

# An integrated model of preeclampsia: a multifaceted syndrome of the maternal cardiovascular-placental-fetal array



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Maternal tolerance of the semiallogenic fetus necessitates conciliation of competing interests. Viviparity evolved with a placenta to mediate the needs of the fetus and maternal adaptation to the demands of pregnancy and to ensure optimal survival for both entities. The maternal-fetal interface is imagined as a 2-dimensional porous barrier between the mother and fetus, when in fact it is an intricate multidimensional array of tissues and resident and circulating factors at play, encompassing the developing fetus, the growing placenta, the changing decidua, and the dynamic maternal cardiovascular system. Pregnancy triggers dramatic changes to maternal hemodynamics to meet the growing demands of the developing fetus. Nearly a century of extensive research into the development and function of the placenta has revealed the role of placental dysfunction in the great obstetrical syndromes, among them preeclampsia. Recently, a debate has arisen questioning the primacy of the placenta in the etiology of preeclampsia, asserting that the maternal cardiovascular system is the instigator of the disorder.

It was the clinical observation of the high rate of preeclampsia in hydatidiform mole that initiated the focus on the placenta in the etiology of the disease. Over many years of research, shallow trophoblast invasion with deficient remodeling of the maternal spiral arteries into vessels of higher capacitance and lower resistance has been recognized as hallmarks of the preeclamptic milieu. The lack of the normal decrease in uterine artery resistance is likewise predictive of preeclampsia. In abdominal pregnancies, however, an extrauterine pregnancy develops without remodeling of the spiral arteries, yet there is reduced resistance in the uterine arteries and distant vessels, such as the maternal ophthalmic arteries.

Proponents of the maternal cardiovascular model of preeclampsia point to the observed maternal hemodynamic adaptations to pregnancy and maladaptation in gestational hypertension and preeclampsia and how the latter resembles the changes associated with cardiac disease states.

Recognition of the importance of the angiogenic-antiangiogenic balance between placental-derived growth factor and its receptor soluble fms-like tyrosine kinase-1 and disturbance in this balance by an excess of a circulating isoform, soluble fms-like tyrosine kinase-1, which competes for and disrupts the proangiogenic receptor binding of the vascular endothelial growth factor and placental-derived growth factor, opened new avenues of research into the pathways to normal adaptation of the maternal cardiovascular and other systems to pregnancy and maladaptation in preeclampsia.

The significance of the "placenta vs heart" debate goes beyond the academic: understanding the mutuality of placental and maternal cardiac etiologies of preeclampsia has far-reaching clinical implications for designing prevention strategies, such as aspirin therapy, prediction and surveillance through maternal hemodynamic studies or serum placental-derived growth factor and soluble fms-like tyrosine kinase-1 testing, and possible treatments to attenuate the effects of insipient preeclampsia on women and their fetuses, such as RNAi therapy to counteract excess soluble fms-like tyrosine kinase-1 produced by the placenta.

In this review, we will present an integrated model of the maternal-placental-fetal array that delineates the commensality among the constituent parts, showing how a disruption in any component or nexus may lead to the multifaceted syndrome of preeclampsia.

**Key words:** cardiac output, cardiovascular adaptation, decidual natural killer cells, diastolic function, exercise in pregnancy, extracellular vesicles, extravillous trophoblast, fetus, great obstetrical syndromes, hypertension, maternal-fetal interface, maternal heart, peripartum cardiomyopathy, peripheral vascular resistance, placenta, placental-derived growth factor, preeclampsia, soluble fms-like tyrosine kinase-1, syncytiotrophoblast, systolic function, trophoblast

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## Introduction

Preeclampsia (PE) is a syndrome characterized mainly by maternal symptoms: hypertension, proteinuria, or, in the absence of proteinuria, effects in target organs. Over the last 3 decades, fetal effects have been enfolded into the definition of PE to designate various phenotypes: PE with or without intrauterine growth restriction (IUGR) as well as the symptom onset time early or late in pregnancy, before or after 34 weeks' gestation.

Nearly a century of extensive research has investigated the role of the placenta in the development of hypertensive disorders and PE during pregnancy. Molar pregnancies, which develop without a fetus, are at very high risk of developing PE and provided the clue to investigate the placenta as a source of the disease.<sup>1</sup> Later investigations by Brosens et al demonstrated that poor placentation, typified by shallow trophoblast invasion and deficient spiral artery conversion, is characteristic of gestational hypertensive disorders and PE.

Healthy pregnancy requires integration of a complex array of crosstalk and interplay across maternal, fetal, and placental systems, to ensure normal embryo implantation and adequate development and maintenance of the placenta and placental bed and appropriate adaptation of the maternal cardiovascular and other systems. Some instances of PE seem to have their source in placental pathology, others have their source in maternal cardiac maladaptation, and perhaps most involve a combination of the 2. This has broader implications than the purely academic. Although the maternal cardiovascular system has a part in the development of the disorder, understanding the role of the placenta is imperative to understanding the full complexity of the maternal-fetal interface. The interface is not a 2-dimensional fabric but rather a multifaceted array.

In this essay, we will attempt to illuminate the importance of appropriate maturation of the maternal-placental-fetal array from the moment of implantation and the mutual crosstalk

between the maternal cardiovascular system and fetal-placental system. Maldevelopment in any of the constituents comprising the array can lead to PE.

## Maternal Cardiovascular Adaptations to Pregnancy and Maladaptation in Preeclampsia

Normal maternal cardiovascular adaptations in pregnancy include increased cardiac output (CO), expanded blood volume, and reduced systemic vascular resistance and blood pressure, which ensure healthy provision of nutrients and gas exchange to the growing fetus and maternal adjustment to the burden of pregnancy.<sup>3</sup> Maternal cardiac transformation resembles the physiological hypertrophic response to exercise in normal individuals, including eccentric ventricular remodeling, enhanced function, and improved metabolism.<sup>4,5</sup> Several studies<sup>6–9</sup> have examined the progressive changes in CO and uterine artery diameter and flow velocity. The proportional distribution of CO to the uterus increases from 3.5% in early pregnancy<sup>6</sup> to 5.6% at midtrimester to approximately 12% at term.<sup>6,9</sup>

Certain conditions, such as chronic hypertension or increased afterload, can lead to pathologic hypertrophy, characterized by concentric remodeling of the left ventricle. In some conditions of pregnancy, the demands exceed the adaptational capacity of the maternal milieu, such as twins and multiples, macrosomia, or prolonged pregnancy. In other conditions, such as prepregnancy chronic hypertension and others, the preexisting condition might predispose to poor maternal response and adaptation.<sup>3</sup>

The necessity of maternal adaptation to pregnancy is evident; CO increases by approximately 45% in normal singleton pregnancy and even more in twins.<sup>3,10</sup> Normal cardiac remodeling and the differences between eccentric and concentric remodeling are measurable via morphometric and functional parameters. Some of the measures being studied include ventricular wall thickness, septal thickness, ventricular diameter, atrial dimensions, and others, and

the indices derived from them that control for maternal body habitus. These evaluate the morphologic modifications brought about by the increasing demands of pregnancy and volume overload and the changes in the milieu of circulating factors. Functional parameters focus primarily on left ventricular function as it adapts to pregnancy. These include stroke volume (the volume of blood pumped at each systole, calculated as end diastolic volume—end systolic volume), CO (stroke volume×heart rate), measures of vascular resistance (systemic vascular resistance or total peripheral resistance, calculated as  $80 \times [\text{mean arterial pressure} - \text{central venous pressure}] / \text{CO}$ ), and isovolumetric relaxation time (measured from the closure of the aortic valve to the onset of filling by opening of the mitral valve).

In a metaanalysis<sup>11</sup> of multiple studies and meta-analyses of maternal cardiac parameters across the trimesters, results were shown to be mixed. From 32 weeks' gestation onward, CO, stroke volume, and heart rate have been shown to increase, remain the same, or decrease. Some of the observed inconsistency seems to stem from differences in populations, approaches, and technologies used to obtain measurements.<sup>11</sup>

Researchers have investigated the link between maternal cardiac adaptation and maladaptation and the subsequent development of PE. In an early study of the changes in cardiovascular function,<sup>12</sup> the authors showed that the changes observed in maternal hearts in their initial pregnancy began early, persisted after delivery, and appeared to be enhanced by a subsequent pregnancy.<sup>12</sup>

Melchiorre et al<sup>13</sup> showed that gravidae with term vs preterm PE had differently adapted hearts. Although both groups showed increases in mean arterial pressure, total vascular resistance index, relative wall thickness, and altered geometry, the preterm PE cases showed increased signs of hypertrophy, impaired relaxation, and measures of diastolic and systolic dysfunctions and decreased stroke volume index and cardiac index, indicative of worsening dysfunction. The group also showed<sup>14</sup> that the impact of

PE, observed during pregnancy, was evident 1 and 2 years after delivery.<sup>14</sup>

Ghossein-Doha et al<sup>15</sup> followed 51 women that formerly developed early-onset PE, defined as the appearance of symptoms before 34 weeks' gestation, in their subsequent pregnancies. PE recurred in 14 women. Compared with women in whom PE did not recur, those with PE had significantly lower prepregnancy left ventricular mass index and stroke volume and higher heart rate. During the course of their pregnancies, the groups displayed similar adaptive trajectories. Maternal cardiac parameters were the only observed difference among the groups. Interestingly, the groups also differed in the rate of persistent chronic hypertension and treatment with antihypertensive medications. Although the recurrent PE group had a higher rate of hypertension, they had lower rates of treatment.<sup>15</sup> Numbers were small, but this may be an interesting avenue of future research, whether interventions for hypertension might improve outcomes in these high-risk gravidae.

These 2 seminal studies demonstrated changes in the maternal cardiovascular system and signs of maladaptation that cannot be explained by placental factors alone. Maternal cardiac maladaptation is shown to have a role in the development of PE.

Further investigation into maternal maladaptation in PE by Valensise et al<sup>16</sup> compared uterine artery Doppler and echocardiographic functional measures of more than 1300 asymptomatic women at 24 weeks' gestation and compared groups that eventually developed early- or late-onset PE. Of the 107 women who developed PE, 75 manifested early-onset disease and 32 late-onset disease. Women with early-onset disease had smaller wall thickness and ventricular diameters than late-onset cases or controls. This, coupled with lower CO, appeared to be the result of underfilling in a state of pressure overload and a concentric hypertrophy pattern. However, late-onset PE showed the largest ventricles, with intermediate wall thickness and high CO, indicative of hypertrophied ventricles in an overfilling state without pressure overload. The

study groups also showed statistically significant differences in total vascular resistance (TVR), with early-onset cases showing high TVR and late-onset cases showing low TVR. Controls were measured at a median level. Early-onset cases showed greater alteration in diastolic function, such as lower atrial measures. Uterine artery notching at 24 weeks' gestation was noted 4 times more in women developing early- vs late-onset disease. The investigators concluded that different hemodynamics came into play for early, placenta-mediated PE, which is linked to defective trophoblast invasion with high percentage of altered uterine artery Doppler, and late-onset PE, which appears to be linked to constitutional factors.<sup>16</sup> This large study demonstrates the combination of maternal cardiac maladaptation and placental factors in the development of the differing phenotypes of PE.

### Cardiac Adaptation to Exercise and Pregnancy and Maladaptation in Preeclampsia

Exercise has known benefits for the cardiovascular and endothelial systems. The observed anatomic and functional adaptations in the heart to exercise are mirrored in many ways by the physiological adaptations observed in normal pregnancy. There are some important differences. For example, exercise creates sporadic volume overload and corresponding adaptation during the resting state, whereas pregnancy is a continuous, progressive state. The cellular and molecular mechanisms and pathways implicated in these comparative states have been reviewed elsewhere.<sup>5</sup>

Exercise has been shown to enhance placentation through alterations in perfusion pressure and oxygen availability that may impact invasion and proliferation of trophoblast cells.<sup>17</sup> The brief bouts of hypoxia and reduced placental perfusion induced by exercise might benefit placental development by promoting cell proliferation and angiogenesis.<sup>18–20</sup> In murine models, improved placentation was shown to lead to better angiogenic-antiangiogenic balance, which in turn may reduce the risk of PE.<sup>21,22</sup>

In nonpregnant animal models, exercise was observed to induce decreased blood flow in the uterine artery as blood was redirected to provide oxygen to the effort. However, during pregnancy, investigators have observed an attenuated decrease in flow, and a greater proportion of blood flow was directed to the fetus than to the uterus in nonpregnant animals.<sup>23,24</sup>

Exercise reduces the risk of gestational hypertension and PE and appears to mitigate the effects of PE when it develops.<sup>4</sup> The adaptation observed in pregnancy differs from the physiological adaptation to physical exercise and from pathologic remodeling resulting from chronic conditions. The basic molecular mechanisms underlying remodeling in each situation are affected by hormonal and other changes in pregnancy.<sup>5</sup> Exercise can impact the angiogenic-antiangiogenic factors profile, and it may be through this reaction that exercise improves cardiac adaptation and maternal outcomes.

Considered together, these observations of differential cardiac effects in pregnancy and their modulation through exercise brought groups around the world to view the maternal heart not only as playing a role in the development of PE but also being the most important player in the pathophysiology of the disease.

These investigators draw parallels between PE and gestational diabetes.<sup>25,26</sup> They contend that both states share characteristics, such as predisposing factors, with the parallel states in nonpregnant individuals, that is, risk factors for type 2 diabetes and cardiovascular disease are shared with gestational diabetes and PE, respectively. In contrast with nonpregnant patients, both syndromes of pregnancy are resolved at parturition. Most patients rapidly return to normotensive or normoglycemic states in the postpartum period but remain at high risk of developing cardiovascular disease or diabetes in later life. However, as most were at increased risk of these diseases before pregnancy, it is not proven that affected pregnancy is the instigator. In addition, important differences between the 2

pregnancy syndromes are the preponderance of nulliparas in PE and the occurrence of type 2 diabetes in males. Unlike diabetes, PE never occurs without a placenta.

### The Imperative Role of the Placenta in Preeclampsia

The cardiovascular model of PE, as presented above, contends that poor prepregnancy cardiovascular reserve or excessive cardiovascular demands in pregnancy are the precursors of PE. This model presents the maternal heart as the “engine” of pregnancy and gestational complications, whereas the placenta is merely the “radiator.”<sup>25,27</sup> However, there are numerous examples of pregnancy complications and experimental research investigations that underline the essential role of the placenta in the development of the disease and serve as a “proof of concept,” substantiating the placenta as the source of PE.

There are many examples of placenta-dependent pathologies that lead to PE, but they do not satisfactorily illustrate other pathways to the disease. Karumanchi et al<sup>28</sup> provide a “missing link” among these varied mechanisms: soluble fms-like tyrosine kinase-1 (sFlt-1). The sFlt-1 receptor is a nonmembrane associated, and therefore free-circulating, antiangiogenic splice variant of the vascular endothelial growth factor (VEGF) receptor 1 (or Flt-1). As sFlt-1 resembles Flt-1 in its extracellular domain, it can compete with Flt-1, binding with the angiogenic factors, VEGF and placental-derived growth factor (PlGF), essentially removing them from circulation and diminishing their angiogenic effects.

In normal pregnancy, the angiogenic factor, PlGF, and the antiangiogenic factor, sFlt-1, are balanced, but unbalanced (with increased sFlt-1 and decreased PlGF) in PE.<sup>28–37</sup> Under hypoxic conditions, cytotrophoblasts up-regulate sFlt-1.<sup>38,39</sup> Sela et al<sup>40</sup> showed that sFlt-14 comes from syncytial knots, which in turn impacts on kidney function. When sFlt-1 and PlGF concentrations are balanced, normal angiogenesis is maintained. Antiangiogenic properties predominate when the balance is skewed.<sup>28,35,36</sup> Women with chronic

hypertension, who are at very high risk of PE, were observed to have reduced first-trimester concentrations of PlGF and sFlt-1, and this was more pronounced in women who developed PE.<sup>37</sup>

In addition, it has been shown that pravastatin may impact the angiogenic-antiangiogenic balance by reducing the release of sFlt-1 from the placenta while increasing PlGF release and circulating PlGF, with potential usefulness in PE prevention.<sup>41</sup>

The case of abdominal pregnancies has been suggested in support of the cardiovascular model of PE. By definition, in abdominal pregnancy, there is no intrauterine placenta or remodeling of the decidual spiral arteries; implantation, trophoblast invasion, and idiosyncratic vascular remodeling seem to arise in an ectopic location.<sup>42</sup> However, despite this lack of spiral artery conversion, changes characteristic of pregnancy have been observed in the uterine and ophthalmic arteries, and uterine artery Doppler indices have been shown to be appropriately adapted during abdominal pregnancy.<sup>43</sup> These pregnancies (although rare) have a high rate of PE. It is argued therefore that spiral artery conversion and shallow invasion are not essential for developing PE. From this, the supporters of the cardiovascular etiology interpret that placentation is not necessary for PE. However, other case reports<sup>44,45</sup> would tend to support the necessity of a placenta (albeit extra-uterine) in the development of PE in these pregnancies. Piering et al<sup>44</sup> described a case of abdominal pregnancy carried to term. After the delivery of a live fetus and the placenta left in situ, PE persisted for more than 3 months after delivery, confirmed by clinical signs and kidney endotheliosis. The disease resolved after the removal of the placenta; kidney biopsy almost 2 years after delivery confirmed the resolution of endotheliosis. The patient was alive and well 25 years later, with normal kidney function and blood pressure.<sup>44</sup> In another case<sup>45</sup> of abdominal pregnancy with PE resulting in the delivery of a live term neonate, with placenta adherent to the broad ligament, cecum, and small bowel, a portion of the placenta was left

in situ. The authors describe “a stormy postoperative course” necessitating anticonvulsants and antihypertensives to control worsening PE.<sup>45</sup>

Pregnancies of fetuses with trisomy 13 have been observed to suffer a 6-fold increase in gestational hypertension and a 12-fold increase in severe PE.<sup>46</sup> The balance between circulating angiogenic and antiangiogenic factors has been shown to differ from euploid cases: the placentas of these pregnancies were shown to have increased sFlt-1, and the mothers had decreased serum PlGF. A case series of trisomy 13 placental mosaicism cases showed that 3 of 6 women developed PE and 1 developed gestational hypertension.<sup>46</sup>

Mirror syndrome is a curious disorder in which maternal symptoms “mirror” those of the fetus, which is affected by hydrops fetalis. The maternal clinical picture may mimic PE and resolve when the underlying fetal cause is treated. Llurba et al<sup>47</sup> examined the sera levels of angiogenic and antiangiogenic factors in mirror syndrome and compared them with preeclamptic and control cases. The investigators showed that sFlt-1, PlGF, sFlt-1-to-PlGF ratio, and soluble endoglin (sEng) in patients with mirror syndrome mimicked those of women with PE, that is, sFlt-1, sEng, and the sFlt-1-to-PlGF ratio were increased, whereas PlGF was decreased compared with controls. However, as mirror syndrome resolved, values gradually returned to levels comparable with controls. The authors note that tracking the level of these factors can differentiate between mirror syndrome and preeclamptic pregnancies.<sup>47</sup>

A recognized puzzle of PE is the clear “protective effect” of cigarette smoking.<sup>48</sup> Llurba et al<sup>47</sup> investigated this clear inverse association as it relates to sFlt-1 and PlGF levels and uterine artery Doppler measures. The investigators found that even in women at high risk of PE based on their uterine artery Doppler screening results, serum PlGF remained higher, and the rate of PE that eventually developed was lower, compared with nonsmokers.<sup>49</sup>

A known complication of twin pregnancy is discordant fetal development.

We and others have reported twin pregnancies complicated by early-onset PE and discordance for IUGR.<sup>40,50</sup> Selective feticide of the affected twin led to eventual resolution of the PE cascade. Cordocentesis performed before the procedure revealed higher levels of sFlt-1 in the circulation of the twin with IUGR. Moreover, maternal serum levels of sFlt-1 returned to normal as the PE symptoms resolved.<sup>40</sup>

Staff et al<sup>51</sup> proposed a model of PE phenotypes based on maternal endothelial response to circulating PlGF. PE and IUGR develop as a result of disturbed endothelial inflammatory response. Vascular endothelium may be characterized by pregestational endothelial inflammatory dysfunction. In this case, placentation may be normal, but owing to disturbed maternal endovascular response to circulating biomarkers, PE may develop without IUGR. In cases with normal pregestational maternal endothelium but poor placentation, an oxidatively stressed placenta and reduced levels of PlGF might lead to a dysfunctional maternal endothelial inflammatory response and ultimately to the maternal syndrome of PE and the fetal syndrome of IUGR. In a parallel scenario, this might lead to an oxidatively stressed placenta, reduced circulating PlGF levels but a maintained normal maternal vascular response, and the development of the fetal syndrome of IUGR in the absence of PE.<sup>51</sup>

As canvased in a recent review,<sup>52</sup> an extreme example of PlGF-sFlt-1 balance and cardiac remodeling is found in cases of peripartum cardiomyopathy, a complication affecting previously healthy women with potential harmful long-term effects on their cardiovascular health. PE was observed at 4-fold the population prevalence, and sFlt-1 was significantly higher and persisted in the circulation significantly longer.<sup>52</sup>

### Maternal-Fetal Crosstalk in Implantation

The extensive work presented above demonstrates the maternal and placental causes and effects involved in the development of PE. The success of pregnancy depends on the integration of maternal

factors and their impact on the fetus, and fetal factors on the uterus and other maternal organs.<sup>53,54</sup> Most fascinating is the part played by the fetus in the creation of a favorable uterine milieu, by crosstalk with and changes to the uterus and the maternal heart. These processes begin with implantation and continue throughout pregnancy.

Implantation and placentation during the first trimester of pregnancy are the foundation of normal fetal development and a healthy pregnancy.<sup>55</sup> Implantation, with subsequent migration of extravillous trophoblast (EVT) into the decidua and first third of the myometrium, includes invasion by EVT into the lumen of the spiral arteries and remodeling of their myometrial and decidual segments. These invaded segments widen and lose their smooth muscle to achieve vessels of low resistance and high capacitance.

Implantation and the initial development of the placenta involve crosstalk among fetal and maternal cells, including trophoblasts and decidual cell types, such as macrophages, dendritic cells, mesenchymal cells, and others. Our findings and those of others reveal the maternal natural killer (NK) cells as holding the principal role in the crosstalk of the maternal-fetal interface.

### Decidual Natural Killer Cell Trophoblast Crosstalk

Immune cells comprise approximately 40% of the cells within the decidua. Obviously, they are needed to protect the placenta and fetus from pathogens. However, within the placental bed, maternal and fetal cells intermingle. The semiallogenic trophoblasts not only cohabit with the maternal cells but also collaborate successfully. They not only tolerate each other but also engage in crosstalk, to balance the activities necessary to lay the foundation for healthy pregnancy. Trophoblasts and decidual NK cells are at the forefront of successful implantation and maintenance of a healthy pregnancy. Trophoblasts are bathed in maternal blood and invade the uterine spiral arteries, evading the attack of resident NK cells, which comprise 50% to 70% of decidual lymphocytes. This is accomplished via

mechanisms that allow the placenta to live harmoniously in a nonallogenic environment: down-regulation of the highly polymorphic human leukocyte antigen (HLA)-A and HLA-B antigens in the syncytiotrophoblast while the invasive trophoblast expresses HLA-G of low polymorphism. Although NK cells are known for their killing properties for immune defense, they are builders at the maternal-fetal interface.<sup>56,57</sup> Chiefly, the decidual NK (dNK) cells produce factors necessary for appropriate placental bed development.<sup>56</sup> Ashkar et al<sup>58</sup> pioneered the seminal work in mice lacking uterine NK (uNK) cells, which showed that their pregnancies developed defective central artery remodeling and growth-restricted pups.<sup>58</sup> Tayade and colleagues<sup>59</sup> further demonstrated a role for PlGF (generally expressed by both uNK and trophoblasts) in uNK cell proliferation, and perhaps differentiation, by employing mice null for PlGF expression.<sup>59</sup> Similarly, in humans, the dNK cells produce chemokines, growth factors, cytokines, and angiogenic factors vital for the appropriate development and maintenance of the maternal-fetal interface.<sup>57</sup> Interestingly, the numbers of dNK are the highest in the first trimester of pregnancy, and by the early second trimester of pregnancy, their numbers steadily decrease, perhaps reflecting the role that they play when conversion of the spiral arteries is completed and remodeling of the placental vasculature ensues. This reciprocal discourse is further reflected in the homing of both trophoblasts and dNK cells to the maternal-fetal interface. Although the trophoblast is intrinsically programmed to invade,<sup>60</sup> the invasive trophoblast is further directed and homed by chemokine signaling of the decidual NK cell (interleukin-8, interferon gamma-induced protein 10) via chemokine receptor expression (CXCR1, CXCR3) on the invasive trophoblast.<sup>56</sup> Likewise, the trophoblast, by expressing chemokine (CXCL12), signals chemokine receptor (CXCR4) expressing decidual NK cells for colocalization to the decidua.<sup>61</sup>

Recently, memorylike properties have been demonstrated in human peripheral blood NK cells, mainly in instances of

viral reinfection.<sup>62</sup> These observations are remarkable because NK cells are part of the innate immune system rather than the acquired immune system. In light of these findings, the role that dNK cells play in remodeling the placental bed may afford an explanation as to why first pregnancy is a risk factor for PE. We and our colleagues found that the dNK cells of parous women showed enhanced expression of certain cell receptors and enriched production of angiogenic factors and cytokines compared with dNK cells of nulliparous women.<sup>63,64</sup> Specifically, these Pregnancy Trained dNK (PTdNK) cells from parous women are primed to act with greater expression of the receptors NKG2C and LILRB1, which bind HLA-G and HLA-E expressed on EVT. These features are stored as epigenetic changes in the NK cells residing in the endometrium between pregnancies, where they remain “on call” to operate more robustly in subsequent pregnancies. PTdNK cells showed superior growth factor production and immune modulation, NK activation, interleukins, hormone regulation, and chemokine ligands and receptors and may act with greater efficiency to remodel the placental bed, resulting in enhanced placentation and hence lower risk of the development of PE.<sup>63,64</sup>

In the context of the above, it is most interesting that the ligands of fetal HLA-E and HLA-G activate via their attachment to receptors on maternal NK cells and production and expression of growth and angiogenic factors and others, which allow placentation and fetal development. During first pregnancy, these processes are less efficient, leading to higher rates of PE in primigravidae.

In a further demonstration of maternal-fetal crosstalk in immune response and balance between the trophoblasts and dNK cells, Moffett and Colucci<sup>65</sup> described coevolutionary development of HLA antigens on invasive trophoblasts (HLA-G, HLA-E, and HLA-C) and specific NK cell receptors (LILR, CD94/NKG2, KIR). Based on the finding that the likelihood of PE is associated with KIRA and KIRB receptors on NK cells that bind particular C1 and C2 classes of HLA-C ligands on

trophoblasts with differing binding affinities and inhibitory and activating properties,<sup>65,66</sup> the coevolutionary development of these NK receptor and trophoblast ligand pairs highlights the balance between maternal-fetal immune inhibition and activation in maintaining a healthy pregnancy.

### Maternal-Fetal Cell Signaling Via Extracellular Vesicle Delivery

In addition to the mechanisms described above, intracellular maternal-fetal crosstalk can also occur via a broad category of molecules termed extracellular vesicles (EVs) that include microvesicles, apoptotic bodies, and exosomes, which differ in their membrane origin<sup>67,68</sup> and are heterogeneous in particle size and cargo. The cargo consists of molecules that the EVs transport to cells, tissues, and organs, either in close proximity or in distant sites, including but not limited to proteins, phospholipids, mRNA, and miRNA. As a mode of intercellular communication, the ability of EVs to transfer molecules in membrane-bound vesicles, protected from degradation, affords a mechanism to regulate divergent cell processes, spanning normal physiology to disease pathogenesis and infection. As a method of maternal-fetal communication, the recipients of EVs, especially placental EVs entering the maternal blood circulation, include but are not limited to the maternal liver, endothelial cells, immune cells, and heart as potential targets.<sup>69</sup> In normal physiological pregnancy, a limited number of placental EVs are found whose release can be governed by oxygen tension and glucose concentration, and their numbers normally increase as gestation progresses.<sup>70–72</sup> These include EVs that are bioreactive, promoting endothelial tube formation,<sup>72</sup> modulating immune function, and promoting metabolic adaptations<sup>73</sup> and spiral artery remodeling and angiogenesis through stimulation of endothelial cells.<sup>74–77</sup> EVs do not function during pregnancy: exosomes carrying miRNAs have been shown to enhance implantation. Here, miRNAs carried within exosomes originating in endometrial epithelial cells (Hsa-miR-30d) and incorporated into the

trophoblast target genes (Hqb3, Hqa7, cdh5) relevant for implantation.<sup>68</sup> The field of EVs and their roles in human reproduction represent a burgeoning field of investigation, highlighting a new mechanism of maternal-fetal cell communication. Molecular signaling by EVs is beneficial in mediating maternal-fetal crosstalk and is engaged in normal placentation and pregnancy. Conversely, cargo carried by EVs has been shown to have a harmful effect on pregnancy, leading to complications, specifically PE. Burton et al<sup>78</sup> have proposed that the nonconverted spiral arteries of PE expel maternal blood into the intervillous space in a turbulent jet fashion with shear stress potential to damage villous structure and release of membrane-bound EVs because of their maladapted narrow structure.<sup>78</sup> This proposal of far-reaching implications would go hand in hand with the observation of increased EVs found in the maternal circulation in PE.<sup>79</sup> The EVs observed in increased numbers in PE include specific miRNAs with harmful potential to endothelial cell function and syncytial apoptotic bodies ferrying cell death signals. These observations have led to the proposal that the cargo of extracellular microvesicles originating from the syncytiotrophoblast circulating in maternal blood may prove useful as a biomarker for PE.<sup>80,81</sup>

Especially significant for maternal-fetal communication with relevance to PE are the findings of Rajakumar et al.<sup>82</sup> sFlt-1 is highly expressed in the syncytial knots of preeclamptic placentas.<sup>40</sup> Rajakumar was able to demonstrate that circulating syncytial aggregates of syncytial knots (from preeclamptic and normal placentas) contain both sFlt-1 protein and sFlt-1 transcriptionally active mRNA. These microparticles of placental origin that harbor sFlt-1 represent a method through which the antiangiogenic signature of PE enters the maternal circulation to target maternal tissues and organs.

### The Impact of the Fetus on Maternal Cardiac Remodeling

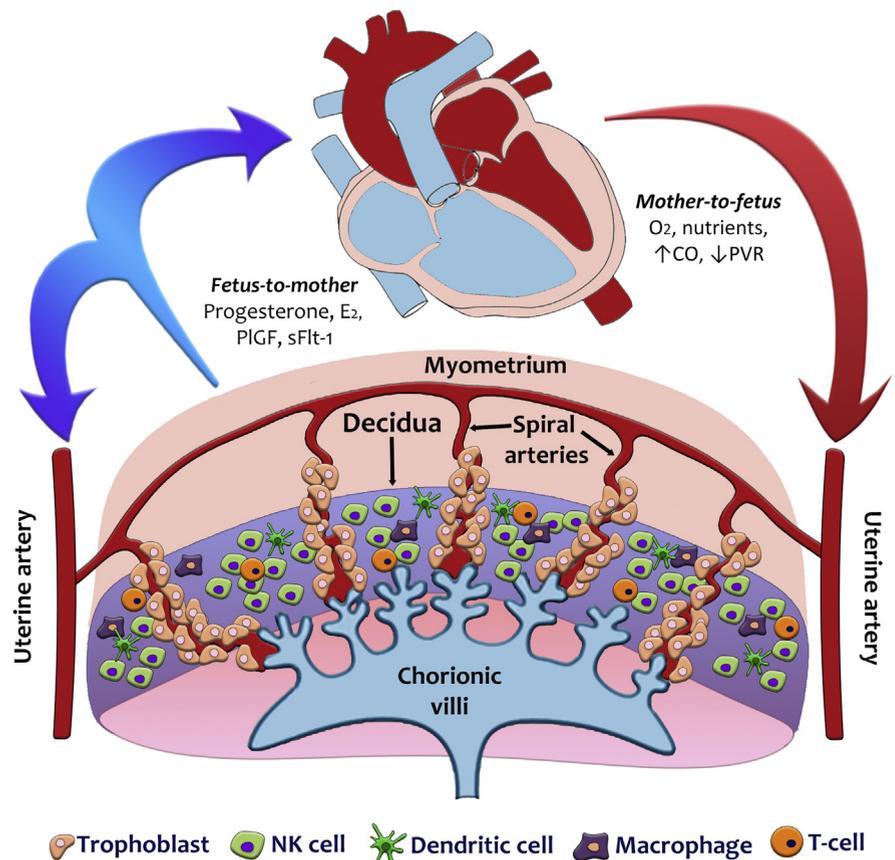
The effect of maternal cardiac function on the development of her fetus is clear:

without the maternal cardiovascular system to supply nutrient and gas exchange, there would be no pregnancy. Perhaps less clear is the effect of the fetus on maternal cardiac remodeling, as has been shown in animal models and in humans. Recently, researchers have demonstrated evidence of maternal cardiac hypertrophy driven by hormones associated with pregnancy, especially progesterone, during the first trimester of pregnancy, before the establishment of the functional placenta. Progesterone induces reduced peripheral vascular resistance (PVR), possibly initiating the increased volume overload and subsequent functional changes. The observed surge in progesterone activates calcineurin, which in turn initiates pathways, such as Akt and its downstream targets,<sup>83,84</sup> and induces cardiac hypertrophy.<sup>83</sup> Estrogens, produced first by the corpus luteum and subsequently chiefly by the syncytiotrophoblast, impact uterine artery vasodilation and other cellular processes in remodeling of the uterine vasculature<sup>85</sup> to increase uteroplacental blood flow and reduce PVR.<sup>53,54</sup> These changes and other adaptations in the maternal renal and pulmonary systems work to increase blood volume and CO.<sup>53</sup>

A recent study in a mouse model showed that PIGF is associated with systemic maternal cardiovascular adaptations to pregnancy.<sup>86</sup> The investigators in the Croy laboratory employed PIGF knockout mice (PIGF negative) and healthy controls to compare virgin, pregnant, and postpartum measures of cardiac and renal size and function. The PIGF-negative mice were found to have higher systolic blood pressure, lower CO, and greater left ventricular mass (LVM), whereas only the healthy control mice showed the expected gestational gain in LVM. By 16 days' gestation (close to term), PIGF knockout mice had hypertrophic kidneys and glomerular pathology.<sup>86</sup>

In humans, Benschop et al<sup>87</sup> measured PIGF at midpregnancy in 5475 singleton pregnancies and followed up maternal blood pressure and cardiac structure and Doppler parameters 6 years after delivery and blood pressure 9 years after delivery. The investigation

**FIGURE**  
**The maternal cardiovascular-placental-fetal array: the integrated model of hemodynamic provision of healthy pregnancy for mother and offspring**



The integrated maternal-placental-fetal milieu is composed of maternal and fetal tissues meeting to mediate the needs of the fetus and ensure maternal survival and adaptation to the demands of pregnancy. This intricate multidimensional array of tissues and resident and circulating factors involve the developing fetus, the growing placenta, the evolving decidua, and the dynamic maternal cardiovascular and other systems. Extravillous trophoblasts mediate remodeling of the maternal spiral arteries to create a conduit of low resistance and high capacitance. Decidual immune cells, dNK being the most prevalent, play an essential role in the appropriate development of the placental bed. Changes to maternal hemodynamics provide increased CO and decreased PVR to meet nutrient and gas exchange demands and other factors through the remodeled uterine arteries. The fetus and placenta supply estrogens, progesterone, and PIGF and its receptor (sFlt-1) to maintain the angiogenic-antiangiogenic balance necessary to mediate adaptational changes to the maternal cardiovascular and other systems. Disruption in any component or nexus among the constituent parts of the array or the commensality may lead to the multifaceted syndrome of preeclampsia.

CO, cardiac output; dNK, decidual natural killer cell; E<sub>2</sub>, estrogen; NK, natural killer cell; PIGF, placental-derived growth factor; PVR, peripheral vascular resistance; sFlt-1, soluble fms-like tyrosine kinase-1.

Yagel. Preeclampsia: a syndrome of the maternal-placental-fetal array. *Am J Obstet Gynecol* 2022.

revealed that quartiles of PIGF level significantly correlated with persistent changes in cardiac remodeling. The lowest PIGF quartile group had significantly higher aortic root diameter, left atrial diameter, LVM, and systolic blood

pressure at 6 years after delivery than the highest quartile. This association was also maintained among women who did not develop pregnancy complications.<sup>87</sup>

All of the above examples testify to the role of the fetus through placental

expression of PIGF, estrogen, and progesterone into the maternal circulation to remodel the uterine and broader maternal milieu to optimize its environment and promote maternal cardiac adaptation and maternal survival to maintain healthy symbiosis (Figure).

### When Things Go Wrong

Many maternal and fetal systems and conditions may be implicated in the development of PE. In many, or even most instances, the proportional contribution of maternal and placental factors in the clinical advent of PE may not be evident. Some are physiological but strain the maternal capability to adapt, such as twins and higher-order multiples, prolonged pregnancy, or fetal macrosomia. Others may hint at an underlying or preexisting difficulty in facing the demands of pregnancy, such as advanced maternal age, obesity, chronic hypertension, diabetes, or other systemic diseases. Placental etiologies of PE include but are not limited to the examples given above: hydatidiform mole, abdominal pregnancy, trisomy 13, and sFlt-1 and PIGF imbalances. Smoking in pregnancy inadvertently provides a “proof of concept” for the role of angiogenic-antiangiogenic factors imbalance in PE.

First pregnancy differs from the other complications described above in that it represents the integration of the maternal-placental-fetal array and involvement of either or both: the maternal side or the fetal-placental side in the development of PE. Whether the maternal heart is inadequately prepared for or unable to adapt to the demands of pregnancy or the maternal-fetal interface is dysfunctional will come into play in first pregnancy in incipient PE (Figure). Contrasting first and subsequent pregnancies reveals the epigenetic memory acquired by the mother, not only at the maternal-fetal interface but also in the maternal cardiovascular system and elsewhere. These myriad adaptations are brought about through crosstalk among many cell types.

### Clinical Significance

Recognition of the interconnected roles played by the maternal and fetal-

placental systems in healthy pregnancies and in the development of PE has important implications for directing future avenues of research and planning screening, diagnosis, treatment, and follow-up approaches and modalities. For example, screening might include not only traditional risk factors for PE but also maternal hemodynamic measures, such as CO and PVR, and the fetal-placental factors PIGF and sFlt-1.<sup>88–90</sup> The integration of maternal and fetal-placental parameters in the success of PE risk prediction,<sup>88–90</sup> reinforces the interdependence of all the maternal-placental-fetal array components in the development of the disease.

In the realm of possible future preventative and therapeutic interventions, there may be a benefit to offering aspirin to all primigravidae and at-risk multigravidae and to prescribing antihypertensive medication where indicated. Pravastatin has shown some promise<sup>91</sup> in preventative and therapeutic studies and may prove to be of benefit pending further study. However, sildenafil, which seemed effective in improving PE phenotypes in preclinical studies and early human trials, was not found to improve outcomes in IUGR, with or without PE.<sup>92</sup> Most recently, researchers showed<sup>93</sup> that in a baboon model of PE, short interfering RNAs (siRNAs) selectively silenced the 3 sFlt1 mRNA isoforms primarily responsible for placental overexpression of sFlt1.<sup>93</sup> Pending further investigations, this may open avenues to the development of an RNAi-based treatment of PE.

In the absence of contraindications, we should encourage all our patients to take moderate daily exercise. During the postpartum period, follow-up could include maternal cardiac assessment so that therapeutic and preventative measures can be started early, with an eye to improving women’s heart health and metabolic status in the reproductive years and beyond.

### Summary and Conclusions

The maternal-fetal interface has been characterized in many ways: as a scene of conflict and competition, danger, immune suppression, commensalism, or mutuality or “an intricate admixture of

cooperation and conflict.”<sup>94</sup> Common to all these representations is the understanding that successful pregnancy and parturition depend on balancing the provision of resources to maintain the mother and fetus, to ensure optimal survival of both. The adaptations necessary to preserve the mother and her offspring have been shown to impact the health of both, far beyond the postpartum period.

Numerous combinations of possible disturbances, evinced as either fetal or maternal maladaptation or maldevelopment from implantation to parturition, can lead to the development of PE. The commonality is a failure of working together. Characterization of PE as solely a failure of placentation is an oversimplification of the maternal-fetal-placental array, whereas portrayal of this complex syndrome as a failure of maternal cardiovascular adaptation ignores reality.

Unmet demand created in the case of a very large fetus or multiple pregnancy can lead to the syndrome of PE, whereas at the other end of the spectrum, poor placental development and deficient maternal vascular remodeling will lead to the appearance of early-onset PE. The importance of understanding this duality is in designing preventative programs and treatment modalities. ■

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