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The placenta in preeclampsia

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Abstract

The root cause of preeclampsia is the placenta. Preeclampsia begins to abate with the delivery of the placenta and can occur in the absence of a fetus but with the presence of trophoblast tissue with hydatidiform moles. In view of this, study of the placenta should provide insight into the pathophysiology of preeclampsia. In this presentation we examine placental pathological and pathophysiological changes with preeclampsia and fetal growth restriction (FGR). It would seem that this comparison should be illuminating as both conditions are associated with similarly abnormal placentation yet only in preeclampsia is there a maternal pathophysiological syndrome. Similar insights about early and late onset preeclampsia should also be provided by such information.

We report that the placental abnormalities in preeclampsia are what would be predicted in a setting of reduced perfusion and oxidative stress. However, the differences from FGR are inconsistent. The most striking differences between the two conditions are found in areas that have been the least studied. There are differences between the placental findings in early and late onset preeclampsia but whether these are qualitative, indicating different diseases, or simply quantitative differences within the same disease is difficult to determine.

We attempt to decipher the true differences, seek an explanation for the disparate results and provide recommendations that we hope may help resolve these issues in future studies.

Keywords

Preeclampsia; Fetal Growth Restriction; Placenta; Pathology; Morphology; Pathophysiology

Introduction

The placenta has long been recognized as the necessary component for the genesis of preeclampsia. Hydatidiform moles with abundant trophoblast but no fetus are associated with an excess incidence of preeclampsia.[1] The unique feature of the placenta proposed to result in preeclampsia is its exposure to reduced placental perfusion. This is supported by clinical, pathological and experimental findings.[2] Preeclampsia is more common in

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diseases that feature microvascular disease (e.g. hypertension, diabetes mellitus), and in obstetric disorders with large placentas (e.g. hydatidiform moles, multiple gestations).[3] The latter association is felt secondary to the inability of even a normal placental blood supply to adequately perfuse the very large placental mass, thus resulting in a relative hypoperfusion. A common pathological feature of preeclampsia is the failure of the maternal arteries supplying the placenta to undergo the physiological adaptations of normal pregnancy that facilitate adequate placental perfusion.[4] Finally, although animal models of preeclampsia are far from perfect, strategies to reduce placental perfusion result in a preeclampsia like syndrome in several species.[5, 6]

We and others have proposed a “Two Stage Model” to explain the relationship of the placenta to the maternal syndrome.[7] This hypothesis proposes that the placenta in response to reduced perfusion produces material(s) that act upon the mother to bring about the clinical findings of preeclampsia. The placenta as the key component of this hypothesis should provide clues about preeclampsia and its genesis. Especially important insights should arise from placental differences between preeclampsia and fetal growth restriction (FGR) without preeclampsia. In both of these conditions there is reduced placental perfusion but only in preeclampsia is there a maternal syndrome. For this reason, throughout this presentation we will where possible compare features of the placenta in these two conditions. Many questions must be answered. What is it about abnormal perfusion that results in preeclampsia? The Two Stage Model proposes placental abnormalities that result from reduced perfusion generated materials that produce maternal disease. What are the important abnormalities of placental function leading to the production of these factors? What is released into the maternal circulation to cause preeclampsia? Furthermore is this one or several agents, and is it the same in all cases of preeclampsia? Finally, it has been suggested that preeclampsia with and without growth restriction or of early or late onset could be different disorders. Is this supported by placental findings?

Abnormal implantation and vascular remodeling

Although not strictly placental, the changes in the vessels supplying the intervillus space are considered to be the key feature in the genesis of preeclampsia. The embryo originally implants in maternal decidua and is not supplied directly by any modifications of maternal vessels. Until about 10 weeks gestation the embryo exists in a low oxygen environment with nutrients provided by endometrial glands. At about 10 weeks, maternal vessels begin to perfuse the embryonic placenta as the intervillus space is vascularized.[8] Placental cytotrophoblast respond to the initial low oxygen environment with proliferation and to the subsequent increased oxygen with reduced proliferation and differentiation to an invasive phenotype.[9] The maternal vessels are invaded by the trophoblast and dramatic modification of the vessels occurs. The spiral arteries, which are initially fairly standard small muscular arteries, dilate strikingly at the decidual end of the vessel. The dilated portions of the vessels lose their endothelium, smooth muscle and inner elastic lamina. This modification extends to the inner third of the myometrium resulting in the terminal portion of the spiral arteries becoming modified to flaccid large diameter tubes unable to constrict in response to humoral or neural signals.[10] These changes do not occur normally in preeclampsia. Some vessels undergo modest remodeling in their decidual segments but this change never extends to the myometrium and some vessels do not remodel.[11–15] For many years the failure to increase the diameter of the terminal spiral artery received greatest attention. The diameter of this section of the spiral artery increases several fold and the impact of this change on flow has been emphasized. However, recent modeling of these changes indicates that dilating only the terminal portion of the vessel as occurs with the remodeling of spiral arteries in normal pregnancy will have little effect on flow.[16] Analogous to the effect of placing a funnel on the end of a garden hose, the flow will not

increase with the fourth power of the radius (Poiseuille's law) but rather may double. Graham Burton has proposed that perhaps a more influential change is the depth of the vascular modification.[16] He points out that in the spiral arteries located at about the inner third of the myometrium in nonpregnant women there is a condensation of vascular smooth muscle proposed as important to stop blood flow at the time of menses. This smooth muscle is lost in normal pregnancy but persists in preeclampsia. The result, he posits, is spiral arteries that remain contractile in the preeclamptic placental vascular bed with the potential for a perfusion/reperfusion scenario with the subsequent generation of oxidative stress. He proposes the main consequence of the terminal vascular dilation is to reduce the rate of flow that would be greatly increased with the striking increase in uterine perfusion that accompanies normal pregnancy. Although this abnormal finding is described in the setting of preeclampsia, it is thought that an identical change occurs in FGR[12] without preeclampsia and in about one third of cases of preterm birth.[17]. Another characteristic change in the untransformed spiral arteries in preeclampsia and FGR is "acute atherosis". This change results in vessels occluded by fibrinoid and surrounded by foam cells. Acute atherosis has been compared to the vascular lesion of atherosclerosis[18] and also is claimed to be similar to changes in vessels of tissues undergoing rejection.[19] Atherosis is found in disorders other than preeclampsia and FGR and can be seen in decidual vessels beyond site of placental implantation.[20]

Morphological changes in the placenta with preeclampsia and FGR

Gross pathological changes are most common with severe preeclampsia occurring preterm. [21]. The characteristic placental changes of preeclampsia would be predicted to be those associated with placental ischemia. Consistent with this prediction, the placenta in preterm preeclampsia is small with several types of infarction. The gross placental changes with severe preeclampsia and FGR are quite similar.

Interestingly, if placental weight is examined as a centile for gestational age, infants with placentas less than the 30th centile were smaller in preeclamptic pregnancies, while those with the placental weight greater than the 90th centile were larger.[22] Thus, there are at least some gross differences in placentas from preeclampsia and FGR. Moreover, the shape of the placenta in preeclampsia may also be characteristic. In a large (n = 6410) series of placental measurements performed in Finland between 1934 and 1944 the placenta was more "oblong".[23] Rather than the circular shape usually present in pregnancy there was a greater discrepancy between the shortest and longest diameter in preeclampsia. Burton has proposed that such an abnormal placental shape is associated with reduced endovascular invasion. [8] The hypothesis proposes that with normal trophoblastic invasion the maternal spiral arteries are "plugged" by trophoblast for a period of time sufficient to allow for vascular remodeling to reduce the velocity of flow into the intervillus space. Normally, invasion is most robust in the center of the placenta and less so moving towards the periphery. In the peripheral areas with reduced invasion and plugging, villi are damaged. This is by mechanical effects as well as by excess oxidative stress with increased oxygenation due to lesser trophoblast invasion and plugging of maternal vessels in the periphery. The resulting villus necrosis leads to the formation of a circular placenta with surrounding chorion laevae. With more generalized reduced plugging because of shallow invasion the regression of the placenta is not circumferential and unusual shapes result. Interestingly, this hypothesis also predicts a thicker placenta in response to damage to cell columns and villi by the high velocity blood flow from untransformed spiral arteries. Consistent with this hypothesis, a thicker placenta was also more prevalent in the placentas from preeclamptic pregnancies. Unfortunately, there was no statement in the presentation regarding placental shape and thickness in isolated FGR.[23]

Histological changes in the placenta with preeclampsia and with FGR are also those of reduced perfusion. These can be found in term but more commonly in preterm preeclampsia as well as with FGR and include accelerated villus branching, large and numerous syncytial knots, and small sclerotic villi.[21] It is suggested that most of these findings are related to low oxygenation secondary to reduced perfusion. However, with the hypothesis forwarded by Burton, hypoxia may not be a major feature of the abnormal vascular remodeling but rather the generation of reactive oxygen species.[16] Syncytial knots, for example, can be induced *in vitro* by either hypoxia or oxidative stress.[24]

Quantitative assessment of placental morphology

Thus, standard histological examinations do not appear to differentiate the abnormal placental findings in preeclampsia and FGR without preeclampsia. Nonetheless, the qualitative assessment of villus vascularity has led to the conclusion that preeclampsia is associated with increased branching of villi that could result in increased surface area for exchange.[25] This would be predicted as an adaptive response to reduced oxygen delivery supporting the hypothesis that hypoxia resulting from reduced oxygen delivery increases branching morphogenesis.[26]

The morphological examination of the placenta has been extended to include quantitative assessments using stereological techniques. However, this approach does not seem to be support increased villus branching in preeclampsia. In a review of the available literature it was concluded that terminal villus volume, terminal villus surface area and terminal capillary surface were similar in preeclampsia without accompanying FGR to findings in normal pregnancy. In preeclampsia with a FGR infant the findings were quite similar to findings with FGR without preeclampsia.[27] In both of these settings terminal villus volume, terminal villus surface area and terminal capillary surface were reduced compared to normal pregnancy.

One study reported differences between preeclampsia and FGR.[28] Syncytiotrophoblast to total villus area was reduced in preeclampsia without FGR but not with FGR with or without preeclampsia. However, even in this study these abnormal groups appear more similar to each other than similar to the control. (control=22±3%, preeclampsia 13±3%, preeclampsia + FGR 14±3%, FGR 16±4%; mean ± standard error of the mean).

The certainty that the quantitative data does not support the preexisting concept of an increase in syncytial surface areas due to increased villous branching must be taken cautiously. These are labor-intensive analyses done on a limited numbers of subjects. In fact, it appears the same 10 preeclamptic women have been assessed for different quantitative morphological measurements in at least 3 studies.[28–30] Also, with the limited numbers of patients that have been studied it is likely that women with severe and mild preeclampsia and preeclampsia of early and late onset were combined and the findings in these two groups are quite different. This is demonstrated in investigation by Egbors who studied placentas from 20 women with preeclampsia of early or late onset with and without FGR. In this study, in preeclampsia in the absence of FGR there were few differences from normal pregnancy.[31] In preeclampsia with FGR the villus volume and terminal villus surface area were reduced compared to placentas from normal pregnancies but were not different than FGR alone. In another publication by the same author with apparently the same subjects, he divided the preeclamptic pregnancies into early onset (≥34 weeks) and late onset.[32] He found that as reported previously the placenta from pregnancies with FGR, whether complicated by preeclampsia or not were very different. For some measurements the preeclampsia with FGR, placental findings were worse than FGR alone but the degree of growth restriction was also greater in this group. The major new finding was that whereas

there was no difference between term preeclampsia without FGR placentas and placentas of term controls, there were differences in the early onset preeclampsia without FGR placentas compared to placentas from preterm controls. Thus, terminal villi volume and terminal villi surface area were reduced in placentas from early onset preeclamptic pregnancies without FGR compared to gestationally age matched control pregnancies. This study raises another problem present in such studies. The early onset control pregnancies are not normal pregnancies but rather pregnancies from preterm births.

In summary, as powerful as is the technique of quantifying key placental morphological features that could influence nutrient and gas exchange, the results currently available are compromised by small numbers, poor definitions and poor controls. With this disclaimer, the consensus of findings is that FGR with and without preeclampsia manifest a similar reduced surface area for exchange. The placentas from preeclamptic pregnancies delivering at term are similar to controls and placentas from preterm preeclamptic pregnancies even without FGR resembles FGR.

Pathophysiological Markers of Placental Dysfunction

Thus, the question as to whether placental morphological differences, qualitative or quantitative, can explain the maternal manifestations of preeclampsia that are not present in FGR is an equivocal no. Are there differences in pathophysiological markers of placental dysfunction?

Inflammation and oxidative stress are proposed as important components of the pathophysiology of preeclampsia. Can differences in these two phenomena explain the systemic findings of preeclampsia that are absent in FGR? Oxidative stress is almost universally demonstrated in the placenta of preeclamptic pregnancies and somewhat less consistently in FGR without preeclampsia.[33–36] Burton has proposed that the reduced uterine perfusion characteristic of preeclampsia and FGR may be a spectrum. Modest reductions of placental perfusion engender endoplasmic reticular stress. Endoplasmic stress with consequent reduced protein synthesis results in a small placenta and baby with FGR. As perfusion is reduced more severely oxidative stress ensues with consequent maternal systemic findings of preeclampsia.[36] The occurrence of oxidative stress in some studies of FGR is not supportive of this hypothesis, although as cited, oxidative stress markers in the placenta with FGR are less prevalent and less severe. Further, many studies of placental oxidative stress are done with placentas delivered after labor that clearly confounds the findings since labor itself induces placental oxidative stress.[36] However, as appealing as is this hypothesis of quantitative differences in oxidative stress in preeclampsia and FGR the story is likely more complex. A systemic marker of oxidative stress, reduced plasma ascorbate is associated with reduced placental perfusion as assessed by Doppler velocimetry of uterine arteries independent of pregnancy outcome. Oxidative stress by this criterion is present in women with abnormal Doppler velocimetry whether they subsequently have preeclampsia, FGR or normal pregnancy outcomes.[37]

Normal pregnancy is associated with increased inflammatory activation, which is accentuated in preeclampsia.[38–41] Morphological changes in the placenta support increased inflammation,[42, 43] as do systemic markers of inflammation.[42, 44] Although there are few, if any, direct comparisons of inflammatory changes of serum markers of inflammation in preeclampsia and FGR it is clear that inflammation is increased in most studies of FGR without preeclampsia.[45, 46]

Although there is evidence that the trophoblast surface is exposed to increased oxygen concentrations with severe FGR because of reduced oxygen extraction,[25] the consequences of reduced extraction is reduced oxygen delivery to the placenta and fetus.[36]

Examination of molecules sensitive to reduced oxygenation suggests differences in FGR and preeclampsia. Analyses, largely by Conrad, and Rajakumar with our group, [47] have indicated that protein concentration for HIF-1 and HIF-2 alpha, the hypoxia responses elements, as well as proteins downstream from HIF-1 and HIF2 alpha, Flt and s-Flt are increased in placentas from preeclamptic women with or without FGR. By contrast, in placentas from FGR infants (< 2.4 centile) whose mothers did not have preeclampsia, HIF-1 alpha and HIF-2 alpha were not higher nor were proteins downstream of these transcription factors greater than in placentas from normal pregnancies. This, despite the fact, that the concentrations of mRNA for HIF-1alpha and HIF-2 alpha were not different in placentas from infants (with or without FGR) of preeclamptic women and of women with FGR without preeclampsia.[48] In another study investigators modified gene expression by exposing early pregnancy trophoblast to hypoxia in vitro and found that genes they identified as activated by hypoxia were increased in late pregnancy placentas from preeclamptic but not FGR pregnancies.[49]. However in an older study HIF-2 alpha but not HIF-1 alpha was increased in FGR without preeclampsia.[50] Other than this last study it would seem there is a striking difference in hypoxia or the response of the placenta to hypoxia in preeclampsia and FGR.

The results with circulating concentrations of putative placentally produced proteins modified by hypoxia are less clear. Circulating s-Flt-1, one of the downstream markers of HIF activation, is increased in preeclampsia, particularly early onset [51] and severe preeclampsia[52] and in early[53] and late onset[54] FGR pregnancies without hypertension. However, in keeping with the lack of difference in placental s-Flt with late onset FGR, our group found no differences in circulating s-Flt in FGR (3.4 centile) near term.[55] In another study with normal pregnant controls, concentrations measured in preeclampsia with and without FGR were not different from each other but were significantly higher than FGR without hypertension[56]. However, other studies report increased s-Flt or reduced PlGF in FGR placentas[57] or maternal blood compared with controls.[53, 58]

Release of placental components into maternal circulation

Almost twenty years ago the Oxford group proposed that microparticles released from placental syncytium, syncytiotrophoblast microparticles (STBM), might be involved in the pathogenesis of preeclampsia.[59] They demonstrated that STBM were increased with preeclampsia with more present in severe preeclampsia but interestingly there was no increase with FGR suggesting a role for these particles in the maternal preeclampsia syndrome.[60] Originally considered as a pathophysiological component of preeclampsia, it has become increasingly evident that circulating microparticles are far more than pathological. Microparticles circulate from many tissues and in pregnancy SBTM are only about 1.5 to 3% percent of circulating microparticles with the majority (97–99%) coming from platelets. Further, included with these shed portions of cells are smaller particles (nanoparticles) that include endosomes, particles with a specific pathway of synthesis and release. Endosomes contain RNA and DNA and appear to provide another method of intercellular communication. It is also speculated that STBM provide a means of immunological communication between mother and fetus. Although most attention has been directed at quantitative differences in STBM with an increase in preeclampsia, the functionality of these particles suggests that qualitative differences are also worthy of study.[61] Qualitative differences could reflect the “toxicity” by modifications to syncytiotrophoblast membranes with the hypoxia, oxidative and mechanical stress but could also include failure of these particles to induce appropriate responses.

The mechanism by which SBTM contribute to the pathophysiology of preeclampsia has been studied extensively.[62] Original in vitro studies suggested a direct effect upon

endothelium to reduce proliferation and disrupt endothelial monolayers.[59] Particles prepared from normal and preeclamptic placentas had similar effects. The endothelial dysfunction of preeclampsia in response to these particles was proposed to be quantitative with more STBM in preeclampsia than normal pregnancies.[60] Subsequently, increased attention has been directed at the inflammatory effects of STBM. STBM prepared by placental perfusion (but not by mechanical means) stimulate inflammatory cytokine release from PBMC's. Monocytes have STBM bound to them in vivo associated with activation. [44]. Other in vitro studies have demonstrated the ability of STBM prepared from placentas or isolated from blood of preeclamptic women to affect coagulation[62] or modify vascular responses.[63] It is important to bear in mind the limitations of these studies, as the activity of prepared STBM varies with preparation (e.g. mechanically or by placental perfusion) and the study of microparticles isolated from blood is confounded by binding of the microparticles to blood products or modifications of their activity by the isolation techniques.[62] Nonetheless, the multiple functions demonstrated and potential of these particles makes them interesting candidates for the placental genesis of the maternal preeclampsia syndrome.

Consistent with this idea of placental syncytial shedding, preeclampsia is associated with high circulating concentrations of cell-free fetal DNA (ffDNA) in maternal plasma[64, 65]. Once again the situation is not clear with FGR[64, 66, 67]. In one study the concentration of fetal DNA was significantly higher in subjects with preeclampsia than with isolated FGR or normal control subjects; while the concentration in the latter two groups were similar[67]. In addition, higher concentrations of ffDNA were associated with preeclampsia severity.[64]

Maternal fDNA is also increased in overt preeclampsia and is felt to be an indicator of maternal tissue injury.[68] Although the increase of fetal and maternal cell free DNA have been primarily considered as markers of disease it is also relevant that the metabolism of DNA generates vasoactive molecules such as adenosine, ADP and ATP.[69] Furthermore, with the placental hypoxia posited to be associated with preeclampsia, ATP is released and its breakdown increased.[70] Supporting this is the observation that adenosine is higher in maternal circulation from preeclamptic compared with normal pregnancies, and the highest concentration is present in severe preeclampsia.[71] This difference has not been reported with FGR. Interestingly the implications of the altered concentration of the vasoactive materials, ATP and adenosine, has received little attention. Suggesting that these might be relevant for the regulation of maternal blood flow, reduced expression of A_{2A} adenosine receptor have been found in microvascular placental endothelial cells[72] while the expression of all adenosine receptors, A_1, A_{2A}, A_{2B} and $A_{3,}$ was increased in placentas from preeclamptic but not FGR pregnancies.[73]

Apoptosis and necrosis

The observation that STBM are increased in the circulation of pregnancies complicated by preeclampsia but not FGR without preeclampsia suggests structural placental differences in the two conditions.[60] The source of these microparticles has been proposed to be due to apoptosis, necrosis and felt by some to represent the shedding of syncytial knots.[74] There is evidence of increased apoptosis as well as necrosis in preeclampsia but the concept that the origin of STBM is solely or primarily syncytial knots has been questioned.[75]

Although apoptosis is increased in placentas from FGR and preeclampsia,[76, 77] necrosis is felt to be more a characteristic of preeclampsia.[78] Apoptosis as the major source for STBM has been disputed by Burton.[75] He proposes that the release of STBM is due to the increased velocity of blood entering the intervillus space with failed spiral artery remodeling. He posits that this leads to the release of placental sprouts and more importantly

necrotic trophoblast into the maternal circulation. Necrotic tissues unlike apoptotic tissue induce an inflammatory response when taken up by endothelial cells and thus would contribute to the pathophysiology of preeclampsia.[79, 80] Implicit in this observation is that somehow the placenta, despite similar exposure to the results of abnormal spiral artery remodeling, is more damaged and is more likely to contain necrotic material with preeclampsia than with FGR. Huppertz has proposed that the excess of STBM in preeclampsia is due to a very early defect in syncytiotrophoblast development that is not present with FGR, emphasizing that the failed remodeling of the spiral arteries in both conditions does not explain the differential release of STBM.[78] The abnormal differentiation of syncytiotrophoblast leads to an excess of necrosis and release of material into the maternal circulation. Since syncytiotrophoblast differentiation in this model is not abnormal in FGR there is no excess STBM release in this condition. Although this speculation seems logical, and explains the dichotomy of STBM it will be difficult to test.

Genomics and proteomics

Genomic and proteomic strategies take a “discovery science” approach to the understanding of altered placental function in preeclampsia.[81–85] Unencumbered by hypotheses these strategies assess differences in gene or protein expression between preeclampsia and other pregnancies. Differential gene and protein expression and modification should then be useful guides for hypothesis generation.[86] Unfortunately, despite this promise, most genomic studies have been performed on placentas obtained at term, sometimes without concern for exposure to labor and findings are not consistent. In one study, for example, expression of genes shown to be up-regulated by hypoxia in placental tissue from early pregnancy was increased in preeclamptic pregnancies compared to placentas from FGR pregnancies with abnormal umbilical artery Doppler determinations.[49] In another study using microarray no differences were present with the two diagnoses.[87]

Of much more relevance would be the expression of genes related to trophoblast invasion and angiogenesis at the time these events are occurring (10–20 weeks gestation) during pregnancy. In keeping with this recommendation, samples remaining after chorionic villus sampling at 10–12 weeks of gestation, were examined by microarray in women who later developed preeclampsia (n=4) or had normal pregnancy outcome (n=8).[88] There were 36 genes differentially expressed in preeclamptic women (five up-regulated and 31 down-regulated). Bioinformatic pathway analysis indicated that the differentially expressed genes were in two signaling networks 1) network: cancer, respiratory disease, and cellular movement and 2) network: inflammatory disease, cellular movement, and hematological system development and function. MMP-12 was the only gene shared between networks 1 and 2[89]. These data and other similar data obtained at a time in pregnancy when what is considered the root cause of preeclampsia is occurring should provide insights and perhaps useful predictors for preeclampsia.[90, 91] It might also be feasible to use these markers to contribute to the understanding of early mechanisms in preeclampsia. Unfortunately we found no study including placental samples from FGR obtained in early pregnancy, thus the question of similarities or differences between FGR and preeclampsia cannot be addressed.

Protein expression, the step beyond gene expression, is also beginning to be assessed in preeclampsia. Proteomic approaches such as microarray with or without mass spectrometry; or specific protein analyses of post-translational modification such as nitration or nitrosylation, or examining specific subsets of proteins with metabolomics have been used with several types of biological samples from preeclamptic pregnancies. Most of these studies have had as their goal to establish predictors, but useful pathophysiological information has also emerged. Focusing on placental tissue, at least 12 proteins were differentially expressed in preeclamptic compared to normal pregnancy. These differentially

expressed proteins included signal transduction and molecular chaperon proteins[92]. In another study utilizing the same approach, at least 11 proteins, which were associated with anti-oxidant activities and altered expression of stress-response proteins were different in preeclampsia[93]. Interestingly, one study examined placental samples from normal pregnancies, early onset preeclampsia, late-onset preeclampsia and preeclampsia associated with FGR. Twelve proteins associated with immune response (i.e., Th1 and mainly Th2), were increased in samples from preeclampsia or FGR in relationship to normal pregnancies. There also appeared to be a different protein pattern with the different disease expression[94]. In another study 11 proteins related with oxidative stress protection were reduced in cells from preeclamptic compared to normal pregnancies.[95] Unfortunately in the reported studies differential expression of the same proteins is not consistently identified; samples are frequently collected after labor while early and late onset preeclampsia are compared without considering the role of differential gestational age on protein expression in the placenta.

Numerous studies of urine, amniotic fluid and serum/plasma have used genomic and proteomic approaches largely assessing prediction. One study took the analysis a step further testing the relevance to placental function. “Finger print” analysis of urine samples by proteomic profiling with mass spectrometry identified 13 peaks that correlated with the severity of preeclampsia.[96]. The authors sought the identity of the proteins to obtain pathophysiological insights (and simplify the identification of the protein predictors). They identified multiple forms of the serine protease inhibitors SERPINA1 and albumin. The SERPINA1 was expressed more in the placentas from preeclamptic women. The multiple protein forms suggested misfolding of proteins. This process is characteristic of endoplasmic reticulum stress that has been suggested as etiological relevant to preeclampsia and FGR. [36] The combination of discovery science and the generation of testable hypotheses with the data generated should hold real promise for increasing the understanding of preeclampsia

Subsets of preeclampsia

It is likely that preeclampsia is not a single disease. The clinical presentations and the wide scatter of virtually all laboratory assessments in the disorder, support this concept. Further, the striking differences in recurrence rate, frequency of later life cardiovascular disease and the likelihood of FGR with early but not late onset preeclampsia, suggest these are different disorders.[97, 98] Might the morphology of the placenta or the placental bed provide further support for subsets of preeclampsia? There does seem to be greater morphological evidence of hypoxia/oxidative stress with consequent infarctions and small placental size in early onset preeclampsia.[21] It is difficult to determine if these are qualitative differences or merely a matter of degree of exposure or perhaps a differential response (adaptation?) to reduced oxygen and nutrient availability. It is disturbing that in recent years the fact that uterine Doppler abnormalities are more likely to precede early than late onset preeclampsia and the increased risk of FGR primarily with early onset preeclampsia have led to the conclusion, largely unsupported by objective data, that only early onset but not late onset preeclampsia is associated with reduced placental perfusion.[78] The definitive proof that this is the case rather than for example a different response to reduced perfusion would come from placental bed biopsy studies. There are very few data in this area. In reviewing the available literature it is difficult to separate results from term and preterm preeclampsia. In most cases mean values of gestational age, which are in all cases less than term, is the only information presented. We identified two papers in which early and late onset preeclampsia could be differentiated. In a study by Moldenhauer, failed remodeling of basal plate spiral arteries was present more often in term preeclampsia than in normal pregnancy but failed remodeling was even more common in preterm preeclampsia.[99] This is likely an

underestimate of the differences in remodeling since the most consistent difference between preeclampsia and normal pregnancy is found in the myometrial (not present in basal plate) rather than decidual segments of the spiral arteries.[100] In another study, myometrial spiral artery invasion was absent in 6 of 12 mild preeclamptics with a mean gestational age of 37 weeks and in 15 of 20 severe preeclamptics with a mean gestational age of 34 weeks.[101] Similarly, spiral artery vascular remodeling was abnormal not only in all 21 cases of preeclampsia with FGR but also in 8 of 9 cases of preeclampsia without FGR.[102] In a study of myometrial spiral artery remodeling, it was absent in 1 of 26 normal pregnancies, 7 of 11 preeclamptics with FGR, and 6 of 22 preeclamptics without FGR.[103]. In a study with a similar endpoint, remodeling was absent in preeclampsia with FGR in 2 of 2 cases and 6 of 6 cases or preeclampsia without FGR.[104] Thus, although the data are sparse it does not appear that failed remodeling of spiral arteries is a feature of only preterm preeclampsia or only preeclampsia with FGR. There may be a difference in the degree of failed remodeling, being more extensive with FGR and preterm but the phenomenon is more common in all forms of preeclampsia compared to normal pregnancy.

Conclusions

Review of the pathology and pathophysiology of the placenta, the organ known to be the proximate cause of preeclampsia, provides some interesting answers but leaves several important questions unanswered. The pathological changes of preeclampsia provide evidence of reduced oxygen delivery and exposure to oxidative and likely endoplasmic reticular stress. The materials released from the placenta into the maternal circulation are compatible with these observations. Some or all of these materials likely serve to link the abnormal placenta to the maternal syndrome (although the disparity of results within and between studies raises the question if this is the same linkage in all subjects). The clinical subtypes of preeclampsia, early onset, late onset and associated or not associated with FGR, present certain differences of placental findings. Nonetheless, it is difficult to determine if these indicate that the subsets are different diseases or are simply quantitatively different. One of the most strikingly different presentations of preeclampsia is the contrast clinically and epidemiologically between early and late onset preeclampsia. Although placentas in term preeclampsia without FGR are only minimally different from control placentas, early onset preeclampsia even without FGR is quite different than the placentas from their “control” (spontaneous preterm birth) placentas (and from term preeclampsia). These findings support that preeclampsia of early and late onset may be more than quantitatively different and provide weak support for the concept that late onset preeclampsia is a maternal rather than a placental disease. However, the concept that the placenta is normally perfused in late onset preeclampsia is not supported by placental bed findings. Failed remodeling of the spiral arteries is present in a percentage of preeclampsia of all varieties, late, early, with and without FGR. The difference in vascular remodeling appears more quantitative than qualitative in these forms of preeclampsia.

The major quandary is the lack of clear and consistent differences between the placenta from preeclamptic pregnancies and pregnancies with FGR without preeclampsia. Despite the presence of a maternal syndrome caused by the placenta in preeclampsia and the absence of this syndrome with FGR, the pathological placental differences do not provide great insights. In almost every case, if several studies are available, some indicate that changes are present only in preeclampsia and not FGR while others of almost equal number find little differences between the two conditions. It is probably not coincidental that the clearest differences come from studies that have not been extensively replicated. The work of Rajakumar et. al. [47, 48]clearly demonstrates that HIF protein and products of HIF activation are increased in the placenta from preeclampsia but not FGR. This finding raises the possibility that the placenta in FGR is either exposed to a lesser degree of oxidative

stress and low oxygen delivery than it is in preeclampsia or that it does not respond to this insult. However, there are numerous studies of the concentration of placental products of hypoxia in the maternal circulation (e.g. leptin, s-Flt etc.), which do or do not indicate differences between the two conditions. Similarly, the quantitation of STBM indicates higher circulating concentrations with preeclampsia but not FGR. Thus far, there are few observations to confirm or refute this finding. There is also the interesting observation of placental/fetal size differences between preeclampsia and FGR with small preeclamptic infants having a smaller fetal/placental ratio than FGR infants from non-preeclamptic pregnancies, but again this has not been replicated. Virtually every morphological or physiological observation comparing FGR and preeclampsia that has been subjected to extensive study arrives at a similar conclusion. FGR with and without preeclampsia are quite similar and preeclampsia without FGR is subtly different from normal.

What is the explanation for this overlap between FGR and preeclampsia? Some portion of the explanation relates to flawed experimental design. In some studies it is not clear whether FGR includes FGR with preeclampsia. In others, the subjects called FGR without preeclampsia, seem more like preeclamptics than normals with, for example, blood pressure, which although not diagnostically elevated, are higher than controls. Also in some placental studies sufficient attention is not directed to whether a sample was taken before or after labor, which can markedly change evidence of hypoxia or hypoxia reperfusion. Another technical issue is how areas to be investigated in the placenta are chosen. Usually, microscopic analyses are representative of a small part of the placenta. Attempts to compare several randomly selected areas reduce bias but still represent only a small proportion of the “universe” of possible pathological findings.

However, this is unlikely the explanation for all of the overlap in placental findings. It is likely that this comes from the real overlap of the two conditions and the fact that there may be multiple routes to preeclampsia and to FGR. Both conditions also suffer from the problem of non-specific findings that arbitrarily divide a continuous outcome. In preeclampsia the selection of blood pressure and proteinuria is purely historical. These were the first two changes identified in women with what at the time was considered a pregnancy specific seizure disorder, eclampsia. They are not specific or sensitive[105] and are not actual direct indicators of the most important pathophysiological changes in preeclampsia. Further the division of 140/90 as blood pressure indicating preeclampsia (while 139/89 does not) is obviously arbitrary. Likewise, even if one takes the conceptual diagnosis of FGR, the failure of the infant to exercise its growth potential, it is unlikely to be due to a single etiology. Most published studies present findings due to failed spiral artery remodeling with reduced nutrient delivery but most FGR worldwide is due to reduced nutrient intake. Is it possible that even in developed countries nutritional abnormalities can be a part of the genesis in some subjects? Attempts to standardize the diagnosis of FGR include the use of abnormal umbilical artery velocimetry to clarify the diagnosis. Interestingly, in a study of infants less than the 5th centile, with middle cerebral artery redistribution half of the infants with normal umbilical artery Doppler had oligohydramnios, head circumference > than the 95th centile and were delivered by C-section for intolerance of labor.[106] This would seem to suggest different forms of FGR even when abnormal spiral artery remodeling rather than reduced nutrient intake is the usual explanation for FGR. The studies from our group stand out as very different than those from other investigators. In our studies we find little difference between SGA infants defined as less than the fifth centile and normally grown infants. The findings of Rajakumar et. al. and and the lack of evidence of circulating markers of hypoxia in our other studies have led us to propose a blunted fetal response to reduced oxygen and nutrient availability in FGR without preeclampsia. These findings are not confirmed in the studies by others of infants with the same degree of FGR and especially when accompanied by abnormal uterine artery velocimetry and with early FGR delivering

prematurely. (e.g. [58]) Our subjects are taken from a prospective collection of “normal” subjects. SGA was not recognized in many of these subjects until delivery, which was frequently at term and rarely accompanied by Doppler assessment. Another differentiation that has received little attention is fetal sex. In epidemiological and animal studies it appears that male and female fetuses respond differently to reduced nutrient availability and the maternal response may also be influenced by fetal sex.[107–109] Also, the definition of SGA is completely arbitrary and depending on the cut off selected will include a greater or smaller number of constitutionally small infants. With these considerations it is not surprising that laboratory or pathological findings do not clearly differentiate the two conditions.

In summary, the participation of the placenta in the pathophysiology of preeclampsia is clear; however, to maximize information gained from study of the placenta we must direct meticulous attention to several issues of analysis and diagnosis.

Recommendations

It seems incontrovertible that the placenta will provide insights into preeclampsia and just as likely that the imprecision of clinical diagnoses will hinder the ability to interpret the findings. In order to maximize the impact of future studies, several points should be considered. In studies of preeclampsia diagnostic precision is mandatory. Criteria used for diagnosis should be included in the presentation. A table should be included that presents the values for these criteria satisfying the diagnosis as well as parity, gestational age at delivery and birth weight centile of offspring. The table should also include data indicating the severity of the preeclampsia (platelet count, liver function and evidence of hemolysis). Sufficient data should be presented about the normal controls to guarantee to the reader that they are normal.

Placental samples should ideally be obtained from pregnancies that have not labored, especially when oxidative stress or hypoxia markers are part of the research. Failing this, information about labor or not laboring before the time of collection should be presented. In identifying controls for placentas from preeclamptic pregnancies delivered preterm, it should be recognized that placentas collected from women delivering preterm are not “normal” placentas. In such studies term control placentas should also be compared to preterm pregnancies. Investigators should be alert for the rare placenta collected preterm from pregnancies without labor or other disease. The samples from preterm labor patients should be carefully defined based on the clinical presentation and pathological evidence of infection or lack of infection.

Currently there are several quantitative morphological studies in which the same samples have been compared in several different ways. If samples are used for several investigations in several publications this information should be presented. This is important to keep findings in different studies in perspective but also to allow the combination of extensive findings in an individual subject. Fetal growth restriction is potentially a valuable control for preeclampsia. Simplistically, findings present in preeclampsia but not FGR may provide insight into the maternal syndrome. As stated, to date it has not been possible to ascertain due to the overlap in the two conditions. Whether this difficulty can be overcome is difficult to determine but it is worth attempting to carefully characterize FGR to aid in this attempt. Maternal BMI should be presented as a crude evidence of nutrient sufficiency. The results of umbilical, and if available, uterine artery Doppler velocimetry should be presented and if not available should be so stated. To increase the likelihood of SGA indicating FGR, birth weight centiles of less than at most the 5^{th} centile should be considered as diagnostic.

However, whatever the cutoff, mean birth weight centile in the SGA group should be presented rather than or in addition to "less than n^{th} centile".

We also recommend continuing with the analysis of the biological activity of the products released by the placenta, which can be a clue to understanding placental response or adaptation. It will also be extremely beneficial to apply state-of-the-art technology in placental analyses such as "omic" and quantitative morphological assessments to the study of the placenta. However, such studies should include individuals with expertise in the relevant clinical areas (e.g. preeclampsia, FGR etc.). Sophisticated analytical strategies and expertise in these approaches cannot substitute for expertise relating to the disorders being studied.

Attention to these considerations we believe will provide the optimum opportunity to fully utilize the power of placental analysis to unravel these (and the other) "great obstetric syndromes".[110]

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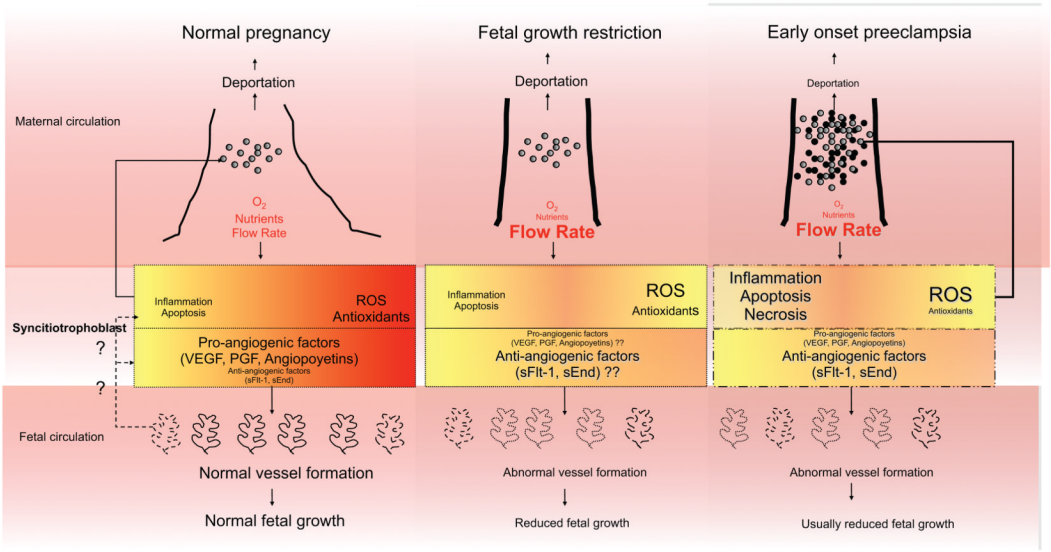

Figure 1. A Schematic Representation of Human Placentation

Based on the available data it appears that the abnormal modification of the maternal vessels supplying the intervillus space is the same in preeclampsia and fetal growth restriction (FGR) without preeclampsia. The placental changes are similar in early onset preeclampsia and FGR (particularly when early onset preeclampsia is accompanied by FGR). The consequences of the reduced nutrient and oxygen delivery and the increased flow of blood delivered to the intervillus space are similar in FGR and preeclampsia but not identical. In FGR, placental inflammation is increased, as is apoptosis. These changes are also present in preeclampsia but may be more severe and are also accompanied by necrosis that is not as prevalent in FGR. Oxidative stress, as indicated by increased reactive oxygen species (ROS) and reduced antioxidants is present in the periphery of the placenta where maternal blood supply is reduced compared with the central region, in either normal or pathological conditions. The degree of oxidative stress is more in FGR than normal pregnancy and even greater in preeclampsia. Data on the response to reduced oxygen in FGR is not consistent (indicated by ??). Hypoxia and the response to hypoxia may be less in FGR than preeclampsia. In response to apoptosis, increased pressure and necrosis, fragments of syncitiotrophoblast are released into the maternal circulation, which are both increased in quantity, and qualitatively different in preeclampsia (necrotic particles indicated by black circles are greater with preeclampsia) compared with normal pregnancy or FGR. It is postulated (?? and dotted line) that apoptosis, or inflammatory and proangiogenic factors from syncitiotrophoblast in normal and pathological conditions regulate placental vascularization. In both FGR and preeclampsia the fetal vasculature responds to reduce the villous surface area. Whether this is quantitatively and qualitatively different in the two conditions is not established, but only in preeclampsia has spotty placental vascular development resulting in an abnormally shaped placenta been reported. The final fetal result is by definition reduced fetal growth in FGR but this is not universally present even with early onset preeclampsia.