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The Two Stage Model of Preeclampsia: Variations on the Theme

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Abstract

The Two Stage Model of preeclampsia proposes that a poorly perfused placenta (Stage 1) produces factor(s) leading to the clinical manifestations of preeclampsia (Stage2). Stage 1 is not sufficient to cause the maternal syndrome but interacts with maternal constitutional factors (genetic, behavioral or environmental) to result in Stage 2. Recent information indicates the necessity for modifications of this model. It is apparent that changes relevant to preeclampsia and other implantation disorders can be detected in the first trimester, long before the failed vascular remodeling necessary to reduce placental perfusion. In addition, although the factor(s) released from the placenta has usually been considered a toxin, we suggest that what is released may also be an appropriate signal from the fetal/placental unit to overcome reduced nutrient availability that cannot be tolerated by some women who develop preeclampsia. Further, it is evident that linkage is not likely to be by one factor but several, different for different women. Also although the initial model limited the role of maternal constitutional factors to the genesis of Stage 2, this does not appear to be the case. It is evident that the factors increasing risk for preeclampsia are also associated with abnormal implantation. These several modifications have important implications. An earlier origin for Stage 1, which appears to be recognizable by altered concentrations of placental products, could allow earlier intervention. The possibility of a fetal placental factor increasing nutrient availability could provide novel therapeutic options. Different linkages and preeclampsia subtypes could direct specific preventive treatments for different women while the role of maternal constitutional factors to affect placentation provides targets for prepregnancy therapy. The modified Two Stage Model provides a useful guide towards investigating pathophysiology and guiding therapy.

Introduction

Several years ago we extended a concept originally introduced by Chris Redman and colleagues 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, Stage 2.(Figure 1) We further proposed that the reduced perfusion, posited as secondary to failed remodeling of the maternal vessels supplying the intervillous space, was not sufficient to cause preeclampsia.[1] It was possible to identify evidence of reduced placental perfusion in women who had growth restricted babies unassociated with maternal signs of preeclampsia.[2] Furthermore, in one third of pregnancies complicated by preterm birth there was pathological evidence of failed placental vascular remodeling.[3] This led to the concept that maternal constitutional factors,

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genetic, behavioral 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 (Figure 2). 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. Several placentally derived “toxins” were suggested, including cytokines,[4] antiangiogenic factors,[5] syncytiotrophoblast microparticles[6](STBM) and formed blood products activated in the intervillous space.[7] Oxidative stress was an attractive component as part of the linkage.[8] Reactive oxygen species could be generated by the reduced perfusion of the placenta with consequent activation of monocytes and neutrophils[7] passing through the intervillous space. Oxidative stress would also stimulate release of cytokines, antiangiogenic factors, microparticles 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.[9] Evidence for the involvement of early placentation is largely the abnormal release of placental proteins as early as the first trimester of pregnancy. Is it possible, as the Two Stage Model would predict, to distinguish markers of the two stages? Secondly, is it possible that what is being produced by the poorly perfused placenta is not principally a “toxin” but rather the result of an adaptive fetal response? Another question is whether there may be more than one linkage between the stages, different in different women. We should also address the suggestion that the constitutional factors that are proposed to interact with Stage 1 to lead to preeclampsia may also contribute to Stage 1. Finally, the necessity of Stage 1 should be considered. Can preeclampsia develop without abnormal implantation and failed vascular remodeling?

When is the placental abnormality of preeclampsia initiated?

Dr. Huppertz champions the concept that the placental abnormality associated with preeclampsia occurs prior completion of the remodeling of the vessels supplying the placental site.[9] He posits, based upon evidence of changes in the release of placental proteins in the first trimester,[10–16] that the initial insults that lead to the clinical manifestations of preeclampsia, occur long before 12 to 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 posits abnormalities of either the differentiation of the morula to trophoblast or the slightly later differentiation of trophoblast to cytotrophoblast and syncytiotrophoblast. Although somewhat circumstantial, the presence of these early markers clearly suggest that there are important differences in placentation prior to deep trophoblast invasion with vascular remodeling. Dr. 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. [2] It is also possible that the placental aberrations in early pregnancy posited as important by Dr. Huppertz may be the root cause of both abnormal implantation/placentation and the abnormal placental bed vascular remodeling occurring in later pregnancy.

Are there different markers for Stage 1 and Stage 2?

It is also important to point out that it has not been established whether the markers released in the first trimester predict preeclampsia specifically as opposed to any disorder associated with abnormal implantation. The available data support the latter possibility.[10–16] In the studies in which IUGR pregnancies (without clinically evident maternal complications) are also examined the early abnormal placental protein release is also present.[10–16] Furthermore, it is also evident that several of the markers preceding preeclampsia but manifesting later than first trimester are not only increased prior to pregnancies that become complicated by IUGR or preeclampsia. Several of these markers are associated with abnormal uterine artery velocimetry even with subsequent normal pregnancy outcomes. Uterine artery Doppler studies are proposed to be abnormal in the second trimester of pregnancy because of increased vascular resistance indicating failed remodeling of the vessels of the intervillous space.[17] This concept is supported by a few studies of placental bed biopsies in women with abnormal uterine artery Doppler waveforms.[18] About half of women with abnormal uterine artery Doppler findings go on to have preeclampsia, preterm birth, or pregnancies complicated by IUGR. The other half go on to normal outcomes.[18] In women with abnormal uterine artery velocimetry compared to those without there is evidence of oxidative stress (reduced circulating ascorbate), [19] increased concentrations of asymmetric dimethylarginine (the endogenous inhibitor of nitric oxide synthase),[20] and an increased prevalence of agonistic autoantibodies against the AT1 angiotensin receptor.[21] These markers are present regardless of whether the pregnancy proceeds to IUGR, preeclampsia or a normal outcome. This raises two possibilities. These factors either cause abnormal vascular remodeling or equally likely they are the result of reduced placental perfusion. In any case, these findings support the concept that poor placentation (Stage 1 of the model) alone is not sufficient to cause preeclampsia.

Are markers uniquely present in preeclampsia (with or without IUGR) and not in IUGR (in otherwise uncomplicated pregnancy) or other settings of abnormal placental bed perfusion? This is not an easy question to answer. Preeclampsia is defined arbitrarily at a given level of blood pressure and proteinuria, making it possible that some women with IUGR also have a mild form of preeclampsia. Therefore, it is not surprising that in many studies the findings in IUGR pregnancies for many markers (as well as blood pressures) are intermediate between normal and preeclamptic pregnancies. In our studies we have rigidly defined IUGR pregnancies as neither having an increase in blood pressure (no greater than 15 mm Hg. diastolic or 30 mm Hg. systolic) nor an absolute increase to either 140 mm Hg. systolic or 90 mm Hg. diastolic. In contrast to preeclampsia, we have found no increase in the antiangiogenic factor s-Flt,[22] cellular fibronectin,[23] or leptin[24] with IUGR. The Oxford group similarly has found the STBM are not increased in IUGR pregnancies.[25] Thus, these findings support the potential role of these pathways specifically in development of Stage 2 of preeclampsia.

What is the placenta releasing to lead to 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. 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, thus 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 remodeling but that has not been the finding in large

series of placental bed biopsies where the vast majority of women with preeclampsia have failed vascular remodeling.[26] 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,[27] these same amino acids are increased in the blood of growth-restricted infants from preeclamptic pregnancies.[28] Finally, we have shown that although System A amino transport is reduced in placentas from growth restricted pregnancies without preeclampsia, this transport is not reduced in the placenta of similarly growth restricted infants from pregnancies with preeclampsia.[29]

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 we have demonstrated that 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.[24] 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. In preeclamptic pregnancies IUGR occurs when the signal is insufficient to overcome the reduced nutrient delivery while IUGR in the absence of a maternal syndrome reflects the absence of the signal. Perhaps our search for a linkage should seek an appropriately released fetal/placental factor to which a subset of women has an inappropriate response.

Is the same factor the linkage in all preeclamptic pregnancies?

Implicit in the Two Stage Model is a common linker for the two stages. Oxidative stress is one proposed linker, as are SBTM and antiangiogenic factors. However, it is important that no such factor has ever been shown to be present in all cases of preeclampsia. Is it possible that there may be different linkages in different women? Endothelial dysfunction seems consistent as a common convergence point for early pathophysiological changes of preeclampsia. Are there several ways to induce this endothelial dysfunction? Are antiangiogenic factors an important precursor of the maternal syndrome in some women while in others oxidative stress serves this role? This possibility has several very important implications. 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. It will be useful to examine the pathophysiology of preeclampsia from this perspective, searching for commonalities in groups of subjects in whom preeclampsia is or is not associated with a putative linker.

Can Stage 2 of Preeclampsia occur in the absence of Stage 1? (Is Stage 1 neither necessary nor sufficient?)

We have discussed the fact that in the model as presented the presence of abnormal placentation/reduced placental perfusion is not always sufficient to result in the maternal changes of preeclampsia (Stage 2). The occurrence of Stage 2 requires predisposing maternal constitutional factors. The heterogeneous nature of preeclampsia is consistent with varying degrees of contribution from mother and infant.[30] Thus, with profoundly reduced placental

perfusion the generation of Stage 2 may require very little contribution from the mother. In this setting almost any woman would get preeclampsia (Figure 3). Conversely, the woman with extensive predisposing constitutional sensitivity could develop preeclampsia with very little reduced perfusion. As the Oxford Group has emphasized, virtually all of the inflammatory changes of preeclampsia are present in normal pregnancy albeit to a lesser degree.[31] Likewise, most of the metabolic changes of preeclampsia are an exaggeration of the changes in normal pregnancy.[32] In both of these cases the difference between normal pregnancy and preeclampsia is often not as pronounced as the difference between pregnancy and non-pregnancy. Similarly even oxidative stress markers are slightly increased in normal pregnancy.[33] It is probably not too great a leap to conclude that in a mother with an abundance of predisposing factors the changes of normal pregnancy are enough to induce Stage 2 of preeclampsia.

Are Stage 1 and Stage 2 completely unrelated?

When we first presented the model we believed that the sole contribution of the maternal constitution to preeclampsia was to interact with the insult(s) associated with reduced placental perfusion to result in the development of preeclampsia in a particular woman. We posited that the abnormal placentation was most likely secondary to reduced immunological interactions between mother and fetus. We felt this was the explanation for the predominance of preeclampsia in first pregnancies. The exposure to paternal antigen that occurred during pregnancy was protective. This concept was supported by the reduced frequency of preeclampsia in women who had been sexually active with the father of the baby for a prolonged time prior to conception[34] including exposure to paternal antigen with oral sex[35], the increased frequency of preeclampsia with barrier contraception,[36] and when there was a different father for the infant or a long interpregnancy interval.[37]

However, certain data are not compatible with this concept. Preeclampsia delivering before 34 weeks gestation is much more likely to recur than preeclampsia occurring near term, a difference not consistent with a purely immunological concept.[38] Furthermore, preeclampsia of early onset is much more likely to be associated with later life cardiovascular disease suggesting extensive involvement of the maternal constitution.[39] We performed a study in which we attempted to determine if the implantation abnormality was present in women who had had preeclampsia in first but not second pregnancies. We found that there was an excess of the implantation related disorders, preterm birth and IUGR, in women with early onset preeclampsia even without preeclampsia in a subsequent pregnancy.[40] Once again this observation suggested that an immunological explanation was less likely in at least early onset preeclampsia. More recently Germain and coworkers followed women with yet another implantation disease, recurrent miscarriage, and found that, as had been reported with women who had previously been preeclamptic, there was increased endothelial dysfunction.[41] Triglycerides, cholesterol and inflammatory markers are higher at 15 weeks gestation in women who subsequently deliver preterm.[42] Furthermore, not only preeclampsia but preterm birth and pregnancies associated with abnormal implantation, placental abruption and infarction, are associated with an increased risk of cardiovascular death in later life.[43] Thus, it seems quite likely that, in at least a subset of women with pregnancy abnormalities associated with abnormal implantation, the same maternal constitutional factors that increase the risk of developing the maternal preeclampsia syndrome (by adversely affecting the maternal response to reduced placental perfusion) also act at the level of Stage 1 as mediators of poor implantation/placentation.

Summary

The modifications of the Two Stage Model have important implications. (Figure 4) Evidence that placentation is abnormal earlier in pregnancy may provide a better opportunity for therapeutic interventions to prevent Stage 2. Evidence that not all pregnancies associated with abnormal implantation (as least as measured by uterine artery Doppler and placental markers) have abnormal pregnancy outcomes suggests a search for what is different in these pregnancies. The possibility that the factors linking Stage 1 and Stage 2 of preeclampsia may be adaptive fetal responses to reduced nutrient availability directs a search for this signal as a potential therapy for IUGR. In addition, the likelihood that there is more than one linkage between Stage 1 and Stage 2 supports the existence of subtypes of preeclampsia that might be identified by the linker. Multiple linkages also raise the possibility of directed therapy for preeclampsia. Although the hypothesis that the factors influencing the maternal response to the reduced placental perfusion are also involved in the genesis of reduced perfusion makes the model “less tidy”, it also raises the possibility of preventive therapy prior to pregnancy to improve implantation. The Two Stage Model as modified remains useful conceptually to approach studies of preeclampsia and other implantation disorders.

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Figure 1.

Preeclampsia: a two stage disorder: Preeclampsia is initiated by reduced placental perfusion (Stage 1). This results in the release of factor(s) that leads to the maternal systemic pathophysiological changes (Stage 2).

Figure 2.

Maternal fetal interactions in the pathogenesis of preeclampsia: This version of the Two Stage Model emphasizes that reduced placental perfusion (Stage 1) is not sufficient to cause preeclampsia but requires interaction with maternal constitutional factors that may be genetic, behavioral or environmental. These are modified by the maternal pathophysiological changes of preeclampsia.

Figure 3.

Different contribution of fetal/placental factors and maternal constitution to Stage 2 of preeclampsia: The contribution of reduced placental perfusion, fetal/placental (●) or the maternal constitution (○) to result in the maternal pathophysiological changes of preeclampsia can vary. It can be primarily fetal/placental (A), equally maternal constitutional and fetal/placental (B) or primarily maternal (C). It is a reasonable extension that some women with exquisite sensitivity to fetal/placental function could respond to the normal physiological changes of pregnancy (D).

Figure 4.

Revised maternal fetal interactions in the pathogenesis of preeclampsia: The original Two Stage Model presented in Figures 1 and 2 is revised to indicate that abnormal placentation (that occurs in the first trimester) is the important contributor to Stage 1. Further, appropriate signals from the fetal/placental unit in response to abnormal placentation (---) modify maternal physiology, which cannot be tolerated by women resulting in preeclampsia. The same maternal constitutional changes that interact with abnormal placentation can also stimulate abnormal placentation (---). Also the linkage between Stage 1 and Stage 2 is likely secondary to many factors (several 305 arrows compared to one in the original model).