

Preeclampsia - What is to blame? The placenta, maternal cardiovascular system or both?

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Author contributions: All authors contributed equally to the preparation of this manuscript; The preparation of the manuscript, tables and figures was done by Vinayagam D and Leslie K; Khalil A provided further input and guidance to the preparation of the manuscript; Thilaganathan B designed the outline of the manuscript and coordinated the writing and revision of the manuscript prior to final submission.

Conflict-of-interest statement: The authors report no conflict of interest with regards to the contents of this minireview.

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Received: May 29, 2015

Peer-review started: June 3, 2015

First decision: August 4, 2015

Revised: September 3, 2015

Accepted: October 1, 2015

Article in press: October 8, 2015

Published online: November 10, 2015

Abstract

Preeclampsia (PE) is a pregnancy-specific syndrome,

complicating 2%-8% of pregnancies. PE is a major cause of maternal mortality throughout the world with 60000 maternal deaths attributed to hypertensive disorders of pregnancy. PE also results in fetal morbidity due to prematurity and fetal growth restriction. The precise aetiology of PE remains an enigma with multiple theories including a combination of environmental, immunological and genetic factors. The conventional and leading hypotheses for the initial insult in PE is inadequate trophoblast invasion which is thought to result in incomplete remodelling of uterine spiral arteries leading to placental ischaemia, hypoxia and thus oxidative stress. The significant heterogeneity observed in pre-eclampsia cannot be solely explained by the placental model alone. Herein we critically evaluate the clinical (risk factors, placental blood flow and biomarkers) and pathological (genetic, molecular, histological) correlates for PE. Furthermore, we discuss the role played by the (dysfunctional) maternal cardiovascular system in the aetiology of PE. We review the evidence that demonstrates a role for both the placenta and the cardiovascular system in early- and late-onset PE and highlight some of the key differences between these two distinct disease entities.

Key words: Preeclampsia; Placenta; Maternal cardiac function; Cardiovascular; Aetiology

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Core tip: The conventional paradigm is that preeclampsia (PE) is solely due to placental dysfunction. However not all cases of placental dysfunction result in the syndrome of PE. Equally, placental dysfunction - as evidenced by impaired uterine artery Doppler indices, low birth weight and abnormal histology - is not always present in PE. Therefore, the heterogeneity observed in PE cannot be solely explained by placental dysfunction. There is now strong evidence supporting the role of the maternal cardiovascular system in PE. In this minireview, we evaluate the evidence supporting a dual

aetiology of PE, involving both the placenta and the maternal cardiovascular system.

Vinayagam D, Leslie K, Khalil A, Thilaganathan B. Preeclampsia - What is to blame? The placenta, maternal cardiovascular system or both? *World J Obstet Gynecol* 2015; 4(4): 77-85 Available from: URL: <http://www.wjgnet.com/2218-6220/full/v4/i4/77.htm> DOI: <http://dx.doi.org/10.5317/wjog.v4.i4.77>

Preeclampsia (PE) is a pregnancy-specific syndrome, complicating 2%-8% of pregnancies^[1]. PE is a major cause of maternal mortality throughout the world. Over half a million women die during or after childbirth every year, and it is estimated that 60000 of these maternal deaths worldwide are attributable to hypertensive disorders of pregnancy^[1,2]. In the United Kingdom, PE/eclampsia was the fourth leading cause of direct maternal deaths between 2009-2011^[3]. In the triennium 2009-2011, 10 deaths in the United Kingdom were attributable to PE, giving a mortality rate of 0.42 per 100000^[3], considerably lower than the mortality figures worldwide. The management of hypertension in conjunction with the use of national and local guidelines are credited with the reduction in morbidity and mortality observed in the developed world.

PE can also result in morbidity to the fetus, including fetal growth restriction, placental abruption and stillbirth. In addition, there is a considerable financial burden as a result of increased antenatal surveillance, investigations and hospital admissions along with an increased risk of operative intervention and peripartum monitoring. Following delivery, prematurity and the associated care costs, both in the short and long term, further contribute to the financial burdens associated with PE. At present, the only recognised cure for PE is delivery of the placenta. As a result, PE is the leading cause for iatrogenic preterm birth^[4], which is associated with greater neonatal morbidity than delivery at term.

The importance and magnitude of PE on maternal health and neonatal morbidity is well accepted. Despite this being such an important disease, our knowledge of its aetiology is still incomplete. Forming a better understanding will aid us in making an accurate diagnosis, perform better screening and improve our ability to triage disease severity, offer targeted preventative and therapeutic measures and formulate appropriate short- and long-term postpartum management plans.

PE is a heterogenous disease exhibiting a diverse range of both fetal and maternal disease presentations. At present, we aim to identify and diagnose PE based on organ dysfunction both in the mother and in the fetus. The timing of onset of PE is as diverse as its organ involvement and can occur from the late second

trimester, through to term and can even present in the postnatal period.

Although often classified as mild, moderate and severe, a newer and perhaps more relevant method of clinical classification would be based upon timing of onset. Early onset PE is thus defined as PE occurring prior to and requiring delivery before 34 wk gestation and late onset PE developing and requiring delivery after this gestational age. There are distinct differences between these two types of PE, in terms of their pathophysiological basis, effects on mother and fetus as well as their long term implications. Late PE accounts for approximately 75% of cases, whilst the remaining 25% are early onset PE^[5,6].

Ten percent to fifteen percent of pregnant women will develop some form of hypertensive disease that requires further assessment and follow up. Currently, United Kingdom guidelines on screening for identification of those at high risk of developing PE is performed in the first trimester and is based on maternal demographics and obstetric/medical risk factors^[7]. The NICE model recommends commencing preventative measures (*e.g.*, low dose aspirin) and formulation of an appropriate antenatal management plan in high risk women. However the NICE model categorises more than 60% of women as high risk, but predicts less than 30% of those destined to develop PE^[8].

PATHOPHYSIOLOGY - THE ROLE OF THE PLACENTA

The precise pathophysiological basis of PE remains an enigma with multiple, plausible aetiological theories involving a combination of environmental, immunological and genetic factors.

The conventional, leading hypotheses, which has stood the test of time, for the initial pathophysiological insult in PE is inadequate trophoblast invasion and thus incomplete remodelling of uterine spiral arteries. This leads to placental ischaemia, hypoxia and thus oxidative stress^[9,10]. The placental hypoxaemia sets off a biochemical cascade of angiogenic/antiangiogenic factors which leads to subsequent endothelial cell dysfunction with its observed maternal signs and symptoms of PE. Whilst placental hypoxaemia and the subsequent oxidative stress is a significant contributing factor, we acknowledge that a definitive link between PE and placental hypoxia is not confirmed and further research is required.

However not every pregnancy characterised by abnormal placentation results in PE - fetal growth restriction is one such example in where there is suboptimal placentation with detrimental fetal effects but minimal maternal effects. Others will go on to develop the syndrome of PE which is characterised by hypertension and proteinuria and multiple organ involvement.

One possible reason for the development of PE is that there is a concurrent maladaptation of the maternal cardiovascular system along with abnormal placentation, and this predisposes an individual to developing PE. This would also explain why not all women with poor placentation with its sequelae (such as fetal growth restriction) develop PE; their cardiovascular system adapts appropriately to the ongoing pregnancy and associated haemodynamic changes.

IS PE SOLELY DUE TO PLACENTAL DYSFUNCTION?

The development of PE does not necessarily require a uterus or indeed a fetus, as the condition has been reported in abdominal^[11] and molar pregnancies^[12] respectively. However, a placenta is essential for the disease to occur, and is therefore central in the pathogenesis. Furthermore, it is well documented that the cure for PE is delivery of the placenta, further supporting the crucial role played by the placenta in the development of PE.

The paradigm is that the "placenta causes PE". Whilst we firmly believe that the placenta is a pre-requisite and therefore crucial to the development of PE, herein we critically review the evidence that the placenta is indeed the only organ of causality in PE.

CLINICAL EVIDENCE FOR THE AETIOLOGY OF PE

The majority of the evidence for the placental origin hypothesis of PE is based on the clinical features of the disorder. Broadly speaking, they constitute clinical risk factors, placental blood flow evaluation, fetal growth restriction and placental biomarkers.

Risk factors for PE

Both PE and fetal growth restriction (FGR) are thought to share clinical risk factors such as increased maternal age, ethnic origin, increased body mass index (BMI), diabetes and other co-morbidities. These associations are conventionally advocated by national guidelines^[7,13] as a method to screen routine populations for their risk of developing PE. However, analysis of data from 40000 pregnancies collected for the World Health Organization Antenatal care trial^[14] showed that surprisingly, PE and fetal growth restriction had different risk factor profiles. Mothers with PE compared with those with fetal growth restriction were more likely to have a history of diabetes, renal or cardiac disease, chronic hypertension, previous PE, increased BMI and extremes of maternal age. Conversely, fetal growth restriction was associated with higher risk of low birth weight in previous pregnancies, but not with previous PE. The same analysis demonstrated that PE

and gestational hypertension shared many risk factors - conventionally associated with cardiovascular disease in the non-pregnant population. These data infer that the aetiology of PE is not necessarily as a result of placental dysfunction.

Placental blood flow

The pathological hallmark of placental insufficiency is incomplete spiral artery remodelling, and this is seen in both fetal growth restriction as well as in some, but not all cases of PE. Uterine artery Doppler waveform studies have been shown to aid in the prediction of pregnancies that will be complicated by fetal growth restriction or PE^[8,15-17]. Increased uterine artery resistance indices are related to incomplete trophoblast invasion of maternal spiral arteries, which results in a high-resistance placental circulation and therefore an underperfused fetoplacental unit. This placental hypoperfusion is a feature seen in both PE and fetal growth restriction.

The association with increased uterine artery Doppler resistance indices and a higher propensity to develop PE and FGR is widely reported and used in current clinical practice in the management of high risk pregnancies. Velauthar *et al.*^[17] carried out a meta-analysis of over 55000 patients looking at the predictive value of performing uterine artery Doppler measurements in the first trimester. The authors reported a sensitivity and specificity of 47.8% and 92.1% respectively for the detection of early onset PE. The sensitivities and specificities for detection of late onset PE were 21.5% and 90.3%; for PE at any gestation these were 26.4% and 93.4%. Although first trimester uterine artery Doppler screening is a highly specific means of screening for early PE, it is less so for late PE.

Verlohren *et al.*^[18] have corroborated this finding in their published data of second trimester uterine artery Doppler screening. The investigators looked at outcomes in over 27000 cases that had uterine artery measurements in the second trimester. They reported that the prevalence of resistance indices above the 90th centile were present in 63.6% of early PE, 15.5% of late PE and 8.8% in the control group. This significant finding shows that increased uterine artery Doppler indices, are a poor predictor of late onset PE.

It is well recognised that increased uterine artery dopplers are an index for inadequate placentation, and thereby a surrogate marker for increased risk of PE and FGR. Data from these large-scale, high quality studies indicate that inadequate placentation is a key feature of early onset PE and FGR. The reduced prevalence of increased uterine artery indices observed in late-onset PE lends further support to the argument that the heterogeneity observed in PE, is due to early onset PE being related to a dysfunctional placenta, whilst late onset PE may not be associated with placental insufficiency.

Fetal growth

The fetal effects of a dysfunctional placenta include fetal growth restriction, and this is seen in many cases of early-onset PE, but less so in cases of late PE. The majority of neonates in late PE are of normal size^[18]. This observation is consistent with the notion that whilst early PE due to placental insufficiency is also closely correlated to FGR, there is an additional aetiological factor to placental insufficiency in late onset PE.

Verlohren *et al*^[18] reported on the distribution of small-for-gestational-age (SGA) neonates in their large cohort. They found the incidence of SGA to be 66.2% in the early PE group, 16.7% in the late PE group and 10.8% in the control group.

The distribution of large-for-gestational age neonates did not observe a similar pattern; the prevalence being greatest in the late PE group as compared to all other groups. Interestingly, both SGA and large-for-gestational-age (LGA) births were more prevalent in the late PE group, demonstrating a bimodal skewed birth weight distribution in late PE. Whilst the association between PE and LGA babies has been observed previously, the bimodal distribution is certainly a novel finding.

The increased incidence of SGA births in early-onset PE, associated with increased uterine artery impedances, is an expected finding given the underlying placental insufficiency, unlike the reported increased prevalence of both SGA and LGA in late-onset PE. The authors postulate that this finding implies that whilst the SGA form of late-onset PE is due to placental insufficiency, the LGA form (with its associated normal uterine artery impedance measurements) is secondary to the inability of the maternal heart to meet the demands of the (oversized) placenta. The subsequent placental hypoperfusion as a result of the inadequate pump action, leads to placental hypoxia and the biochemical cascade that leads to endothelial cell dysfunction observed in PE.

Placental biomarkers

The oxidative stress in the placenta leads to an imbalance in angiogenic and antiangiogenic factors. An imbalance in these factors can adversely affect vascular homeostasis, and therefore contribute to the array of symptoms displayed in PE. The angiogenic factors that are believed to play a role include vascular endothelial growth factor (VEGF) and placental growth factor (PIGF)^[10,19,20], the latter being used as a potential diagnostic biomarker for PE^[19,20]. PIGF is produced by trophoblasts and interacts with cell surface receptors such as Flt-1. The soluble form of this, soluble fms-like tyrosine kinase-1 (sFlt-1) is an antiangiogenic factor which has also emerged as a key factor and potential biomarker in PE. sFlt-1 has been shown to block PIGF and therefore play a causative role in the development of PE^[10,21]. Maynard *et al*^[10] demonstrated a rise in arterial pressures and proteinuria with exogenous

administration of sFlt-1. Furthermore, uteroplacental ischaemia has been shown to increase sFlt-1 levels in experimental models, as well as a decrease in VEGF/PIGF^[22,23].

Another biological factor that has been studied and may have a role in PE is Heme Oxygenase-1 (HO-1). HO-1 and its metabolites carbon monoxide (CO) and bilirubin exert protective effects against oxidative stimuli, and *in vitro* studies have reported that HO-1 downregulates sFlt-1^[24]. HO-1 has been shown to inhibit sFlt-1 release^[24,25] and it is possible that a loss of HO-1 plays a part in the pathophysiology of PE. There are no published studies looking at the differences in the expression of HO-1 in early-onset vs late-onset PE.

Poon *et al*^[26] conducted a first trimester screening study using uterine artery Doppler indices, serum pregnancy associated plasma protein A (PAPP-A) and placental growth factor measurements in a large cohort of over 57000 cases. They found that in the pre-term SGA group, serum PAPP-A and PIGF were reduced, indicating an underlying pathology of impaired placentation. The authors reported that for a false-positive rate of 5%, the detection of early-onset PE (< 34 wk gestation) using PIGF was 59.3%, however in all cases of PE below 42 wk gestation, the detection rate was significantly lower at 29.1% - this figure included all of the early-onset along with late-onset cases of PE. The evidence suggests that placental biomarkers have a good performance for screening for early-onset PE, but a poor performance when screening for late-onset PE.

The biomarkers discussed above have been used in clinical trials as a potential screening tool for the detection of PE. Elevated sFlt-1/PIGF ratios have been observed in early-onset PE^[19,20]. Chappell *et al*^[19] published data from a multicentre trial using a PIGF assay (Triage, Alere, California, United States). PIGF concentrations below the 5th centile had a sensitivity of 96% and a negative predictive value of 98% for PE requiring delivery within the next fourteen days, in gestational ages below 35 wk. Beyond 35 wk, the test was not as good at excluding PE. This further strengthens the argument for a role of placental insufficiency in early cases of PE, with a weaker association between PIGF and late-onset PE.

PATHOLOGICAL EVIDENCE FOR THE AETIOLOGY OF PE

Many scientific evaluations of the pathology associated with PE have been used to justify the placental origins hypothesis of PE. These may be genetic, molecular or histological in nature.

Genetic

There is an unquestionable link between the development of PE and subsequent cardiovascular disease. Despite the incomplete understanding of the aetiology

of PE, familial clustering has been observed^[27,28] and reported in PE and therefore supports a genetic link. Many susceptibility genes for PE have been reported in the literature - the function of the majority of these loci remain unknown. The very few PE genetic loci with known associations have previously been implicated in adult cardiovascular disease. Despite further work in this field being required, it does seem entirely plausible that due to the similarities between PE and cardiovascular disease with clinical risk factors and postpartum cardiovascular legacy, there is indeed a shared genetic link between PE and cardiovascular disease.

Molecular

Recently published data on the molecular biology, also provide insightful evidence. Yung *et al.*^[29] investigated whether there was molecular evidence of a difference in placental stress response between cases of early and late PE. Investigating multiple stress-signalling pathways, the investigators demonstrated that activation of stress-signalling pathways was negatively correlated with gestational age, with a clear inflection for placentae beyond 34 wk gestation. Activation of these pathways was significantly higher in early PE than in late PE or controls. The authors reported no difference between placentas in late PE and normotensive controls. It appears that this group of investigators have provided the first molecular evidence of placental stress response in early PE with a lack of such a response in cases of late PE. This supports a placental cause for early PE, but further suggests that placental dysfunction may not necessarily be implicated in late onset PE.

Histological

Histopathological studies of placentae have also reported a difference between early and late PE^[30-32]. Whilst in the majority of cases of PE the placentae are histologically normal, it is also found that histopathological lesions are mainly seen in preterm PE^[22]. Pathak *et al.*^[33] carried out a blinded analysis and reported that placental hypoperfusion in the form of massive perivillous fibrin deposition was much more frequent in those with PET (OR 20.2) and SGA (8.9). However we acknowledge that this was in a small sample of pathological cases. Ogge *et al.*^[32] demonstrated the prevalence of placental hypoperfusion lesions were greatest in cases of early-onset PE (58%), as compared to 33% in late onset PE and 16% in term controls.

An interesting, recent study investigated placental perfusion using magnetic resonance imaging in early and late PE^[34]. The study reports that women with early PE did indeed show smaller placental perfusion fractions when compared to controls. Interestingly, women with late onset PE had a larger placental perfusion fraction when compared to matched controls for gestational age. The increased placental perfusion

fraction seen in late PE further supports the argument that late-onset PE is associated with larger placentae and babies, and therefore is unlikely to be due to placental insufficiency.

PATHOPHYSIOLOGY - THE ROLE OF THE CARDIOVASCULAR SYSTEM

The maternal cardiovascular system undergoes a series of changes in pregnancy, all of which have a role in ensuring adequate uterine perfusion, oxygen delivery and provision of nutrients to meet the demands of the growing fetus. These adaptations enable the pregnancy and the growth of the fetus to continue unimpaired. They include a rise in cardiac output, heart rate and plasma volume and a concomitant fall in total vascular resistance (TVR).

Despite a significant volume of literature regarding placental dysfunction in PE, data regarding the cardiac changes associated with PE are more scant, and also more controversial. The conventional belief was that early-onset PE is associated with reduced cardiac output and increased total vascular resistance, with maternal cardiac function succumbing early in the disease process. With regard to late-onset PE, the original data implied that this was a condition of raised cardiac output and reduced total vascular resistance, however this model has not been reported consistently^[35,36]. The discrepancies reported in the cardiovascular profiles in women who present with PE can be attributed to certain confounding factors - antihypertensive medication, co-morbidities, different gestational ages and stages of labour.

Another significant reason for the discrepancies reported in the literature with regards to haemodynamics in PE is the use of cardiac output instead of the corrected index for body surface area, cardiac index. Cardiac index (CI) represents the cardiac output per square meter of body surface area. We believe that using this corrected index is superior to using cardiac output, which does not factor in height or weight of the subject. As human beings come in different shapes and sizes, with varied metabolic demands, we feel that comparison of cardiac output without correcting for body surface area is both inadequate and inaccurate.

Prior to the onset of symptoms of early-onset PE, there is a shift towards a reduced cardiac index in conjunction with a raised total vascular resistance, increased mean arterial pressure, contracted intravascular volume and reduced venous reserve capacity^[37-42]. These findings suggest that the high resistance/low volume haemodynamic profile observed in women destined to develop early-onset PE is observed in the latent phase of the disease at mid-gestation^[39,40].

In a study by Melchiorre *et al.*^[39] women who subsequently developed late-onset PE presented with raised total vascular resistance, but importantly, there was no difference in cardiac index between late-onset

PE and control groups. Whilst these findings have not been reported consistently in the literature, it is worth noting that in studies that did not corroborate the findings observed by Melchiorre *et al.*^[41], corrected cardiac indices were not employed.

In preeclamptics medicated with anti-hypertensives, the CI normalises and is comparable to CI in normotensive controls. The observed reduction in arterial compliance, has also been shown to be corrected following antihypertensive treatment in patients with PE^[42].

Although some of the initial work into cardiac changes in PE showed conflicting results, more recent work has demonstrated a more consistent collection of findings. This is in part due to improved and newer techniques such as colour tissue Doppler and 2-dimensional speckle tracking derived strain and strain rate imaging, which are able to detect early and subtle changes in myocardial function in an objective manner, when used in conjunction with validated diagnostic algorithms.

Prior to the onset of clinical symptoms in women who develop early onset PE, there is an abnormal remodelling of the left ventricle which consists of concentric remodelling and hypertrophy^[39,41]. Moreover in this group of women, there is evidence of mild diastolic dysfunction as well as impaired myocardial relaxation^[39,41]. This impaired diastolic function is thought to be associated with the increased cardiac afterload (increased TVR) and abnormal left ventricular remodelling^[39,41]. The abnormal pattern of remodelling observed in PE is similar to that observed in non-pregnant individuals with essential hypertension and is consistent with an impairment that is afterload-induced^[39,41,43].

Studies assessing early myocardial changes, have reported that mild-moderate isolated left ventricular diastolic dysfunction is seen in approximately half of women with early onset PE^[39,41,43] with one in five women having biventricular systolic dysfunction with associated left ventricular hypertrophy^[41,43]. Melchiorre *et al.*^[39,41] have also demonstrated impairment in myocardial contractility in early onset PE using colour tissue Doppler and 2-D speckle tracking. Left atrial remodelling in PE has also been reported. These findings suggest that the pregnant heart in PE is working at its maximum potential capacity, and any additional stress could result in a deterioration of cardiovascular function.

Other authors have suggested raised intra-abdominal pressure (IAP) as a major aetiological factor to the development of PE^[44,45]. They hypothesize that women with raised IAP will have compromised venous return to the heart, which will result in decreased blood flow in the vascular beds of the placenta, uterus, kidneys and liver. The result of this impaired blood flow and venous congestion would include placental ischaemia, oedema of the lower extremities, glomerulopathy associated with hypertension

and proteinuria and hepatic dysfunction^[44,46]. This hypothesis is in concordance with the cardiovascular origin of PE proposed in this review. The myocardial dysfunction of PE noted in many studies will also compound the compromised venous return to the heart. These two theories are therefore not mutually exclusive.

WHAT IS THE CARDIAC LEGACY OF HAVING PE?

Although we have classically believed that treatment of PE is by delivery of the placenta in order to avoid impending maternal harm, the subtle, subclinical cardiac changes associated with a diagnosis of PE are not cured by birth of the infant or delivery of the placenta. Melchiorre *et al.*^[47] showed that at 1 year postpartum 56% of women with early onset PE had asymptomatic left ventricular dysfunction compared to 14% of women with late onset PE and 8% of healthy controls. The same authors also reported a 40% incidence of essential hypertension at 2 years post-delivery.

Indeed a diagnosis of PE is considered a risk factor for long term cardiovascular disease^[48,49]. Following a diagnosis of PE, in particular early onset PE, it therefore seems prudent that these patients are adequately risk assessed in the years following pregnancy, in order to address and mitigate future cardiovascular risks.

CONCLUSION

Herein we argue that in order for PE to manifest in an expectant mother, there is an element of both a dysfunctional placenta as well as an abnormal cardiac response. Figure 1 depicts the common and specific key components of impaired placentation and cardiovascular dysfunction. We cannot ignore the role of the maternal cardiovascular system in the development of PE, and thus PE must be recognised and managed, both in the acute and in the long term phases, as a cardiovascular-placental syndrome.

PE is a heterogenous disorder. There is an abundance of evidence supporting the role of the placenta in PE. The evidence indicates that placental dysfunction is prevalent in early-onset PE, however this is not as clear in cases of late-onset PE, as evidenced by uterine artery Doppler indices, birthweight distribution, placental biomarkers, histological and pathological studies. Table 1 summarises the main differences in placental and cardiovascular parameters observed in early-onset vs late-onset pre-eclampsia

The majority of PE is late-onset, and has classically been described as "maternal" or "heterogenous" PE. By and large, maternal PE remains unexplained. Several theories involving an exaggerated maternal systemic inflammatory response and increased systemic levels of oxidative stress have been published in the past^[50].

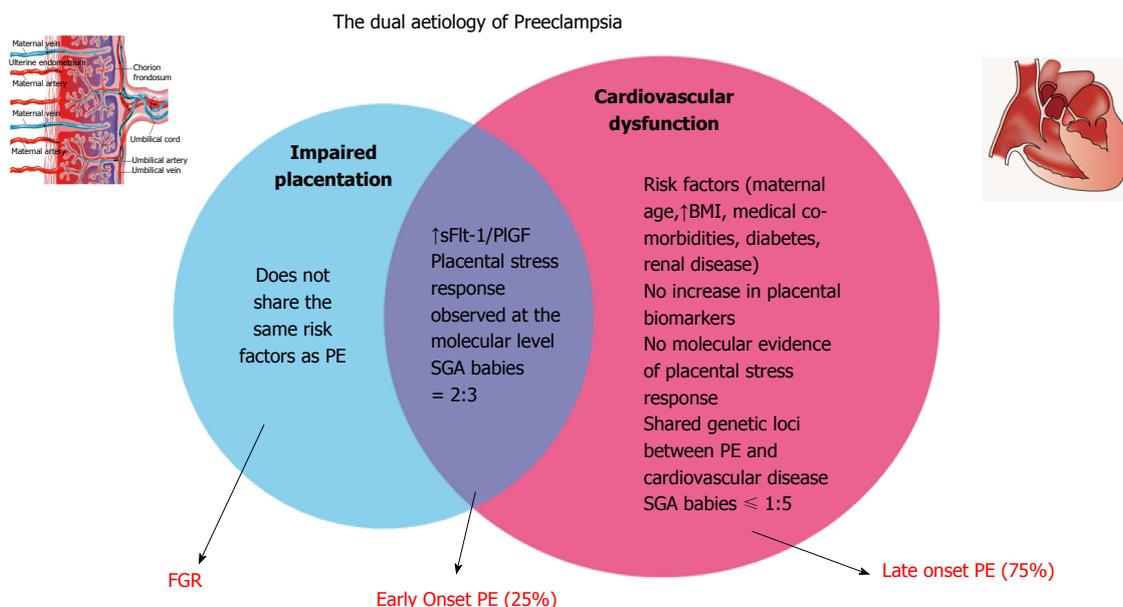


Figure 1 Illustration of the key components, both specific and common to impaired placentation and cardiovascular dysfunction and their presence in fetal growth restriction, early-onset and late-onset preeclampsia. FGR: Fetal growth restriction; PE: Preeclampsia; PlGF: Placental growth factor; sFlt-1: Soluble fms-like tyrosine kinase-1; SGA: Small-for-gestational-age; BMI: Body mass index.

Table 1 A summary of the key differences observed in placental and cardiovascular parameters in early-onset vs late-onset preeclampsia

	Early onset PE	Late onset PE
Fetal growth restriction	↑↑↑	↑
Hormones - PlGF	↓	↔
Hormones - sFlt-1	↑	↔
Hormones - PAPP-A	↓	↔
Uterine artery Doppler resistance	↑↑↑	↑/↔
Molecular stress response	↑	↔
Histological evidence of hypoperfusion	↑↑	↑/↔
Haemodynamics - Cardiac index	↓	↔
Haemodynamics - TVR index	↑↑	↑
Left Ventricular geometry - concentric remodelling	↑↑	↑↑
Left Ventricular geometry - concentric hypertrophy	↑	↓
Chamber diastolic function	↓↓	↓
Chamber systolic function	↓	↔

PE: Preeclampsia; PlGF: Placental growth factor; sFlt-1: Soluble fms-like tyrosine kinase-1; PAPP-A: Pregnancy associated plasma protein A; TVR: Total vascular resistance.

Whilst this is supported by the observed increase in PE in women with certain pro-inflammatory systemic conditions (autoimmune disease, renal disease, etc.)^[51], another, and we believe stronger, argument can be made for the role of the maternal cardiovascular system in the development of PE.

PE is a complex disorder which is no doubt closely related to placental insufficiency. However we strongly believe that the placenta is not the only culprit; the inability of the maternal heart to adapt to placental dysfunction also forms a significant, however as yet incompletely understood, part of the enigma.

We propose that whilst intrinsic placental dysfunction

and the mal-adaptation of the maternal cardiovascular system leads to early-onset PE, late PE is associated with an acquired placental dysfunction as a result of the maternal heart not being able to meet the demands of the placenta. Both the intrinsic and acquired placental dysfunction results in placental hypoxia which sets off a cascade of events result in the multisystem disorder of PE. In view of the evidence, we propose a paradigm shift of our current understanding of pre-eclampsia, as a disease entity not solely due to the placenta, but as a cardiovascular-placental syndrome. In answer to our original question which forms the title of this review, the answer is both - as an element of dysfunction in both the cardiovascular system and the placenta are required in order for PE to develop.

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P- Reviewer: Wong RJ, Xu XH S- Editor: Ji FF L- Editor: A
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