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Preeclampsia: Syndrome or Disease?

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Abstract The focus on disease mechanisms underlying the hypertension and proteinuria defining preeclampsia has increased knowledge of the pathophysiology yet we lack both therapy and predictors. We propose this is in part due to the fact that diagnostic findings identify a "preeclampsia syndrome" but do not necessarily indicate the most important pathophysiology nor if organs are involved as cause or consequence. The increased risk for later life cardiovascular disease in women who develop preeclampsia suggests the stress test of pregnancy exposes pre-existing subclinical vascular disease. The dogma that inadequate trophoblast invasion and ischemia/reperfusion injury to the placenta is "the" cause of preeclampsia is more relevant to early onset preeclampsia (<34 weeks). There is much less evidence for defective placentation in late onset preeclampsia where maternal constitutive factors or susceptibility to vascular damage is more relevant. The contribution of differing disease phenotypes to the syndrome may explain the inability of biomarker studies to identify all preeclampsia. Identification of phenotypes will require large amounts of prospective clinical data and biospecimens, collected in a harmonized manner with analysis in an unbiased discovery approach.

Keywords Preeclampsia · Placenta · Pregnancy · Cardiovascular disease · Biomarkers · Angiogenic factors

This article is part of the Topical Collection on *Preeclampsia*

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Introduction

Preeclampsia is a serious pregnancy problem, components of which have been recognized for 2000 years. It is relatively common, occurring in 3 to 6 % of pregnant women. As a leading cause of maternal mortality in low- and middle-income countries, it accounts for more than 75,000 maternal deaths yearly. The availability of prenatal care in developed countries is associated with a dramatic reduction of maternal mortality [1, 2]. Observation as part of prenatal care exploits the progressive nature of preeclampsia and the fact that acute features terminate with delivery. This prevents maternal death by expeditious delivery of increasingly ill women with preeclampsia. Nonetheless, infant mortality is increased with preeclampsia even in high-income countries, in some cases because of these indicated deliveries, and maternal morbidity is greatly increased over normal pregnancy [2].

In recent years, there has been an explosion in our knowledge (but not necessarily understanding) of the pathophysiology of the disorder. Despite this increased knowledge, definitive management remains delivery, and we have identified no preventive therapy or clinically useful predictors to direct such therapy. In this presentation, we suggest this may be at least in part due to a misguided view of preeclampsia. We suggest that we look at preeclampsia from perhaps a different perspective, as a syndrome rather than as a disease.

First, some historical perspective is appropriate. For over a hundred years, preeclampsia has been diagnosed and defined

as the new onset of hypertension and proteinuria appearing after mid-pregnancy. For many years, it was considered a pregnancy-specific renal disease leading to pregnancy-induced hypertension. How did this concept originate and evolve? Over 2000 years ago, it was recognized that pregnant women could present with seizures that terminated after delivery. These pregnancy-specific fits were referred to as "eclampsia," a Greek word indicating "lightning like." Thus, for almost 2000 years, eclampsia was viewed as pregnancy-specific seizure disorder. In the late nineteenth century, the similarity of the edematous appearance of the eclamptic woman to that of individuals with Bright's disease (acute glomerulonephritis) led care providers to check for protein in the urine of eclamptic women. Protein was present, as it was in the urine of Bright's disease patients. At about the same time, it became possible to non-invasively measure human blood pressure, and blood pressure was found to be increased in eclamptic women. It was then noted that in eclamptic women, these findings were present before seizures, hence preeclampsia. The next insight was that proteinuria and hypertension even without seizures indicated a potentially progressive condition with associated maternal and infant death. Thus, preeclampsia as a unique "disease" was defined. Note that these findings were chosen serendipitously not because they were the most important pathophysiological changes or the most sensitive or specific indicators of risk. Yet these features that we now know indicate a more general systemic pathophysiology were taken as the pathognomonic findings responsible for adverse outcomes. For years, almost all research studying preeclampsia was guided by concepts relevant to hypertension and renal disease. It is now evident that preeclampsia is far more than hypertension and proteinuria. However, we persist in considering preeclampsia as a unique disease.

Syndrome vs a Disease

The remarkable toll that preeclampsia exerts in terms of maternal and fetal mortality together with its profound impact on perinatal morbidity naturally conceptualizes it as a disease. However, it is worthwhile reminding ourselves that the condition of "preeclampsia" is indeed a syndrome. A syndrome is a group of symptoms that commonly occur together or a condition that is characterized by a set of associated features. Syndromes we are all familiar with include AIDS, Down's syndrome, and Asperger's. Syndromic findings allow us to recognize the presence of a disease or diseases but tell us nothing about pathophysiology and are not themselves necessarily the most important feature of the disorder(s). Traditionally, preeclampsia is defined by the appearance of elevated blood pressure and proteinuria, which identifies a group of pregnant women at high risk for adverse outcomes. The clinical features of preeclampsia led early investigators to concentrate on dysfunction of the vascular (blood pressure) and renal (proteinuria) systems. There is however involvement of other organ systems e.g., coagulation system, liver, and brain that are better markers of the severity or worsening of the condition. While the preeclampsia syndrome is associated with dysfunction of several organs, it is still unresolved which is the primary disease state(s) at play and if a particular organ involvement is a cause or consequence.

Pregnancy as a Stress Test

An alternative way of looking at this is that pregnancy per se is a stress test for the maternal vascular and metabolic systems [3, 4]. Are women who fail the respective stress tests i.e., those who develop preeclampsia or gestational diabetes, those who indeed have pre-existing sub-clinical vascular or metabolic disease? Pregnancies in women with chronic hypertension, pre-gestational or gestational diabetes, and previous preeclampsia have a higher rate of preeclampsia [5]. These women are characterized as responding to pre-existing vascular dysfunction. Is the threshold for the stress test lower in these women [6]? It is now becoming increasingly clear that women who developed preeclampsia are at greater risk of developing cardiovascular disease, stroke etc. later in life [7, 8]. This may validate the hypothesis that pregnancy is a stress test that exposes those with underlying sub-clinical vascular disease (Fig. 1). However, such findings would also support the idea that pregnancy per se may damage the maternal vasculature, causing preeclampsia and leading to vascular disease later in life.

It is clear that women who have had preeclampsia manifest changes in many organ systems long before clinically evident cardiovascular disease. Thus, blood pressure, endothelial function, and subtle aspects of cardiovascular function, although in many cases not clearly abnormal, are less normal than in women who have had normal pregnancies [9–14]. This could represent residual damage from preeclampsia or be changes that antedated pregnancy. The fact that many of these changes are also present in women with other prior pregnancy disorders that have no maternal syndrome would argue for the latter [15–17]. However, the definitive answer requires information obtained before pregnancy, which is difficult to acquire in a disorder with an incidence of 3–6 %. There is nonetheless some data available collected in a Norwegian longitudinal assessment of cardiovascular health, the HUNT study [18] where men and women are re-evaluated every 10 years. In 3356 women, pregnancy occurred between two assessments, and 261 women developed preeclampsia. As expected, after pregnancy, the women with preeclampsia manifested less normal lipids, blood pressure, and BMI. When pre-pregnancy values were compared many, but not all, of the differences were present prior to the preeclamptic pregnancy. It appears

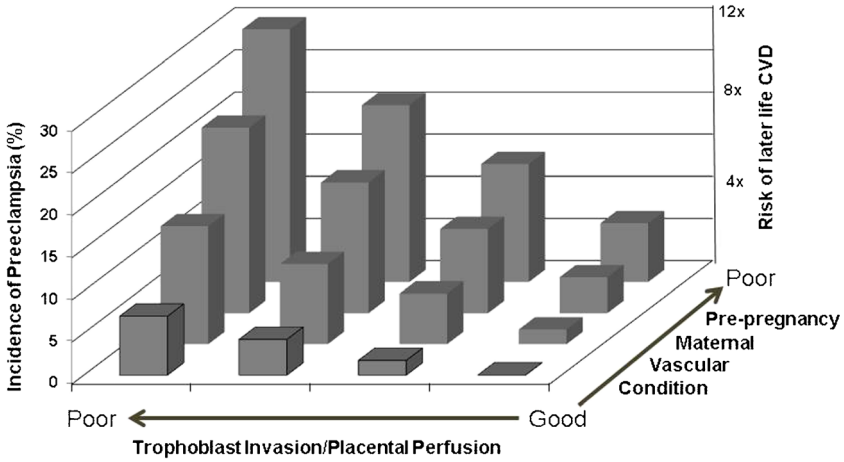

Fig. 1 Relationship of maternal vascular condition and placental perfusion to development of the preeclampsia syndrome and later life cardiovascular disease

that primarily common risk factors (failing the stress test) but also some residual "injury" account for the increased cardiovascular risk with preeclampsia,

The Relationship of Placenta and the Vasculature

Based on the historical primacy of blood pressure in the definition of preeclampsia, it is quite difficult to determine whether other syndromic findings might be as important. For example, we know that in HELLP syndrome women with low platelets and liver dysfunction are at increased risk even without hypertension. However, the later life manifestations of increased cardiovascular disease suggest that either there is a central etiologic role of the vascular system or that underlying etiologies ultimately converge on the vasculature to present the syndrome. The fact that preeclampsia can be resolved by removal of the placenta is taken as proof of the central role of the placenta in preeclampsia. This is supported by the increased rate of preeclampsia with large placentas such as with multiple gestations [5]. This view is extended by the oft-recanted dogma that abnormal trophoblast invasion, failed remodeling of the spiral arteries supplying the placenta and resultant placental ischemia reperfusion injury is the sine qua non of preeclampsia [19]. Thus, the inability to adequately perfuse the placenta because of its large size or inadequate development of the blood supply to the placenta is considered the inciting feature. Indeed, early onset preeclampsia is reportedly associated with a more profound incidence of abnormal trophoblast invasion and increased uteroplacental vascular resistance [20] pointing to the primacy of this theory. The link between the placenta and the vasculature is explained by release of placental factors that damage the maternal vasculature. While many factors have been suggested as the etiologic agents over the years [21], currently angiogenic factors released by placenta and which act on the vascular endothelium are thought to comprise at least some of the injurious agents [22]. However, despite the convincing information supporting relative or absolute reduced perfusion of the placenta that argues for the role of the placenta and of placental-derived factors, abnormal trophoblast invasion is also reported in intrauterine growth restriction (IUGR), preterm birth, and stillbirth [20]. Furthermore, there is much less evidence that late onset preeclampsia is associated with abnormal trophoblast invasion suggesting that additional factors are necessary to cause preeclampsia. This is elegantly explained by the concept of maternal constitutive factors [23] or the pre-existing susceptibility of the maternal vasculature to damage [21]. Under this scenario, those with an extremely susceptible vasculature may become preeclamptic simply by the normal adaptation to pregnancy while those with a healthy vasculature who become preeclamptic may only do so when faced with a major insult arising from defective placentation. The worst case scenario might be the individual with poor placentation and a susceptible vasculature [21] (Fig. 1). Models that involve the variable interaction of placenta and maternal vascular systems can also incorporate the effect of modifiers e.g., obesity or smoking on the individuals risk of developing the preeclampsia syndrome.

Biomarker Studies

As the reader is doubtless aware, the literature contains a vast number of cross-sectional studies measuring a wide range of molecules that are altered in tissues and fluids of women who present with a diagnosis of preeclampsia. This association with the established syndrome does not prove that they are primary etiologic factors rather than a late manifestation of the full-blown syndrome akin to multi-organ involvement. Indeed, our inability to prevent preeclampsia by correcting imbalances in some of these factors [5, 24, 25] perhaps reflects that they are not etiologic but rather late-stage manifestations. However, discovery of alterations in such molecules in established preeclampsia and their association with putative

mechanistic pathways quickly led to their adoption as predictive biomarkers. Disappointingly, the more recent prospective large-scale biomarker studies [26•, 27] have not yielded any useful biomarkers to predict preeclampsia nor have they yet yielded additional information re etiology. They have however yielded large amounts of data that can perhaps be used in a systems biology and pathway analysis approach to define different phenotypes or subtypes of preeclampsia and potential etiologic pathways.

Is Preeclampsia More than One Disease?

The heterogeneity of presentation of preeclampsia including time of onset and severity, with or without IUGR, coupled with the variable involvement of different organ systems finally led investigators to postulate that there might be different underlying etiologies that ultimately presented as the preeclampsia syndrome. Examination of the ontogeny of appearance of preeclampsia across gestation, both in low-risk nulliparous women and in high risk nulliparous women, fails though to show a clear dichotomy of timing or severity of appearance [28, 29] that would suggest different underlying etiologies. However, as explained in more detail below, the failure of prediction studies to identify those women who will ultimately develop preeclampsia coupled with the increased recognition that not all women with preeclampsia share the same profile of altered biomarkers has led to increasing focus on the concept of differing disease subtypes or phenotypes of preeclampsia [21, 30, 31]. Efforts to elucidate the different disease types have though so far proven elusive.

Placental Disease

Several factors feed into the concept that has gathered momentum over recent years that preeclampsia is more than one disease. Preeclampsia can occur, by definition, from 20 weeks of gestation onwards, although >75 % of cases occur at greater than 37 weeks [21]. Early onset preeclampsia, which in the past has been defined as <37 weeks, but now generally accepted to be <34 weeks gestation (<1 % of nulliparous women) [32], shows a greater association with defective trophoblast invasion, placental ischemia, and IUGR than late onset disease [20] and has poorer perinatal and maternal outcomes i.e., it identifies a group at greater risk of adverse outcome. The long range relationship to cardiovascular disease is also strikingly different with a tenfold increased risk with early onset vs. a less than twofold increase with term preeclampsia [33, 34]. This has led to the suggestion there are at least two etiologies distinguishing early vs late onset preeclampsia. Recent placental histology studies show differences in placental pathology between early and late preeclampsia, with early onset preeclampsia being associated with more syncytial knotting, villous hypoplasia, and vascular lesions in the placenta [35, 36]. Early onset preeclampsia shows a greater incidence of abnormal uteroplacental flow waveforms, an indirect measure of abnormal trophoblast invasion, again supporting the concept of placental disease. There is a close relationship between placental and fetal size with placental size being considered a surrogate for placental dysfunction and early onset preeclampsia is often associated with IUGR. Term preeclampsia is interestingly associated with both low (4.5-fold) and high birth weight (2.6-fold) in a U shaped association [31]. However preterm, only low birth weight was associated with a greater risk of preeclampsia (9.9-fold) [31]. In a study of over 317,000 pregnancies, no association was found between placental size and risk of preeclampsia, indicating that placental weight per se is not a useful indicator for placental dysfunction in preeclampsia and that some other factor is causing low birth weight [37]. Together, this data supports the concept that early and late preeclampsia are two different diseases at the placental level. Consistent with this, tests that measure placental function, including doppler flow indices and angiogenic factors, better predict early rather than late onset preeclampsia. While an increasing number of studies are published advocating measuring biomarkers, uteroplacental resistance, and clinical characteristics to identify early onset preeclampsia [38], it is important to recognize this only affects up to 1 % of the pregnant population making screening of this population expensive that large trials are needed to generate adequate numbers of cases for statistical analysis and that there is a danger of over-fitting analyses on small datasets.

Angiogenic Factors: Markers of Placental Function and/or Mediators of Vascular Injury

A cardinal feature of preeclampsia is endothelial injury/dysfunction that can be assessed by measurement of endothelin, fibronectin, von Willebrand factor, increased oxidative stress, and cytokines [39] or by functional studies of endothelial function [40]. The increased incidence of preeclampsia seen in chronic hypertensives, previous preeclamptics, and pre-gestational diabetics [5] suggests vascular/endothelial dysfunction may pre-exist in some women and make them susceptible to development of preeclampsia. What though causes preeclampsia in low-risk women? In 1989, the concept of the "toxin" of preeclampsia was formalized into the idea that circulating factors released by placenta damaged the vascular endothelium [41]. Since then, a multitude of studies have identified activities in maternal blood that affect vascular function. More recently, the pro- and anti-angiogenic factors synthesized and released by the placenta have come to the fore as the candidates for the placental

molecules that damage the vasculature [22]. Angiogenesis is the branching of blood vessels to form new blood vessels, but the angiogenic factors have other actions including vasoactivity, the control of proliferation of endothelial cells, and of vascular permeability. The orchestrated patterns of secretion of pro-angiogenic (VEGF and PLGF) and anti-angiogenic (sFlt and sEng) factors by placenta throughout gestation are important for the development of both uteroplacental and fetal-placental vasculatures and the control of vascular tone and permeability. Dramatic differences in the balance of pro- and anti-angiogenic factors secreted by the placenta have been reported to precede and accompany development of preeclampsia [22]. Murine models with injection or overexpression of anti-angiogenic factors are able to recapitulate the features of preeclampsia [42] implicating these molecules centrally in the pathophysiology. The stimulus to altered release of these molecules from placenta is still actively sought. In vitro and in vivo studies have shown hypoxia and placental ischemia will stimulate their release linking back to the concept of defective trophoblast invasion and uteroplacental insufficiency [43]. However, in keeping with the syndromic nature of preeclampsia and consistent with subtypes of preeclampsia, not all women presenting with preeclampsia have altered pro- and anti-angiogenic molecules [44•]. Thus, the imbalance of pro- and anti-angiogenic factors is unlikely to be a primary pathophysiologic feature of preeclampsia but rather a target of underlying pathophysiology similar to liver or renal dysfunction or there may be angiogenic and non-angiogenic forms of preeclampsia [44•]. Differences in angiogenic factors have also been seen in pregnancies complicated by IUGR [45] suggesting it is not a specific feature of preeclampsia but more likely an index of placental growth, development and function.

Other Disease Processes in Preeclampsia

A variety of cross-sectional studies have shown an association of preeclampsia with altered immune responses [46] and inflammation [47] and with insulin resistance or metabolic syndrome [48]. However, in a prospective study, Founds et al. [49] saw no dichotomous subsets of preeclampsia by inflammation vs insulin resistance; hence, distinct subsets could not be identified. Given the known heterogeneity of presentation of preeclampsia, it is perhaps not surprising that cross-sectional or prospective studies with small number of patients did not identify subsets. In a modest-sized longitudinal study, Powers et al. [44•] found two distinct patterns of circulating concentrations of the angiogenic factor PlGF. Approximately half of preeclamptic women had normal PlGF across pregnancy while the other half had very low (less than 5th centile of normal) concentrations throughout pregnancy. The clinical features of the disorder were different with significantly higher blood pressure in early pregnancy and, after diagnosis, earlier gestational age at delivery ($P<0.05$) and more preterm birth ($P<0.05$) in preeclamptic women with low PlGF compared to those with high PlGF [44•]. However, the analysis of data from two large prospective cohorts, CAPPS [27] and SCOPE [26•] that measured multiple analytes, failed to show the ability of any combination of biomarkers and clinical data measured in the late first or early second trimester to have clinically useful predictive capability. The predictive value for early onset preeclampsia was better than that for preeclampsia overall but still not clinically useful. Interestingly, although the samples were collected longitudinally, the analysis was cross sectional. Again, this highlights the heterogeneity of the syndrome if large panels of biomarkers do not have predictive capacity. However, the results of analysis by Powers et al. [44•] of individual patients over time suggests that subsets of patients with different pathophysiologies may cloud the predictive value of biomarkers in even large datasets. Interestingly, a report of a distinct profile of biomarkers associated with poor uteroplacental vascular flow index was recently presented [50]. Obviously, other approaches are needed to identify diseases subsets if they exist.

Bioinformatic or Systems Biology Approaches

These findings suggest that analytical strategies would best recognize the syndromic nature of preeclampsia with the likelihood of multiple subtypes. This requires large amounts of data and an unbiased "discovery" based assessment of data clusters. The generation of increasing volumes of "omics" data has driven the development of analytical tools that allow integration of genome, transcriptome, proteome, and metabolome data to identify biological processes or pathways involved in various situations including preeclampsia. There is a strong genetic component to development of preeclampsia, and numerous, mainly maternal, candidate genes have been proposed based on genetic linkage or candidate gene association studies [51, 52]. There are also an increasing number of studies, mainly in intrauterine tissues, of gene expression in the setting of preeclampsia [53–56]. Recently, a genome-wide transcriptome pathway analysis of previously identified maternal preeclampsia susceptibility genes was performed in decidual tissue from women with or without preeclampsia in an attempt to identify functional roles of these genes [57] and revealed that apoptotic and cell signaling pathways, which were targets of the susceptibility genes, were significantly altered in preeclampsia. A recent cluster analysis of seven placental microarray datasets women with preeclampsia revealed three distinct molecular subclasses of placental gene expression defining preeclampsia [58•]. This revealed a

"canonical" preeclampsia subclass with increased expression of angiogenic factors, poor oxygenation, and increased secretion, one potentially representing a poor maternal response to pregnancy and another which was immunologic. It is increasingly clear that at least at the placental level, many pathologic features are shared by the obstetric syndromes, preeclampsia, IUGR, preterm birth, and stillbirth. Women who suffer these unfortunate outcomes also seem to share a common risk for poor outcomes later in life further indicating common antecedents. Analysis of molecular pathways in this aggregate of poor outcomes may be useful in identifying the nuances that lead to each clinical outcome.

Conclusion

Preeclampsia as currently diagnosed is a syndrome not a disease. We have no idea which of the myriad of pathophysiological changes are causal and which are secondary to a primary pathophysiology(ies). The existence of several pathophysiologies converging on a common readout (syndrome) is supported by much current data. Addressing this possibility requires a new mindset at all levels of investigation. Animal models allow testing of one pathway to disease but do not exclude other pathways. Biomarkers of pathophysiology should as much as possible consider patients as individuals and examine changes before and during disease to test the existence of subsets. At a minimum, epidemiological studies should attempt to evaluate differences in obvious subsets of preeclamptic women. Genetic studies must resist the urge to loosen diagnostic criteria to increase power but rather should demand rigid diagnostic criteria with obvious subsets looked at separately. It is quite likely that discovery studies of large numbers of subjects and biological samples looking for unbiased patterns and clusters will be required to unravel the complexity of preeclampsia. All of these human studies would benefit from (indeed should demand) sharing of data and biological samples to have sufficient power to decipher the disease complexities.

Compliance with Ethics Guidelines

Conflict of Interest Drs. Myatt and Roberts declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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