**Scientific Impact Paper (New)**

**Peer review draft – October 2024**

**Pre-eclampsia and maternal cardiovascular function: Insights into pathophysiology and management**

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**Plain-language summary**

Pre-eclampsia is a pregnancy complication that involves the development of high blood pressure in pregnancy and other features such as protein in urine, kidney or liver problems, or poorer growth for the baby. It typically presents after 20 weeks of pregnancy, either mid-pregnancy or more commonly, later in pregnancy, after 34 weeks of pregnancy.

Different blood pressure medications can be used to treat this condition, but not all women respond in the same way, probably due to differences in the function of their heart and blood vessels.

Over the last two decades, technological developments have meant it is now possible to measure these important aspects of maternal cardiovascular health using simple non-invasive tests. Studies in these areas have shown two distinct patterns of abnormal measurements of blood circulation and cardiac health in the pregnant woman that can occur with pre-eclampsia, with some changes detectable before the condition becomes obvious. For example, we understand that some pregnant women have less volume of blood being pumped out of their hearts per minute, and these pregnant women are more at risk of being affected by pre-eclampsia earlier in pregnancy, and more likely to have a baby with a low birth weight. Recognising these patterns of blood flow provides an opportunity to individualise treatment plans for pregnant women, such as utilising drugs that are tailored to restore balance to their circulatory system. Early recognition also allows treatment to be commenced sooner, in turn reducing the incidence of serious manifestations of pre-eclampsia.

1. **Introduction**

Pre-eclampsia (PET) is one of the most common obstetric disorders, and arguably the most elusive in our understanding of its pathophysiology. The classical view of the cause of PET is that of a two-staged model, initially proposed by Redman in 19911. This model was subsequently revised by Staff in 20192; it proposes that that both early and late onset PET result from placental syncytiotrophoblast stress which is the end point of stage 1 of the disease. This stress then leads on to the clinical manifestation (stage 2) of PET.

While placental stress is classically attributed as the origin of PET, evidence over the last three decades strongly suggests that maternal cardiovascular dysfunction is central in the development of PET. More importantly, the evidence of this dysfunction is found prior to the clinical manifestation of PET, and even prior to pregnancy, implying that it is aetiological in the disease.3-5 Furthermore, profiling of maternal cardiac output, vascular resistance and arterial function demonstrates differing mechanisms of hypertension that is characteristic of PET, strongly suggestive that PET is not a singular disease process if viewed from the standpoint of the woman’s cardiovascular function.6

This paper aims to summarise and put in perspective the concept of different phenotypes of PET, distinguishable and treatable by addressing the specific cardiovascular dysfunction in the pregnant woman.

*Within this document we use the terms woman and women’s health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women’s health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth*

* 1. **An introduction to assessment of maternal cardiovascular function**

Successful maternal cardiovascular adaptation to pregnancy is an essential component of healthy pregnancy. In contrast, a significant body of data now demonstrates that inadequate physiological adaptation of cardiac and circulatory function in response to pregnancy predisposes both woman and child to adverse pregnancy outcomes.7-11 A range of cardiovascular indices (also known as haemodynamic indices) can be assessed safely in pregnancy. These have the potential to provide a comprehensive overview of the maternal cardiac, arterial and venous adaptation to pregnancy.

**Blood pressure:** Frequent blood pressure (BP) measurement is crucial for the diagnosis and management of hypertensive disorders in pregnancy, such as PET. BP can be measured in various settings, such as in the clinic, using both attended (clinician/observer present in the room) and unattended (clinician/observer leaves the room) approaches, ambulatory readings (e.g. 24-hour BP monitoring) or self‐measurement at home. Different measurement methods are also available, such as using auscultatory or automated (oscillometric) measurement devices. Various oscillometric BP devices have been validated specifically for use in pregnancy12-15, and protocols for measurment in early pregnancy have been published.16 Thresholds for categorising high blood pressure into mild, moderate and severe categories are outlined in NICE guidance.17

**Cardiac output:** Cardiac output (CO) is one of the most important indicators of maternal haemodynamic function and undergoes significant changes during pregnancy.18 A variety of techniques are available to assess CO during pregnancy, as listed in Table 2 and outlined in this consensus review.19 Important considerations when choosing a method to assess CO in pregnancy include the invasiveness of the procedure, operator-dependency, requirement for intermittent (i.e. discrete, serial measurements throughout a pregnancy) versus continuous (i.e. during an acute event within pregnancy) measurements. Few techniques have been validated specifically in pregnancy.

**Total peripheral vascular resistance:** Total peripheral vascular resistance (TPVR), or the resistance to the flow of blood through the systemic arterial vasculature, is a key determinant of the static component of BP i.e. the mean arterial pressure (MAP). Indeed, TPVR is not measured directly, but is typically derived from measurements of CO and MAP. Like CO, TPVR changes significantly during pregnancy, but in the opposite direction. Thus reductions in TPVR, particularly in early pregnancy, serve to accommodate increases in CO resulting largely from significant changes in blood volume, while maintaining the MAP.

**Arterial function:** A range of parameters relating to arterial function have been assessed in pregnancy, including arterial stiffness, wave reflections and endothelial function. Each provides different information concerning the state of the vasculature and non-invasive methods are available for all three, making them attractive measurements for inclusion in pregnancy studies. The extent to which arterial stiffness changes during healthy pregnancy and in pregnancy disorders is controversial, since arterial stiffness is heavily dependent upon BP, which changes significantly in pregnancy. In contrast, the available evidence supports the view that pregnancy-induced changes in wave reflections and endothelial function are independent of confounders and are altered in pregnancies complicated by PET, and can predict PET earlier with greater ability compared to BP measurements, ultrasound indices and angiogenic biomarkers.20 Commonly used techniques to assess arterial function are detailed in Table 2 and in Figures 1a and 1b.21

**Venous haemodynamics:** Venous haemodynamics play an essential role in pregnancy, particularly in relation to volume homeostasis and the control of venous return, which, in turn, determines the CO. However, indices relating to venous haemodynamics are often overlooked by investigators, most likely due to the difficulty associated with assessing venous physiology and the relative lack of simple, non-invasive techniques. Nevertheless, several techniques do exist, as detailed in Table 2, and which provide important information concerning venous vascular tone and plasma volume, allowing the investigator to examine the balance between stored and circulating blood volumes in pregnancy.22

**1.2 Two phenotypes of pre-eclampsia based on maternal cardiovascular function**

PET is a pregnancy-induced endothelial disorder characterised by hypertension, proteinuria and/or systemic dysfunction (renal, liver, coagulation), and in a proportion of cases, fetal growth restriction (FGR).23 Gestational age has been identified as the most important clinical discriminator in predicting both maternal and perinatal outcomes.24 This has led to the approach of stratifying PET into two phenotypes based on gestational age of diagnosis: early-onset (before 34 weeks’ gestation) and late-onset PET (after 34 weeks’ gestation).25

Over the last three decades, research into maternal cardiovascular function in PET suggests that two phenotypes of PET can be differentiated by maternal cardiovascular or haemodynamic status, based on whether the pregnant woman has a hypo-or hyper-dynamic circulation. Some of these cardiovascular profiles can be identified weeks before symptom onset and significantly, in a subset of patients, are present from prior to pregnancy.8 Further detail on common maternal haemodynamic parameters used in research settings is detailed in section 1.2.

The first, and less common, of the two phenotypes is that which occurs earlier in gestation. This is typically associated with FGR and abnormal uterine artery Doppler resistance indices.26-28 Maternal profiling finds that this phenotype occurs in patients with normal body mass index (BMI), with a haemodynamic pattern of low cardiac output (CO) and high total peripheral vascular resistance (TPVR), in other words a *hypodynamic* *circulation*.4,29,30 Additionally, evaluation of the venous compartment and body water volume load in the first trimester has shown higher extracellular body water volumes, compared to unaffected pregnancies, as well as normotensive FGR cases.31 Links between a hypodynamic maternal circulation and concurrent FGR has been described since the early 2000s32,33, with increasing supporting evidence in the last decade.32,34-37 Interaction between maternal and fetal haemodynamics seems to be at the basis of this finding, with descriptions of a hypodynamic maternal circulation leading to lower fetal umbilical vein blood flow and slower fetal growth velocity.38 Management including Doppler investigation of FGR is outside the scope of this document, however is discussed in detail in an RCOG guidance.39

In contrast, the more common PET phenotype occurs later in gestation, and is not associated with FGR.26 The maternal haemodynamic pattern is one of normal or high CO, low TPVR and increased intravascular volume state; a *hyperdynamic circulation.4* These patients are often overweight or obese.4

Hypodynamic PET associated with FGR or low birth weight is therefore often referred to (without clear justification) as ***placental PET***, and hyperdynamic circulatory PET as ***maternal PET.*** It is important to state that maternal phenotype based on haemodynamics should be determined by findings at the time of diagnosis. This is because maternal haemodynamic patterns have been found to cross over between the pre-clinical to clinical stage of PE, from a hyper to hypodynamic state.40

The relationship between angiogenic biomarkers and maternal cardiovascular function remains uncharacterised. Studies on angiogenic markers, specifically PlGF and sFlt-1, have shown a clear association in adverse pregnancy outcomes in patients affected by PET, high sFlt-1 and low PlGF being pathognomonic of placental dysfunction. The clinical use of PLGF and sFlt-1 has mostly been focused on late PET as a ‘rule out’ test.41 However, biomarkers show potential utility in predicting adverse neonatal outcome in early onset PET.42 There is little published on the association of biomarkers with different maternal haemodynamic profiles, in particular the low cardiac output, high vascular resistance phenotype that is characteristic of early PET or PET with FGR. In a recent study at mid-gestation PlGF and sFlt-1 were associated with subclinical cardiac function alterations.43

* 1. **Clinical utility in identifying maternal cardiovascular dysfunction** 
     1. Therapeutic opportunities during pregnancy

Healthy pregnancy is normally accompanied by major changes in maternal haemodynamic function that benefit the uteroplacental circulation.44 The drop in vascular resistance in early pregnancy triggers an increase in plasma volume and cardiac output, to maintain adequate blood pressure and uterine perfusion.44,45 Women who develop gestational hypertension exhibit non-physiological haemodynamic changes with heterogeneous patterns depending on the clinical phenotype of either a hypo- or hyperdynamic circulation. Understanding the underlying cardiovascular profiles of different phenotypes of PET will not only allow better identification of women who are at a higher risk of developing PET but provide insights to mitigate the associated complications for woman and baby.46-48

PET developing as a result of these cardiovascular changes can have a significant impact on both maternal and fetal morbidity and mortality.49 As women exhibit aberrant haemodynamic changes long before clinical disease, timely antihypertensive therapy may well impede the deterioration in circulatory changes that contribute to the development of preeclampsia.50 This information would also be of value in stratification of antenatal monitoring and enabling targeted early intervention to modify disease progression.50,51 In women presenting with overt PET, haemodynamic and echocardiographic assessment can help identify those at highest risk of severe cardiovascular complications, enabling interventions targeted at preventing complications such as acute kidney injury and pulmonary oedema.52 Feasibility studies on tailoring management based on maternal haemodynamics are elaborated on in Section 1.4.

1.3.2. Postnatal maternal cardiovascular health

The effects of maladaptive cardiovascular changes in PET persist postpartum and lead to poorer future cardiovascular health. There is robust evidence that maternal cardiovascular morbidity and mortality risk is at least doubled after preeclampsia. This risk starts immediately postpartum and remains increased for decades afterwards; linked directly to the cardiovascular dysfunction and maladaptation that occurred during the pregnancy.53-57

In the short term, blood pressure stays elevated and cardiac diastolic function remains impaired. In a proportion of patients this cardiovascular dysfunction does not resolve resulting in an increased risk of cardiovascular disease.46,47 More than ten years postpartum, hypertension is two to four times more likely in women who had PET compared to those with normotensive pregnancies.48,55 Similarly, heart failure occurs twice as often and appears to be driven by the persisting hypertension55,58, and women who have had PET are six-fold more likely to develop end-stage kidney disease.59

These findings highlight that PET has a significant and continued impact on postnatal maternal cardiovascular health, and identifying maternal cardiovascular dysfunction provides opportunities to intervene with risk-reduction strategies.

* 1. **Therapy based on maternal cardioavascular profiling**

1.4.1 Treatment of severe hypertension

Severe hypertension in pregnancy (BP>160/110mmHg), whether secondary to PET, pregnancy-induced hypertension or an exacerbation of chronic hypertension, needs to be managed effectively to prevent maternal end organ damage, without compromising utero-placental perfusion and fetal wellbeing.17 In accordance with National Institute for Health and Care Excellence (NICE) guidelines, severe hypertension can usually be safely lowered with oral hypotensive agents, while avoiding a profound and acute BP drop.60 Indeed, intravenous administration of the vasodilator hydralazine can have a rapid and unpredictable hypotensive effect.61 Injudicious use risks maternal cerebral infarction, utero-placental hypoperfusion, fetal bradycardia and intra-uterine demise. These adverse outcomes are more likely to occur when PET is associated with intravascular hypovolaemia.

Ideally, the choice of hypotensive agent will be guided by non-invasive cardiovascular monitoring.62,63 Measures of TPR, CO, sympathetic tone and intravascular volume would allow targeted treatment with a vasodilator, beta-blocker or diuretic, as appropriate64, with the aim to normalise cardiac output and peripheral resistance, and preserve circulatory volume to maintain renal, cerebral and utero-placental perfusion.19,22,62,63

Tailoring anti-hypertensive management based on cardiovascular profiling is a tried and tested strategy in the cardiology field. In a randomised study on a non-pregnant cohort of patients with treatment resistant hypertension, Taler et al. demonstrated superior blood pressure control when therapy was guided by serial cardiovascular function tests based-algorithms, compared to specialist clinician decisions alone.65

Translating that to obstetric cohorts, an early concept study by Easterling et al analysed outcomes in patients at risk of PET who had serial measurements of cardiac output. The authors found that failure to adjust therapy in response to excessive fall in cardiac output or increase in vascular resistance was associated with reduced fetal growth velocity. Furthermore commencing anti-hypertensive therapy in early pregnancy was associated with a lower rate of developing severe hypertension and requiring preterm delivery.66 A more recent study by Stott et al utilised a treatment algorithm that was constructed based on cardiovascular profile response to common drugs used in pregnancy to treat PET. The authors demonstrated that treatment based on serial cardiovascular monitoring reduced the rate of severe antenatal hypertension from 18% to 3.8%.67

1.4.2 Cardiovascular function considerations with arterial hypertension

Management of maternal arterial hypertension needs to consider both arterial and venous systems. The maternal arterial system can be high-resistance and low-output, or low-resistance and high-output. The venous reserve, that powers stroke volume, can be relatively or absolutely under-filled, over-filled or normovolaemic.19,22,62,68 Changes to maternal arterial characteristics induced by anti-hypertensives, must be counterbalanced by measures to maintain or improve venous return. Otherwise, there is a physiological increase in the renin-angiotensin-aldosterone system (RAAS) and increased sympathetic activity, which may paradoxically increase arterial tone.

Dalla et al. compared invasive arterial blood pressure recordings to automated oscillometric blood pressure monitoring in patients with severe PET admitted to an obstetric critical care unit.69 There was a weak association between systolic blood pressure with the mean difference around 24± 17 mmHg. When protection against cerebral haemorrhage is paramount, intra-arterial measurement of systolic values is best. Intra-arterial blood pressure monitoring combined with titrated continuous infusion of antihypertensive drugs should be considered in PET patients with severe hypertension and organ dysfunction.69

* + 1. Management of fluid balance

Fluid management in patients with severe PET remains challenging, especially in those with oliguria. These women will routinely be monitored and managed as in-patients, even with close cardiovascular function monitoring. The current gold standard for the assessment of fluid responsiveness in non-pregnant people is assessment of the change in the stroke volume after fluid bolus administration.70 Lamia et al studied fluid responsiveness in patients with sepsis using changes in the echocardiographic sub-aortic VTI (velocity time integral). A passive leg raising induced increase in stroke volume of 12.5% or more predicted an increase in stroke volume (VTI × cross-sectional area) after crystalloid volume expansion.71 More recently the same method was used in predicting fluid responsiveness in people with severe pre-eclampsia and oliguria. Only 52% of those with oliguria responded to a 500ml fluid bolus. The important finding was that during passive leg raising an increase of more than 12% in the VTI accurately predicted fluid responsiveness.72 This non-invasive test could be tested within future algorithms for fluid management in PET.

Injudicious fluid replacement in women with PET and leaky capillaries readily leads to pulmonary oedema and sometimes death. This outcome was a consequence of PET management that prioritised urine output.73 Clinician acceptance of transient oliguria and haemoconcentration with raised haemoglobin and creatinine has been a characteristic s strategy in the management of fluid balance in peri-partum PET.74 Such a compromise can however induce acute pre-renal kidney injury, reduce utero-placental blood flow, and critically reduce maternal cerebral and hepatic perfusion. As described above, fluid restriction can activate the renin-angiotensin-aldosterone system (RAAS) leading to unintended vasoconstriction.

Rates of acute kidney injury (AKI) in pregnancy have risen up to four-fold in women with hypertension75-77 in the last three decades, and long-term effects of AKI are recognised, including increased future cardiovascular morbidity, chronic kidney disease77 and risk of pre-eclampsia in future pregnancies.78 Women with late onset PET are commonly volume replete and diuretics may play a role if there are signs of volume overload.6 However, many women with early onset PET, particularly if associated with FGR, have the opposite findings: reduced plasma volume expansion and are fluid deplete.6 This means that a strategy of fluid restriction may lead to oliguria and rising creatinine, findings that are iatrogenic but can be confused with a worsening of the underlying PET.

Pragmatically, fluid depletion is deduced from clinical symptoms such as postural dizziness (although symptoms may not manifest until large fluid losses have occurred), skin turgor and assessment of fluid balance from intake/output monitoring. It can also be assessed by additional devices if available such as point-of-care ultrasound79, bioimpedence80 or non-invasive cardiac monitoring. Whilst pulmonary oedema remains an ever present risk with fluid resuscitation, it is also important to avoid reduced renal perfusion, oliguria and consequent kidney injury. Cautious fluid replacement (bolus with assessment of response, rather than continuous infusion) can be administered in those with suspected volume depletion, regulated by cardiovascular monitoring that at a minimum should include regular measures of heart rate, blood pressure, pulse oximetry, pulmonary auscultation, urine output and measures of fetal wellbeing.

More detailed cardiovascular tests could include monitoring of intravascular blood volume via central venous pressure and pulmonary capillary wedge pressure assessments. A central venous pressure line provides right atrial pressures that are a good indicator of intravascular volume. This allows intravenous fluids to be administered in bolus doses until a sustained improvement in venous pressure can be achieved.81 However, in the context of PET, there are concerns that the use of central venous pressure monitoring might be risky as the bolus doses of fluid could lead to a sharp rise in pulmonary capillary wedge pressure that could precipitate pulmonary oedema.82 This is thought to be attributed to changes in left ventricular compliance in PET. Thus, the use of pulmonary artery catheters should be confined to circumstances where large volumes of intravenous fluid replacement is required, but it is worth noting that the utilisation and safety of pulmonary artery catheterisation is mostly drawn from anecdotal clinical experience. Randomised studies that demonstrate a significant benefit in invasive cardiovascular monitoring in the management of severe PET are lacking.

Diuretics should be administered only in women who are volume replete but are considered regardless of volume status in those with pulmonary oedema. Concurrent administration of fluids and diuretics to ‘drive’ urine output should be avoided.

Angiotensin 2 receptor blockers and angiotensin converting enzyme inhibitors are feto-toxic and therefore avoided during pregnancy but not postpartum.83 A feasibility study has demonstrated improved echographic measurements in patients affected by PET and treated with enalapril in the post-natal period.84 Magnesium sulfate for prophylaxis against eclampsia or to reduce the risk of neonatal cerebral palsy, relaxes vascular smooth muscle and is a useful adjunct to hypotensive treatment.

1.4.4 Clinical application of utilising cardiovascular function for treatment

At present, facilities to perform comprehensive non-invasive cardiovascular monitoring are rarely available outside research settings. The clinician is therefore left with a pragmatic choice that usually lies between an oral calcium channel blocker, such as Nifedipine (slow release), an alpha and beta-blocker such as Labetalol or Doxazocin (alpha 1 receptor antagonist) or the centrally-acting vasodilator, Methyldopa. Given orally, these three agents will have a maximum hypotensive action within approximately 1.5 hours, 2 hours and 5 hours respectively. In most cases, the hypotensive effect of oral Nifedipine SR (slow release formulation) and Labetalol is effective while keeping the pregnant woman safe and will not lead to reduced utero-placental perfusion. A large first dose of methyldopa (1000mg), which, as it relies on conversion to a false-transmitter catecholamine (alpha methyl noradrenaline), will not usually have a quicker hypotensive effect than a lower dose but will be associated with more side effects after 5 hours.

In guiding decisions where no cardiovascular function monitoring is available, we suggest an approach that is based on an understanding of the two key clinical phenotypes of PET that relate to underlying cardiovascular dysfunction as explained in section 1.2. To illustrate this further we present the following case examples in the infographic below.

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* 1. **Future therapies and research**

The acknowledgement of two differing phenotypes of PET based on maternal cardiovascular dysfunction is the starting point for the design of future therapies and research. We now enter the era where research into maternal cardiovascular assessment can improve prediction of PET and direct antihypertensive treatment in preclinical and clinical phases of the condition.19,62

Targeted adjustment of maternal cardiovascular dysfunction from early pregnancy seems to improve trophoblast invasion and subsequent placental function as well as reduce stress on the cardiovascular system. The occurrence and severity of early onset PET are thus reduced by selectively influencing the underlying pathophysiological mechanisms as well as disease process.44 Cardiovascular techniques detecting cardiovascular fragility or subtle dysfunction in pre-clinical stages after early-onset PE can also be used to direct programs aiming to improve long-term cardiovascular health.85,86 Several therapies with the potential to reduce anti-angiogenic factor production (sFlt-1,s-Eng), oxidative stress or inflammation, influence immunologic adaptation to a semi-allogenic fetus and placenta, or enhance pro-angiogenesis (Plgf, VEGF, nitric oxide donors or angiotensin) pathways are being or are to be investigated for their potential in the prevention or treatment of early-onset PET.87 These include medications that are used for other indications in pregnancy (e.g. proton pump inhibitors, statins, low molecular weight heparin (LMWH), metformin, sulphasalazine, monoclonal antibodies) whose safety in pregnancy is already established.87-95

Another potential avenue of developing therapy is in addressing imbalances in nitric oxide (NO). NO is a potent vaso-dilator, and has anti-platelet activity, and NO deficiency at the vascular endothelial level has been demonstrated in animal PET models and human studies. NO donors such as glyceryl tri-nitrate (GTN) and penta-ethyl-tetranitrate (PETN) shows some promise in prophylaxis of PET and its complications in high risk women.96 The NO donor S-nitrosoglutathione GSNO has shown potential therapeutic efficacy in early phase studies in severe early onset PET.97 Its effects are particularly on the vascular endothelium and activated platelets and with intravenous infusion it demonstrated improvements in arterial stiffness, reversal of proteinuria and improvement in platelet count in severe PET +/-HELLP syndrome.98

LMWH was postulated as a potential therapeutic agent, as it provides possible anti-inflammatory effects by reducing the levels of TNF-alpha, interleukins, receptors for advanced glycation end products (RAGE) and neutrophil activity.99 A meta-analysis estimating the impact of adding LMWH or unfractionated heparin to low dose aspirin on the prevalence of PET suggested a possible reduction in the development of PET, however only contained a small number of studies (eight RCTs) that did not allow sensitivity analyses and evaluation of publication bias.100

Further avenues of research into PET therapy is within the area of vitamins, calcium and food supplementation. However, limited or no evidence of benefit reported in several trials101 should lead towards studies addressing the whole nutritional exposome and not just singular supplements. Future research is required to investigate the link between nutritional profile, the gut microbiome, inflammation and maternal cardiovascular function.

Innovative techniques such as the development of short interfering RNAs (siRNAs) that selectively silence messenger RNA isoforms primarily responsible for placental overexpression of soluble vascular endothelial growth factor receptor (sFLT1) has been shown to reduce clinical signs of PET in animal models.102 These results are exciting potential future treatment options for patients with early/placental PET.

* 1. **Opinion**
* There are two distinct phenotypes of PET that can be distinguished based on maternal cardiovascular profiling.
* Early-onset and late onset PET are considered to occur before and after 34 weeks, respectively, however this is to some extent an arbitrary threshold.
* Simple non-invasive techniques can be used to study maternal cardiovascular status in pregnancy. Early onset PET is frequently associated with a hypodynamic maternal circulation with raised vascular resistance, particularly if associated with FGR. Conversely, late-onset PET phenotypes demonstrate a hyperdynamic circulatory pattern with low or normal vascular resistance.
* Understanding maternal cardiovascular status allows targeted therapeutic intervention to address circulatory imbalances
* There is a clear rationale for the management of severe PET to be guided by maternal cardiovascular monitoring, at present these assessments are only utilised in a research setting. Clinical application of these assessments would allow targeted treatment with anti-hypertensives and fluid management.
* The continuation of abnormal cardiovascular function post-pregnancy highlights the need to introduce risk reductions strategies for long-term maternal health.
* Future research involves the exploration of therapies involved in improving cardiovascular adaptation in pregnancy. Likely this will include interventions involving lifestyle modificationssuch as nutritional influences, weight management and improved cardiovascular fitness, pharmacological manipulation of inflammatory and oxidative stress pathways.

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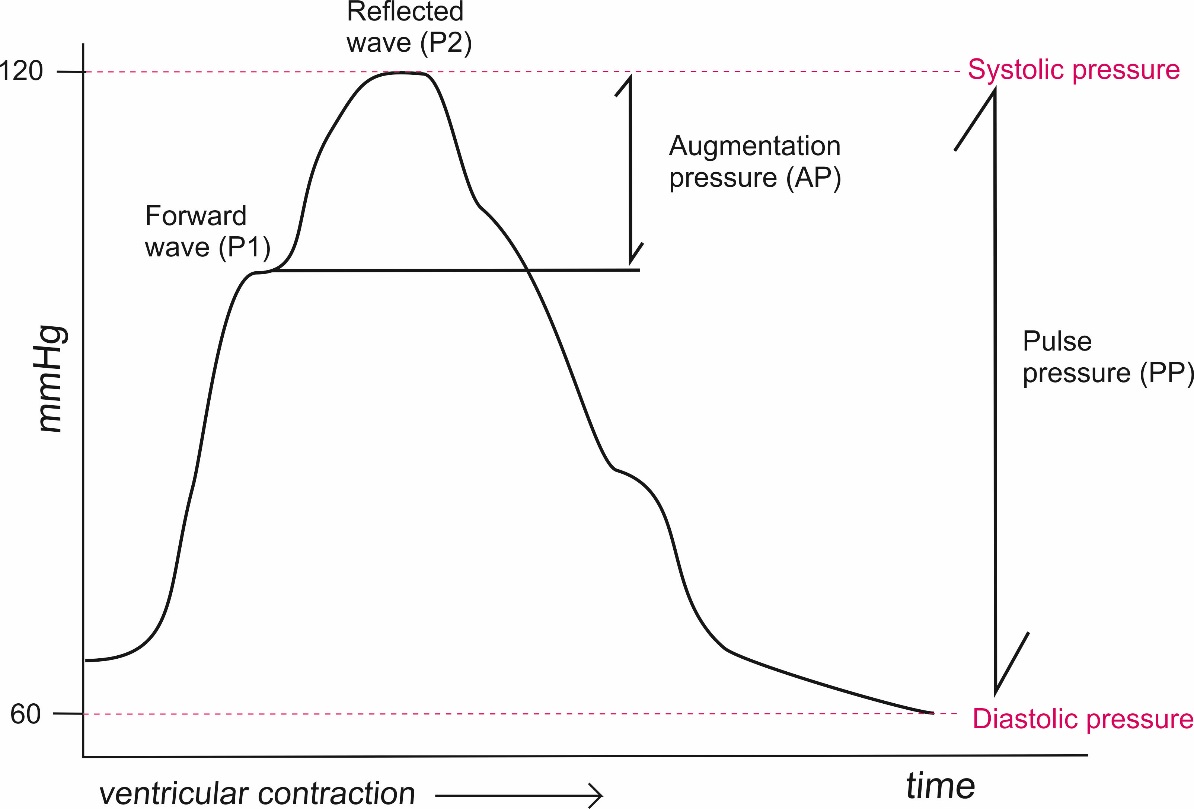
**Table 1.** **Maternal and fetal characteristics in two phenotypes of PE**

|  |  |  |
| --- | --- | --- |
|  | **PLACENTAL/EARLY PE** | **MATERNAL/LATE PE** |
| **Maternal haemodynamics** | Hypodynamic circulation | Hyperdynamic circulation |
| **Fetal growth** | Restricted | Normal |
| **Maternal BMI** | Normal | Overweight/ Obesity |

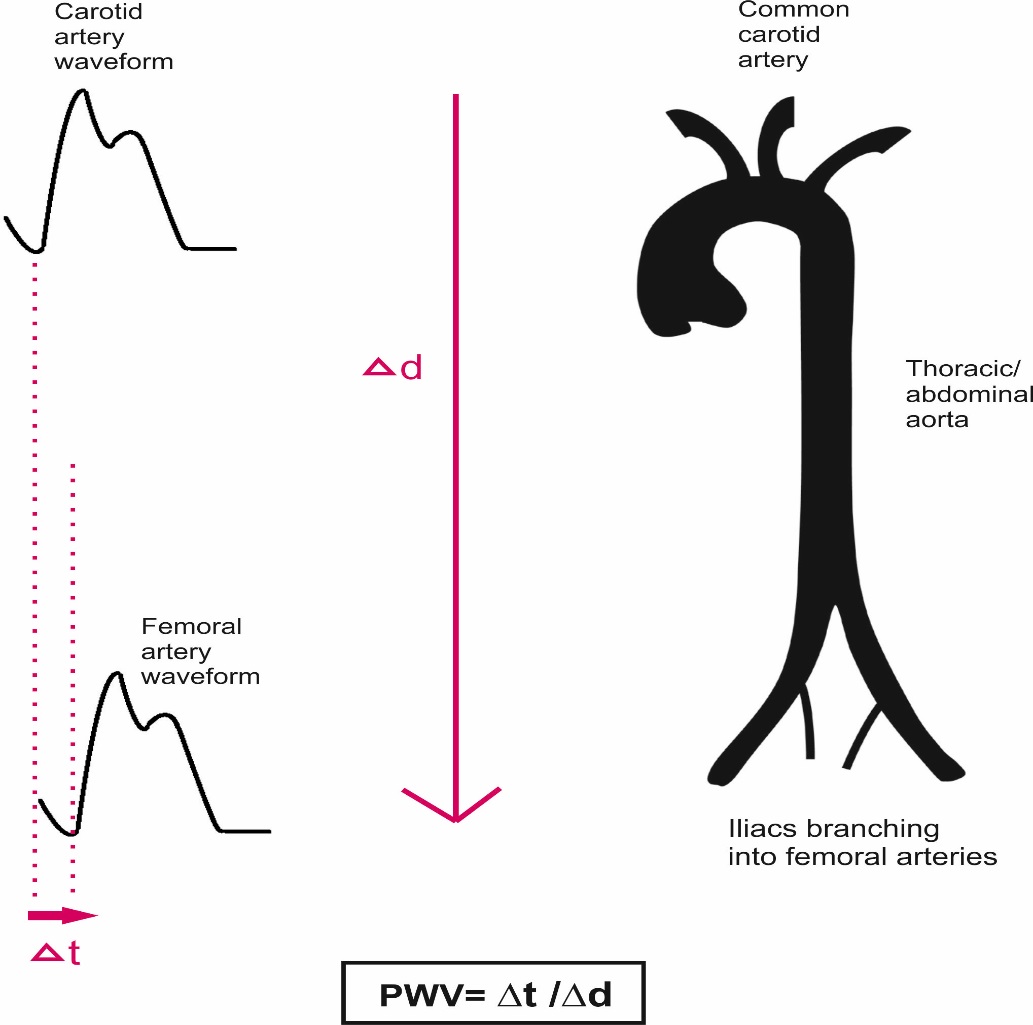
**Table 2. Techniques and Approaches to the Assessment of Maternal Haemodynamics**

**Table. Common non-invasive (or minimally invasive) methods to assess maternal haemodynamics during pregnancy**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Technique/Approach** | **Suitability in pregnancy** | **Validation in pregnancy** | **Comment/Recommendation** |
| Blood pressure | Oscillometry   * Clinic (office)-based (attended and unattended) * Ambulatory * Home | Oscillometric devices suitable in pregnancy.  Auscultatory devices less suitable for ‘out of office’ readings. | Several devices specifically validated in pregnancy. See Bello et al, 201815 for recent review. | Automated/oscillometric devices easy to use and widely available.  Carefully measured BP should be the foundation of all cardiovascular assessments in pregnancy. |
| Cardiac output | Cardiac magnetic resonance imaging (MRI)  Transthoracic Echocardiography (TTE)  Inert gas re-breathing  Bioimpedance and Bioreactance  Continuous-wave Doppler  Pulse contour analysis | Considered safe for use in 2nd and 3rd trimesters of pregnancy; expensive.  Safe for use in pregnancy but requires extensive training.  Safe for use in pregnancy and operator-independent. May not be feasible for assessing acute changes e.g during labour.  Safe for use in pregnancy  Safe for use in pregnancy and easier to learn than TTE.  Safe for use in pregnancy | Previously compared with TTE 103.  Previously compared with invasively determined cardiac output in pregnancy 104.  Not specifically validated.  Previously compared with TTE105-107.  Previously compared with TTE, with good reproducibility106,108.  Not specifically validated in pregnancy. | Considered non-invasive “gold-standard” for assessment of CO in non-pregnant individuals. Possible reference method for non-invasive CO assessment in pregnancy.  Alternative to cardiac MRI as reference method for non-invasive CO assessment in pregnancy.  Technique previously validated against invasive CO determinations in non-pregnant individuals109. Good indicator of “true” CO.  Easy to use, but lacking in accuracy and precision. Better suited to monitoring short-term or acute changes.  Easy to use with appropriate training, but variable accuracy and precision.  Previously compared with thermodilution110 and TTE111 in non-pregnant patients. Insufficient accuracy for determination of “true” CO. |
| Arterial stiffness | Pulse wave velocity (PWV) | Non-invasive, widely used and suitable for use in pregnancy. | Not specifically validated in pregnancy. | Carotid-femoral PWV considered non-invasive ‘gold-standard’ method for assessing arterial stiffness.  Care should be taken when measuring arterial path lengths in pregnancy. |
| Wave reflections | Augmentation index (AIx) | Non-invasive, widely used and suitable for use in pregnancy. | Not specifically validated in pregnancy. | AIx is not a measure of vessel stiffness and should not be used interchangeably with PWV. |
| Endothelial function | Ultrasound-based measure of flow-mediated dilatation (FMD)  Venous occlusion plethysmography-based measure of forearm blood flow (FBF) | Non-invasive, widely used and suitable for use in pregnancy.  Minimally invasive, involves local infusion of challenge agents to assess endothelium-dependent and independent vasodilatation. | Not specifically validated in pregnancy.  Not specifically validated in pregnancy. | Widely used method in pregnancy and non-pregnancy settings, although requires expensive equipment and intensive training. Less operator-dependent devices now available112.  Considered minimally-/non-invasive gold standard method for assessing endothelial function, but time-consuming and specialist equipment required. |
| Venous haemodynamics | Abdominal ultrasound and doppler sonography | Non-invasive and suitable for use in pregnancy | Not specifically validated in pregnancy. | Techniques allow assessment of inferior vena cava dimensions and collapsibility index, together with venous flow measurements.  Further confirmation of existing data required and a need for further non-invasive techniques. |
| Plasma volume | Indicator dilution  Bioimpedance | Non-radioactive labels suitable for use in pregnancy (e.g dextran or non-radioactive dyes)  Non-invasive and suitable for use in pregnancy | Not specifically validated in pregnancy.  Not specifically validated in pregnancy | Gold-standard for plasma volume measurement (radio-iodine labelled human serum albumin unsuitable for use in pregnancy.  Bioimpedance represents a promising approach but validation studies in pregnancy are needed. |

**Figure 1A Measures of arterial stiffness: Determinants of arterial augmentation index**

**Figure 1B Measures of arterial stiffness: Assessment of carotid-femoral pulse wave velocity (PWV)**



**Comments on: (New)** **SIP** **Pathophysiology of Early Onset Pre-Eclampsia and Insights to Management: Joint with British Hypertension Society (SIP Proposal)**

Date: September–October 2021

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| **Name of Reviewer** | **Comments** | **Action taken by lead proposer (Christoph Lees)** |
| RCOG Clinical Quality Assurance Group (CQAG) | The following external individuals/organisations (not included in the development team) should be approached at external consultation stage:   * International Society for the Study of Hypertension in Pregnancy (we are now following the revised version of definition of pre-eclampsia which was released by ISSHP in 2018 and adopted by NICE in 2019. This SIP will add value particularly when new definition is based on multi-organ involvement). * Professor Basky Thilaganathan as Clinical Director of Tommy’s National Centre for Maternity Improvement (unless he remains as one of the development team) * British Heart Foundation | Editorial to coordinate – no action by developers required |
| RCOG CQAG | With reference to any risks/controversies that may be associated with this paper – NICE primarily recommends the use of beta-blockers for treatment of pre-eclampsia and does not categorise early or late. BNF mentions that this drug category can influence the uteroplacental function. They both are contradictory to each other. In my practice I have observed that the higher doses of labetalol (>200 BD) can detriment the uteroplacental flow leading in higher Doppler values in umbilical arteries.  Methyldopa should also be mentioned in the treatment options along with the other drugs in this SIP. |  |
| RCOG CQAG | Give consideration with reference to ethnicity whether differing efficacy or changes in maternal haemodynamics is observed with certain drugs. |  |
| RCOG CQAG | On publication, consider whether there should be any additions made to the existing RCOG patient information on pre-eclampsia. | Editorial to refer to PIC – no action by developers required |
| Michelle Sadler, RCOG Guidance Editorial Manager | Title: Pathophysiology of Early Onset Pre-Eclampsia and Insights to Management  Preferred usage is the word 'Care' instead of Management; consider if this is appropriate in this instance. |  |