The placenta and preeclampsia: villain or victim?

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Preeclampsia is a disease whose characterization has not changed in the 150 years since the cluster of signs associated with the disorder were first described. Although our understanding of the pathophysiology of preeclampsia has advanced considerably since then, there is still little consensus regarding the true etiology of preeclampsia. As a consequence, preeclampsia has earned the moniker "disease of theories," predominantly because the underlying biological mechanisms linking clinical epidemiologic findings to observed organ dysfunction in preeclampsia are far from clear. Despite the lack of cohesive evidence, expert consensus favors the hypothesis that preeclampsia is a primary placental disorder. However, there is now emerging evidence that suboptimal maternal cardiovascular performance resulting in uteroplacental hypoperfusion is more likely to be the cause of secondary placental dysfunction in preeclampsia. Preeclampsia and cardiovascular disease share the same risk factors, preexisting cardiovascular disease is the strongest risk factor (chronic hypertension, congenital heart disease) for developing preeclampsia, and there are now abundant data from maternal echocardiography and angiogenic marker studies that cardiovascular dysfunction precedes the development of preeclampsia by several weeks or months. Importantly, cardiovascular signs and symptoms (hypertension, cerebral edema, cardiac dysfunction) predominate in preeclampsia at clinical presentation and persist into the postnatal period with a 30% risk of chronic hypertension in the decade after birth. Placental malperfusion caused by suboptimal maternal cardiovascular performance may lead to preeclampsia, thereby explaining the preponderance of cardiovascular drugs (aspirin, calcium, statins, metformin, and antihypertensives) in preeclampsia prevention strategies. Despite the seriousness of the maternal and fetal consequences, we are still developing sensitive screening, reliable diagnostic, effective therapeutic, or improvement strategies for postpartum maternal cardiovascular legacy in preeclampsia. The latter will only become clear with an acceptance and understanding of the cardiovascular etiology of preeclampsia.

Key words: cardiovascular function, change in partner, etiology, ovum donation, parity, placentation, preeclampsia, spiral artery transformation, uterine Doppler

Introduction

Preeclampsia (PE) is a multiorgan disorder, which presents as a well-recognized clinical syndrome characterized by predominantly cardiovascular manifestations attributable to systemic inflammation, endothelial dysfunction, and generalized vasoconstriction resulting in hypertension and multiorgan hypoperfusion.[1] PE is defined as new-onset hypertension arising after 20 weeks' gestation with multiorgan system involvement resulting in complete resolution by 12 weeks after birth.[1] The maternal vascular inflammatory syndrome characteristic of PE is thought to be triggered by abnormal levels of soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF)—commonly referred to as an angiogenic imbalance.[2] These angiogenic factors are known to be secreted into the maternal circulation by the dysfunctional placenta as a consequence of cellular oxidative or endoplasmic reticulum stress resulting from ischemia-reperfusion injury related to the impaired endovascular invasion of the spiral arteries by trophoblast seen in defective placentation.[2,3] Such defective placentation is thought to be caused by an abnormal maternal immune response to the invading trophoblast—principally driven by the clear epidemiologic observations relating risk of PE to primiparity, partner change, and ovum donation fertility treatment.[4–11] Although, there are plenty of published literature supporting the immunologic origin of PE,[4–11] the specific underlying biological mechanism is yet to be elucidated.[12] We propose that PE is primarily a consequence of a cardiovascular disorder, and in this review, we will examine the evidence in support of this hypothesis.

Placental Development and Spiral Artery Transformation

The conventionally accepted hypothesis for the etiology of PE paradigm considers extravillous trophoblast remodeling of the uterine spiral arteries as essential for

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promoting blood flow to the placenta. A defect in spiral artery remodeling underpins the development of placentally mediated disorders of pregnancy, notably early-onset PE and fetal growth restriction.

Uteroplacental hypoperfusion and maternal cardiovascular function

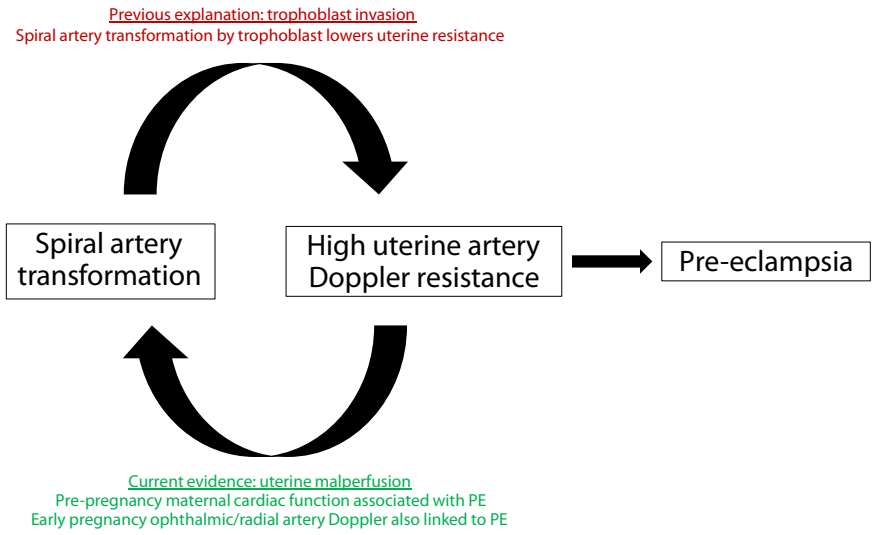
The only histologic lesions consistently found more often in the placentae derived by pregnancies complicated by PE and in isolated fetal growth restriction are those associated with maternal underperfusion of the placenta, such as massive perivillous fibrin deposition.[13,14] Uterine malperfusion may be a prepregnancy phenomenon caused by a dysfunctional maternal heart as indirectly demonstrated by several studies showing a higher prevalence of PE and fetal growth restriction in women with congenital heart disease (CHD).[15−17] A recent study on more than 3.6 million admissions for birth in California during a 7-year period, including 3189 women with noncomplex CHD and 262 with complex CHD, demonstrated that noncomplex CHD was significantly and independently associated with increased odds of PE.[18] Specifically, the prevalence of PE or eclampsia was 7.3% in women with complex CHD, 5.7% in noncomplex CHD, and 3.4% in women without CHD. Even after multivariate logistic regression with numerous covariates, noncomplex CHD remained significantly associated with increased odds of PE or eclampsia (odds ratio [OR], 1.3; 95% confidence interval [CI], 1.1−1.5; P=.003). The authors speculated that reduced placental perfusion may cause PE, which was more common in women with CHD than in women without heart disease.[18] Another study on 1302 completed pregnancies in 714 women with CHD showed that the most important obstetrical complications were hypertension-related disorders occurring in 12% of pregnancies and that these disorders occurred mainly in women who had uncorrected CHD.[16] Similarly, women with unrepaired atrial septal defects (ASDs) have also been shown to be at higher risk of PE than the general population, but this difference was not seen in women who had undergone prepregnancy ASD repair.[19,20] The additional finding that women with an unrepaired ASD also had a higher incidence of other placenta-related adverse outcomes, such as miscarriage, fetal growth restriction, and stillbirth, supports the proposed cardiovascular mechanism for developing placenta-related pregnancy complications.[21,22]

Consistent with the hypothesis of maternal uteroplacental malperfusion as a precursor to placental dysfunction and development of PE, Wald et al[23] demonstrated that the decline in maternal cardiac output (CO) during pregnancy was independently associated with neonatal complications in pregnant women with cardiac disease. Pieper et al[24] in their prospective study on 209 women with CHD and 70 healthy women demonstrated that abnormal placentation and related adverse pregnancy outcome were associated with suboptimal prepregnancy cardiovascular function. Several prepregnancy cardiovascular parameters (tricuspid annular plane systolic excursion; high N-terminal pro−B-type natriuretic peptide; systemic and pulmonary atrioventricular valve regurgitation) were associated with abnormal uteroplacental blood flow at 32 weeks' gestation and abnormal pregnancy outcome.[24] The association between poor prepregnancy cardiovascular function and subsequent uteroplacental dysfunction leading to placentally mediated disorders is not exclusive to women with CHD. Foo et al[25] has demonstrated that healthy women destined to develop PE or fetal growth restriction had poorer prepregnancy hemodynamic indices than women destined to have an uneventful pregnancy. Specifically, these women had lower prepregnancy CO, higher mean arterial pressure and systemic vascular resistance (SVR)—all features that induce peripheral organ malperfusion.[25] A recent metaanalysis investigating the association between maternal cardiac function, abnormal uteroplacental flow, and poor perinatal outcome demonstrated a relationship between abnormal uteroplacental Doppler flow patterns and cardiac function before and during pregnancy.[26] Abnormal uterine artery impedance indices and pregnancy complications demonstrated cardiac dysfunction (adverse remodeling and abnormal hemodynamic profile) from the preclinical phase of pregnancy complication to the postpartum period.[26,27] These findings suggest that abnormal prepregnancy maternal cardiovascular function may lead to trophoblast malperfusion and may be the origin of PE (Figure 1). When one considers that poor trophoblast development and placental dysfunction may result from cardiovascular dysfunction rather than cause it, a new paradigm to understand the etiology of PE becomes evident.

Uterine artery Doppler and spiral artery transformation

Uterine artery Doppler impedance indices reflect vascular resistance in the uteroplacental circulation and are thought to be an accurate proxy for the degree of trophoblast invasion. The latter hypothesis is the rationale for the use of uterine artery Doppler assessment to assess remodeling of maternal spiral arteries as a screening test for PE.[28] However, uterine artery Doppler indices in pregnancy are determined not only by the degree of trophoblast development but also by maternal cardiac function.[29] This assertion is supported by 2 unique case observations. The first is an acute improvement in uterine artery Doppler indices in a woman with severe aortic regurgitation who underwent aortic valve replacement at 19 weeks' gestation.[30] Preoperatively, uterine artery pulsatility index (PI) was 3.9 (normal, 0.5−1.5 at 20 weeks), falling to 1.0 in the postoperative period after successful surgery. Another case described a paradoxical fall in uterine artery resistance indices in the case of an abdominal pregnancy with placental implantation into the omentum.[31] These observations are supported by large population studies that have shown a substantial and independent association between uterine artery Doppler impedance indices in pregnancy and maternal cardiovascular hemodynamic parameters.[32] Furthermore, the relatively frequent finding of de novo increase in third-trimester uterine artery resistance indices is unlikely to be related to changes in trophoblast invasion, because

FIGURE 1
Cardiac maladaptation to pregnancy and uteroplacental circulation



Convention dictates that trophoblast invasion results in spiral artery transformation and the development of a low resistance uterine artery circulation—explaining the strong relationship between early pregnancy uterine artery Doppler indices and the subsequent development of PE. The strong association of ophthalmic and radial artery Doppler with PE in the absence of spiral artery transformation and the effect of prepregnancy maternal cardiovascular function on development of PE point toward poor uteroplacental perfusion as the primary event resulting in poor trophoblast development.

PE, preeclampsia.

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this would require a biologically implausible "deconversion" of the spiral arteries in the third trimester of pregnancy.[33] Doppler studies of other peripheral waveforms, such as in the ophthalmic and radial arteries, also demonstrated abnormal indices several months before the onset of PE.[34] Early pregnancy ophthalmic artery and radial artery Doppler evaluation is as effective as uterine artery Doppler assessment in screening for PE.[35] These findings support the concept that abnormal high resistance uterine artery Doppler indices reflect suboptimal cardiac performance and cardiac maladaptation to pregnancy rather than inadequate trophoblast invasion—consistent with the fact that the uteroplacental circulation has a limited autoregulatory mechanism and is directly dependent on cardiac performance.

Maternal Cardiovascular Function

If the assumption that maternal cardiovascular function plays an important role in the pathophysiology of PE is true, then studies of maternal cardiac function before the onset of, at presentation of, and during postpartum recovery from PE should consistently reflect the cardiovascular deficit in women (Figure 2).

Maternal cardiovascular function before development of preeclampsia

Abnormalities in several cardiac parameters (left ventricular remodeling, diastolic dysfunction, increased SVR, reduced cardiac index, contracted intravascular volume, and reduced venous reserve capacity) are evident at midgestation in women several weeks before they develop clinical signs and symptoms of PE.[36,37] This finding has now been reported in several studies and suggests that unfavorable cardiac adaptation to pregnancy predates the clinical manifestations of PE, supporting the hypothesis that disadvantageous functional cardiac changes could be the cause of PE. The finding that suboptimal morphofunctional cardiac changes precede the onset of PE was consistently reported predominantly in preterm or early-onset PE, but recently, it has been reliably demonstrated also in term or late-onset disease. Garcia-Gonzalez et al[38] reported that—despite a low clinical PE risk score—women destined to develop term PE demonstrated increased chamber-filling pressure (E/e′ ratio) and left ventricular mass index (LVMI) at 35 weeks' gestation. Specifically, women with an E/e′ ratio of $\geq$7.3 and an LVMI of $\geq$63.2 g/m^2 at 35 weeks' gestation were more likely to develop PE (hazard ratio, 20.1; 95% CI, 10.5−38.7; $P<.001$).[38] These findings support the hypothesis that maladaptation of maternal cardiovascular system (CVS) precedes the development of PE and may play a central role in the pathophysiology of this disease. The precise mechanism by which the adverse maternal cardiac and hemodynamic profiles could cause PE is not yet known, but the most promising hypothesis is that this occurs secondary to organ hypoperfusion, including the placenta (as described above), kidney, liver, brain, and heart itself.

Cardiovascular function in women with preeclampsia

It is now evident that the CVS is markedly compromised in PE and play a major role in the development of PE complications.[39] Numerous studies have consistently demonstrated that women affected by preterm or early-onset PE present mainly with a hemodynamic pattern of high SVR and low cardiac index (also termed a high resistance-low output circulation). The hemodynamic profile of term or late-onset PE has confusingly been referred to as exhibiting a low resistance-high output pattern because the CO was erroneously classified relative to a nonpregnant standard. Compared with women of similar age, stature, and gestational age, a high resistance-low output circulation is also evident in term PE.[38,40] Women with preterm PE also exhibit mild-to-moderate biventricular diastolic dysfunction and biventricular remodeling with preserved radial function. A small proportion of preterm women with preeclampsia also show

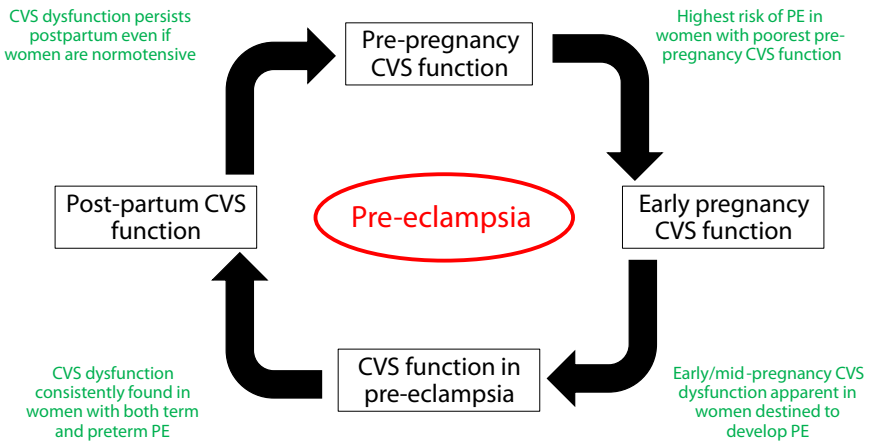
biventricular chamber longitudinal systolic dysfunction, severe biventricular hypertrophy, and chamber dilatation. Specifically, cardiovascular dysfunction seen in PE is associated with segmental impaired myocardial relaxation and high amplitude postsystolic shortening index—both indirect signs of myocardial fibrosis and ischemia. Cardiac findings are similar but less frequent and less severe in term PE. In conclusion, well-characterized morphofunctional cardiovascular changes occur in women presenting with PE.

Postpartum cardiovascular function after preeclampsia

Numerous studies have shown that changes in both the arterial and venous systems seen in acute PE and functional and geometric heart alterations persist for years after birth.[41,42] A prospective longitudinal case-control echocardiographic study demonstrated that asymptomatic biventricular diastolic dysfunction, impaired myocardial relaxation, and chamber remodeling persisted 1 year after birth, with more than half of the women who had preterm PE developing chronic hypertension within 2 years of giving birth. The persistence of adverse cardiac morphologic and functional changes after PE increased the risk of developing chronic hypertension within 2 years by 15-fold even after adjusting for confounding risk factors. These features are more prevalent in preterm vs term PE or matched controls and reflect the different long-term outcome of these 2 entities.[43] Consistent with the latter findings, epidemiologic studies have demonstrated that women with preterm or early-onset PE have a higher risk of developing congestive heart failure and coronary artery diseases than women who had term or late-onset PE or had an uncomplicated pregnancy.[44]

The persistence of postpartum adverse morphofunctional cardiac changes is unexpected given that the mother does not have the additional oxygen demands and volume load of the fetoplacental unit and her blood pressure has returned to normal. This implies that either prepregnancy or de novo PE-related cardiovascular dysfunction persists in the postpartum period in these women. The most relevant of these findings is the asymptomatic diastolic dysfunction and impaired myocardial relaxation, which has been demonstrated in the preclinical phase of PE and persist several years after birth and has recently been shown to be present at preconception in women destined to develop PE.[25,26,36–38,43] Outside pregnancy, diastolic dysfunction and impaired myocardial relaxation can occur as a result of regional desynchrony (myocardial infarction), reduction in energy supply (myocardial ischemia), or abnormal myocardial milieu (myocardial fibrosis of diabetes, metabolic syndrome, and obesity). Asymptomatic diastolic dysfunction can cause "cardiac inability" to tolerate exercise and even symptomatic heart failure if exercise is performed. It is therefore a biologically plausible hypothesis that the volume and resistance load of pregnancy may result in marked cardiovascular dysfunction and uteroplacental malperfusion.

FIGURE 2
Maternal cardiovascular function findings in women affected by preeclampsia



Suboptimal maternal cardiovascular function predates the pregnancy, is clear in early pregnancy, predominates in the clinical syndrome of PE, and persists in the postpartum period long after the resolution of maternal hypertension.

CVS, cardiovascular system; *PE*, preeclampsia.

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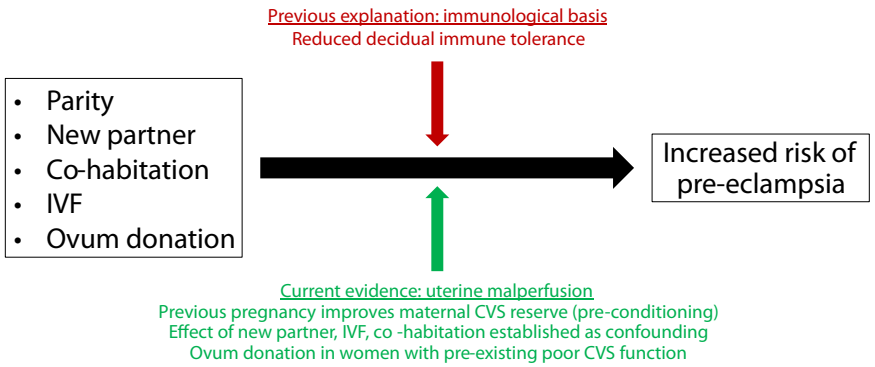
Epidemiology of Preeclampsia

The epidemiologic associations of PE played an important role in the inferences leading to the popular hypothesis of an abnormal maternal immune response to the invading trophoblast for the etiology of PE. A comprehensive understanding of maternal cardiovascular adaptation to pregnancy and maladaptation with PE has only been recently developed over the last decade, thereby justifying a reexamination of these epidemiologic associations (Figure 3).

Influence of parity

In normal pregnancy, an increase in volume load prompts a remodeling response, which consists mainly of left ventricular geometric changes, enhancing myocardial contractility (increasing CO) and enabling the CVS to cope with the extra work required in pregnancy. To understand the extent of this response, it is useful to compare the 35% increase in left ventricular mass (LVM) in pregnancy to the 25% increase in LVM reported in elite athletes on an intensive, year-long training program.[45] The protective effect of parity on the development of PE may be because of the persistence of maternal cardiac adaptation from previous pregnancy—referred to as "preconditioning" in

FIGURE 3
Reconsideration of the epidemiology of preeclampsia



Impaired placentation from reduced decidual immune tolerance to nulliparity, limited cohabitation, new partner, IVF, and ovum donation has been used to explain the clear increase in risk for preeclampsia. Pregnancy has been shown to result in improved maternal cardiovascular conditioning and better function in a subsequent pregnancy, and ovum donation is usually performed in women with poor cardiovascular function, such as mosaic Turner syndrome, PCOS, or premature ovarian failure. Large prospective epidemiologic studies have demonstrated that the effect of a new partner, IVF, and cohabitation are explained by statistical confounding, such as advanced maternal age and multiple pregnancy.

CVS, cardiovascular system; *IVF*, in vitro fertilization; *PCOS*, polycystic ovarian syndrome.

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cardiology or commonly understood as training. The assumption that preconditioning in pregnancy can result in improved tolerance to the hemodynamic load posed in the subsequent pregnancy is, in fact, supported in several studies demonstrating better cardiovascular responses to pregnancy in multiparous vs nulliparous women. Clapp et al[46] undertook echocardiographic evaluation from prepregnancy and found that ventricular volumes and CO in pregnancy were significantly greater by 15% to 20% in multipara vs nullipara. A subsequent large echocardiographic study of 4689 women found that maternal cardiovascular indices (CO, SVR, and uterine artery pulsatility) in the first trimester of pregnancy improved with increasing parity and that parity independently contributed on the advantageous cardiovascular adaptation.[47] A more recent longitudinal prospective study by Ling et al[48] examined the effect of parity on maternal hemodynamics distinguishing between parous women with and without a history of PE or small-for-gestational-age birth. They found that in parous women with previous uncomplicated pregnancy compared with nullipara, there was a more favorable cardiac adaptation, reflected in higher CO and lower peripheral vascular resistance. In contrast, multipara with previous complicated pregnancy exhibited a poorer hyperdynamic profile of lower CO and higher peripheral vascular resistance from midgestation compared with nullipara and multipara without a history of a complicated pregnancy. The incidence of PE and small-for-gestational-age birth was highest in women with a previous history of PE who exhibited the poorest cardiovascular profile in pregnancy, leading the authors to conclude that there are parity-specific differences in maternal cardiac adaptation in pregnancy.[48] This pattern of hemodynamic response related to parity is consistent with the hypothesis that the maternal heart is conditioned in the first pregnancy, thereby eliciting improved maternal cardiovascular responses and improved placentation and lower PE rates in subsequent conceptions.[48]

Change in partner

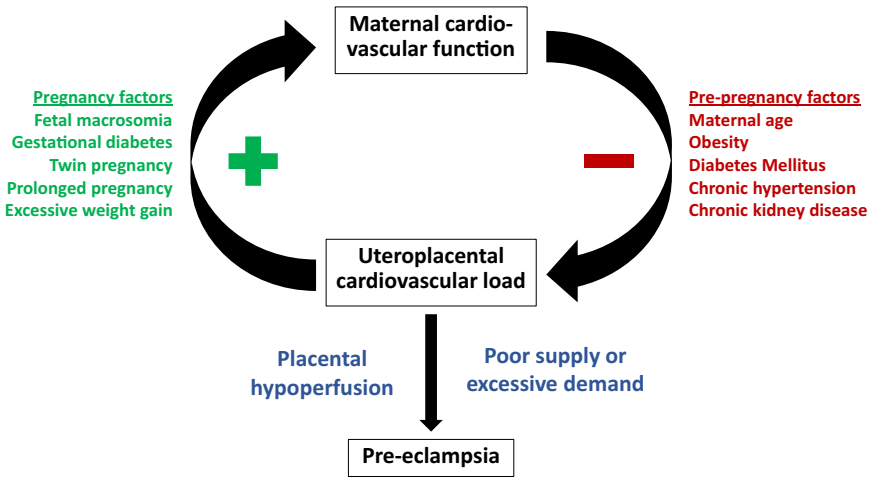
There are now several large and well-conducted epidemiologic studies that contradict the previously held belief that new paternity increases the risk of PE. A Medical Birth Registry of Norway study on 547,238 women who had registered 2 births was the first to demonstrate that change of paternity for the second pregnancy was actually associated with a reduced risk of PE after controlling for the time since first birth (adjusted OR [aOR], 0.80; 95% CI, 0.72−0.90).[49] Another population-based Scandinavian registry study on 760,901 women who had 2 or more births found that in unadjusted analyses, a pregnancy involving a new partner was associated with higher risk of PE, but after adjustment for the interbirth interval, the risk of PE was reduced (aOR, 0.73; 95% CI, 0.66−0.81).[50] Despite these consistent findings and concordance from a similar epidemiologic study on Danish women,[51] proponents of the immunologic basis of PE have always claimed that population-based registry studies lack robustness to confirm alleged paternity.[52] However, a subsequent Norwegian cohort study of women with spontaneous (n=489,326) or assisted reproductive conceptions (n=12,440) found that the prevalence of PE was explained by interbirth interval and advanced maternal age but unrelated to change of partner.[53] Therefore, the increase in PE risk previously ascribed to changing paternity leading to the immunologic theories of PE appears to be explained by the fact that new paternity was a proxy marker for interpregnancy interval in older epidemiologic work that failed to statistically correct for such confounding.

Cohabitation and prolonged sperm exposure

It has been proposed previously that sexual cohabitation protects against the development of PE by inducing desensitization of the maternal immune system to paternally derived fetal antigens.[7,8] However, a well-designed retrospective study examined the outcomes of pregnancies of women who conceived by donor insemination

compared with women who conceived after in vitro fertilization (IVF) with own partner's spermatozoa.[54] The prevalence of hypertensive disorders in pregnancy was not different between the 2 groups (22% and 24%, respectively).[54] The authors concluded that insemination by the partner's spermatozoa was not associated with a reduction of hypertensive disease and neither was donor spermatozoa associated with an increased incidence.[54] The role of barrier contraception in preventing sperm exposure was tested in a study of 2211 women who recorded preconception contraception and timing of first sexual intercourse with the father of the pregnancy.[55] The authors demonstrated that women using barrier contraception before conception were no more likely than women not using barrier contraception to develop PE (aOR, 1.0; 95% CI, 0.6−1.6) and concluded that their findings do not support the immune maladaptation theory of PE.[55] In a study of 5591 nulliparous women from the Screening for Pregnancy Endpoints study, compared with women who had a duration of sexual relationship of >12 months, the risk of PE was ascertained for women who had a duration of sexual relationship of ≤3 months, 4 to 6 months, 7 to 9 months, and 10 to 12 months.[56] The latter is the only prospective study to evaluate this relationship, showing that duration of sexual relationship was not associated with PE after adjusting for confounders.[56]

FIGURE 4
Interaction between maternal cardiovascular supply and uteroplacental cardiovascular load



Prepregnancy risk factors for PE are associated with poorer cardiovascular function and pregnancy risk factors with increased cardiovascular load. A mismatch between cardiovascular supply and demand will lead to placental hypoperfusion, leading to the placental syndrome recognized clinically as PE. The gestational age at presentation will depend on the predisposing factors, and their influences on cardiovascular supply and load. Poor supply (chronic hypertension) matched with increased demand (twin pregnancy) will predispose to early PE. Good maternal cardiovascular health matched with excessive pregnancy demand (fetal macrosomia) is likely to present as term PE.

PE, preeclampsia.

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Ovum donation

The increase in risk of PE in pregnancies conceived through IVF has been consistently explained by advanced maternal age and multiple pregnancy—except in the case of ovum donation. Pregnancies achieved by oocyte donation confer a 2- to 3-fold increase in the likelihood of developing PE compared with those achieved by homologous IVF.[57] Recent metaregression analyses have shown that even after adjustment for maternal age, gravidity, parity, and chronic hypertension, oocyte donation was independently associated with a higher rate of hypertensive diseases of pregnancy.[58] The latter observation has been used to support the immunologic origins of PE based on the differences in human lymphocyte antigen compatibility between a hemiallogenic fetoplacental graft in natural conception and a completely allogenic conception with ovum donation. An alternative explanation for the association between ovum donation and PE is evident if one considers that women who undergo ovum donation are typically affected by premature ovarian insufficiency, polycystic ovarian syndrome (PCOS), or even mosaic Turner syndrome. All of these conditions are strongly associated with the development of metabolic syndrome or increased cardiovascular risk.[59,60] It is therefore entirely plausible that prepregnancy asymptomatic cardiac dysfunction or metabolic derangement in these women may play a role in increasing the risk of PE in ovum donation pregnancies. A recent study has shown that more than 90% of women with PCOS required lifestyle or medical intervention for cardiovascular disease (CVD) prevention when following the American Heart Association guidelines.[61] The latter findings indirectly support a hypothesis of cardiovascular maladaptation to pregnancy and increased risk of uteroplacental dysfunction in women with PCOS.

Preeclampsia and cardiovascular risk factors

The major established risk factors for PE, such as obesity, physical inactivity, hypertension, dyslipidemia, metabolic syndrome, diabetes, and other maternal comorbidities, are also related to increased cardiovascular risk in later life.[62] Obesity, metabolic syndrome, diabetes, and dyslipidemia are known to be associated with asymptomatic diastolic dysfunction and adverse cardiac remodeling in nonpregnant individuals.[63] The commonality of these risk factors for PE

with those for CVDs supports the hypothesis for a central role of impaired maternal cardiovascular function in determining poor placentation by malperfusion, with dysfunctional trophoblast leading to the systemic vascular inflammatory syndrome of PE (Figure 4). Prepregnancy physical activity was found to have a protective effect against PE, which could be mediated by the reduced inflammation, decreased oxidative stress, and improved endothelial function known to characterize physically active women; furthermore, physical activity predisposes the heart to favorable maternal cardiovascular adaptation to pregnancy and successful trophoblast implantation.[64] Familial clustering has also been reported in PE, supporting a link to genetic causality.[65] The limited number of genetic loci that have been consistently and reproducibly linked to PE has also been implicated in adult CVD, suggesting a genetic link between PE and CVD.[66]

Screening and Therapy in Preeclampsia

Proposing a cardiovascular etiology for PE has profound implications not only on our understanding of the disease course but also on several aspects of clinical management, such as screening, diagnostic and preventive strategies for PE.

Screening for preeclampsia

In a recent randomized controlled trial (RCT) of first-trimester early screening followed by targeted and effective pharmacologic prophylaxis of preterm PE, an integrated prediction model was used, which included historic risk factors, blood pressure, uterine artery PI, and PlGF concentration.[28] Of note, with the exception of uterine artery Doppler indices (covered earlier), cardiovascular risk factors and blood pressure are used routinely in assessing CVDs in the nonpregnant state.[67–69] For example, in children with CHD, serum PlGF levels correlated with the degree of the ventricular volume overload and persistent hypoxia after corrective surgery.[70] Although PlGF is known to be mainly secreted by the placenta in pregnancy, its putative role is cardiac protection from myocardial ischemia secondary to circulatory overload.[71] A recent study demonstrated that third-trimester assessment of cardiac function—specifically LVMI and E/e′ ratio—was superior to clinical PE risk stratification using sFlt-1 and PlGF in screening for the development of PE at term.[38] The authors appropriately speculate that more aggressive blood pressure treatment in identified high-risk women could modify the maternal cardiac adaptation and prevent the development of late-onset PE and potentially reduce the risk of developing severe hypertension and organ damage later in life. The prognostic value of cardiovascular indices is highlighted in a study of women with gestational hypertension in which a point-of-care noninvasive CO monitor was used to obtain cardiovascular variables of CO and SVR. Women with high SVR and low CO (adjusted HR, 7.79; 95% CI, 1.94−31.24) cardiovascular profiles had a significantly higher risk of earlier PE than women with normal SVR and normal CO—with median survival times without developing PE being 2 weeks and 11 weeks, respectively.[40]

Preeclampsia prevention therapies

There are now numerous RCTs demonstrating the efficacy of low-dose aspirin in reducing the incidence of preterm PE, and this has been shown to be equally effective when introduced into routine care in a public health setting.[28] It is clear to most readers that apart from its analgesic properties, aspirin is commonly used for its cardioprotective effects. We propose that it is no coincidence that most therapeutic prevention strategies for PE employ drugs used to reduce the incidence of CVDs in nonpregnant adulthood, such as calcium, statins, metformin, and antihypertensive medications.[72] The commonalities in screening modalities and prevention strategies for both PE and adult CVD further strengthen the hypothesis of a cardiovascular origin for PE.

Birth as a cure for preeclampsia

It has been a long-standing belief that the harmful maternal consequences of PE are completely reversible with termination of pregnancy.[12] However, there are now several studies and systematic reviews in pregnancies complicated by PE, which have consistently demonstrated postnatal biventricular remodeling and diastolic dysfunction from as early as 3 months after birth persisting for several decades after that.[42,43] These subclinical features of cardiac dysfunction are associated with increased risk for developing a range of adverse cardiovascular outcomes, including hypertension, cardiomyopathy, myocardial infarction, stroke, and vascular dementia.[72–75] For example, women who had hypertensive disorders in pregnancy have as high as a 30% risk of postpregnancy hypertension in the decade after birth—with the highest risk of onset being in the first 1 to 2 years after birth.[74,75] The long-term maternal cardiovascular risks following PE are greater than for smoking, and the American Heart Association effectiveness-based guidelines for preventing CVDs in women now recognize PE as an independent risk factor for CVD and have introduced this complication of pregnancy in the algorithm for the evaluation of the 10-year Framingham cardiovascular risk score.[76] These findings emphasize the extraplacental nature of PE and mandate that women who have had PE should be advised about their cardiovascular risks and be offered advice on prevention and increased surveillance for cardiovascular morbidity.

Conclusion

Although abnormal trophoblast invasion possibly of immunologic origin has been proposed as the cause of poor placentation in PE, this review suggests that suboptimal cardiovascular performance is more likely to be the cause of poor placentation because of uteroplacental malperfusion. Placental malperfusion—occurring either because of suboptimal cardiac performance due to asymptomatic cardiac dysfunction or from excessive pregnancy demand in the normally functioning heart—may lead to PE following exactly the same translational mechanisms previously described for the placental etiology

hypothesis. For example, primary maternal cardiovascular dysfunction through uteroplacental malperfusion may still induce syncytiotrophoblast damage by ischemia-reperfusion injury with consequent abnormal placental-maternal signaling and development of the overt systemic inflammatory syndrome of PE. Despite the seriousness of the maternal and fetal consequences of PE, we are still developing effective screening, diagnostic, therapeutic, and improvement strategies for postpartum maternal cardiovascular legacy. These will only become clear with an acceptance and understanding of the cardiovascular etiology of PE.

This continued lack of certainty is particularly concerning when PE is the cause of a considerable annual global toll in maternal death. ■

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