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Review article

The two-stage placental model of preeclampsia: An update*

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ABSTRACT

Early-onset preeclampsia has been linked to poor placentation and fetal growth restriction, whereas late-onset preeclampsia was suggested to result from maternal factors. We have proposed an alternative model, suggesting that both early- and late-onset preeclampsia result from placental syncytiotrophoblast stress. This stress represents a common endpoint of several Stage 1 processes, promoting the clinical stage 2 of preeclampsia (new-onset hypertension and proteinuria or other signs of end-organ dysfunction), but the causes and timing of placental malperfusion differ.

We have suggested that late-onset preeclampsia, without evidence of poor spiral artery remodelling, may be secondary to intraplacental (intervillous) malperfusion due to mechanical restrictions. As the growing placenta reaches its size limit, malperfusion and hypoxia occurs. This latter pathway reflects what is observed in post-mature or multiple pregnancies.

Our revised two-stage model accommodates most risk factors for preeclampsia including primiparity, chronic pre-pregnancy disease (e.g. obesity, diabetic-, chronic hypertensive-, and some autoimmune diseases), and pregnancy risk factors (e.g. multiple or molar pregnancies, gestational diabetes or hypertension, and low circulating Placental Growth Factor). These factors may increase the risk of progressing to the second stage of preeclampsia (both early- and late-onset) by affecting one of or both pathways leading to Stage 1, as well as potentially accelerating the steps towards Stage 2, including priming the maternal cardiovascular susceptibility to inflammatory factors shed by the placenta.

This paper reviews previous preeclampsia findings and concepts, which fit with the revised two-stage model, and argues that "maternal" preeclampsia does not exist, as all preeclampsia requires a placenta.

1. Why the need for improved pathophysiological understanding of preeclampsia?

Preeclampsia is a common and potentially lethal multisystem disorder of pregnancy defined by new-onset hypertension and proteinuria after gestational week 20, or new onset preeclampsia-associated signs in the absence of proteinuria (Brown et al., 2018).

Preeclampsia presents in heterogeneous forms, where the early-onset form (often defined as premature delivery prior to 34 weeks' gestation), is associated with a high rate of fetal growth restriction (FGR), in contrast to the late-onset form (delivery after 34 weeks' gestation) in which neonates generally are not growth restricted, and may even be large for gestational age (Xiong et al., 2002). Late-onset preeclampsia is, however, not without danger. Eclampsia and HELLP (haemolysis, elevated liver enzymes, and low platelets) are examples of life-threatening crises that are more common in late gestation- and post-term manifestations of preeclampsia, when the rates are calculated per "on-going pregnancies" (Caughey et al., 2003). The preeclampsia/eclampsia health burden is especially high in low- and middle-income settings (Bilano et al., 2014).

The heterogeneous preeclampsia syndrome is poorly understood, and its onset and progression is unpredictable. Furthermore, preeclampsia does not only represent a major health threat to the woman and her fetus during pregnancy and labour, it also confers an increased long-term risk of cardiovascular disease in both the mother and child (as reviewed in (Staff et al., 2010, 2016)). Prevention is key, but with today's medicine our options for efficient prevention are limited.

Known risk factors include primiparity, renal disease, chronic hypertension, obesity, advanced maternal age, multiple- or molar pregnancy, and pre-gestational- or gestational diabetes mellitus. Though

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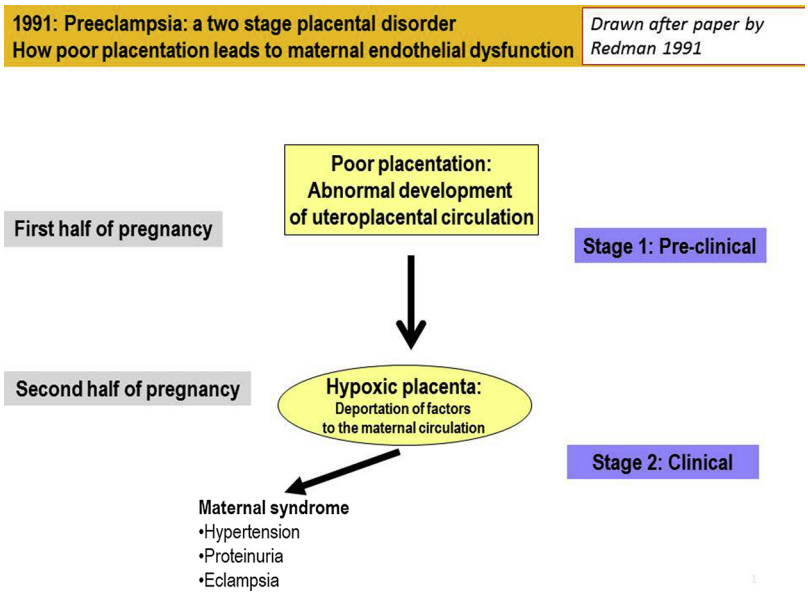

Fig. 1. The original 1991 two-stage placental model of preeclampsia.
Figure drawn from the text of Redman's paper (Redman, 1991). This original two-stage model of preeclampsia (Redman, 1991) proposed "poor placentation" with unremodelling of spiral arteries as the pathway to Stage 1 preeclampsia (placental dysfunction). Stage 1 represented the preclinical stage before development of maternal clinical signs (Stage 2).

these may be contributing factors, they are not sufficient; preeclampsia requires the presence of a placenta (or a recently delivered placenta, as in postpartum preeclampsia). The interactions between and pathophysiological effects of maternal predisposition and factors shed by the placenta are not, however, well delineated (Redman et al., 2014).

This paper will discuss how a revised two-stage model of preeclampsia fits with known risk factors and findings of circulating maternal biomarkers derived from the placenta. Improving our understanding of the pathophysiology underlying preeclampsia will hopefully promote the development of novel preventive and therapeutic measures, to ultimately improve short- and long-term maternal- and offspring health outcomes after preeclampsia.

2. The original 1991 two-stage model of preeclampsia and previous concepts

The classical two-stage model of preeclampsia was introduced by Redman in 1991 (Redman, 1991), and is depicted in Fig. 1. This model changed the paradigm of its time; prior to which preeclampsia was just considered to be a "hypertensive disease "of pregnancy. The secondary maternal manifestations of preeclampsia, new onset hypertension and proteinuria, were mistakenly regarded as primary. The two-stage model expanded on Redman's previously published concept (Redman, 1990) postulating that "in its origins preeclampsia is a trophoblastic disease, not a disorder of the haemodynamic, renal, or even endothelial system, although processes involving these systems may be essential to its evolution". He further argued that the disordered tissue must be the placental (fetal) trophoblast, as a fetus is not needed (the same syndrome occurs with a complete hydatidiform mole), nor is the uterus (as women with abdominal pregnancies may develop preeclampsia) (Redman, 1990).

Evidence of the placenta being important in preeclampsia was presented more than a hundred years previously, by Schmorl in 1893, in a report describing trophoblasts in the lungs of women who had died of eclampsia (as referenced by Redman: (Redman, 1991)). Later, it became well acknowledged that deportation of trophoblasts also occurred in normotensive pregnancies, albeit to a lesser extent than in preeclampsia (and eclampsia). The increased transport was assumed to be a consequence of placental ischemia. In 1967, Robertson and Brosens presented their seminal findings showing that preeclampsia is associated with poor placentation, observed as shallow remodelling of the uteroplacental spiral arteries (Robertson et al., 1967). In 1989, Roberts and **co**-workers introduced the concept of preeclampsia being a disorder of endothelial cell dysfunction (Roberts et al., 1989), suggested to explain the various clinical presentations of preeclampsia.

The 1991 Redman placental model of preeclampsia proposed two connecting stages: the first, the placental stage, was caused by shallow spiral artery remodelling during the first half of pregnancy, leading to "structural defects in the spiral arteries supplying the intervillous space", in turn causing "placental ischemia". It was recognized that poor placentation was not specific to preeclampsia, as it could also occur in pregnancies with FGR without a maternal syndrome. Furthermore, uteroplacental malperfusion secondary to poor placentation was proposed to cause increased release of "placental products or activities" into the maternal circulation. The second stage, the clinically overt maternal illness, was postulated to be a consequence of Stage 1; "a sequel of placental ischemia, secondary to spiral artery insufficiency" (Redman, 1991).

3. Further refinements of the two-stage model of preeclampsia

Rather than refuting the two-stage preeclampsia model presented in 1991, extensive preeclampsia-research has since refined our understanding of Stage 1 and Stage 2. Redman proposed in 1992 that immune mechanisms are involved in placentation and spiral artery insufficiency (Stage 1) and clinical preeclampsia development (Stage 2) (Redman, 1992). In 1993, Roberts and Redman together provided a synergistic understanding of preeclampsia in their seminal paper "Preeclampsia: more than pregnancy-induced hypertension" (Roberts and Redman, 1993). They suggested that endothelial dysfunction is the link between poor placental perfusion (Stage 1) and systemic maternal disease (Stage 2), specifically that the maternal endothelium represents the primary target (leading to Stage 2 development of hypertension and proteinuria) of factors derived from the placenta (produced in Stage 1). They argued that systemic endothelial dysfunction leads to loss of normal endothelial depressor functions and increases sensitivity to normally circulating pressor agents. The loss of endothelial integrity was suggested to underlie the heterogeneous clinical presentations of preeclampsia (Roberts and Redman, 1993).

Ness and Roberts made a substantial contribution to the development of the concept of preeclampsia in 1996, postulating the existence of two types of disease: the "placental" type and the "maternal" type (Ness and Roberts, 1996). They proposed that the "placental" type was linked to early-onset disease and high rates of fetal growth restriction (FGR), defining it as the form with a "placental circulation problem". The "maternal" type, linked to late-onset disease and lower rates of

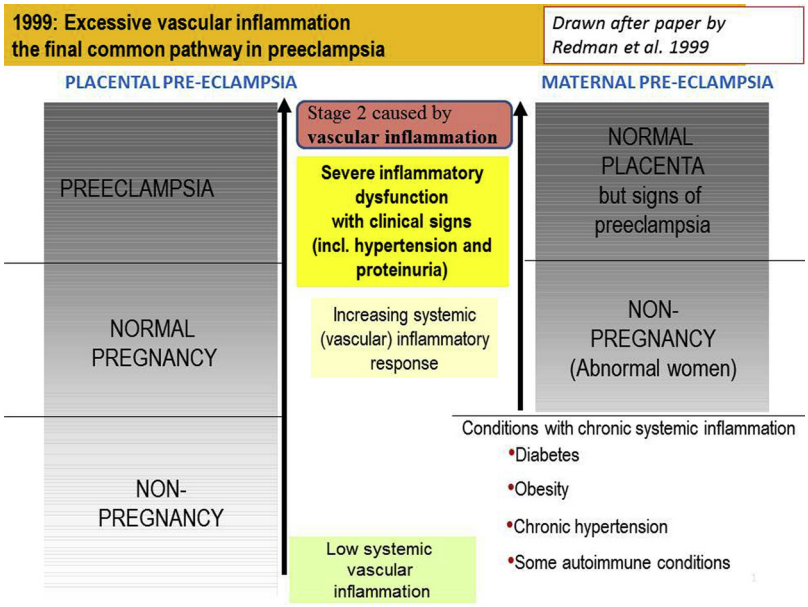

Fig. 2. Preeclampsia 1999 model: an excessive vascular inflammatory response to pregnancy.
The figure is derived from the text of Redman's paper (Redman et al., 1999), explaining how maternal risk factors promote development to Stage 2 (clinical preeclampsia). The paper argued that maternal endothelial dysfunction is a part of the more generalized vascular inflammatory response of preeclampsia (Redman et al., 1999). It also argued that this vascular inflammatory response is not an epiphenomenon, but represents the cause of the preeclampsia clinical syndrome. Maternal diseases involving ongoing vascular inflammation were suggested to lower the threshold for the inflammatory effects of pregnancy. The paper argued that poor placentation is not the cause of preeclampsia, but a strong predisposing factor, and that no single preeclampsia gene, no single specific predictive test nor single effective measure will be devised, due to the heterogeneity of the syndrome.

FGR, was defined as preeclampsia occurring in spite of normal placentation and a normal placental circulation, and rather due to predisposing inflammatory conditions in the woman causing her vessels to react abnormally to the "stress of pregnancy", including diabetes mellitus, chronic hypertension, obesity, and autoimmune disorders.

In 1999, Redman and co-workers (Redman et al., 1999) further refined Stage 2 by proposing that vascular inflammation (rather than isolated endothelial dysfunction) is the cause of the clinical manifestations of preeclampsia. Endothelial activation is intrinsic to the systemic inflammatory response, which involves leukocyte and complement activation, the acute phase response, perturbed complement and coagulation function, insulin resistance, and hyperlipidaemia. Generalized vascular inflammation, caused by several potential proinflammatory stress factors from the placenta (e.g. syncytiotrophoblast microvillous fragments (Redman et al., 1999), more recently named syncytriotrophoblast extracellular vesicles (Tannetta et al., 2015)), was suggested to explain the features of the multi-organ syndrome preeclampsia. As depicted in Fig. 2, the "maternal" form of preeclampsia was integrated into the two-stage model by suggesting that women with chronic systemic inflammation (such as diabetes, obesity, chronic hypertension, and autoimmune conditions) start their pregnancies with an elevated level of maternal vascular inflammation as compared to healthy women. Consequently, as pregnancy progresses and shedding of inflammatory placental factors increases, predisposed women will more rapidly reach a level of severe inflammatory dysfunction (Stage 2) and thereby display the clinical signs of preeclampsia, including new onset hypertension and proteinuria, even in pregnancies with normal spiral artery remodelling and placentation.

Research in the field of pregnancy immunology has contributed major advances to the field since the birth of the two-stage model in 1991. In 1996, Robillard and collaborators published their important observations that preeclampsia is associated with a shorter period of sexual cohabitation prior to conception (Robillard and Hulsey, 1996), suggesting that primipaternity rather than primigravidity is a risk factor for preeclampsia (Robillard and Hulsey, 1996). This suggests a preconceptional stage of preeclampsia (Redman and Sargent, 2010) that modifies the risk of poor placentation and other Stage 1 problems. Maternal interaction with fetal (paternal) alloantigens, facilitating local maternal-fetal immunotolerance, is today viewed as essential for normal human placentation. Immune priming by seminal plasma has been demonstrated in mice (Robertson et al., 2009). A prior pregnancy with the same conceiving father generates memory Treg cells (Rowe et al., 2012), that presumably decline over time, which explains why protective benefit is lost after a long inter-pregnancy interval (Skjaerven et al., 2002). The last decade has pinpointed the importance of decidual regulatory T cells (Tregs) for maternal immune tolerance to ensure a robust placenta (Robertson et al., 2018). As well as mediating tolerance, Treg cells are anti-inflammatory, conferring protection against inflammatory injury. An active state of maternal immune tolerance to maintain the allogenic pregnancy is essential. A reduction in Treg number or function is observed in preeclamptic pregnancies (Sasaki et al., 2007; Tsuda et al., 2018), as is a Treg/Th17 imbalance (Saito et al., 2011). Treg dysfunction is implicated in dysfunctional trophoblast invasion and spiral artery remodelling problems across several clinical variants of placental dysfunction, including preeclampsia and FGR (Robertson et al., 2018). Such immunological findings are in line with epidemiological observations that the risk of preeclampsia is elevated in pregnancies achieved after insemination with donor sperm, or after using barrier methods of contraception (as reviewed in (Redman and Sargent, 2010)).

Seminal publications by Moffet and others have highlighted the importance of the local uterine lining's (decidual) immune system in successful placentation. Maternal uterine natural killer (uNK) cells contribute to the early stages of spiral artery remodelling (Robson et al., 2012). Interactions between killer-cell immunoglobulin-like receptor (KIR) proteins, expressed on the uNK cells, and fetal HLA-C proteins, expressed on invading trophoblasts, are important for the placentation process. The consequence of maternal and fetal interactions is reflected in the effect that differing KIR genetics world-wide has on baby weight percentiles and preeclampsia rates (Nakimuli et al., 2015). The importance of maternal KIR and fetal HLA-C interaction for preeclampsia development was however questioned in a study by Saito et al, as data from Japan might be in contrast to these findings (Saito et al., 2006). Recently, it was also shown that human uNK cells may develop trained memory after a first pregnancy, potentially promoting more efficient placentation in subsequent pregnancies (Gamliel et al., 2018). A recent paper highlights the intimately link between the immune and cardiovascular systems. Care et al recently described that Treg deprivation in a mouse model reduces maternal vascular adaptations in pregnancy. As the uNK cells are essential for this pregnancy remodelling of uterospiral arteries, it is proposed that Tregs interact with uNK cells to facilitate such vascular remodelling (Care et al., 2018).

In 2009, Burton et al (Burton et al., 2009a) refined our views of how insufficient remodelling of uteroplacental spiral arteries could lead to

abnormal uteroplacental perfusion and placental (dys)function in preeclampsia. It was previously assumed that failure of deep endovascular invasion and remodelling would lead to "placental under-perfusion" and resulting chronic hypoxia. In the model by Burton et al, it was argued that flow volume is not largely affected by unsuccessful spiral artery remodelling in pregnancy, but that the quality of uteroplacental perfusion through non-converted spiral arteries has a more pulsatile and higher pressure flow compared to what is observed in normally remodelled arteries. This abnormal flow resulting from suboptimal remodelling is predicted to injure the chorionic villi, both hydrodynamically and biochemically, generating ischemia-reperfusion injury and placental oxidative stress, rather than chronic hypoxia per se (Burton et al., 2009a). The same year, Burton et al (Burton et al., 2009b) also demonstrated that placental malperfusion secondary to poor placentation was linked to increased placental endoplasmic reticulum (ER) stress and activation of the unfolded protein response, a cellular pathway that halts protein synthesis in the event of unsuccessful protein folding, which they argue contributes to the development of the small placenta phenotype observed in FGR and early-onset preeclampsia. They suggested pregnancies with maternal clinical symptoms of preeclampsia were secondary to a severe degree of placental ER stress and oxidative stress.

Several scientific controversies regarding the dysfunctional spiral artery remodelling in preeclampsia have been raised since 1991, and were reviewed by Pijnenborg et al in 2006 (Pijnenborg et al., 2006). One common misunderstanding is that both the interstitial and endovascular depth of trophoblast invasion are altered in preeclampsia. As summarized by Pijnenborg et al, interstitial invasion occurs prior to endovascular invasion, but it is only the depth of the latter that is reduced in preeclampsia as interstitial trophoblast invasion depth remains normal. This finding of shallow invasion only by endovascular (and not interstitial) trophoblasts in preeclampsia was confirmed in detailed placental bed studies by Lyall and co-workers (Lyall et al., 2013). Another misconception, still presented in many papers, is that endovascular trophoblast invasion results in permanent replacement of maternal spiral artery endothelial cells by invading fetal trophoblasts (Pijnenborg et al., 2006). This misconception is based on findings by Zhou et al (Zhou et al., 1997a, b) showing that endovascular trophoblasts normally "transform their adhesion receptor phenotype" and begin to express endothelial markers, whereas those in preeclampsia fail to do so. As argued by Pijnenborg et al (Pijnenborg et al., 2006), findings from term placenta bed specimens rather suggest that the endothelial cell replacement by trophoblasts is only temporary, and intramural embedment of these cells follows. Re-endothelialisation with maternal endothelial cells likely occurs in all pregnancies; immunohistochemical findings of third trimester biopsies show that all spiral artery endothelial cells are cytokeratin-negative and therefore not likely trophoblast-derived (Pijnenborg et al., 2006). In their 2006 review, Pijnenborg et al also discuss their original "two-wave" hypothesis of trophoblast invasion, based on hysterectomy specimens. This hypothesis has been refuted in light of placental bed findings by Lyall, concluding with a continuous endovascular migration from decidual to myometrial arteries, rather than two distinct trophoblast invasion waves (Lyall, 2002).

Another major modification to the two-stage preeclampsia model of 1991 is the increasing understanding that poor placentation involves much more than trophoblast-associated spiral artery remodelling. Pijnenborg et al predict (Pijnenborg et al., 2006) that several of these non-trophoblastic remodelling features may be affected in preeclampsia. These steps include early decidual vascular remodelling (prior to trophoblast invasion) and vascular plugging by trophoblasts. The plugging by cytotrophoblasts of maternal vessels helps to maintain a state of physiological hypoxia early in the placentation process, favouring cytotrophoblast proliferation rather than differentiation and invasiveness, as reviewed by Red-Horse et al in 2004 (Red-Horse et al., 2004).

In 2008, Huppertz proposed a new concept by suggesting that early failures in the different trophoblast lineages could mediate the clinical heterogeneity seen in FGR and preeclampsia (Huppertz, 2008). He suggested that early *villous* cytotrophoblast failure could result in placental pathology and release of inflammatory factors that would mediate a systemic maternal inflammatory response, and thereby the clinical signs of preeclampsia, whereas early failure in the *extravillous* cytotrophoblast lineage would result in the clinical features of FGR (Huppertz, 2008). It could be argued, however, that severe failure of the villous trophoblast cell line is also likely to result in distal villous hypoplasia, a condition associated with severe FGR, as well as hypertensive pregnancies (Veerbeek et al., 2014). Factors impacting the various trophoblast precursors may also interact, thereby resulting in mixed clinical presentations.

A major improvement to the concept of how Stage 1 and Stage 2 of the placental preeclampsia model interconnect, was made by Karumanchi and his team in 2003. They discovered that some trophoblast-derived markers were closely associated with preeclampsia, the so-called anti-angiogenic factors (e.g. soluble VEGF receptor 1; sFlt1, and soluble Endoglin; sEng) and pro-angiogenic factors (e.g. placenta growth factor; PlGF) (Maynard et al., 2003; Levine et al., 2004). Placental villous syncytiotrophoblast (STB) secrete PlGF and sFlt1, the latter representing a soluble decoy receptor for VEGF and PlGF. A relatively anti-angiogenic imbalance (elevated levels of maternally circulating sFlt1 and sEng, and low PlGF) is found in overt preeclampsia (Stage 2), as compared to most normotensive pregnancies. Also, an increasing anti-angiogenic pattern in the first two trimesters significantly increases the risk of early-onset preeclampsia (Levine et al., 2004; Vatten et al., 2007; Erez et al., 2008). However the question of whether these factors represent early in pregnancy simply biomarkers of placental dysfunction or whether local decidual dysregulation of such anti-angiogenic factors mediates early dysfunctional placentation and thereby Stage 1, has not yet been answered. Besides being a major controller of angiogenesis, sFlt1 represents an important link from placental dysfunction (Stage 1) to the clinical stage (Stage 2) of preeclampsia development as it affects normal endothelial structure function through reducing available (free) PlGF and VEGF. Unlike free PlGF, the concentration of free VEGF in blood is too low in pregnancy to be measured reliably with today's immunoassay methodologies, even in normotensive pregnancies.

The discovery of an anti-angiogenic pathway to preeclampsia by Karumanchi and co-workers has led to many biomarker studies attempting to predict the onset of preeclampsia early in pregnancy (Myers et al., 2013) as well as the absence of preeclampsia in women with suspected disease, not fully meeting diagnostic criteria (Zeisler et al., 2016). We have ourselves suggested that maternally circulating biomarkers mostly derived from the placenta, like PlGF, could be used to further subdivide the heterogeneous preeclampsia syndrome into more pathophysiologically similar subgroups (Staff et al., 2013a).

In 2014, we (Staff et al., 2014) extended the two-step model of preeclampsia into a multi-step model, as shown in Fig. 3. The dysregulated local maternal tolerisation to allogeneic trophoblasts previously suggested as one aspect of poor placentation (Redman, 1992) were named Stages 1 and 2 in this new multi-step model. Impaired immune tolerance would impair placental development and promote dysfunctional uteroplacental perfusion (here named Stage 3) through reduced vascular adaptation and elevated inflammation, leading to placental release into the maternal circulation of inflammatory factors and ensuing generalized maternal inflammatory vascular stress and overt clinical preeclampsia (Stage 4). In addition, pre-pregnancy maternal vascular inflammation (named pathway B in Fig. 3), including that observed in chronic hypertension, some autoimmune disorders, and obesity, might also dysregulate placentation (named pathway A in Fig. 3) as well as increase maternal vascular susceptibility to factors shed by the placenta in late pregnancy, the latter promoting the maternal clinical signs. In addition, we speculated that excessive decidual

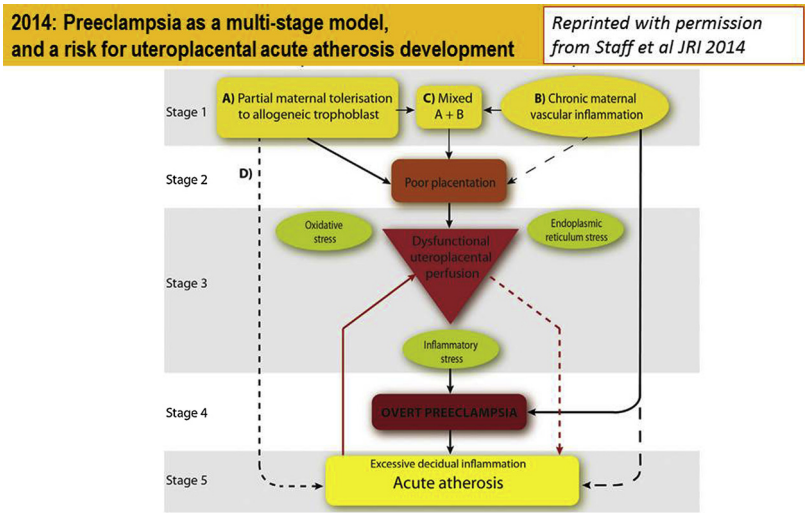

Fig. 3. A multi-stage 2014 Preeclampsia placenta model.
Reprinted (own figure) with permission from the Journal (Staff et al., 2014). The model recognizes preplacentation factors leading to poor placentation and suggests uteroplacental acute atherosis as part of a multistep pathway of preeclampsia (Staff et al., 2014)

inflammation in late pregnancy could predispose to the development of decidual acute atherosis, an arterial foam cell lesion akin to the early stages of atherosclerosis, which is commonly observed in preeclampsia (Staff et al., 2013b, 2014; Alnaes-Katjavivi et al., 2016). It is obstructive, associated with spiral artery thrombosis and would be expected to worsen placental intervillous perfusion beyond that caused by poor placentation. We also hypothesized that uteroplacental acute atherosis could develop at any stage of pregnancy in the setting of sufficient decidual inflammation (Staff et al., 2014), including in normotensive pregnancies. In term decidual tissue, we found that 11% of normotensive pregnancies were affected by acute atherosis (Alnaes-Katjavivi et al., 2016). The finding of first trimester decidual acute atherosis in a woman with concurrent systemic lupus erythematosus and antiphospholipid syndrome (Nayar and Lage, 1996) suggests that massive pre-pregnancy vascular inflammation may be sufficient for generating inflammatory arterial pregnancy lesions, even very early on in pregnancy.

4. Recent improvements to the 2-stage preeclampsia model

In the original two-stage model of preeclampsia (Redman, 1991) it was assumed that poor placentation occurs in all preeclampsia. But in most cases of late-onset preeclampsia delivering at or beyond term, the neonates are not growth restricted, which is incompatible with poor placentation. The original 2-stage model was therefore applicable mainly to early-onset preeclampsia. A unifying model of placental dysfunction was lacking. In 2014 (Redman et al., 2014), we suggested a second placental etiology of preeclampsia. This comprised uteroplacental malperfusion at term, without poor placentation, occurring when the placenta outgrows uterine capacity, such that the terminal villi are compressed, impeding intervillous perfusion. This causes syncytiotrophoblast hypoxia and stress in the same way as does dysfunctional perfusion associated with early-onset disease. Hence these two pathways have different time courses and causes, but trigger similar maternal responses, both mediated by syncytiotrophoblast stress. Poor placentation comprises an “extrinsic cause” of placental dysfunction. Placental compression at term suggests the concept that Stage 1 (placental dysfunction), previously presented as an early event in pregnancy, may also occur, as a late event, for another reason, at or beyond term, even in relatively large placentas, by way of an “intrinsic” pathway (Fig. 4, pathway B). This concept is consistent with the fact that the ultrastructural changes of villous trophoblasts in post-term pregnancies is strikingly similar to that of preeclampsia (Jones and Fox, 1978).

The revised two-stage preeclampsia model explains why FGR is more associated with early- than late-onset preeclampsia. The effect is a function of the duration of the problem of dysfunctional uteroplacental perfusion. In the context of poor placentation this is longer, starting in the first trimester, therefore the insult is more severe. With late-onset preeclampsia FGR can occur, but it is mitigated by its short duration and the fact that it is rapidly treated by inducing labor. The two placental forms of preeclampsia may occur together with moderately preterm preeclampsia, fitting with the clinical heterogeneity of the disease (Redman et al., 2014). Placental compression is more likely in women with larger placentas at term, who have been observed to have an increased risk of developing late-onset preeclampsia (Dahlstrom et al., 2008).

Poor placentation is now known to be associated with a spectrum of poor obstetric outcomes beyond early onset preeclampsia (Fig. 5), as was predicted by Redman already in 1991 (Redman, 1991). These include (recurrent) pregnancy loss, FGR, preterm premature rupture of membranes, intrauterine fetal death, and placental abruption (Avagliano et al., 2011). Similarly to dysfunctional spiral artery remodelling not being the obligatory prerequisite for all forms of preeclampsia, it is well documented that FGR and other placental syndromes may occur without these remodelling problems.

Fig. 4 illustrates a 2019 updated two-stage model of preeclampsia. Here, the poor placentation pathway (Fig. 4, pathway A) and the congested placenta pathway (Fig. 4, pathway B) can both lead to syncytiotrophoblast (STB) stress of preeclampsia (Stage 1), representing the common endpoint of several processes. However, there may be several other hitherto unknown factors important for reaching Stage 1 (STB stress). Excessive trophoblast senescence (Cox and Redman, 2017) may possibly add to placental cellular stress (illustrated by a clock in Fig. 4, pathway C), and this potential pathway to preeclampsia deserves further investigation

The original two-stage model did not incorporate maternal risk factors. In an alternative model, Ness and Roberts (Ness and Roberts, 1996) proposed the concept of “maternal type” preeclampsia, in which the development of hypertension and proteinuria was considered not to be linked to placental dysfunction or an altered uteroplacental circulation. The updated two-stage model of preeclampsia (Fig. 4) incorporates that maternal factors may affect multiple steps in the pathways leading to preeclampsia, potentially affecting both main common stages of preeclampsia development. The model also predicts that there is no “maternal” preeclampsia, without the presence of a placenta. We

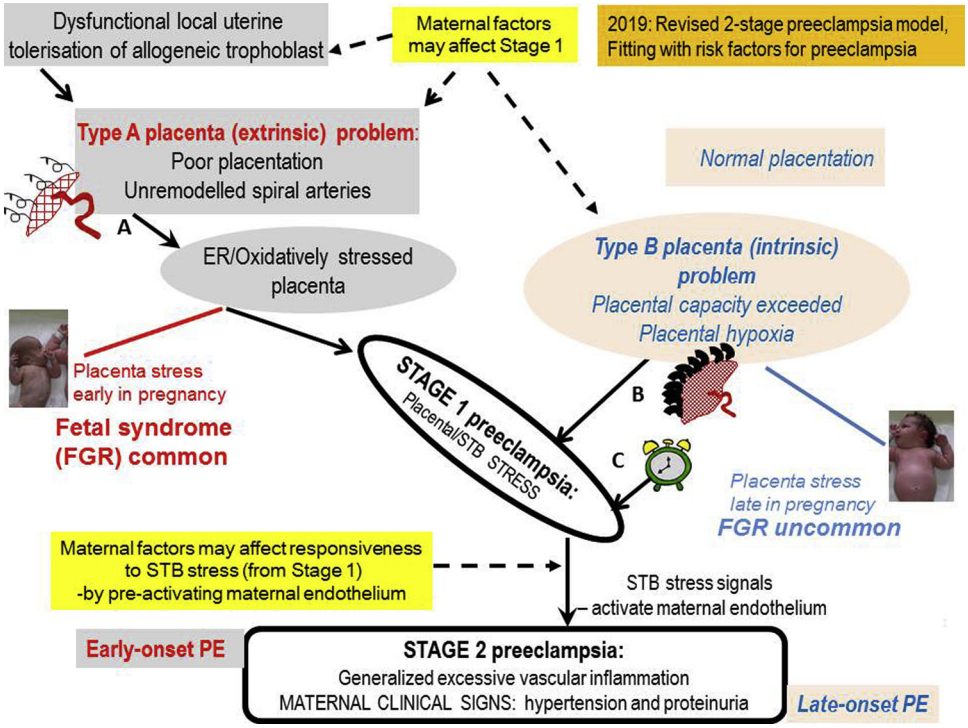

Fig. 4. The 2019 revised two-step model of preeclampsia, integrating maternal risk factors and two main placental pathways to clinical preeclampsia.
The figure is further developed from our previous papers (Redman et al., 2014; Redman and Staff, 2015; Staff and Redman, 2018). This unifying model suggests how maternal and placental factors contribute to both stages of the disease; STAGE 1 represents the placental dysfunction stage (STB-syncytiotrophoblast stress) and STAGE 2 represents the maternal clinical syndrome. Pathway A illustrates the classical dysfunctional placentation pathway to STAGE 1 ("extrinsic placental pathway") and Pathway B illustrates the "intrinsic placental pathway", typically of late pregnancy and larger placentas.
Pathway C illustrates other potential pathways to Stage 1, including ageing/senescent placentas (Cox and Redman, 2017), a pathway deserving further investigations. Yellow boxes illustrate that maternal factors, such as chronic inflammatory diseases, may affect several steps of both placental pathways as well as affecting the cardiovascular receptivity to STAGE 1 produced inflammatory factors, promoting the development towards clinical recognized preeclampsia with new onset hypertension and proteinuria (STAGE 2 preeclampsia).

propose that maternal factors (e.g. chronic arterial disease, obesity, and some autoimmune diseases) may impact multiple aspects of placentation, placental size, and placental function, converging on the Stage 1 pathology of placental dysfunction, in addition to amplifying maternal cardiovascular sensitivity to factors shed by the placenta to generate the maternal clinical signs (Stage 2).

Maternal obesity, a well-known risk factor for both early-and late preeclampsia (Egeland et al., 2016) and chronic vascular inflammation, has indeed been shown to be an independent risk factor for poor spiral artery remodelling across several placental syndromes (Avagliano et al., 2011). It is likely that obesity and other risk factors for preeclampsia affect the periconceptual endometrial function. Although studies of pre-pregnancy spiral arteries and endometrial tissue in women who develop preeclampsia are lacking, a recent study of chorionic villous samples

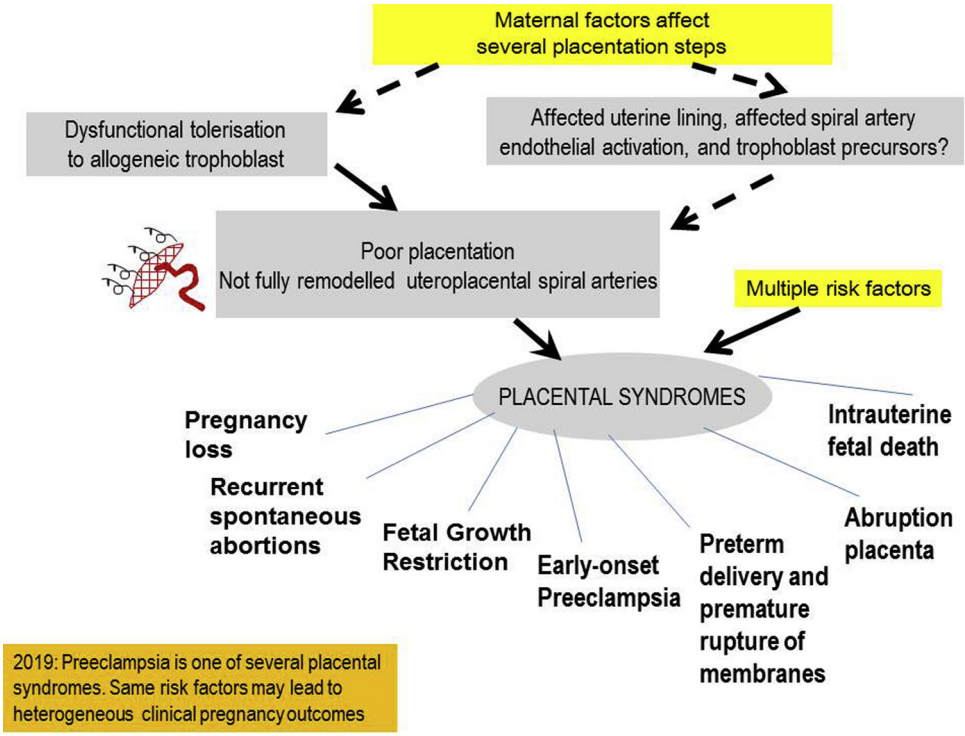

Fig. 5. Placental syndromes are more than preeclampsia. Placentation problems are associated with several placental syndromes, not exclusively preeclampsia. All these placental syndromes, including preeclampsia, may however also have other causes for placental dysfunction than spiral artery remodeling problems.

Table 1
Risk factors for preeclampsia (hypertensive disorders of pregnancy).

Risk factor start	Increases risk for preeclampsia/gestational hypertension (Visintin et al., 2010; Nelson-Percy, 2015)
Pregestational factors	Primiparity/primigravidity
	Advanced maternal age (> 40 years)
	Maternal overweight/obesity (risk increases linearly from BMI 28 (Egeland et al., 2016)
	Chronic hypertension (by definition not a risk factor for gestational HT)
	Pregestational diabetes mellitus
	Renal disease (incl. kidney transplantation)
	Autoimmune diseases (e.g. Systemic Lupus Erythematosus and Antiphospholipid syndrome)
	Short pre-pregnancy duration of sexual cohabitation (with conceiving father). Long inter-pregnancy interval (> 10 years). Barrier contraception
	Women of African (genetic) descent
	Previous severe/early-onset preeclampsia (delivery prior to gestational week 34) and/or fetal growth restriction.
	Preeclampsia in mother/sisters
	Lack of smoking
Pregnancy factors	Large placentas, including multiples and moles
	Fetal Growth Restriction (FGR)
	Gestational diabetes mellitus
	Uterine artery notch/elevated PI
	Dysregulated angiogenic factors (e.g. Low circulating level of Placenta Growth Factor in first trimester)
	Assisted Reproductive Technology

from early pregnancy indicates that insufficient or defective maturation of endometrial and decidual NK cells during the secretory phase and early pregnancy respectively can indeed precede the development of preeclampsia (Rabaglino et al., 2015), supporting the important role of the periconceptional endometrium in mediating adverse pregnancy outcomes such as preeclampsia.

Maternal obesity also increases risk for chronic hypertension. Chronic hypertension, even on non-obese women, is also a strong risk factor for developing preeclampsia (named “superimposed” preeclampsia), as much for early- as for late-onset disease (Lisonkova and Joseph, 2013). Early-onset superimposed preeclampsia is associated with FGR, a primary feature of underlying poor placentation. So it can be deduced that maternal prepregnancy hypertension predisposes to poor placentation. However the precise mechanisms whereby maternal arterial dysfunction inhibits early placentation are yet to be defined. If it were the maternal hypertension itself, then its early treatment would be expected to reduce the risk of later superimposed preeclampsia, for which there is little evidence. Hence it is more likely to be mediated by increased vascular inflammation in the spiral arteries, either directly or indirectly. How this interacts with the processes of spiral artery remodelling, including the shallow endovascular trophoblast invasion seen in early-onset preeclampsia, is yet not clear.

The updated model offers a possible explanation why maternal risk factors may lead to abnormal uteroplacental circulation even in late pregnancyby placental compression, for example- as in the context of large and post-term placentas (Fig. 4, pathway B). Obese women, term pregnancies, and pregnancies with multiple fetuses are more likely to have larger placentas, and also have an increased risk of late-onset preeclampsia, which is consistent with the model. The angiogenic biomarker studies have deomonstrated a progressively increasing circulating maternal sFlt1 level in all pregnancies in third trimester (Levine et al., 2004), also in pregnancies remaining normotensive till delivery. It is likely that this increasing sFlt1 level sensitizes the maternal endothelial cells to any pro-inflammatory factors shed from the (ageing) placenta, similarly to what is demonstrated in vitro (Cindrova-Davies et al., 2011). Pregnancy is a race against time (Redman and Staff, 2015), in which delivery at term or preterm will “save” many post-term pregnancies from developing preeclampsia (and fetal demise).

The maternal risk factors may also affect maternal vascular responsiveness to inflammatory factors shed by the placenta. An elevated level of maternal vascular inflammation at onset of pregnancy, due to maternal risk factors (e.g. diabetes, hypertension, or obesity), could explain why even a moderate degree of STB stress (whether secondary to dysfunctional placentation or placental size problems) could result in clinical disease (Stage 2). Fig. 4 suggests an alternative pathway to STB stress, independent of spiral artery remodelling problems (pathway A) or placenta constraint (pathway B). Pathway C suggests that placentas with normal ageing, but in the extreme end of pregnancy (as in post-term placentas) may cause excessive STB stress as compared to younger placentas, also when the placenta size is not big (as in pathway B). Another pathway to STB stress may be an excessive trophoblast senescence or other causes of trophoblast dysfunction (e.g. infections with Parvovirus (Zaki et al., 2003)), likely leading to increased shedding of inflammatory factors, such as increased sFlt1 (Goa et al., 2013), to the maternal vasculature. Even a relatively low degree of STB stress could be sufficient to reach the clinically overt Stage 2 of preeclampsia in women who are susceptible for excessive inflammatory substances, such as women with prior chronic vascular inflammation, or due to pregnancy-related excessive vascular inflammation, such as in gestational diabetes mellitus (as suggested by increased inflammatory markers TNF-alpha and hsCRP (Salmi et al., 2012)). The more excessively inflamed the maternal vasculature is by prior “non-placental” maternal factors, the less inflammatory stimuli from the placenta is likely needed to reach the clinical Stage 2.

5. Does the revised two-stage model fit with preeclampsia risk factors and heterogeneity?

Table 1 lists the major epidemiological risk factors for preeclampsia. The updated 2019 two-stage model of preeclampsia, as presented in Fig. 4 with many potential combinations of maternal and placental risk factors and pathways, explains much of the heterogeneity observed in the preeclampsia syndrome, including explaining why FGR is a more common feature in early- than late-onset disease.

When it comes to explaining why primiparity, a new sexual partner, long interpregnancy time (Skjaerven et al., 2002), and use of barrier contraception all confer a risk of developing preeclampsia, the previous two-stage model of preeclampsia is sufficient. All of these risk factors involve periconceptional and pregnancy-related effects on the local uterine environment, and thereby contribute to “classical” dysfunctional uteroplacental spiral artery remodelling, presumed to be mediated largely by uterine NK cells (Harris, 2011). In addition, work by Khong et al has demonstrated that the myometrial sections of spiral arteries of parous uteri are more likely to sustain some of the remodelling occurring during pregnancy, which could possibly explain some of the reduced risk of preeclampsia in parous women, along with explaining why birth weights in general increase with increasing parity (Khong et al., 2003).

The revised two-stage model is consistent with other

epidemiological risk factors for preeclampsia. Examples of maternal pre-pregnancy factors affecting preeclampsia rates include short sexual cohabitation prior to pregnancy, autoimmune diseases and obesity, that we suggest may impact on decidual immune factors that are important for placentation (Fig. 4, pathway A). As mentioned above, recent studies indeed support that altered maturation and immune cell properties of the endometrium can precede the development of preeclampsia (Rabaglino et al., 2015), in line with the concept of modifiable endometrium prior to pregnancy.

The revised two-stage model (Fig. 4) fits with obesity being a risk factor for all forms of preeclampsia, not only the late-onset form, as demonstrated in a population-based study with adjusted risk analyses (Egeland et al., 2016). It may therefore seem contradictory that in spite of increasing obesity rates, countries with highly developed antenatal and obstetric care are experiencing a small decline in preeclampsia rates, as seen in Northern Europe and Australia (Roberts et al., 2011; Klungsoyr et al., 2012; Roberts et al., 2015). Two clinical trends may have contributed to reducing the negative effects of increasing BMI; post-term pregnancies are more aggressively induced than before (to reduce rates of fetal demise) and low-dose aspirin for prevention of preeclampsia in women at high risk is increasingly being used.

The revised two-stage model could also explain the rare forms of postpartum preeclampsia and eclampsia observed, and even eclampsia diagnosed prior to the agreed upon 20 gestational week threshold for diagnosing preeclampsia, as well as abdominal pregnancies complicated by preeclampsia. As seen from Fig. 4, any extreme forms of pre-pregnancy vascular inflammation, such as in systemic lupus, could result in accelerated development of Stage 1 and Stage 2, explaining the rare forms of eclampsia seen very early in pregnancy in some of these patients. As for the very rare, but well documented, postpartum cases of eclampsia and preeclampsia (reviewed in (Redman, 1991)), they all have in common that placental tissue was recently present in the mother. Although placentally derived, maternally circulating biomarkers such as sFlt1 fall rapidly after delivery of the placenta (Reddy et al., 2009), some inflammatory mediators from the placenta persist for a while postpartum, as the vaginal bleeding (the “lochia”) of any postpartum woman contains decidual remnants. Also, since parturition in itself may invoke unspecific vascular inflammation (demonstrated by clinical findings of CRP elevation postpartum), excessive inflammation following operative deliveries, postpartum endometritis, and increased postpartum vascular inflammation of any “non-placental” cause, Stage 2 may occur postpartum due to enhanced vascular susceptibility to remnant placental factors (clinically observed as postpartum pre-eclampsia/eclampsia) despite prior delivery of the placenta.

Our revised two-step model may also account for why some pregnancies only present with fetal signs of growth restriction, and lack the maternal signs of new-onset hypertension and proteinuria, despite the presumably similar placentation-based etiology of the two. Some cases of FGR/small for gestational age (SGA) pregnancies are due to fetal genetics or malformations, and are not discussed further here. Amongst normotensive pregnancies complicated by FGR without fetal malformations or genetic aberrations, many could represent pregnancies that have reached Stage 1 (placental dysfunction and ER/STB stress), but not yet Stage 2 of preeclampsia development. We suggest that the predisposition to maternal inflammation may be low/normal in some of these women, but the degree of Stage 1 placental dysfunction may be high (either due to remodelling problems and subsequent ER stress or villous trophoblast dysfunction, the latter not in itself necessarily associated with poor spiral artery remodelling); the net result is FGR and absence of maternal hypertension and proteinuria. Clinically, these pregnancies may be “rescued” by iatrogenic delivery when severe FGR is detected clinically, often through antenatal screening by way of symphysis-fundus height measurement and subsequent diagnosis through targeted specialist follow-up with serial ultrasound assessment of fetal growth and blood flow. In countries with adequate antenatal care, severe FGR is treated by delivery of the baby to avoid severe fetal complications, including intrauterine fetal death. Our revised pre-eclampsia model suggests that many of these women would eventually have developed clinically overt preeclampsia (Stage 2), but are “saved” by the removal of the dysfunctional placenta through preterm delivery. Some women may also have a vasculature that is very resistant to placental-shed inflammatory factors, and may therefore take longer time to develop clinical Stage 2 as compared to women with less resistant vasculature.

The “smoking paradox” of preeclampsia is another complex and puzzling phenomenon. The previously noted “beneficial” risk reduction for preeclampsia in smokers is not a straight-forward association, and is not necessarily present in all populations today (Jeyabalan et al., 2010). Smokers run a largely increased risk of having pregnancies complicated by FGR, intrauterine fetal death, and increased infant morbidity and mortality. Recent population-based studies suggest that smoking (and the cessation of smoking) at different gestational ages, affects the risk of preeclampsia differently (Wikstrom et al., 2010). Nicotine inhibits normal first trimester cytotrophoblast invasion in vitro (Genbacev et al., 1995), and placentas from women who smoke display a reduction in cell columns, in line with smoking increasing the risk of several placental syndromes listed in Fig. 5. Angiogenic factor levels also differ between smokers and non-smokers both prior to and during pregnancy. In pregnancy, this effect is possibly secondary to carbon monoxide reducing placental sFlt1 production (Cudmore et al., 2007), but reports of dysregulated angiogenic factors differ between publications. Differences in production of placental angiogenic factors (in Stage 1) may be one of the reasons why some smokers are less at risk of developing clinically manifest maternal signs of preeclampsia (Stage 2), despite evidence of dysregulated placentation (Fig. 4, Pathway A to Stage 1).

6. Conclusions and future research needed

In conclusion, the revised two-stage preeclampsia model differs from the original one in that it encompasses more than one cause of placental dysfunction (Stage 1 of the syndrome). The effect of Stage 1 may depend on the degree of preset inflammation of the maternal vasculature, potentially culminating in the excessive vascular response and the clinical full-stage preeclampsia Stage 2. The revised two-stage model of preeclampsia is consistent with current scientific findings and preeclampsia epidemiology and pathophysiology and begins to explain aspects of the heterogeneity of the clinical presentations, including its presentation solely with maternal signs or in combination with FGR. As previously proposed (51), anti-angiogenic biomarkers are biomarkers of syncytiotrophoblast (STB) stress, not of preeclampsia as such.

There are still however many miles to go, as we are far from understanding all molecular, immunologic, genetic, and environmental mechanisms leading to the different clinical presentations of the placental syndromes, of which preeclampsia is one. The statement by Redman in the original 1991 two-stage preeclampsia paper is still highly relevant: “At the moment the final proof is lacking that the model is correct. But it is clear that the placenta will reward those who want to understand preeclampsia better”. The conclusion remains the same in 2019: further placenta-related research is needed to promote the understanding of human health and disease, including how the heterogeneous syndrome of preeclampsia develops and how it mediates long-term health effects on mother and offspring. Researchers in the field are especially encouraged to further dissect the various factors promoting pre-implantation heterogeneity and decidua-related (“trophoblast-independent”) vascular remodelling processes, decidual and immune cell interactions, as well as cytokine and growth factor production prior to and during trophoblast invasion. Emerging studies demonstrating accelerated placental ageing in early-onset preeclampsia as well as autophagy (Saito and Nakashima, 2014; Aoki et al., 2018) are also highly worth pursuing, as oxidatively stressed placentas (Stage 1) would be expected to increase the rate of placental ageing, thereby accelerating the speed towards a clinically overt Stage 2.

As for the previous concepts of “maternal” and “placental” pre-eclampsia, the revised preeclampsia model implies there is no form of preeclampsia that does not involve the placenta (Fig. 4, Stage 1). Even an apparently “normal” placenta is an inflammatory burden to the pregnant woman, and this burden increases with advancing gestational age as the placenta grows and ages. Hence, it can be argued that pre-eclampsia is not a fundamentally different state compared to normal pregnancy, but one in which placentally induced changes are ex-aggerated to the point of decompensation.

In light of the heterogeneous nature of the preeclampsia syndrome, and the several potential pathways depicted in our two-stage model, it is unlikely that one isolated main factor, whether genetic or other, could explain all forms of preeclampsia. Preeclampsia represents a complex and multifaceted syndrome, as it involves several genomes; the maternal (oocyte and uterine), paternal, and fetal genomes. Dissecting its molecular pathology and interaction with environmental and mod-ifiable risk factors is likely to uncover biological understanding relevant to many human diseases, in addition to refining our preeclampsia concepts and models.

Declaration of Competing Interest

The authors declare no conflict of interest. Anne Cathrine Staff has received recompensation from Roche (Norway) for advisory board service in 2018 regarding preeclampsia screening. She has also received from Roche International (Rotkreuz, Switzerland) and Roche Norway in-kind reagents for sFlt1 and PlGF biomarker analyses for obstetric research purposes.

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