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Maternal hemodynamics: are we changing obstetrical care?

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M

2021

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INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

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Artigo de Revisão Bibliográfica

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar, da Universidade do Porto

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Aluna do 6º ano do Mestrado Integrado em Medicina (nº aluno 201505666)

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Maio, 2021

Porto, 12 de Maio de 2021

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Agradecimentos

Gostaria de agradecer a todos aqueles que contribuíram para o meu percurso ao longo destes 6 anos de muita aprendizagem. Sou grata pela forma singular como cada um me ajudou a vivê-los.

Um agradecimento especial à Prof.ª Doutora Inês Nunes, pela excelência como docente, que me fez cultivar um encanto sublime pela área de Obstetrícia, pela confiança depositada, pelo apoio prestado como orientadora, pela partilha de conhecimento e ainda por todo o incentivo transmitido, fundamentais para a elaboração deste trabalho.

À Dra. Cristiana Moreira, por toda a disponibilidade, amabilidade e dedicação como coorientadora, bem como pelo apoio e incentivo preciosos ao longo do processo.

Ao Instituto de Ciências Biomédicas Abel Salazar, a casa que me recebeu nestes 6 anos e me proporcionou uma formação médica de excelência. Aos docentes, colaboradores e utentes com quem cruzei o meu caminho, por todos os ensinamentos transmitidos.

À minha família, por todo o amor e apoio incondicionais, por caminharem a meu lado em todos os momentos, por vibrarem com todas as conquistas e por serem conforto nos momentos mais desafiantes.

À minha mãe, por me inspirar e por todo o carinho e incentivo desmedidos em mais uma importante etapa da minha vida.

Aos meus avós, pelo exemplo de vida, por terem um papel tão importante na minha vida e formação como pessoa e por serem fonte de uma imensa força vital: os laços familiares.

Aos meus amigos, pelas pessoas incríveis que são, por me nutrirem do melhor que a vida tem para dar e pelo companheirismo fiel em todos os momentos.

Ao Daniel, por ser um porto seguro e por todo o apoio.

Resumo

Introdução: O surgimento de técnicas não invasivas simples possibilitou a avaliação do perfil hemodinâmico materno ao longo da gravidez, tanto no campo da investigação como na prática clínica. Desta forma, contribuiu para o conhecimento da fisiologia cardiovascular na gravidez normal e nas gravidezes complicadas por pré-eclâmpsia (PE) e restrição de crescimento fetal (RCF). A elevada carga global destas patologias, relacionada com desfechos maternos e perinatais adversos, juntamente com o facto do tratamento se limitar à terminação da gravidez (principalmente devido à limitação na compreensão da sua fisiopatologia), impulsionaram uma vasta investigação nesta área, nas últimas décadas. A tríade clássica - placentação inadequada, insuficiência uteroplacentária e cascata de reação vascular - parece não explicar a totalidade dos casos de PE e RCF. Recentemente, tem surgido evidência de que a má-adaptação cardíaca e a disfunção vascular maternas subjacentes a estas patologias serão as peças que faltavam para explicar a sua fisiopatologia.

Objetivo: Conduzir uma revisão da literatura sobre o papel da hemodinâmica materna nos cuidados obstétricos atuais, contemplando o seu contributo no rastreio, diagnóstico e tratamento da PE e da RCF, bem como marcador de risco cardiovascular materno futuro.

Métodos: Revisão abrangente e integrativa de publicações científicas indexadas na PubMed. Artigos de investigação originais, revisões sistemáticas e meta-análises publicadas, em inglês, entre 2000 e 2021, foram selecionados de acordo com a relevância e a qualidade científicas. Adicionalmente, outras referências bibliográficas foram obtidas através de referenciação cruzada.

Desenvolvimento: Estudos recentes evidenciam diferenças significativas na hemodinâmica materna entre grávidas normotensas e hipertensas ou com RCF, que apoiam a integração da avaliação de parâmetros hemodinâmicos maternos nos protocolos de rastreio do primeiro trimestre para estas patologias, altura em que poderão ser implementadas medidas profiláticas para reduzir a sua ocorrência. O perfil hemodinâmico materno apresenta valor prognóstico, permitindo a distinção entre 2 'fenótipos cardiovasculares' que diferem em relação à idade gestacional de início, envolvimento fetal e desfechos maternos e perinatais adversos, beneficiando de um tratamento individualizado. Um perfil hemodinâmico hipodinâmico e vasoconstritivo (baixo débito cardíaco e elevada resistência vascular) associado a elevada rigidez arterial confere pior prognóstico – a PE surge mais cedo, com consequente maior impacto materno-fetal, incluindo maior incidência de RCF. Este subgrupo de grávidas beneficiará de terapia vasodilatadora adicional. Por outro lado, nas grávidas com um perfil hiperdinâmico (alto débito cardíaco, baixa resistência vascular), a utilização de beta-bloqueadores é suficiente para um bom controlo tensional. O tratamento anti-hipertensivo guiado pelo perfil hemodinâmico reduz a incidência de PE severa e

otimiza o tratamento, preservando o débito cardíaco materno adequado ao crescimento fetal. No caso de fetos pequenos para a idade gestacional, a avaliação do perfil cardiovascular pode ajudar a distinguir os fetos restritos de fetos pequenos saudáveis, evitando decisões inadequadas relativamente a prematuridade iatrogénica nos fetos constitucionalmente pequenos. Finalmente, as medidas capazes de modificar a disfunção hemodinâmica materna são valiosas, podendo ajudar a prevenir o desenvolvimento de disfunção cardíaca no futuro – para alcançar este objetivo, a implementação de programas eficazes de rastreio e 'follow-up' cardiovascular no pós-parto é crucial.

Conclusão: Considerando a recente evidência sobre a hemodinâmica materna, a prática obstétrica atual não pode negligenciar o estudo da função cardíaca e vascular maternas em face da PE e da RCF, com vista a melhorar os desfechos maternos e perinatais. De facto, à luz do conhecimento atual, a avaliação abrangente da função cardiovascular materna deverá integrar os cuidados obstétricos de rotina num futuro próximo.

Palavras-Chave: Hemodynamics, maternal; preeclampsia; fetal growth restriction; diagnosis; cardiovascular disease.

Abstract

Introduction: The emergence of simple non-invasive techniques has allowed serial measurement of maternal hemodynamics throughout pregnancy, both in research and in clinical practice. Thus, knowledge regarding maternal cardiovascular physiology in normal pregnancy and in pregnancies complicated by preeclampsia (PE) and fetal growth restriction (FGR) has improved. The great clinical burden of these disorders, related to important adverse maternal and perinatal outcomes, along with the lack of effective treatment beyond termination of pregnancy, mainly due to inconsistency regarding the understanding of its pathophysiology, propelled an extensive investigation in this area over the recent decades. As the classical triad of inadequate placentation, uteroplacental insufficiency and vascular reactivity cascade fails to fully explain PE and FGR, evidence has emerged supporting the theory that underlying maternal cardiac maladaptation and vascular dysfunction could be the missing piece to explain all the picture.

Objective: To conduct a literature review on the potential role of maternal hemodynamics in modern obstetrical care regarding the screening, diagnosis and treatment of preeclampsia and FGR, along with the prediction of long-term maternal cardiovascular disease.

Methodology: A comprehensive and integrative literature review was conducted using PubMed. Original research articles, systematic reviews and meta-analysis published, in English, between 2000 and 2021, were selected by relevance and scientific quality. Additionally, other bibliographic references were obtained by cross-referencing.

Development: Studies have demonstrated significant differences in maternal hemodynamics between normotensive and hypertensive or FGR pregnancies, supporting the integration of maternal hemodynamic parameters in first-trimester screening protocols for PE and FGR, when preventive measures can still reduce their occurrence. Maternal hemodynamic profile presents prognostic value, allowing the distinction between 2 ‘cardiovascular phenotypes’ that differ regarding gestational age at onset, fetal involvement and adverse maternal and perinatal outcomes, in which treatment has to be individualised. Women with a hypodynamic-vasoconstricted hemodynamic profile [low cardiac output (CO) - high systemic vascular resistance (SVR)] and high arterial stiffness present worse prognosis, developing PE sooner with a higher incidence of FGR. These patients will benefit from additional vasodilator therapy. In contrast, women with a hyperdynamic profile (high-CO-low-SVR) will most likely achieve BP control using only beta-blockers. A hemodynamic-guided antihypertensive treatment reduces the incidence of severe PE and may prompt treatment adjustments to preserve adequate maternal CO for optimal fetal growth. In pregnancies complicated with a small-for-gestational-age (SGA) fetus, evaluation of the cardiovascular profile may also help distinguishing growth restricted from healthy SGA

fetuses, avoiding inadequate decisions regarding preterm deliveries in SGAs. Finally, all measures capable of modifying abnormal maternal hemodynamics are valuable and may help prevent the development of unfavourable cardiac profiles in the future – to achieve this goal the implementation of effective cardiovascular screening and follow-up programmes soon after delivery is crucial.

Conclusions: According to recent evidence on maternal hemodynamics, modern clinical practice cannot neglect the study of maternal cardiac and vascular function, when considering PE and FGR, in order to improve maternal and perinatal outcomes. Therefore, comprehensive maternal cardiovascular assessment in obstetrics may be standard-of-care in the near future.

Keywords: Hemodynamics, maternal; preeclampsia; fetal growth restriction; diagnosis; cardiovascular disease.

Abbreviations

% - Percentage
< - “Less than” or “Before”
> - “Higher than” or “After”
≥ - Higher or equal to
ABPM - Ambulatory blood pressure monitoring
ACC/AHA - American College of Cardiology/American Heart Association
ACOG - The American College of Obstetricians and Gynecologists
AIx - Augmentation Index
AIx-75 - Augmentation index at a heart rate of 75 beats per minute
BMI - Body mass index
BP - Blood pressure
CH - Chronic hypertension
CO - Cardiac output
CVD - Cardiovascular disease
DR - Detection rate
FGR - Fetal growth restriction
FMD - Flow-mediated dilation
GH - Gestational hypertension
HDP - Hypertensive disorders of pregnancy
HF-B - Stage B asymptomatic heart failure
HR - Heart rate
ISUOG - The International Society of Ultrasound in Obstetrics & Gynecology
LDA - Low-dose aspirin
LV - Left ventricle
MAP - Mean arterial pressure
NICE - The National Institute for Health and Care Excellence
PAT - Peripheral arterial tonometry
PE - Preeclampsia
PlGF - Placental growth factor
PWA - Pulse wave analysis
PWV - Pulse Wave Velocity
RCT – Randomised controlled trial
sFlt-1 - Soluble fms-like tyrosine kinase-1
SGA - Small-for-gestational-age
SUA - Spiral uterine arteries
SV - Stroke volume
SVR - Systemic vascular resistance
UK - United Kingdom
UtA - Uterine artery
UtA-PI - Uterine artery pulsatility index

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I. Introduction

The use of hemodynamic profile assessment in pregnant women has assumed an increasingly significant role in obstetrical care, both in research and in clinical practice. A comprehensive maternal hemodynamic assessment comprises an integrative evaluation of the maternal heart and vascular tree, potentially including both arteries and veins, as well as the uteroplacental circulation.

To understand the overall maternal cardiac profile, the heart rate (HR), stroke volume (SV), cardiac output (CO) and systemic vascular resistance (SVR) are the most important hemodynamic parameters (Figure 1). Vascular function can be assessed through measures of arterial stiffness, wave reflection and endothelial function, although there is fewer knowledge and validation regarding these.

A variety of blood vessels can be reproducibly examined, including the aorta, the brachial, radial, carotid, femoral and uterine arteries, along with the maternal microcirculation.

Regarding vascular function assessment, the '*gold-standard*' measurement of arterial stiffness is the aortic or carotid-femoral pulse wave velocity (PWV), which is inversely related to vessel elasticity and compliance. Pulse wave analysis (PWA) is another modality that derives variables from arterial waveforms using applanation tonometry or oscillometry. As arterial resistance builds up, the proportion of the reflected pulse wave attributed to the pulse pressure, known as augmentation index (AIx), increases alongside.[1]

Arterial dysfunction, translated by abnormal PWV and AIx, is recognised as an important 'risk marker' and an independent predictor of sub-clinical organ damage and cardiovascular events.[1]

Brachial artery flow-mediated dilatation (FMD), generally considered the '*gold-standard*' for endothelial function assessment, also correlates inversely to cardiovascular risk.[2] It measures endothelial-dependent dilatation mediated by nitric oxide release in response to increased shear stress using ultrasonography. Additionally, peripheral artery tonometry (PAT) measures endothelial reactive hyperemia induced by blood flow occlusion using an inflatable cuff.

The emergence of non-invasive techniques (Figure 2) has allowed feasible serial measurements of maternal hemodynamics, which improved the understanding of cardiovascular physiology throughout normal pregnancy.

It has also clarified concepts regarding pregnancy complications that may arise from maternal cardiac maladaptation and arterial dysfunction, such as hypertensive disorders of pregnancy (HDP) and fetal growth restriction (FGR), providing valuable information that may help improving their clinical management.[3–5]

In clinical practice, maternal hemodynamic assessment may be easily performed using simple, validated and reproducible non-invasive methods and devices. However, there is no consensus on which method or device is most valid in pregnancy.

Studies regarding maternal hemodynamics have focused mainly on preeclampsia (PE), FGR and preterm birth, which are associated with an increased risk of cardiovascular disease (CVD) later in life.[6] Preeclampsia, a multisystem hypertensive disorder complicating about 2-8% of pregnancies[7], and FGR, which is estimated to complicate about 10% of pregnancies, are major causes of maternal and perinatal mortality and morbidity.[8,9] Besides being linked to potentially severe obstetrical outcomes, such as preterm birth, stillbirth, placental abruption, eclampsia, and maternal pulmonary oedema and cardiac failure, PE lacks effective treatment due to poorly understood pathophysiological mechanisms.[10] The classical triad of inadequate placentation, uteroplacental insufficiency, and vascular reactivity cascade (Figure 3) fails to fully explain most of PE cases that occur at term. Hence, broader investigation on PE pathophysiology identified angiogenic imbalance,[11] systemic endothelial dysfunction,[12] decreased vascular compliance resulting in volume expansion intolerance,[13] and cardiovascular dysfunction[5] as contributors to PE development.

The high burden of these obstetric disorders, along with an increased and comprehensive knowledge regarding maternal hemodynamics, propelled an extensive investigation in this area over the recent decades.

Aim

To conduct an integrative literature review on the potential role of maternal hemodynamics in modern obstetrical care regarding the screening, diagnosis and treatment of PE and FGR, as well as the prediction of long-term maternal cardiovascular disease.

Methods

A comprehensive and integrative literature review was conducted using PubMed, using the following keywords: hemodynamics, maternal; preeclampsia; gestational hypertension; fetal growth restriction; diagnosis; therapeutics; cardiovascular disease. Along with indexed scientific articles, other documents issued by international scientific organizations were also reviewed.

Original research articles, systematic reviews and meta-analysis published, in English, between 2000 and 2021 were selected by relevance and scientific quality. Additionally, other bibliographic references were obtained by cross-referencing.

II. Maternal hemodynamics in normal pregnancy

Throughout pregnancy, major maternal cardiovascular adaptations are required to ensure optimal uteroplacental blood flow and fetal growth and to meet the increased circulatory and metabolic demands. Pregnancy is considered a high-flow and low-resistance physiological state. Most of these normal structural and functional changes (Table I, Figure 4), occurring early in the first trimester, are hormone-mediated and reversible after delivery.[14]

The new non-invasive cardiovascular assessment tools have facilitated simple, bedside evaluation of maternal hemodynamics, providing extensive information regarding the physiology of uncomplicated pregnancies.[15]

There is evidence that the very first maternal hemodynamic changes occur shortly after embryo implantation, prior to the placental development and the establishment of the low-resistance uteroplacental circulation. Furthermore, most hemodynamic changes are induced well before the exponential increase of fetal and placental demands, that prevail in the second half of pregnancy.[14]

In normal pregnancy, preload indicators are expected to progressively increase, while afterload determinants decrease.[16] Indeed, normal fetal growth and birthweight correlate positively with CO increase and SVR reduction.[17]

An adequate continued plasma volume expansion (up to a 45% increase) is accommodated by early and profound maternal vascular changes, characterised by vascular relaxation along with increased arterial compliance and venous distensibility.[16] Systemic and pulmonary vascular resistances decrease significantly (nadir of circa 35% less than baseline at 20 weeks' gestation), leading to a fall in aortic stiffness (PWV, AIx-75) and an increase in FMD, counteracted by a cardiac preload rise.[18–20] Conversely, maternal CO increases steadily, augmenting circa 45% by 24 weeks' gestation, with a greater contribution of increased SV, despite concomitant increase in HR.[21] CO rise is not sufficient to prevent BP fall, thus, mean arterial pressure (MAP) decreases during the first trimester, reaching a nadir by midpregnancy, and then gradually increases, approaching or exceeding pre-pregnancy levels at term.[18] These changes reach a peak in the midthird trimester before CO falls. SVR increases towards 40 weeks' gestation, returning to baseline values in the postpartum period.[15,21]

Most of the morphological heart changes become significant around 12 weeks.[22] Compensatory eccentric cardiac remodelling, promoted by volume overload and neurohormonal factors, is characterised by an excessive increase in the left ventricular mass and associated diastolic dysfunction. It is present in a significant proportion of women at term, but it is, in most cases, physiological and reversible, without any long-term cardiac consequences.[23]

This demanding process places strain on the maternal cardiovascular system. Hence, pregnancy has been described as a stress test, unmasking women who have poor cardiac reserve or vascular dysfunction. Indeed, whenever maternal cardiovascular maladaptation to pregnancy occurs, it favours the onset of disorders such as PE and FGR.[3–5]

III. Role in screening

One of the biggest challenges of modern obstetrics is to identify high-risk women and predict pregnancy complications as early as possible, a concept known as 'inversion of the pyramid of prenatal care'.[24]

However, regarding PE and FGR, the poor understanding of their pathophysiology and the lack of effective treatment have compromised the development of effective screening tools, which would enable adequate implementation of preventive measures and closer monitoring.

Although the complex pathophysiology of PE is not entirely understood, poor placentation has been considered a cornerstone. It is believed to be a two-stage process (Figure 3) initiated by shallow trophoblast invasion into the decidua, which results in inadequate remodelling of the spiral uterine arteries (SUA). Thereby, uteroplacental vessels are unable to become enlarged capacitance vessels, as required to accommodate the massive increase in uterine perfusion throughout pregnancy (Figure 5).[25] The resulting persistent placental hypoperfusion causes release of antiangiogenic and proinflammatory factors into the maternal circulation. These placenta-derived factors induce an early-stage of systemic vascular dysfunction, which can further lead to PE development. Maternal response to endothelial dysfunction and imbalance between angiogenic and antiangiogenic factors (Figure 6) results in the second stage of the disease, responsible for the clinical features of PE.[26] Also, the diminished blood flow through uteroplacental vessels can compromise fetal growth and consequently lead to FGR.[27]

Besides the historically undeniable role of the placenta in PE, growing evidence shows that maternal predisposition to vascular hypersensitivity and other underlying cardiovascular abnormalities contribute upstream to the development of PE. This may provide a window for pre-pregnancy screening of susceptible women.[5,28]

The concepts of early and late PE are now widely accepted as being two different entities with distinctive pathophysiology, biochemical, histological, hemodynamic and clinical features.[29]

Early-onset PE (developing before 34 weeks) is the most severe clinical variant, occurring in 5-20% of all PE cases. Previously considered a 'placenta-mediated disease', it is more commonly associated with abnormal uterine artery (UtA) Doppler, FGR, iatrogenic preterm delivery and worse adverse maternal and neonatal outcomes.[30]

In contrast, late-onset PE (after 34 weeks) is the most prevalent, accounting for 75-80% of all PE cases. It is related to maternal morbidity (such as obesity, dyslipidaemia, chronic hypertension, impaired glucose tolerance and cardiovascular dysfunction) and leads to placental insufficiency due to higher feto-placental demands that exceed the supply. As placental development seems to occur

normally, late-onset PE is associated with normal or slightly increased UtA resistance index, normal birthweight and more favourable maternal and perinatal outcomes.[30]

Therefore, when evaluating the prediction value of a given test or combination of tests for preeclampsia a clear distinction must be made between these two distinct disease phenotypes.

Regarding prevention, in the last decade, several meta-analysis suggested that early-onset (before 16 weeks' gestation) low-dose aspirin (LDA) improves placentation and UtA blood flow, and, therefore, reduces the risk of severe PE, providing a stepping stone for PE prevention.[31,32] Its proangiogenic, antithrombotic, and anti-inflammatory effects favour placentation and represent plausible mechanisms for PE prevention.

The 2017 ASPRE trial, a multicenter, double blind, RCT included 1,776 women at high-risk for PE based on a first-trimester combined screening algorithm, that were randomised to low-dose aspirin (150 mg) or placebo. They found that daily LDA from 11-14 weeks' gestation until 36 weeks' gestation in women at high-risk for PE reduces the incidence of early-onset PE by > 80% and preterm PE by > 60%, with no adverse perinatal outcomes. However, it doesn't seem to significantly prevent term preeclampsia (after 37 weeks), which highlights that mal-placentation is not implied in the development of late-onset PE.[33]

The indications, ideal dosage, and gestational age to start aspirin prophylactic treatment are still being debated. In the literature, dosage recommendations range from 60 mg/d to 150 mg/d; nevertheless, after the publication of ASPRE trial, the biggest RCT conducted to date, the use of 150 mg/d of aspiring has been widely adopted.

Regarding FGR, in the absence of high-risk factors for preeclampsia, current guidelines do not recommend the use of prophylactic LDA for its prevention.[34]

III.1. Screening in the general population

All pregnant women are potentially at risk for preeclampsia and FGR, and should be screened in the first trimester, so that preventive measures can be promptly initiated.

Despite the growing number of prediction models created over the years (some of which are discussed below), to date, no single test is able to accurately predict these diseases. Furthermore, recommendations from scientific organizations vary.

Maternal risk factors

Several professional organizations, such as the National Institute for Health and Care Excellence (NICE) and the American College of Obstetricians and Gynecologists (ACOG), have proposed screening criteria for women at high risk for preeclampsia at 11-13+6 weeks' gestation based on

maternal demographic characteristics and medical history, establishing indications for LDA prophylaxis (Table II).[35–38]

Despite changes in their recommendations over the years, PE screening based on NICE and ACOG criteria presents suboptimal performance (Table II). Their approach considers each risk factor as a separate screening test with additive detection rate (DR) and screening-positive rate to calculate an *a priori* risk for PE, reaching high detection rates (> 80%) but also high false positive rates (~ 60%).[39,40]

As an alternative, studies have reported better results when combining these risk factors using multivariate logistic regression analysis, reaching up to 50% and 30% detection rates for early-onset PE and late-onset PE, respectively, with a 5% false positive rate (FPR).[41]

Combined algorithms

Recognition of maternal risk factors alone, although useful in clinical practice, is considered not sufficient for the effective prediction of PE. Thus, the current approach to risk assessment relies on the identification of well-established maternal risk factors, along with biophysical and biochemical markers, and has shown superior performance to the traditional recommended criteria.[39,42,43]

Indeed, FIGO supports an alternative screening model for preterm PE, developed by *The Fetal Medicine Foundation* (FMF), known as the '*triple test*'. It consists of a one-step algorithm combining maternal risk factors and measurements of MAP, uterine artery pulsatility index (UtA-PI) and serum placental growth factor (PIGF) applied to all pregnant women between 11–13 weeks of gestation. The risk calculator is freely available on the FMF mobile app or webpage (https://fetalmedicine.org/research/assess/preeclampsia).[44]

The FMF first trimester combined test, reporting a DR of 90% (95% CI, 78-96) and 75% (95% CI, 62-85%) for early and preterm preeclampsia, respectively, at a 10% FPR, has undergone extensive successful internal and external validation.[39,45,46]

Secondary analysis of the ASPRE trial data provided definitive evidence that effective screening for preterm PE can be achieved with the combination of maternal factors and biomarkers at 11–13 weeks, ensuring that early aspirin prophylaxis can significantly reduce the risk of developing preterm PE.[47,48]

While first trimester predictive algorithms seem promising for early-onset PE and FGR detection and prevention, their accuracy for late-onset PE and FGR at term is not satisfactory, as well as the prevention with LDA in these groups.[47]

Nevertheless, even women who screen positive for preterm PE but in the end do not develop PE or deliver a small-for-gestational-age (SGA) neonate have impaired cardiac adaptation in pregnancy and lower birthweights. Therefore, they should not be regarded as normal despite

remaining normotensive as they are at greater risk of occult placental insufficiency at term (they present an increased rate of emergency caesareans and operative vaginal deliveries for fetal distress in labour).[49]

- **Combined algorithms with biochemical markers**

Recently, as the role of angiogenic factors in the development of placenta-related diseases is better understood, placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) have demonstrated a major contribution in the combined prediction of PE and FGR.[51]

Women who develop PE present increased levels of sFlt-1, accompanied by reduced levels of free PlGF, earlier and to a greater extent, compared to normotensive women. These changes favour anti-angiogenic imbalance, and are greater in those with subsequent early-onset PE and/or FGR, as a direct result from mal-placentation.[52]

The use of the sFlt-1/PlGF ratio improves prediction and diagnostic accuracy of PE (for example, before 34 weeks' gestation, an sFlt-1/PlGF ratio ≥ 85 achieves 88% sensitivity and 99.5% specificity).[53] This helps distinguishing women with clinical PE – those who need hospitalization and an early delivery from those who may be monitored in an outpatient setting and that will benefit from a later delivery.

- **Combined algorithms with biophysical markers**

Since early hemodynamic changes in women predisposed to develop PE or FGR differ from those occurring in healthy pregnancies, the role of cardiovascular function assessment has been studied in their prediction.

Blood pressure (BP) measurement using validated automated devices is mandatory as part of routine surveillance during antenatal care, due to its feasibility and diagnostic performance.

A large study in the UK has shown that MAP at 11–13 weeks predicted early-onset and late-onset PE with a DR of 59.5% (95% CI, 42.1–75.2) and 36.7% (95% CI, 28.4–45.7), respectively, for a FPR of 10%.[54] Nevertheless, as an isolated marker for the prediction of PE, the performance of MAP is low in healthy nulliparous women.

PE screening by MAP is better when measurements are taken at both 11-13 and 20-24 weeks' gestation. The first defines the high-risk group that benefits from prophylactic treatment with LDA, and the second improves the prediction capacity and identifies the group in need of closer maternal and fetal surveillance, helping to better define the time of delivery.[55]

Uterine artery Doppler velocimetry, so far the most promising screening test for PE, SGA and preterm birth, is a non-invasive operator-dependent method for the assessment of the uteroplacental circulation, reflecting impaired placentation.

Impaired uteroplacental perfusion, predisposing to the development of PE and/or FGR, is reflected in increased UtA resistance and pulsatility indices (RI and PI, respectively) and/or the presence of bilateral early diastolic notches (Figure 7).[56]

Consistent with the pathophysiology of PE, UtA Doppler performs better in the prediction of early-onset PE and PE associated with FGR.[41,57] Furthermore, it is associated with both birthweight and gestational age at delivery.[58]

As a single predictor for PE and FGR, UtA Doppler using flow velocity waveform has poor accuracy, detecting less than 50% of early-PE cases and no more than 40% of pregnancies affected by early-FGR, but presents high specificity for both conditions [92.1% (95% CI, 88.6–94.6) and 93.1% (95% CI, 90.6–95.0), respectively].[41,57] On the other hand, the presence or absence of diastolic notching as a marker of vascular resistance has low sensitivity and specificity, mainly in the first trimester, when it is present in more than half of the pregnancies.[57]

UtA Doppler contribution to the predictive models that combine maternal characteristics, maternal history and other biophysical and biochemical markers, such as the FMF triple test and many others, is promising.[41,46,59–61] When all markers are used, 90% of PE cases that require delivery before 32 weeks, 75% of PE cases that require delivery before 37 weeks, and 55% of FGR cases that require delivery before 34 weeks can be identified in the first trimester.[43,62]

Although the assessment of UtA Doppler velocimetry requires specific training and should be performed following a standardised technique, it is feasible and inexpensive when incorporated in the routine first trimester scan. Thus, even in low-resource settings where biochemical tests may not be available, the combination of maternal factors with MAP and UtA Doppler detects a large proportion of PE cases.[41,43]

Maternal hemodynamic assessment has improved the understanding of maternal cardiovascular adaptation, in both normal and complicated pregnancies. Challenging the placental origin hypothesis, PE may indeed be regarded as a cardiovascular syndrome.

Once placental blood flow is dependent on adequate maternal circulation, maternal cardiovascular maladaptation also plays a vital role in the pathophysiology of HDP and SGA, from as early as the first trimester of pregnancy, leading to secondary placental dysfunction.[14,63] Actually, there have been demonstrated pre-pregnancy differences in the hemodynamic profile of women who had subsequently developed PE and/or FGR.[5,64,65]

Thus, new non-invasive cardiovascular monitoring methods may open new perspectives on early screening, months before the clinical onset of pregnancy complications. *The International Working Group on Maternal Hemodynamics* provided recommendations on several non-invasive techniques (Figure 1) available for the measurement of cardiovascular parameters in pregnant women, such as thoracic bioreactance, non-imaging continuous-wave Doppler, bioimpedance and non-invasive pulse-contour analysis.[66]

Traditionally, PE has been regarded as a condition of hypoperfusion with increased SVR, resulting in hypertension. According to the former concept of a hyperdynamic disease model, the preclinical phase of PE was characterised by a hyperdynamic state (high-CO profile), with a subsequent hemodynamic crossover to a hypodynamic-vasoconstricted state (low-CO and high-resistance profile) at the onset of the clinical syndrome.[67]

Conflicting results regarding CO measurements were later interpreted considering the modern concepts of early and late PE, which are two distinct acknowledged phenotypes of the disease. In fact, early and late PE appear to develop from divergent maternal hemodynamic states in the latent phase of the disease. Early-onset PE expresses through a high-SVR-low-CO response, whereas late-onset PE is characterised by a low-SVR-high-CO profile.[29]

Recently, some studies have clarified the idea that, although early- and late-onset PE are considered to be different diseases, hemodynamic adaptation in pregnancies developing PE were unrelated to gestational age at onset, but rather strongly associated with the presence or absence of FGR. Thus, overall, PE is associated with high CO, but if PE coexists with FGR, which is more common in early-onset PE, then low CO is present.[68–70]

These hemodynamic differences help distinguishing HDP with a predominantly maternal component (PE only, chronic hypertension, gestational hypertension), from PE with a predominantly fetal component (PE-FGR).

Studies on the screening capacity of maternal hemodynamic for pregnancy complications are scarce. In a prospective study, Mahendru et al. measured maternal CO prior to pregnancy and in mid-pregnancy and reported an association between the change in this parameter during pregnancy and birthweight.[17] Thus, maternal cardiovascular changes in the first half of pregnancy may play an important role in determining fetal growth.

De Paco et al. demonstrated that the combination of CO measurement and maternal risk factors in the first trimester achieved a DR of 43.4% (95% CI, 32.5–54.7) for PE and 52% (95% CI, 36.9–67.1) for PE without SGA, for a 10% FPR.[71] In the third trimester, the assessment of maternal cardiac function is unlikely to improve the prediction performance established before.[72,73]

Gagliardi. et al. proposed that assessment of maternal hemodynamics and bioimpedance, at the time of combined screening for PE in the first trimester, could identify early markers of impaired cardiovascular adaptation that may lead to complications in the third trimester of pregnancy.[74]

Recently, a prospective, longitudinal observational study demonstrated that women screened in the first trimester as high-risk for preterm PE exhibited impaired cardiovascular adaptation with worsening CO and SV and persistently higher SVR and MAP throughout pregnancy when compared with low-risk women. Furthermore, the prophylactic use of aspirin (150 mg/day from 11–14 to 36 weeks' gestation) in this group did not appear to alter the maternal hemodynamic profile, which reassures the consensual safety of LDA in pregnancy.[75]

Pulse wave analysis (PWA) and velocity (PWV) are other promising non-invasive techniques, that reflect vascular compliance and endothelial function. Arterial PWA is inexpensive, easy to learn and apply, and seems to predict PE in the first trimester.[76] Moreover, the analysis of distal vasculature, such as the radial artery pulse waveform, can provide information on central hemodynamics.

Many studies have confirmed reduced arterial compliance and, therefore, increased arterial stiffness and endothelial dysfunction in women with clinically established PE, in agreement with the known pathophysiology of the disease.[77,78] Moreover, the degree of arterial stiffness, measured through carotid-femoral or carotid-radial PWV, central augmentation pressure (AP) and augmentation index at heart rate of 75 beats per minute (AIx-75), correlates with the clinical severity of the hypertensive disorders.[79]

Similar magnitude of aortic PWV and AIx increases can be seen in early sub-clinical stages (as early as 11 weeks).[76,80,81] In a prospective screening study on 210 low-risk women, radial artery PWA between 11+0 and 13+6 weeks of gestation achieved an 88% DR for early-onset PE, for a FPR of 11%.[82] These findings suggest that this technique provides a more accurate estimation of central vascular pressure than conventional blood pressure screening and could be used as a first trimester predictor of PE.

It has become increasingly evident that the uteroplacental blood flow relates as much to factors pertaining to maternal systemic vascular and endothelial function as to the 'downstream' placental bed. Everett et al. demonstrated an important association between raised UtA impedance and increased maternal arterial stiffness in the late second trimester, which in turn correlates to lower birthweight.[83]

Beyond a higher risk of PE, women with stiffer arteries in the first trimester are found to have a higher risk of SGA babies.[81,84] Indeed, a relationship between PWV and birthweight was found, with an increase of 1 m/sec in PWV associated with a decrease in birthweight centiles by 17.6%.[85]

However, studies examining PWV in isolated FGR are lacking, since a proportion of SGA babies are constitutionally small, healthy and grow normally.

Overall, current evidence shows that maternal hemodynamics may earn a place in the selection of high-risk women early in pregnancy. However, to date, improvements to the current combined screening methods have not been demonstrated.

III.2. Screening in hypertensive patients (chronic hypertension, gestational hypertension)

Accurate identification of women at high risk of experiencing complications is crucial in higher-risk populations, such as women with chronic hypertension (CH) and gestational hypertension (GH), to allow judicious allocation of monitoring resources and preventive treatment.

Current standard-of-care screening in this high-risk population relies on clinical risk factors, BP monitoring (i.e., MAP) and UtA Doppler imaging, of which second-trimester UtA-PI is the best predictor of superimposed PE.[86] However, the screening models in place perform poorly in high-risk pregnancies.[86–88] In addition, preventive therapy such as aspirin is less effective in reducing PE incidence in this group.[89] Thus, different screening tools and interventions are required in pregnancies at high-risk for PE and FGR.

Some centers have integrated maternal angiogenic markers testing (e.g., sFlt-1/PIGF ratio), which has proven useful in predicting the development of PE, iatrogenic preterm delivery and other adverse outcomes in pregnancies complicated by hypertension before 35 weeks' gestation.[90,91] The additive value of angiogenic biomarkers was reinforced by the recent update of NICE guideline, which includes PlGF testing in the management of women with suspected preeclampsia.[38]

Comprehensive maternal cardiovascular assessment is not currently standard-of-care screening in high-risk pregnancies. Furthermore, only a limited number of studies addressed its use in the screening for PE and FGR among high-risk populations. A recent prospective study performed a complete hemodynamic assessment (including MAP, HR, CO and SVR) using non-invasive devices on pregnancies complicated by hypertension and controls. It was found that hypertensive women with a low-CO-high-SVR hemodynamic profile had a higher risk of developing earlier PE (adjusted hazard ratio, 7.79 [95% CI, 1.94-31.24; P=0.003]).[92] Besides, the association between cardiovascular profile and earlier development of PE was stronger than the traditional risk factors (such as maternal age, body mass index, or antihypertensive use) and persisted after adjusting for maternal and pregnancy characteristics (such as ethnicity, MAP and gestational age at assessment, and initial diagnosis).[92]

Another promising hemodynamic parameter in the prediction of PE in women at increased a-priori risk for PE is aortic AIx-75.[93] This vascular compliance measurement appears to be also a

determinant of birthweight in women with CH who subsequently develop both PE and FGR.[94] As for screening of isolated FGR in hypertensive pregnancies, elevated AIx-75 and low CO in the first trimester seem to be the most sensitive measurements.[69,94]

Maternal cardiovascular assessment presents prognostic value, having the potential to detect subgroups of women with CH and GH associated with poorer outcomes and higher risk of developing PE and/or FGR. These will require closer antenatal surveillance and potentially targeted antihypertensive therapy to treat inherent cardiovascular dysfunction. A model combining both angiogenic markers and maternal cardiovascular assessment might be clinically useful.[95]

IV. Role in diagnosis

IV.1. Early and late preeclampsia

Traditional diagnosis of PE is based on the demonstration of hypertension and proteinuria after 20 weeks' gestation in a previously normotensive patient.[35,96,97]

Recently, in order to reduce delayed diagnosis, this definition was revised and broadened (Table III) to include cases without proteinuria but with evidence of other maternal end-organ or uteroplacental dysfunction, commonly present before the hallmark of proteinuria is detectable. Broader definitions significantly improve the detection of adverse outcomes, particularly when uteroplacental dysfunction is added, using fetal growth assessment and angiogenic markers' evaluation.[98]

Consequently, the term 'severe preeclampsia' has fallen out of favour in clinical practice, and new prediction models for adverse outcomes in preeclamptic pregnancies were created by the PIERS (**P**re-eclampsia **I**ntegrated **E**stimate of **RiS**k) group: full-PIERS and mini-PIERS. Clinical decision-making guided by a risk stratification approach allows timely and effective interventions, especially remote from term when potential perinatal gains are greater.[99,100]

As for the definition of hypertension in pregnancy, guidelines on HDP do not incorporate the most recent hypertension criteria by the 2017 ACC/AHA clinical practice guideline on hypertension.[101] Implementation of broader definitions of PE, now adopted by most international clinical practice guidelines, results in an increased incidence of diagnosis, without significant decrease in the performance of first-trimester screening for PE.[34,96,98,102–105] However, because the additional detected cases tend to be milder, doubts to whether this will improve outcomes in clinical practice have arised.[103,105]

Controversy remains regarding how maternal end-organ dysfunction should be defined, whether uteroplacental dysfunction should be included in the diagnostic criteria for PE, and if so, how it should be defined. Furthermore, preeclampsia and subsequent multiorgan dysfunction have been, perhaps erroneously, attributed purely to placental maldevelopment, rather than the manifestation of underlying cardiovascular dysfunction. Cardiovascular abnormalities associated with PE have been observed both before and after the index pregnancy, sustaining that the cardiovascular system may actually play a pivotal role in PE pathogenesis and that maternal cardiovascular dysfunction may in the future earn a place in the diagnostic criteria of preeclampsia.[5]

The evolving knowledge of preeclampsia as a heterogeneous HDP highlights an obvious limitation of current definitions: women with identical systolic BP and complications are viewed as equals, irrespective of their hemodynamic profile (CO, SV, HR, SVR and arterial function). Thus,

hemodynamic assessment of pregnant women may distinguish between 2 'clinical phenotypes' of PE that arise from opposing hemodynamic profiles in the latent phase of the disease and different pathogenic pathways, which are unlikely to benefit from the same treatment.[29]

These differences have been previously attributed to gestational age at onset, but recent evidence has clarified that, although early and late PE are considered to be different diseases, the hemodynamic phenotype in pregnancies developing PE was instead strongly associated with the presence or absence of FGR, due to placental insufficiency.[68–70]

Early-onset PE or PE with a predominantly fetal involvement (PE accompanied by FGR), previously interpreted as placenta-mediated disease, is characterised by constricted intravascular volume, with a shift towards low CO and HR, persistently high SVR and increased MAP, as well as cardiac remodelling with left ventricular concentric hypertrophy and asymptomatic global diastolic dysfunction.[3,68,106–109] This is the most severe clinical variant, commonly associated with abnormal UtA Doppler, higher incidence of induced premature delivery, and adverse maternal and neonatal outcomes.[30]

In contrast, late-onset PE or PE with a predominantly maternal component, related to maternal constitutional factors, expresses through a low SVR-high CO profile.[29] This is the most prevalent clinical variant, associated with normal or slightly increased uterine resistance index, normal birthweight and more favourable perinatal outcomes.[30]

In summary, PE is overall associated with high CO, but if PE coexists with FGR, which is more common in early-onset PE, low CO is present.[68–70] Lastly, the uterine and fetal Doppler changes contemplated in current criteria for the diagnosis of PE are significantly influenced by maternal hemodynamics. Thus, maternal cardiovascular maladaptation should be considered alongside malplacentation to understand the pathogenesis of uteroplacental dysfunction and may precede FGR.[110] Accordingly, identification of an unfavourable hemodynamic profile may earn an important role in the early diagnosis of uteroplacental dysfunction, the differential diagnosis of the 2 'clinical phenotypes' addressed and the risk stratification of preeclamptic pregnancies, allowing better surveillance and individualised treatment.

IV.2. FGR

SGA pregnancies, in particular those with FGR, are associated with an increased risk of adverse fetal and neonatal outcomes, which are significantly related to gestational age at onset.[111]

The diagnostic criteria of FGR vary among different guidelines, but *The International Society of Ultrasound in Obstetrics & Gynecology* practice guideline 2020 on the diagnosis and management of the SGA fetus and FGR recommends the Delphi consensus criteria (Table IV).[112,113]

Recently, many studies have demonstrated that pregnancies affected by compromised fetal growth are associated with a high-SVR-low-CO static maternal hemodynamic profile.[107,114–118] Furthermore, UtA-PI seems to correlate positively with maternal SVR and negatively with maternal CO, while the opposite occurs for birthweight.[17,71,110,119]

Evidence of hemodynamic differences in preconception and early pregnancy, along with persistent postpartum cardiovascular dysfunction after pregnancies complicated by FGR, supports the contribution of the cardiovascular system to the development of FGR.[5,17,120] However, only recently, clear differences were demonstrated between pregnancies with SGA and FGR using non-invasive maternal hemodynamic assessment, as previously denoted using maternal ecocardiography.[121,122]

In a prospective study on a large cohort of normotensive pregnancies (102 FGR, 64 SGA and 401 controls), *Perry et al*. assessed maternal hemodynamic indices at the time of diagnosis of SGA during pregnancy. They found that impaired maternal hemodynamic function (lower HR and CO, together with higher MAP, SVR and UtA resistance) was only present in pregnancies complicated by FGR. Those delivering a SGA neonate and healthy control pregnancies had a normal maternal hemodynamic function.[123]

Thus, maternal cardiovascular function assessment may therefore be of value in the clinical management of SGA pregnancies, along with fetal biometry and Doppler evaluation, to obtain diagnostic and prognostic information.

Inclusion of maternal hemodynamic assessment into routine clinical care of pregnancies complicated by SGA could perhaps help distinguishing between those with growth restriction and those who will reach their full genetic growth potential being SGA. This may reduce iatrogenic prematurity of small fetuses, and also allow earlier interventions before maternal or fetal compromise ensues.

V. Role in treatment

Despite intense research, there is still no effective treatment for PE or FGR, rather than elective delivery. Growing data on maternal hemodynamic assessment has revealed that the cardiovascular phenotype differs according to the underlying pathology (GH, PE, FGR or PE with FGR), providing a rational basis for individualised therapeutic management.[29,106,124]

Out of pregnancy, there is well-established guidance to individualise antihypertensive treatment based on empirical hemodynamic profile, according to specific characteristics such as age, ethnicity and body mass index (BMI). [125,126]

Targeted therapy according to the hemodynamic phenotype seems to be more effective than therapy guided by physician preference or standard recommendations in achieving BP goals and decreasing hypertensive complications and related diseases.[127–129]

In pregnancy, current recommendations do not differentiate therapy based on additional maternal physiological characteristics apart from BP. This is partly related to the criteria currently used in clinical practice to define and diagnose GH, PE and FGR. Moreover, there is no consensus on the threshold above which empirical antihypertensive treatment should be initiated and BP targets when hypertension is not severe.[37,101] There is also no agreement on the most effective antihypertensive therapy when managing HDP. Although oral labetalol is recommended as the first-line agent for all pregnant women in the UK, ACOG does not state a preference.[10,37]

V.1. Gestational hypertension (GH)

Maternal cardiovascular assessment has the potential to identify subgroups of GH associated with poorer outcomes and higher risk of developing PE, which benefit from closer antenatal surveillance and targeted antihypertensive therapy.

Maternal hemodynamic assessment allows women with HDP to be sorted into 2 subgroups: those with low SVR, who can be treated successfully with beta-blockers such as labetalol (with both vasodilator and negative inotropic effect), and those with high SVR, who have worse prognosis and will likely require additional vasodilator therapy.[130,131] Furthermore, the use of serial hemodynamic monitoring to guide treatment throughout pregnancies complicated by hypertension significantly reduces severe hypertension rates from 18% to 3.8%, and performs better than occasional hemodynamic profiling before initiating first-line antihypertensive therapy or shortly after acute labetalol therapy.[130,132] However, maternal hemodynamics in GH have not been as thoroughly investigated as in PE, limiting conclusions about the best therapeutic management to implement.

V.2. Preeclampsia (early and late onset)

Compared with women with GH, those with PE seem less likely to respond to labetalol monotherapy and most often require additional vasodilator therapy.[130]

Pregnant women who subsequently develop early-onset or late-onset preeclampsia and/or FGR exhibit distinct hemodynamic profiles early in pregnancy before the development of clinical hypertension and even before pregnancy.[5,29,68] Thus, hemodynamic-guided antihypertensive therapy may improve BP management, as patients with hyperdynamic circulation (higher CO and HR and lower SVR) will benefit more from a beta-blocking effect, while patients with a hypodynamic-vasoconstricted profile will benefit more from a potent alpha-blocking effect.[130–132]

Assuming that early and late onset PE have different underlying pathophysiologic mechanisms, not related with primary placental disfunction but rather with maternal hemodynamic phenotype, the use of maternal hemodynamic assessment to guide individualised antihypertensive treatment will contribute to a better control of maternal BP. This will also affect fetal hemodynamic markers and will indirectly contribute to avoid unnecessary preterm terminations of pregnancy.

V.3. FGR

In FGR with associated PE, antihypertensive treatment ignoring maternal cardiovascular function raises concerns regarding adequate uteroplacental perfusion and fetal growth: a well-maintained maternal CO is essential for consistent and appropriate growth.

There is evidence connecting the reduction of maternal BP or treatment with negative inotropic agents (such as beta-blockers) with subsequent slowing of fetal growth, FGR and stillbirth.[133–135] However, when a hemodynamic-guided treatment approach was used, women did not exhibit a steep CO drop and delivered appropriate-for-gestational-age babies. This corroborates the hypothesis that maternal hemodynamic monitoring may prompt adequate treatment adjustments as to preserve maternal CO that do not jeopardise fetal growth.[130,136]

In addition, the combination of vasodilator therapy (including NO donors) and intravascular volume expansion in hypertensive pregnancies with high SVR complicated by FGR and abnormal UtA Doppler may optimise fetal growth and prolong pregnancy, as it may improve both maternal and fetal hemodynamic indices.[116,137]

Recent evidence has contradicted the previous view on conditions thought to be due to irreversible placental disease, allowing new approaches to fetal therapy. If maternal cardiovascular function, rather than the placenta, does indeed modulate uteroplacental perfusion in conditions characterised by abnormal fetal Doppler indices, targeted therapeutic intervention before or after

established PE and/or FGR may optimise maternal cardiovascular and uteroplacental function, and hence fetal condition.[110,138]

VI. Role in the prediction of cardiovascular disease (CVD) in the future

In addition to increased perinatal adverse outcomes, women with previous pregnancies complicated by hypertensive disorders have an increased later-life cardiovascular risk, especially in cases of early-onset PE, severe PE or recurrent PE, denoting a dose-response relationship between exposure to even modest BP elevations and future CVD risk.[139–141] This includes an almost fourfold increased risk of chronic hypertension and heart failure, and twofold increased risk of ischaemic heart disease, stroke, and premature mortality.[142,143]

The exact pathophysiological mechanism leading to increased CVD risk remains unknown and might, in fact, be multifactorial. The current literature suggests three pathways: pregnancy-induced CVD risk, pre-pregnancy underlying predisposition, or a combination of both.[144]

Despite general agreement on women's benefit from early postpartum cardiovascular risk assessment, after pregnancies complicated by HDP (Figure 8), only recently considered an independent risk factor for CVD, the guidelines show different recommendations.[145–147]

The classical used risk score models, such as the Framingham Risk Score, fail because of their young age and premenopausal state, leaving these women currently outside the scope of most of the preventive programs.[148]

Therefore, new biomarkers for postpartum risk stratification are currently being investigated, such as carotid intima-media thickness, coronary artery calcification, or cardiac and vascular function assessment.

VI.1. Blood pressure

Although the increased cardiovascular risk persists in long term, the risk of developing hypertension after HDP is greater within the first 2 years after delivery (six-fold), especially during the early postpartum period (more than ten-fold in the first 6 months).[149]

The speed of resolution of raised BP after delivery and the prevalence of persistent hypertension depends on the underlying or pre-existing diagnosis. In previously normotensive women, hypertension and proteinuria should resolve up until 6 to 12 weeks postpartum, which is noted as the ideal window for revaluation and CVD risk assessment after pregnancies complicated by HDP.[38,104] Approximately 50% of women will have persistent hypertension at 12 weeks postpartum, and the risk is higher in women with previous CH, long duration of antihypertensive treatment in pregnancy, higher maximum systolic and diastolic BP, higher BMI, or preterm PE.[150,151]

Using 24-hour ambulatory blood pressure monitoring (ABPM), 40% of women with previous severe PE will have hypertension at 1 year after delivery and will need antihypertensive

treatment.[152,153] BP monitoring in the early postpartum period may define a subgroup of women for whom targeted BP lowering therapy will be successful in reducing their long-term cardiovascular risk.

However, it is becoming clear that a significant proportion of women with severe or preterm PE, despite becoming normotensive and asymptomatic, present persistent or residual endothelial and cardiac dysfunction.[154–156] Non-invasive assessment of women's cardiovascular profile in the postnatal period may identify women at risk for short and long-term cardiovascular morbidity. This will allow adoption of appropriate follow-up and prevention protocols adapted to young women's CVD risk profile.

VI.2. Vascular function

Parameters obtained from vascular function assessment using PWV, PWA, PAT and FMD may offer an opportunity for the early identification of premenopausal women with cardiovascular risk after preeclampsia in pregnancy. In fact, these potential biomarkers have been associated with left ventricular hypertrophy, CVD events, and all-cause mortality, in the general population.[157–160]

PWV measures arterial stiffness, whereas PWA measures aortic AIx and central pulse pressure, which is a better predictor of cardiovascular outcome than traditional peripheral BP.[161]

Women with previous preeclampsia in pregnancy exhibit lower brachial artery FMD and increased carotid-femoral PWV and AIx from prior to preeclampsia onset until 3 years postpartum, when compared with normotensive controls.[162,163]

While low brachial artery FMD predicts cardiovascular risk in low-risk populations, with a 1% decrease in FMD being related to an 8% increase in future CVD events' risk, its association with elevated rates of premature CVD seen in this high-risk group (with stiffer brachial arteries) remains unclear.[162,164]

Compared to endothelium-dependent FMD, PAT is a more reproducible and practical non-invasive technique for endothelial function assessment in clinical practice. A recent prospective case-control study performed non-invasive vascular assessment at one-year postpartum after preeclampsia and uncomplicated pregnancies using PAT to measure microvascular vasodilatory response to postischemic hyperemia and arterial stiffness. Significant differences were found in vascular function associated with prior preeclampsia, including higher vascular resistance and increased arterial stiffness.[165]

More research is needed to determine long-term persistence of endothelial dysfunction following preeclampsia in pregnancy and whether it has lasting effects on cardiovascular risk. This would improve postpartum management, including the efficacy of early targeted treatment. The

use of statins in the treatment of preeclampsia, to reduce endothelial dysfunction and consequently future adverse cardiovascular events, has been suggested as a candidate.[148,166]

Gestational age at preeclampsia onset might be helpful in directing postpartum CVD prevention strategies, since according to some studies only early-onset or severe PE are associated with impaired vascular function and subclinical atherosclerosis later in life.[120,167]

One major limitation in current literature is the lack of knowledge about the vascular health of women prior to the affected pregnancy. Whether postpartum vascular dysfunction results from lasting cardiovascular damage caused by PE or precedes a preeclamptic pregnancy is yet to be defined.[144] However, women with no pre-existing conditions still develop preeclampsia and, although a prior pregnancy complicated by PE is a risk factor, PE doesn't always recur in subsequent pregnancies.

VI.3. Cardiac function

Immediately after birth, concomitantly with the resolution of preeclampsia symptoms, SV, CO and MAP decrease, returning to healthy pregnancy ranges within 3 to 4 days. Despite apparently supporting the clinical paradigm that birth solves preeclampsia by making BP values return to normal, SVR and MAP remain significantly higher compared to healthy pregnancies.[168]

Although some women present left ventricular (LV) contractility and diastolic function within normal reference ranges, the incidence of asymptomatic ventricular dysfunction is increased in the immediate postpartum period after pregnancies complicated by PE (specially severe or preterm).[155] Melchiorre et al. conducted a prospective, longitudinal case-control study, over a 3-year period, showing that the majority of preterm preeclamptic women have stage B asymptomatic heart failure (HF-B) at 1 year postpartum (56% compared to 14% of term preeclamptic and 8% [$P < 0.001$] of normotensive controls), and 40% develop hypertension within 2 years.[153] The structural changes consistent with HF-B may persist until at least 4 years after delivery.[169]

In PE, the vascular "overfill" arising from intolerance to volu me expansion sets up a vicious circle where systemic hypertension leads to further vascular damage and increases in BP. Abnormal cardiac adaptation, besides favouring the development of FGR and/or PE during pregnancy, may also lead to vascular damage that persists into later life.

However, Breetveld et al. did not observe any association between endothelial dysfunction and the prevalence of HF-A or HF-B in formerly preeclamptic women, suggesting different mechanisms underlying the subclinical stages of HF, which are not yet uncovered.[169]

Nonetheless, the subclinical cardiac abnormalities observed (diastolic dysfunction, LV remodelling and reduced LV contractility) are used in cardiovascular risk stratification for

nonpregnant patients and, thus, may be unique markers to identify women at higher risk for future premature CVD.

VII. Research agenda

To allow widespread implementation of non-invasive maternal hemodynamic assessment, further validation studies on these emerging techniques and devices in pregnant women are required, as well as reports on device-specific reference ranges in pregnancy.

Most studies refer to narrow time periods and pre-conception cardiovascular data is lacking. Thereby, additional longitudinal studies on hemodynamic changes, starting prior to conception or early in pregnancy and continuing to the delivery and the postpartum period, will be extremely valuable to establish early screening protocols and to allow early risk reduction interventions. They may also help to determine whether the cardiovascular dysfunction observed prior to preeclampsia is due to pre-existing maternal risk factors or is attributable to early stages in the disease process.

Data on longitudinal hemodynamic changes that occur as a consequence of hemodynamic-guided antihypertensive therapy may reinforce its efficacy and safety on HDP.

Also, future studies will confirm whether proper BP control using individualised targeted approaches is successful in PE and future CVD prevention, with favourable modification of maternal and perinatal outcomes.

Further insight into the hemodynamic changes in complicated pregnancies and the pathophysiological or molecular links between PE and CVD may also provide rational basis for the identification of potential targets for novel preventive and treatment strategies for both conditions.

Finally, research should also focus on developing effective screening for women at increased risk of cardiovascular diseases in the postpartum period, after preeclampsia, required to establish appropriate long-term cardiovascular follow-up programmes and individualised targeted interventions to improve outcomes.

VIII. Conclusion

Unfavourable maternal cardiovascular adaptation to pregnancy predisposes women to the development of complications, such as PE or FGR, as well as increased risk of future CVD. Emerging evidence on maternal hemodynamics confirms significant differences between normotensive and hypertensive pregnancies.

Comprehensive hemodynamic assessment may, in the future, integrate first trimester screening for PE and FGR, as it is able to identify high-risk pregnancies with subclinical cardiovascular impairment, which will benefit from low-dose aspirin initiated before 16 weeks' gestation and closer prenatal surveillance.

Furthermore, maternal hemodynamic profile presents prognostic value in these pregnancy complications, allowing distinction between 2 'cardiovascular phenotypes' that differ regarding gestational age at onset (early vs late PE), fetal involvement (isolated PE, PE and FGR) and adverse maternal and neonatal outcomes, in which treatment has to be individualised. Women with a low-CO-high-SVR hemodynamic profile and elevated AIx-75 present worse prognosis, developing PE sooner with an associate adverse impact in feto-maternal health.

Serial hemodynamic assessment may be useful when selecting a particular type of antihypertensive drug therapy. Distinction of women with low vascular resistance who respond to first line treatment, labetalol, from those who will need additional vasodilator therapy, reduces the occurrence of severe preeclampsia. Also, a hemodynamic-guided treatment approach may prompt adjustments to preserve maternal CO, preventing jeopardised fetal growth.

In pregnancies complicated by SGA, inclusion of maternal cardiovascular profile into routine care may also help distinguishing growth restricted fetuses from healthy SGA fetuses. This is of utmost importance to avoid inadequate preterm iatrogenic delivery in SGAs and to allow timely intervention in FGR, avoiding related adverse outcomes.

Preeclampsia offers a unique window of opportunity to identify maternal endothelial dysfunction and pre-existing cardiovascular abnormalities, which may have serious implications in the cardiovascular system later in life, and to provide timely cardiovascular risk reduction protocols.

Therefore, while we remain unable to effectively prevent all types of preeclampsia, attempts to reduce its long-term impacts are of potential importance. All measures capable of modifying abnormal maternal hemodynamics are valuable and may help prevent the development of unfavourable cardiac profiles in the future – to achieve this goal the implementation of effective cardiovascular screening and follow-up programmes soon after delivery is crucial.

For all these reasons, modern obstetrics cannot afford anymore neglecting the study of maternal cardiac and vascular function in order to improve maternal and perinatal outcomes. This is probably one of the most important clinical challenges that will change obstetrics in the next couple of years.

IX. Appendix

Table I Overview of early cardiovascular changes in normal pregnancy. *(Adapted from Vonck et al. 2016[170])*

		Early first trimester (5-7 weeks' gestation)	Late first trimester (8-12 weeks' gestation)
Plasma	Volume	↑	
Arteries	SVR	↓	
	PWV	↓	
	Compliance	↑	
	BP	↓	
Veins	Venous return	↑	
	Distensibility	↑	
	Capacitance	↑	
Heart	HR	↑	
	SV	↑	
	CO	↑	
	Cardiac filling pressure	↑	
	Inotropy		↑
	Heart surface area		↑
	Atrial-ventricular dimensions		↑
	Ventricular wall		↑

BP, blood pressure; CO, cardiac output; HR, heart rate; PWV, pulse wave velocity; SV, stroke volume; SVR, systemic vascular resistance.

Table II Different screening models for preeclampsia, based on maternal risk factors.

		ACOG 2013[35] (USA)	ACOG 2018[36] (USA)	NICE 2010 and 2019 [37,38] (UK)
Maternal risk factors	**High-risk factors**	• History of early-onset PE requiring preterm delivery before 34 weeks of gestation • More than one previous pregnancy complicated by PE (recurrent PE)	• Previous pregnancy with PE • Chronic hypertension • Systemic lupus erythematosus • Type 1 or type 2 diabetes mellitus • Renal disease • Multifetal gestation • Antiphospholipid syndrome	• Previous pregnancy with PE • Chronic hypertension • Autoimmune disease • Type 1 or type 2 diabetes mellitus • Chronic kidney disease • Antiphospholipid syndrome
	Moderate-risk factors		• Nulliparity • Age ≥ 35 years • Interpregnancy interval >10 y • BMI >30 kg/m2 • Family history of PE (mother or sister) • History of SGA or adverse outcome • Sociodemographic characteristics (African American race or low socioeconomic status)	• Nulliparity • Maternal age ≥ 40 y • Multifetal pregnancy • Interpregnancy interval >10 y • BMI at first visit ≥ 35 kg/m2 • Family history of PE
Indications for low-dose aspirin prophylaxis (women at high risk for preeclampsia)		• History of early-onset PE requiring preterm delivery before 34 weeks of gestation • More than one previous pregnancy complicated by PE • Dose: 81 mg/d initiated between 12-28 wks, optimally before 16 wks • Continue daily until delivery	• 1 or more high-risk factors • Consider if 2 or more moderate risk factors • Dose: 81 mg/d initiated between 12 and 28 wks, optimally before 16 wks • Continue daily until delivery	• 1 or more high-risk factors • 2 or more moderate risk factors • Dose: 75 to 150 mg/day from 12 wks • Continue daily until delivery
Detection rates [39]	**Preterm PE**	5% (95% CI, 2-14%)	90% (95% CI, 79-96%)	39% (95% CI, 27–53%)
	Term PE	2% (95% CI, 0.3-5%)	89% (95% CI, 84-94%)	34% (95% CI, 27-41%)
	FPR	0.2%	64,2%	10,2%

ACOG, The American College of Obstetricians and Gynecologists; BMI, body mass index; FPR, false positive rate; NICE, The National Institute for Health and Care Excellence; PE, preeclampsia; SGA, small-for-gestational-age; UK, United Kingdom; USA, United States of America; Wks, weeks of gestation.

Table III Diagnostic criteria for the hypertensive disorders of pregnancy. *(Adapted from ACOG Practice Bulletin No. 202, 2019[96] , ACOG Practice Bulletin No. 222, 2020[171], Brown et al., 2018[104], and Webster et al., 2019[34]).*

New Classification of the Hypertensive Disorders of Pregnancy	
Condition	**Diagnostic criteria**
Chronic hypertension	Hypertension (SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, on two occasions at least 4 hours apart) present before 20 weeks' gestation or persistent beyond 12 weeks postpartum
Gestational hypertension	New onset of hypertension after 20 weeks' gestation in previously normotensive women Without end-organ dysfunction
Preeclampsia	New onset of hypertension after 20 weeks' gestation in previously normotensive women With end-organ dysfunction: • **Proteinuria** (on the following): Protein ≥ 300 mg on 24-hour urine Urine protein/creatinine ratio ≥ 0.3 Urine dipstick reading ≥ 2+, if quantitative testing is not available Or ≥ 1 of the following: • **Renal insufficiency**: Serum creatinine > 1.1 mg/dL or doubled, in the absence of other renal disease • **Impaired liver function**: Elevated blood concentrations of liver transaminases at least to twice normal concentration (> 40 IU/L) with or without right upper quadrant or epigastric abdominal pain • **Hematologic complications**: Thrombocytopenia (platelet count less than 100 x 10^9/L) Disseminated intravascular coagulation Hemolysis • **Pulmonary oedema** • **Neurological complications** (e.g. eclampsia, altered mental status, stroke, clonus, new-onset severe headache, and visual symptoms such as persistent visual scotoma and blindness) • **Uteroplacental dysfunction**: fetal growth restriction, abnormal uterine and umbilical artery Doppler waveform analysis, or intrauterine fetal death.
Superimposed preeclampsia	New onset of maternal end-organ dysfunction (as described above) after 20 weeks' gestation, in previously hypertensive women

DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a] In the presence of SBP ≥160 mmHg and/or DBP ≥110 mmHg, severe hypertension should be confirmed within 15 minutes to facilitate timely antihypertensive therapy.

Table IV Definitions of early- and late-onset fetal growth restriction (FGR) in the absence of congenital anomalies, based on the international Delphi consensus. (Adapted from *Gordjin et al., 2016*[112])

Early FGR (GA < 32 weeks)	Late FGR (GA ≥ 32 weeks)
AC/EFW < 3rd centile or UA-AEDF Or 1. AC/EFW < 10th centile combined with 2. UtA-PI > 95th centile and/or 3. UA-PI > 95th centile	AC/EFW < 3rd centile Or at least two of the following: 1. AC/EFW < 10th centile 2. AC/EFW crossing > 2 quartiles on growth centiles* 3. CPR < 5th centile or UA-PI > 95th centile

* Growth centiles are non-customised centiles.

AC, fetal abdominal circumference; AEDF, absent end-diastolic flow; CPR, cerebroplacental ratio; EFW, estimated fetal weight; GA, gestational age; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.

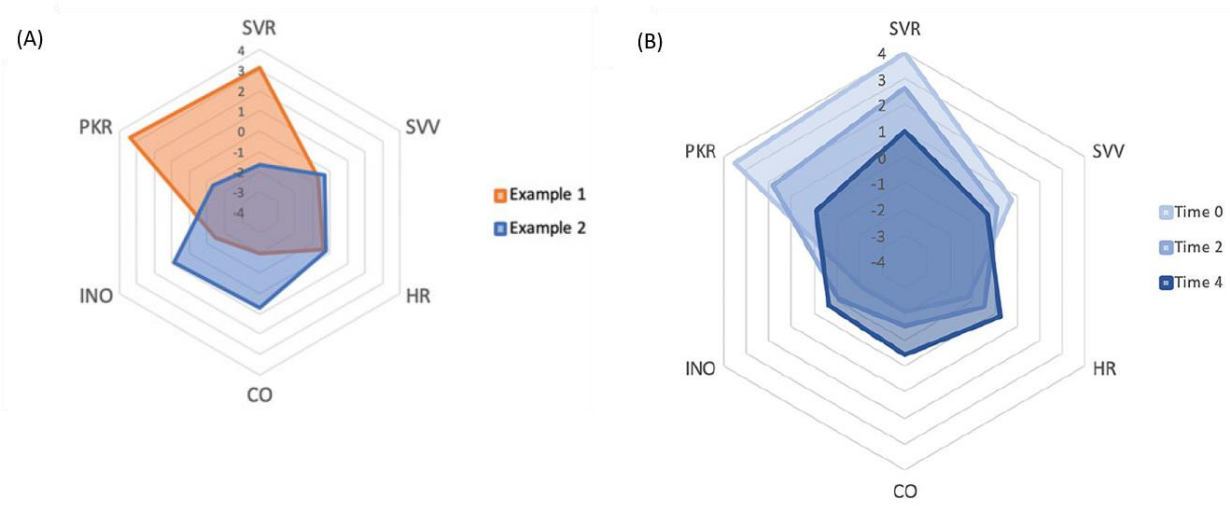

Figure 1 Radar chart: a simple graphing technique to display multiple hemodynamic parameters and easier analysis of the patient's hemodynamic profile. (*copyright* Valensise et al., 2019[172])

CO, cardiac output; HR, heart rate; INO, Smith–Madigan inotropy index; PKR, potential-to-kinetic energy ratio; SVR, systemic vascular resistance; SVV, stroke volume variation.

(A) Radar chart comparing two different hemodynamic profiles: Example 1 (e.g., patient's hemodynamic profile) versus Example 2 (e.g., optimal hemodynamic profile).

(B) Radar chart illustrating hemodynamic modifications over time in the same individual or group (e.g., during antihypertensive treatment).

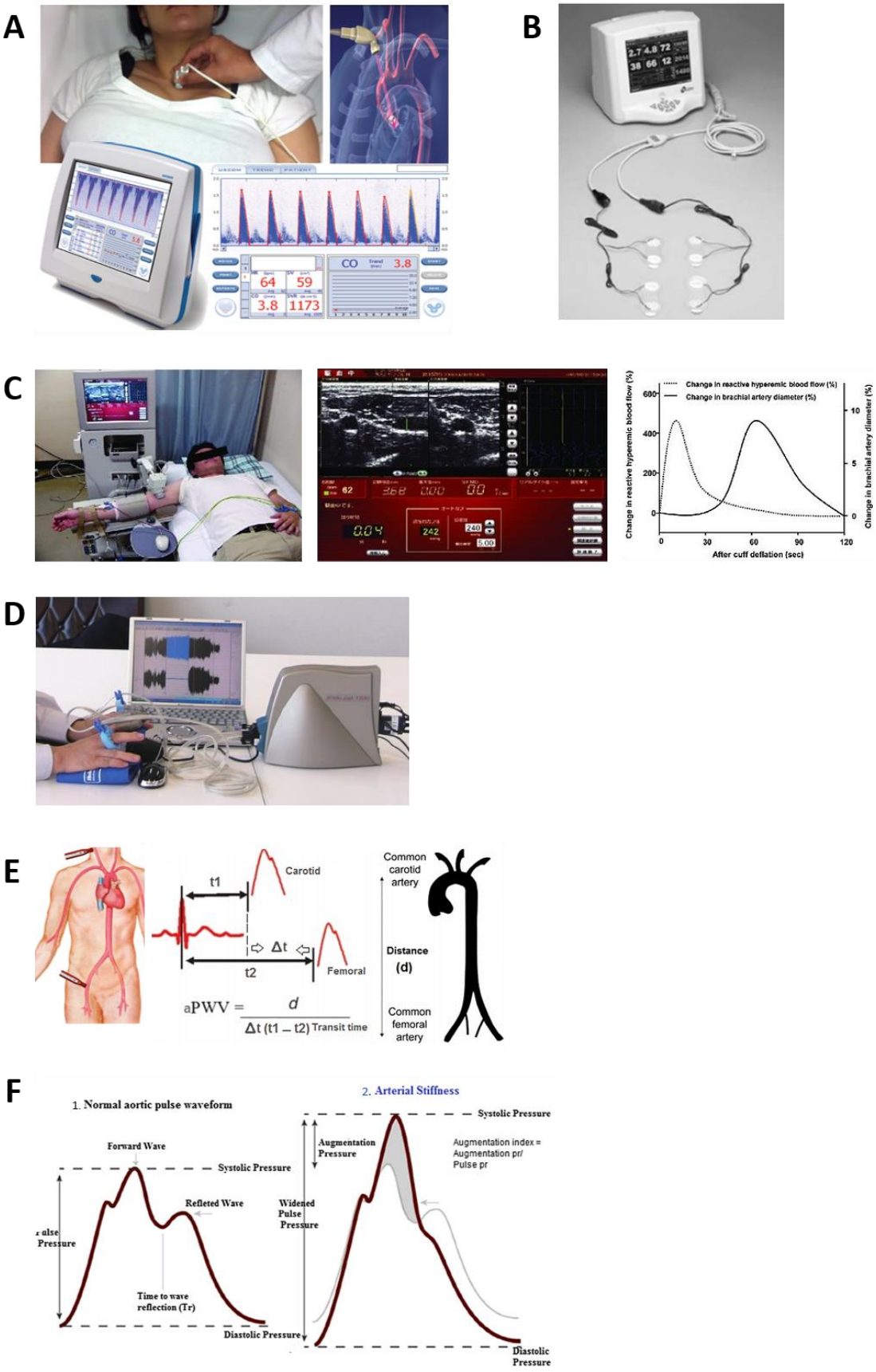

Figure 2 New non-invasive techniques and devices used for hemodynamic assessment.

(A) Ultrasonic Cardiac Output Monitor device (USCOM-1A®, Uscom Ltd.), which uses a non-imaging continuous-wave Doppler transducer placed on the suprasternal notch. It is user-friendly, less operator dependent than echocardiography and can provide measures of CO, HR, SVR and inotropy index. *(copyright* Perry et al., 2020[123]*)*

(B) Non-Invasive Cardiac Output Monitor (NICOM, Cheetah Medical), which is based on bioreactance technology. (c*opyright* www.cheetah-medical.com)

(C) Measurement of flow-mediated vasodilation (FMD), using change in reactive hyperemic blood flow and change in brachial artery diameter after cuff deflation obtained by Doppler imaging. (*copyright* Higashi Y., 2015[173])

(D) Measurement of reactive hyperemia using peripheral arterial tonometry (RH-PAT). (*copyrigh*t Higashi Y., 2015[173])

(E) Aortic pulse wave velocity (aPWV) measurement using mechanoreceptors: aPWV is calculated by dividing the distance (d) between the two arterial sites by the difference in time of pressure wave arrival between the carotid (t1) and femoral artery (t2) referenced to the R wave of the electrocardiogram. (*copyright* Refaat et al., 2015[174])

(F) Hemodynamic changes in arterial stiffness, obtained by computerised oscillometry or applanation tonometry; (1) In normal aortic pulse waveform: forward wave precedes backward wave, (2) In arterial stiffness: due to increased aPWV, forward wave and reflected wave are integrated producing augmented pulse pressure. (*copyright* Refaat et al., 2015[174])

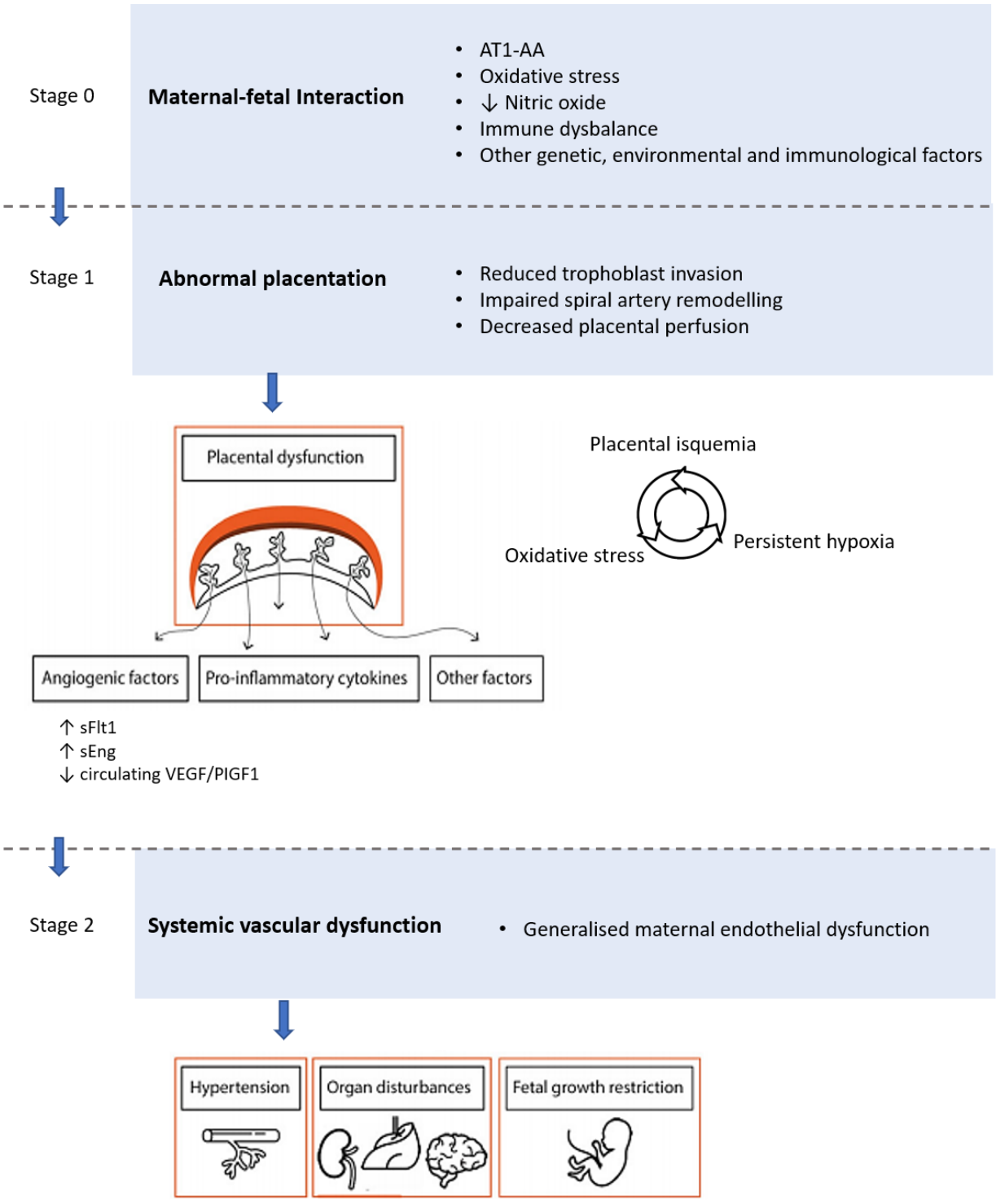

Figure 3 Scheme of the complex pathogenesis of preeclampsia: a two-stage model. (Adapted from Paauwy N.D., Lely A.T., 2018[27] and Belinda Jim B., Karumanchi S.A., 2017[175])

Genetic, immunological and other maternal factors induce early abnormalities at the maternal-fetal interface (stage 0), causing placenta dysfunction (stage 1) and leading to the release of antiangiogenic factors (such as sFLT1 and sENG) and other inflammatory mediators, which consequently induce the maternal syndrome (stage 2).

AT1-AA, autoantibodies to angiotensin receptor 1; PIGF1, placental growth factor 1; sFLT1, soluble fms-like tyrosine kinase 1; sENG, soluble endoglin; VEGF, vascular endothelial growth factor.

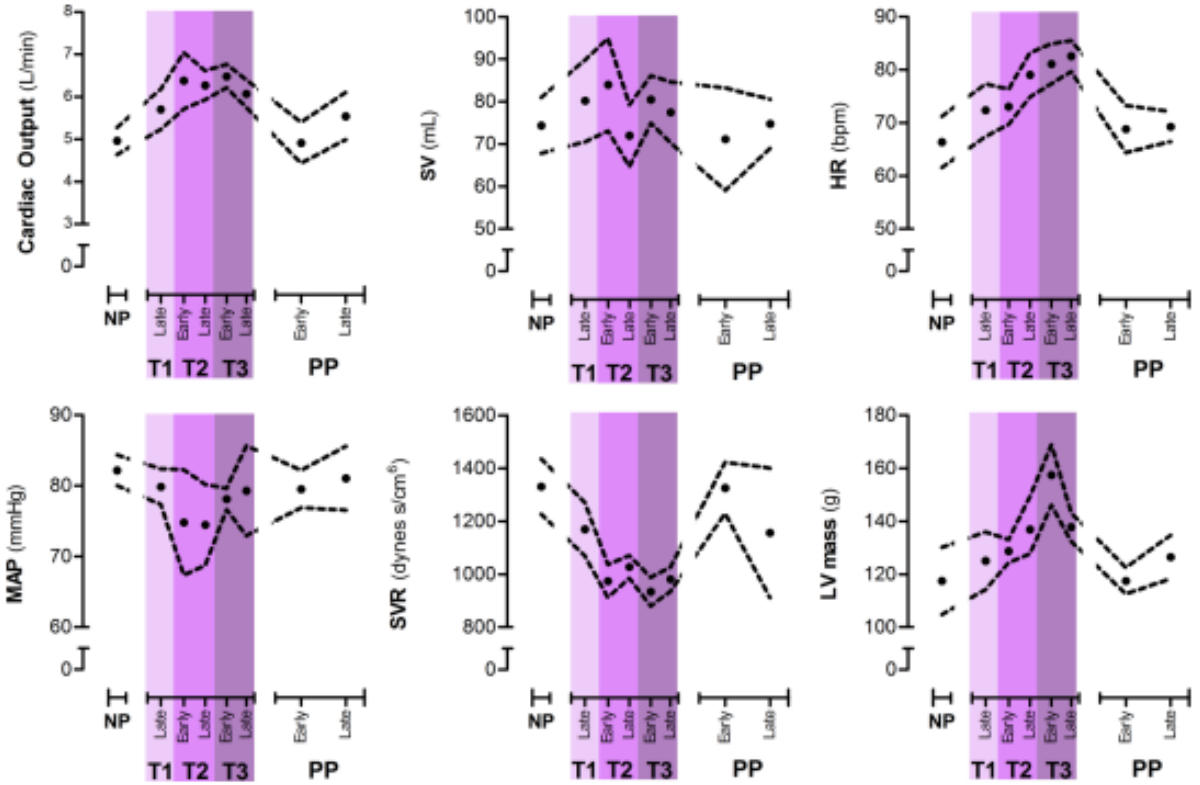

Figure 4 Longitudinal hemodynamic changes throughout healthy pregnancy *(Copyright* Meah et al. 2016 [21])

HR, heart rate; LV, left ventricular; MAP, mean arterial pressure; NP, non-pregnant; PP, postpartum; SV, stroke volume; SVR, systemic vascular resistance; T1, first trimester; T2, second trimester; T3, third trimester.

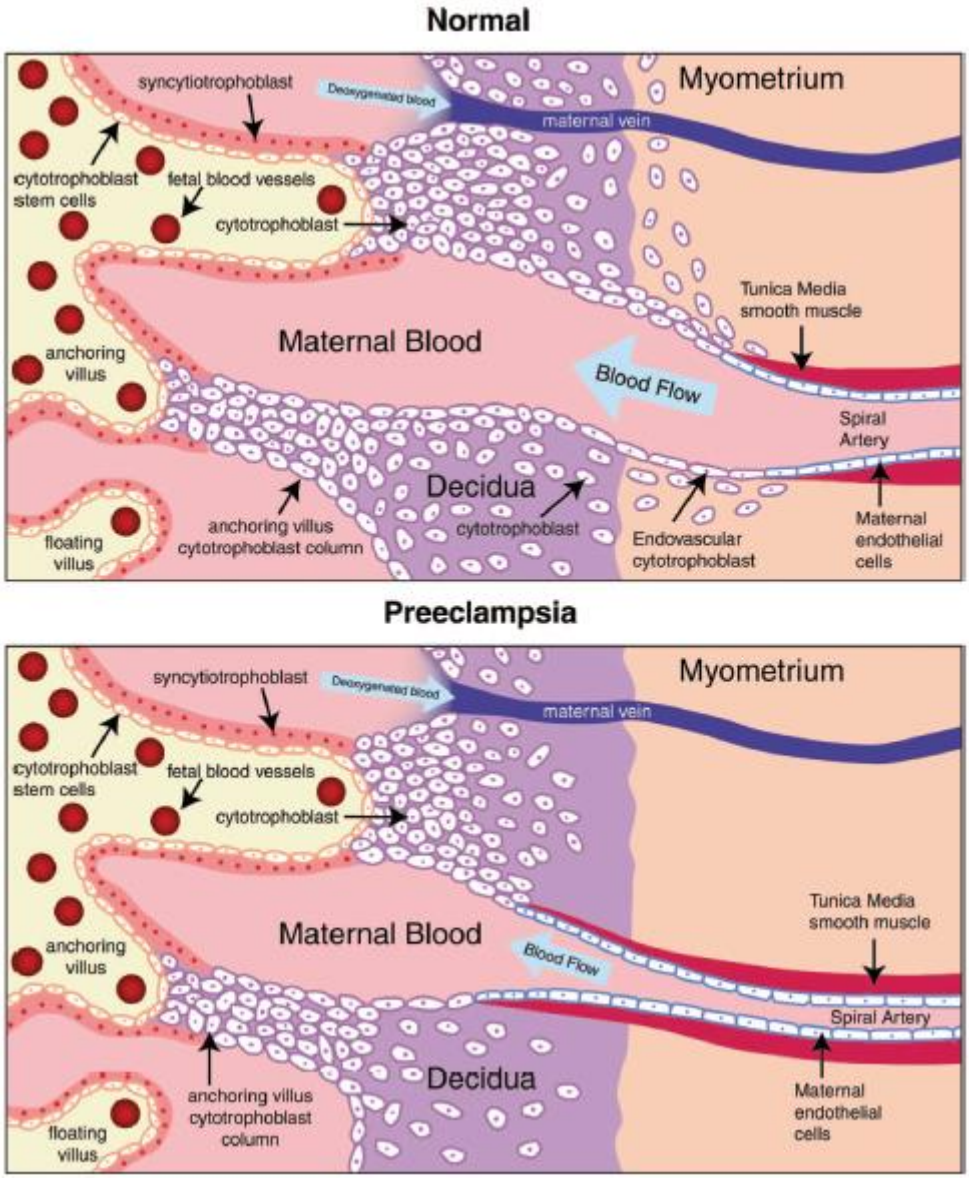

Figure 5 Abnormal placentation in preeclampsia. (Reprinted from Lam et al.,2005[11])

In normal placental development, fetal invasive cytotrophoblasts invade the maternal spiral arteries, transforming them from small-caliber resistance vessels to high-caliber capacitance vessels capable of providing adequate placental perfusion to sustain fetal growth. During the process of vascular invasion, the cytotrophoblasts differentiate from an epithelial phenotype to an endothelial phenotype, a process referred to as “pseudovasculogenesis” (upper panel).

In pregnancies affected by preeclampsia, impaired cytotrophoblasts’ phenotype switch from proliferative to invasive leads to a shallow invasion into the myometrial segment of the spiral artery. The consequent failure of physiological transformation of the spiral arteries results in narrow spiral arteries, a disturbed pattern of blood flow and reduced uteroplacental perfusion (lower panel).

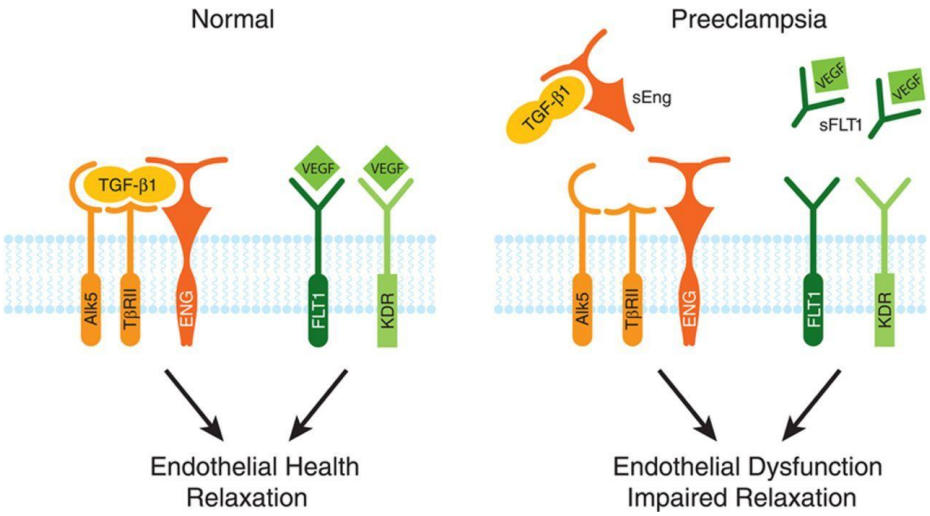

Figure 6 Angiogenic imbalance and endothelial dysfunction in preeclampsia. (Reprinted from Powe et al., 2011[176])

VEGF and TGF-β1 are required to maintain endothelial health. During normal pregnancy vascular homeostasis is maintained by physiological levels of VEGF and TGF-β1 signalling in the vasculature (left). In pregnancies complicated by preeclampsia, due to excessive placental secretion of potent endogenous circulating antiangiogenic factors, high levels of circulating sFLT1 and sENG inhibit VEGF and TGF-β1 signalling, respectively, in the vasculature. This results in endothelial dysfunction, including decreased prostacyclin, nitric oxide production, and release of procoagulant proteins (right).

sENG, soluble endoglin; sFLT-1, soluble fms-like tyrosine kinase 1; VEGF, vascular endothelial growth factor; TGFβ1, transforming growth factor β1.

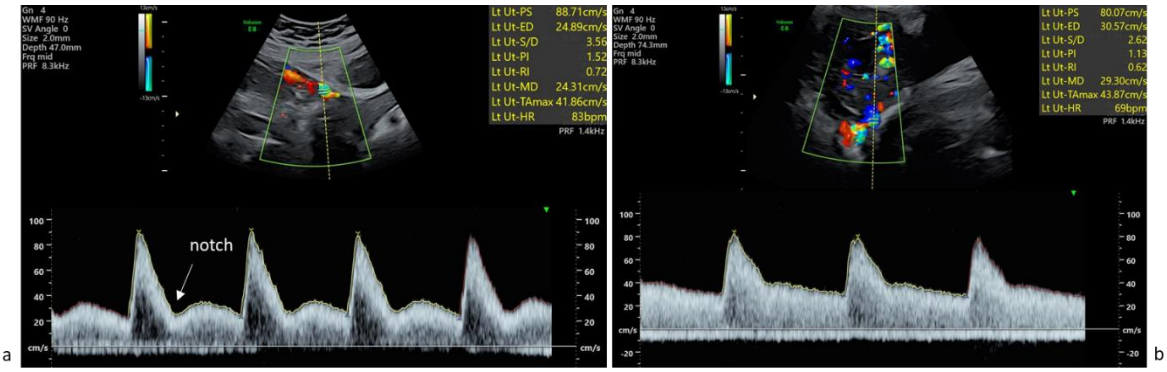

Figure 7 Doppler velocimetry of the uterine arteries. (from the authors' original bank of images – by Cristiana Moreira)

(a) High resistance pattern with notching between the systolic and the diastolic components of the wave, characteristic of the first trimester of pregnancy.

(b) Low resistance pattern, characteristic of the second trimester of pregnancy.

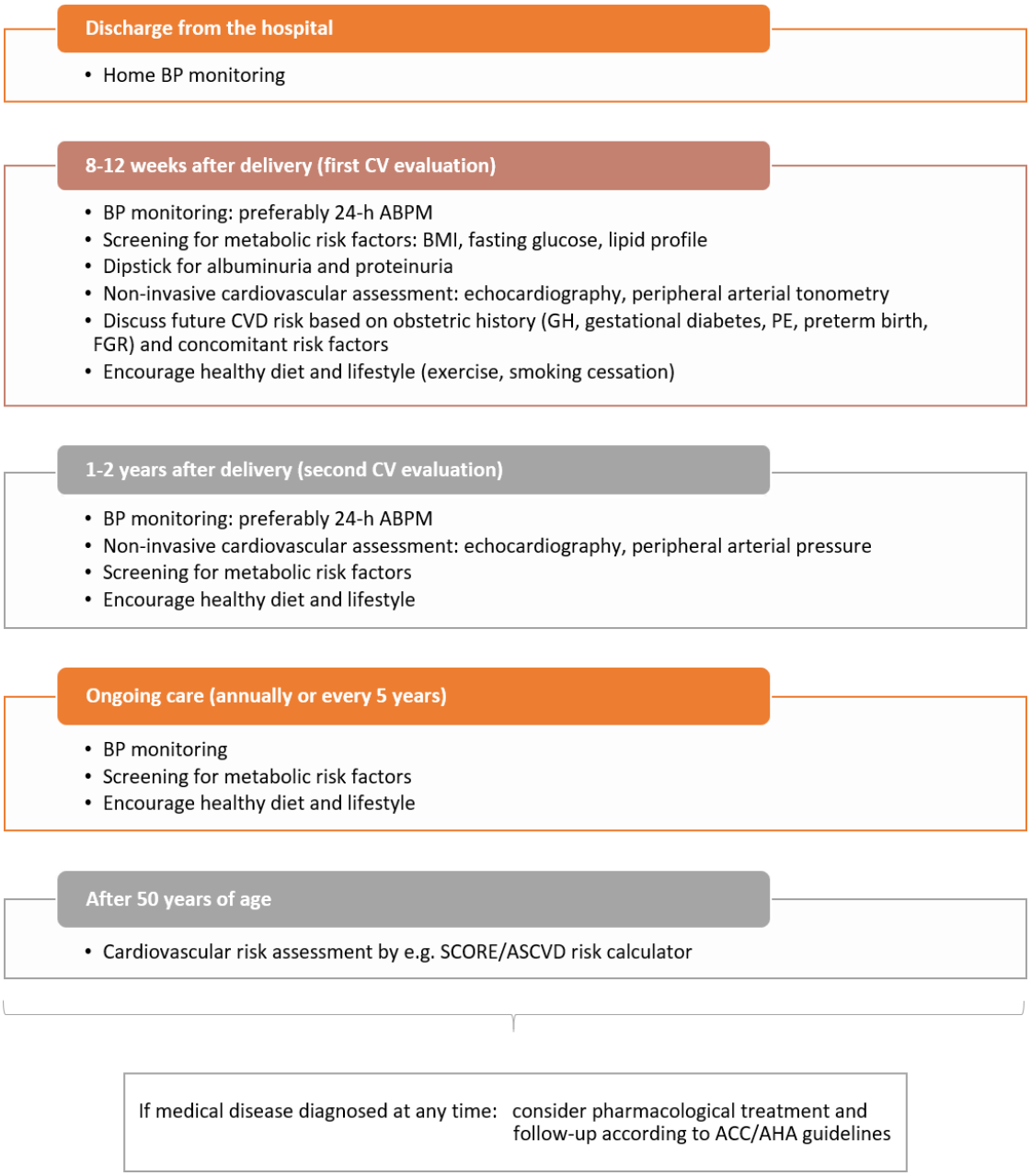

Figure 8. Example of cardiovascular risk management after hypertensive disorders of pregnancy, in a multidisciplinary setting. (Adapted from Benschop et al., 2019[147] and Giorgione et al., 2021[149]).

Women with a history of HDP, especially preterm PE, benefit from formal cardiovascular risk assessment within the first 2 years after delivery to identify those who benefit from close monitoring and targeted therapeutic intervention, such as intensive primary prevention and control of modifiable risk factors.

ABPM, ambulatory blood pressure monitoring; ACC/AHA, American college of Cardiology/American Heart Association; BMI, body mass index; BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease; FGR, fetal growth restriction; GH, gestational hypertension; SCORE, Systematic Coronary Risk Evaluation; ASCVD, atherosclerotic cardiovascular disease;

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