that are capable of inducing an oxidative insult and can produce their own oxidants as well. Oxidative stress is an example of a pathological process whereby multiple factors converge to cause endothelial cell dysfunction [28, 30].

Pro-oxidants include free radicals such as superoxide anions ( $O_2^-$ ), hydroxyl radicals ( $-OH$ ), nitric oxide (NO), and other reactive oxygen species (ROS). A free radical contains one or more unpaired electrons. ROS is the collective term for oxygen-derived free radicals as well as non-radical derivatives of oxygen such as hydrogen peroxide ( $H_2O_2$ ). ROS are continuously produced *in vivo*. They are a view metabolic pathways that can lead to the production of oxygen-derived free radicals. Mitochondria, endoplasmic reticulum, and nuclear membranes have been shown to produce superoxide anions as a consequence of auto-oxidation of electron transport chain components. Oxygen-derived free radicals also are produced as the result of arachidonate metabolism by prostaglandin H synthase, lipoxygenase, cytochrome p450. Nitric oxide synthase can generate superoxide anions and hydrogen peroxide, particularly if the intracellular concentration of L-arginine (the precursor for the synthesis of nitric oxide) are low. It is important to note that oxygen-derived free radicals can be produced at a number of subcellular compartments, such as the mitochondria, endoplasmic reticulum, peroxisomes, phagosomes, plasma membrane, nuclear membrane, and cytoplasm. Therefore, the ability of antioxidants to quench free radicals depends on dietary intake, production, localization as well as the type of oxidative insult [6, 11, 31].

Several factors in circulation produce oxygen free radicals that react with endothelial cells. This raises the

possibility of free radical-dependent vascular dysfunction at sites distant from the primary source or insult. This is important since the placenta is central for the development of preeclampsia. As a consequence of endothelial cell dysfunction, the perfusion of many organs, including the placenta, is reduced. This, in turn, could lead to feed-forward progression for further endothelial cell dysfunction thereby accelerating the symptoms of preeclampsia until the placenta has been removed [6, 11, 31].

In women with preeclampsia, superoxide generation from circulating neutrophils is enhanced. As previously noted, cytokines such as TNF- $\alpha$  can either directly or indirectly initiate oxidate. TNF- $\alpha$ , which is elevated in preeclampsia, has been shown to directly induce oxidative damage as well as increase endothelial cell-induced oxidation of low-density lipoproteins (LDL). TNF- $\alpha$  can also increase free radical production through the xanthine oxidase pathway and concentrations of the latter enzyme are increased in women with preeclampsia. NAD(P)H oxidase appears to represent the most significant source of superoxide anion production in endothelial cells. As previously noted, many of the circulating factors that are increased in women with preeclampsia can activate NADPH oxidase. In preeclampsia, it has been suggested that certain anti-oxidant mechanisms are not adequate to compensate for an overwhelmed oxidant response. Re-establishing a balance between ROS and antioxidant protection in women with preeclampsia via vitamin therapy may protect the vascular endothelium. Unfortunately, this is a complex system. Reactive oxygen species contribute to normal metabolic processes in the body and have physiologic roles as second messengers, in addition to their potentially pathogenic role. Ultimately, antioxidant protection will depend on the compartment and type of oxidative insult imposed on cell. Moreover, oxidative stress in preeclampsia is most likely the result of multiple pro-oxidant pathways; therefore concerted action of multiple antioxidants may be necessary to afford protection [26, 30].

The etiology of preeclampsia remains elusive but appears to be a defect in placentation involving a failure in trophoblast differentiation. There is clear evidence for an increased placental oxidative stress in preeclampsia although the cause of this still remains uncertain [9]. It has long been considered that the placenta is hypoxic in preeclampsia due to reduced perfusion following deficient trophoblast invasion, however, there is no firm evidence to substantiate this claim.

This is especially true in the majority of cases, characterized by late onset of symptoms with normal pla-

central development. Recently, Burton and coworkers have suggested that fluctuating oxygen concentrations within the intervillous space caused by intermittent perfusion from the spiral arteries may be an essential trigger. This hypothesis is supported by their *in vitro* experiments which clearly demonstrate that hypoxia is indeed a potent stimulus [3, 9].

It has also been shown that preeclampsia is associated with increased apoptosis within the syncytiotrophoblast layer, while the interstitial extravillous trophoblast shows a reduced rate of apoptosis within the uterine wall [7, 10]. Since the release of material generated by apoptosis into the maternal circulation should not be associated with an inflammatory response, it is most likely that the activation of the maternal endothelial cells observed in preeclampsia is brought about by the necrotic and aponecrotic release syncytial debris rather than by the apoptotic release of syncytial knots [7, 10, 11].

### **Fetal cells and preeclampsia**

Although the pioneering reports by Schmorl, and later by Attwood and Park had served to indicate that trophoblast deportation is elevated under conditions of preeclampsia or eclampsia, it was only in the 1990s that Redman and colleagues started to examine this issue in detail [11, 12]. Their studies indicated that while these cells could be detected in uterine vein samples, they were not present in samples taken from the antecubital vein. This implied that these large cells were filtered out very rapidly by the lungs. In their study, they did, however, notice that trophoblast (mononucleate cells and oligonucleate syncytial fragments) were more prevalent in pregnancies affected by preeclampsia than in normal ones. In preeclampsia the median amount of trophoblast per milliliter of uterine vein blood was 37 times higher compared to the median of control cases [11, 12].

One of the first studies to address the issue of fetomaternal bleeding was performed by Jones and coworkers, who used the Kleihauer-Betke staining technique (which enabled fetal erythrocytes to be distinguished from maternal ones). These authors showed that fetal erythrocytes were indeed more frequent in maternal blood in pregnancies affected by preeclampsia. A remarkable observation made during these studies was that fetal erythrocyte numbers were already elevated in samples taken before 36 weeks of pregnancy in pregnancies which subsequently developed preeclampsia. Thus there was an increase in fetal cell traffic already prior to onset of clinical symptoms [12].

### **Fetal DNA in preeclampsia**

By the use of real-time PCR technology, Lo and colleagues were able to demonstrate that free fetal DNA levels were elevated in cases with manifest preeclampsia when compared to normotensive pregnancies. The investigations into this phenomenon, allow the novel observation that preeclampsia was associated with a significant elevation in both cell free fetal DNA and cell free maternal DNA levels.

Maynard et al indicated that the increments in cell free fetal and maternal DNA species corresponded to the degree of disease severity and, furthermore, that these levels corresponded to each other in pregnancies affected by preeclampsia but not in normal pregnancies [5, 13, 14].

An advantage of cell free DNA analyses is that they are far more reproducible than studies concerning the analysis of fetal cells. As such, these data have been confirmed by numerous other independent studies [14, 15]. In one of these, Swinkels and coworkers specifically examined pregnancies complicated by the HELLP syndrome and were able to confirm. In this study, it was also observed that circulatory fetal and maternal DNA elevations correlated with the severity of preeclampsia [14, 15].

### **The role of circulating angiogenic factors in etiopathology of preeclampsia**

One of the strongest factors inducing systemic immune response is SVEGFR-1 (sFlt1) (Soluble Vascular Endothelial Growth Factor Receptor – 1, soluble fms-like tyrosine kinase-1). It binds VEGF and placental growth factor (PlGF) and in this way takes away from endothelium necessary factors for growth. sFlt1 has got strong anti-angiogenic effects. Maynard et al claims that in serum of preeclamptic patients there is increased serum concentration on VEGFR-1 in comparison to normotensive patients [5].

### **The genetic influences on development of preeclampsia**

Preeclampsia and eclampsia are family, as genetic research on these conditions over the last century has shown. Due to monumental improvements in neonatal care and decreased mortality rates of newborns over the last 50 years, generational trends can now be observed: eclamptic and preeclamptic mothers, aunts, and grandmothers have had female descendants who shown an increased risk of preeclampsia. Preeclampsia tends to

cluster in families: a heritability study using a Utah genealogy database determined the coefficient of kinship for preeclampsia cases to be more than 30 standard deviations higher than for controls. The recurrence risk for preeclampsia in the daughters of either eclamptic and preeclamptic patients is in 20-40% range [16, 17].

For sisters it is in the 11-37% range. Much lower rates are seen in relatives by marriage, such as daughters-in-law and mothers-in-law. African American mothers at all socio-economic levels experience a higher rate of preeclampsia than the general population in the United States, suggesting that ethnicity, rather than socio-economic status, has a greater impact on incidence of preeclampsia. And finally, twin studies estimate the heritability of preeclampsia to approximately 22% to 47%.

Any genetic hypothesis of preeclampsia must explain the first pregnancy effect. It is widely known that most women will not have preeclampsia with future pregnancies unless another condition exists (e.g. underlying renal disease, twins, diabetes). This has suggested an immunogenetic mechanism to many investigators, in the form of desensitization or tolerance to paternal antigens in subsequent gestations. An increased risk for first pregnancies with new partners (i.e. new paternal antigens presented in the placenta) has also been noted [16, 17].

The genetic reasons for preeclampsia seem to be true to the certain limits. There are two basic genetic models: maternal and fetal.

There are a lot of evidences that among women with preeclampsia the frequency of Leiden factor and 5,10-methylenetetrahydrofolate mutations is much more higher. In 1999 Kupfermic et al. described association between polymorphism of prothrombin and higher frequency of preeclampsia [1].

The first researcher who started analysis of human genom was Hayward in Scotland in 1992. Two Australian researchers Arngrimsson and Moses described chromosom 2 and 11 as a responsible for development of preeclampsia. They called locus on the chromosom 2 as "PREG1" (preeclampsia – ecpampsia gene 1).

In 2005 was finished multicenter genom research in preeclampsia in Great Britain. 675 preeclamptic patients were analysed and no genetic pattern of increased risk of preeclampsia was detected [1, 2].

### **Intrauterine growth restriction and preeclampsia**

The factor linking the two stages of preeclampsia has usually been considered as a pathogen increasing activated blood components, excess syncytiotrophoblast

fragments (STBM), activating immune cells and transmitting oxidized lipids, or excess inflammatory cytokines [1, 2, 6].

Another possibility is that in a setting of reduced placental perfusion and subsequent reduced delivery of nutrients, the fetal-placental unit may release materials intended to overcome this deficiency. Perhaps the placental-to-maternal linkage is a factor(s) that modifies maternal metabolism to increase nutrient availability and acting on the placenta to facilitate nutrient transfer. Women who could not tolerate this modification would be much more likely to develop preeclampsia. Evidence consistent with this hypothesis is that 70% of infants who are born of preeclamptic mothers are not growth restricted. It is possible that those 70% of pregnancies do not have failed vascular remodelling but that has not been the finding in a large series of placental bed biopsies where the vast majority of women with preeclampsia have failed vascular remodelling [6]. Whether there are fetal/placental signals that increase nutrient availability is not yet proven. Nonetheless, several of the metabolic changes of preeclampsia including increased triglycerides, fatty acids, and insulin resistance are appropriate modifications to increase nutrient delivery. Furthermore, whereas infants that are growth restricted in pregnancies without preeclampsia have reduced amino acid concentrations in their blood [1, 2, 6], these same amino acids are increased in the blood of growth restricted infants from preeclamptic pregnancies. If preeclampsia results from the release of an appropriate signal then IUGR without preeclampsia might develop as a result of the absence of this signal. This should be associated with blunting of the normal fetal supply-related metabolic changes of pregnancy in women destined to have IUGR infants. Consistent with this premise women with growth restricted infants have lower plasma triglycerides than women with normally grown (AGA) infants. In addition, as early as 18 weeks gestation women who will subsequently have infants of less than the 5th centile have lower LDL cholesterol values than women whose pregnancies result in AGA infants [6]. Also, the findings in growth restricted infants of low circulating amino acids when growth restriction is not accompanied by preeclampsia versus high amino acids when growth restriction is accompanied by preeclampsia are consistent with the prediction by the model of a very different genesis of growth restriction in these two settings [6].

In etiopathology of preeclampsia the two stage model seems to answer to many questions but there are a lot waiting to be uncovered.

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✉ Mateusz Madejczyk  
Department of Perinatology and Gynecology  
University of Medical Sciences  
60-535 Poznań, Polna 33, Poland