Ultrasound Obstet Gynecol 2025
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.70040.

isuog

CONSENSUS STATEMENT

ISUOG Consensus Statement on maternal hemodynamic assessment in hypertensive disorders of pregnancy and fetal growth restriction

Clinical Standards Committee

The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) is a scientific organization that encourages sound clinical practice, and high-quality teaching and research, related to diagnostic imaging in women's healthcare. The ISUOG Clinical Standards Committee (CSC) has the remit to develop Practice Guidelines and Consensus Statements as educational recommendations that provide healthcare practitioners with a consensus-based approach, from experts, for diagnostic imaging. They are intended to reflect what is considered by ISUOG to be the best practice at the time at which they are issued. Although ISUOG has made every effort to ensure that Guidelines and Consensus Statements are accurate when issued, neither the Society nor any of its employees or members accepts any liability for the consequences of any inaccurate or misleading data, opinions or statements issued by the CSC. The ISUOG CSC documents are not intended to establish a legal standard of care because interpretation of the evidence that underpins them may be influenced by individual circumstances, local protocol and available resources. Approved Guidelines and Consensus Statements can be distributed freely with the permission of ISUOG (info@isuog.org).

INTRODUCTION

Pregnancy presents a unique cardiovascular challenge. Profound maternal hemodynamic adjustments result from a complex interplay between the maternal cardiovascular system and uteroplacental perfusion, which permits fetal development while maintaining healthy maternal homeostasis[1–5]. Failure to meet this challenge can lead to maternal hypertensive complications (hypertensive disorders of pregnancy (HDP)) and/or fetal growth disorders (fetal growth restriction (FGR))[6–9].

Monitoring and management of HDP and FGR has been based largely on maternal blood pressure (BP) monitoring and fetal growth assessment[10]. Promising research offers the prospect of a less reactive and more proactive approach. Maladaptation to the requirements of pregnancy can be detected in a preclinical phase of HDP and FGR by maternal hemodynamic assessment, offering opportunities for targeted hemodynamic interventions[11–15]. Pregnancy also serves as a stress test for future cardiovascular health, especially if superimposed upon subclinical cardiometabolic or cardiovascular vulnerabilities[11,16–19].

This Consensus Statement provides an update on the role of maternal hemodynamic assessment in HDP and FGR.

METHODS

A proposal for this Consensus Statement was submitted to and evaluated by the ISUOG CSC. The authors of this Consensus are members of the International Working Group on Maternal Hemodynamics (https://maternalhemodynamics.com/) and were involved in both the development and the writing stages. Members of the International Working Group on Maternal Hemodynamics who were not involved in the writing of this Consensus were invited to review the document (reviewing group) and those who responded are acknowledged. Stakeholders were not included in the writing process.

This process was not intended to represent a systematic review. The preselected topics were divided among the authors, who worked in pairs and performed a literature search. T.S. collated the document and proposed the key points. The final document and key points were revised by all authors. Several meetings were organized to discuss any points on which there was not initial consensus, until complete agreement was reached. The document was then finalized after comments from the reviewing group, the ISUOG CSC and the ISUOG Board of Trustees.

The authors of this Consensus Statement are experts in the field of maternal hemodynamics and have expressed their opinion based on the available literature and evidence. Any clinician applying this Consensus is expected to use their independent medical judgement in the context of the individual clinical circumstances to determine patient care.

MATERNAL HEMODYNAMIC ASSESSMENT: METHODOLOGY AND REPRODUCIBILITY

Traditionally, peripheral BP is measured by auscultation using an arm cuff connected to a manometer. Increasingly, automated oscillometric devices, validated for pregnancy, are becoming the recommended standard[20,21]. Further developments have allowed additional analysis of the arterial waveform for estimation of central BP and arterial function. Markers of arterial stiffness and compliance, such as pulsed-wave velocity and the augmentation index (AIx)[22,23], help to understand the pathophysiology behind HDP and FGR, predict cardiovascular complications, and evaluate and direct prevention and treatment[24–26].

Cardiac output

Assessment of central hemodynamic factors that determine BP (cardiac output (CO, in L/min) and systemic vascular resistance (SVR, in dyne.s/cm^5)) is increasingly accessible using easily operable devices[27]. Considering the pivotal role of central hemodynamic functioning, this Consensus Statement focuses primarily on CO assessment.

CO is the product of stroke volume (SV) and heart rate (HR) (CO = SV × HR). Accuracy of its evaluation is improved by averaging measurements over several heartbeats[3–5], to compensate for respiratory variations. After 20 gestational weeks, CO is best evaluated with the woman in a left lateral position, to minimize caval and aortic compression by the gravid uterus[28,29]. The heart can rapidly modulate CO in order to meet the demands of pregnancy, with a wide range of normality (4–20 L/min) depending on activity level, age, fitness, body size, gestational age and metabolic rate. While trimester-specific reference ranges exist, device-specific normalization, that takes into account maternal age and posture, does not. Indexing for actual or prepregnancy body surface area or height may be of additional value when comparing measurements between individuals[27,30–32]. Individual or separate CO measurements can be of value for instant hemodynamic assessment, while repeated or continuous measurements are appropriate for trend analysis.

With knowledge of CO and BP, SVR can be calculated ((SVR = 80 × (MAP − RAP)/CO) in dyne.s/cm^5), where MAP represents mean arterial pressure and RAP is right atrial pressure. RAP (or central venous pressure) is usually low in pregnancy (0–5 mmHg) and therefore is usually omitted from the calculation[33,34]. Arterial function can also be evaluated by Doppler assessment of peripheral vessels, for example the uterine and/or opthalmic arteries.

Reference techniques

CO is determined most accurately by invasive measurements using thermodilution or indicator (lithium) dilution, or by cardiac magnetic resonance imaging (MRI). The former require insertion of intracardiac, central venous and/or arterial catheters (e.g. pulmonary artery catheters), limiting their indication to critically ill pregnant women in an intensive care unit setting[33,34] . Cardiac MRI is non-invasive, but its limited availability and high cost restrict its use in an obstetric context[28,35].

Ultrasound

Transthoracic echocardiography permits non-invasive assessment of CO by measuring the left ventricular outflow tract diameter and pulsed-wave Doppler outflow signal along with HR. It has been validated against invasive measurements in severely ill pregnant women and can be considered an alternative reference technique[36,37]. Transthoracic echocardiography enables evaluation of systolic and/or diastolic function (assessing ejection fraction using two-dimensional and/or M-mode imaging, strain and strain rate using speckle tracking, tricuspid annular plane systolic excursion (TAPSE), and mitral inflow using pulse-wave and tissue Doppler imaging) and preload assessment (atrial size and inferior vena cava size and collapsibility)[38–40].

Other techniques

Another means of assessing CO is with a non-invasive mobile device, using a continuous-wave Doppler transducer placed in the suprasternal notch[40]. This technique is limited by assumptions regarding the left ventricular outflow tract diameter and acoustic guidance for probe orientation. However, by including more heartbeats in the calculation, the accuracy is enhanced.

An inert gas rebreathing technique can be used to calculate CO based on Fick's principle[41]. A blood-soluble and an insoluble gas are delivered though a closed breathing assembly and relative levels over a few respiratory cycles are measured by a gas analyzer in the mouthpiece. As with pulmonary artery catheters, pulmonary blood flow or right ventricular output is measured, which is usually identical to left ventricular output. In obstetrics, this technique is more suited for research than clinical practice[42].

With impedance and reactance cardiography, a very-low-amplitude high-frequency current is transmitted between skin electrodes on the thorax. CO can be estimated by calculating differences in impedance (bioimpedance) or phase shifts (bioreactance) induced by changing blood flow during the cardiac cycle[43,44]. Pulse-contour analysis estimates CO from a peripheral arterial waveform, which can be obtained invasively or non-invasively[33,45]. Both impedance and reactance cardiography and pulse-contour methods are operator-independent and permit continuous monitoring for trend analysis, but their algorithms to calculate CO are based on assumptions that may affect accuracy.

Most non-invasive techniques lack validation in pregnancy against reference techniques. The few that have been compared with reference techniques often fail the current rigorous standards for absolute values and trend

analysis[46]. Consequently, CO values obtained with one technique are not comparable with those obtained using another technique, and the techniques cannot be used interchangeably. Still, it would be unwise to disregard the benefits from these devices, as their accessibility permits the gathering of large amounts of valuable hemodynamic information. In addition, using a single device repeatedly in the same patient overcomes the differences between techniques and allows the investigation of changes over time. As such, these techniques may be valuable for monitoring changes as pregnancy progresses.

Key points

- After 20 gestational weeks, the assessment of maternal CO should be performed with the woman in a left lateral position.
- While no non-invasive technique is a true gold standard for CO assessment in pregnancy, transthoracic echocardiography has undergone extensive validation.
- Different techniques for non-invasive assessment of maternal CO cannot be used interchangeably.
- Despite the lack of rigorous standardization and systematic differences between techniques, evaluation of the changes in maternal CO over time might be valuable in obstetric practice.

MATERNAL HEMODYNAMIC ADAPTATION TO HEALTHY PREGNANCY

During pregnancy, the mother's body undergoes cardiovascular changes leading to hemodynamic adaptations required to respond to the increasing metabolic and oxygen demands from the uterus, placenta and fetus and to prepare the mother for possible blood loss during delivery (Figure 1). To understand the possible role of maternal hemodynamics in pathological conditions, it is important to understand these changes in healthy pregnancy, as normal maternal hemodynamic adaptation is a prerequisite for development of a normal pregnancy[42,47].

Maternal hemodynamic changes in healthy pregnancy

Maternal hemodynamic changes can be observed during the menstrual cycle. Compared to the follicular phase, during the luteal phase, the HR, plasma volume (PV), CO and central and peripheral arterial compliance are increased, while the MAP and SVR are decreased[48]. Similar changes are present early in pregnancy, from 6 weeks of gestation, prior to the development of a placental circulation[42,48,49].

The hypothesized mechanism underlying maternal hemodynamic changes in early pregnancy (Figure 2) is that a fall in SVR, by up to 20–25%[50], acts as the trigger event, most likely due to reduced vascular

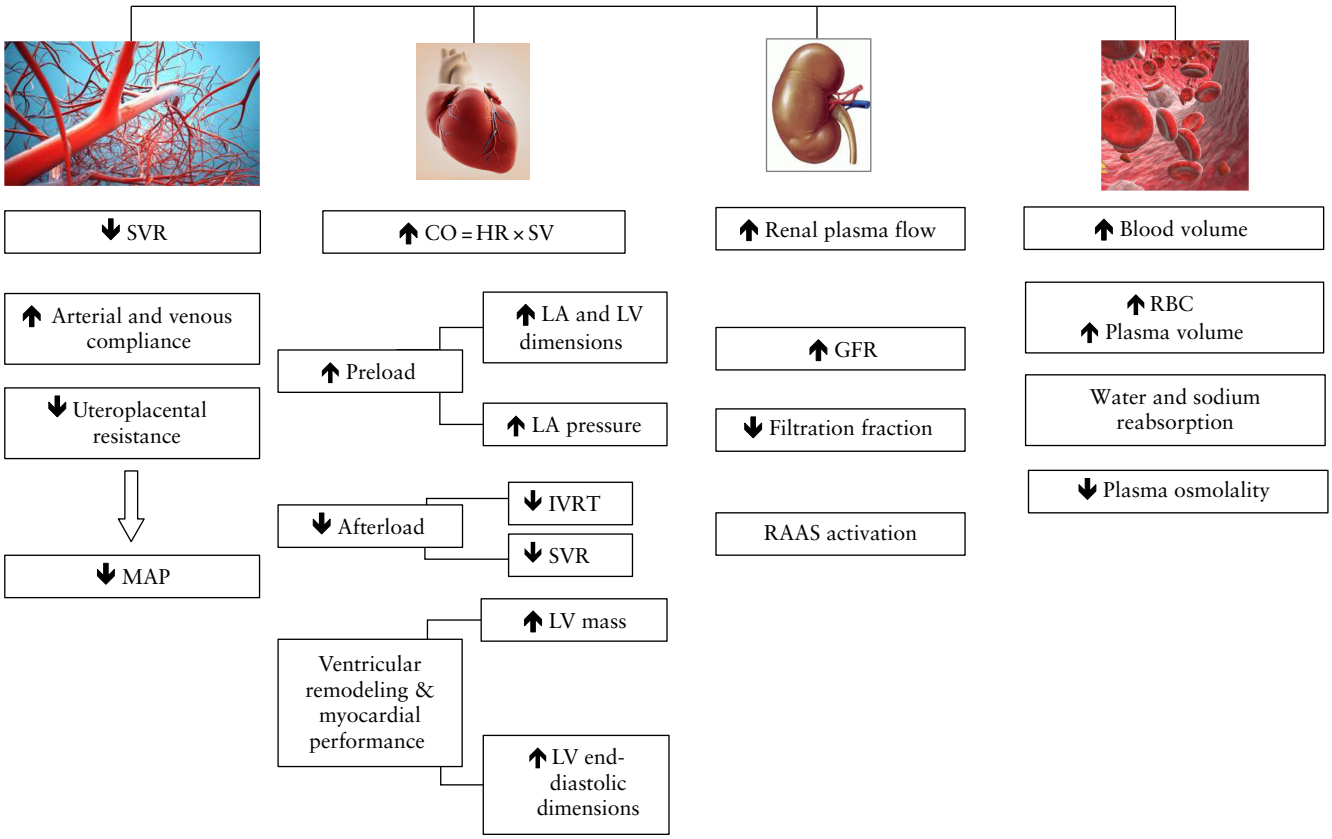

Figure 1 Major maternal hemodynamic changes in healthy pregnancy. CO, cardiac output; GFR, glomerular filtration rate; HR, heart rate; IVRT, isovolumetric relaxation time; LA, left atrial; LV, left ventricular; MAP, mean arterial pressure; RAAS, renin–angiotensin–aldosterone system; RBC, red blood cells; SV, stroke volume; SVR, systemic vascular resistance.

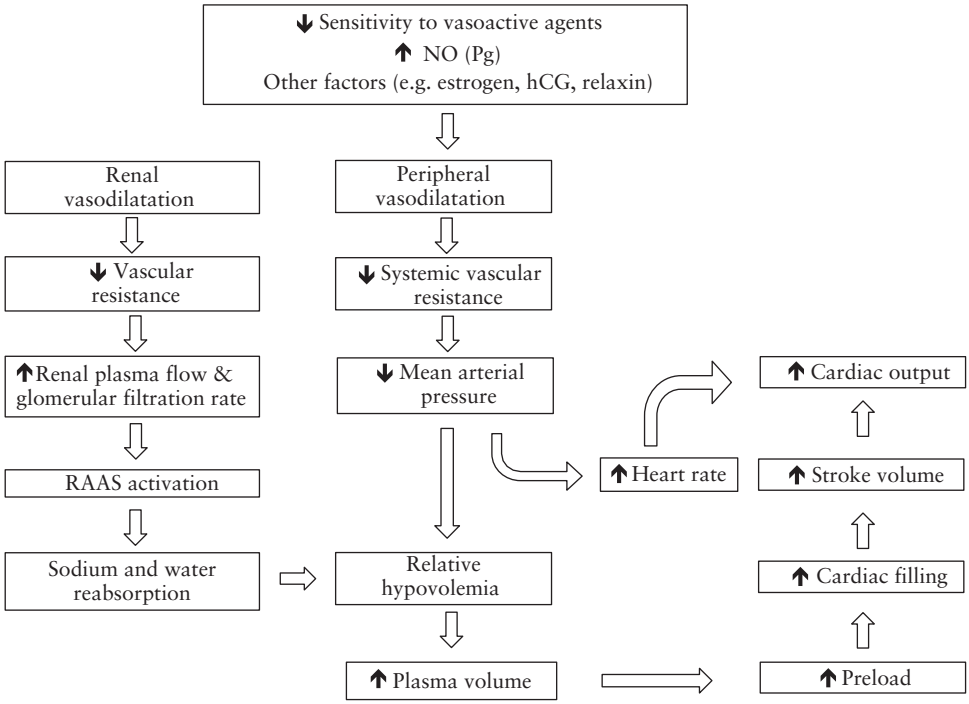

Figure 2 Early maternal hemodynamic changes in healthy pregnancy. hCG, human chorionic gonadotropin; NO, nitric oxide, Pg, progesterone; RAAS, renin–angiotensin–aldosterone system.

tone, leading to a decrease in MAP and a compensatory increase in CO[51]. The initial increase in CO is caused by an increase in HR[48]. These changes are accompanied by renin–angiotensin–aldosterone-system (RAAS) activation due to increases in renal plasma flow and glomerular filtration rate and reduction in MAP[48,51]. The result of RAAS activation is sodium and water reabsorption, with consequent PV expansion, hemodilution and increased preload[52]. The increased preload leads to improved cardiac filling during diastole. Together with decreased cardiac afterload, this results in increased SV and, consequently, in increased CO[48]. As a result of increased preload, the maternal heart undergoes changes: the left atrial diameter, left ventricular diastolic and systolic dimensions and ventricular wall thickness all increase, resulting overall in increased cardiac mass, surface area (so-called myocardial eccentric hypertrophy) and performance[5,53]. Maternal cardiac morphological changes start at around 8 weeks of gestation, but become significant at around 12 weeks of gestation[52].

The maintenance of CO is also guaranteed by decreased cardiac afterload, which is accomplished by the decrease in SVR, while the normal perfusion pressure is associated with higher arterial compliance[54]. Concomitantly, increased venous compliance accommodates a higher quantity of PV, contributing to preload increase and further maintenance of CO[48].

A detailed discussion of molecular pathways is beyond the scope of this document, but it has been hypothesized that hormonal influences, including estrogen and human chorionic gonadotropin secreted by the synciotrophoblast, and other factors (e.g. relaxin, vascular endothelial factor, nitric oxide (NO)) play a role in physiological maternal hemodynamic adaptation early in pregnancy[48], which would mean that the earliest maternal hemodynamic changes in pregnancy develop independently from the fetoplacental unit.

After the early first-trimester changes, healthy pregnancy is characterized by various hemodynamic adaptations, including further increases in CO and PV, decreases in SVR and MAP, and changes in maternal cardiac function.

Cardiac output

Increasing cardiac preload and concomitant decreasing afterload result in progressively higher SV and CO in the first trimester of pregnancy. SV increases by 15–25% early in pregnancy and plateaus by about 20 weeks[55,56]. In the second half of pregnancy, the increase in SV is reversed, so that near term there is no difference between pregnant and non-pregnant women[56]. The increased CO is also caused by the higher maternal HR, which increases by 15–30% early in pregnancy and continues to increase gradually until term. The CO increases overall by 20–50% and peaks by mid to late pregnancy, reaching a maximum mean difference of 1.41 L/min between 29 and 35 weeks of gestation[55,56]. It remains controversial as to whether CO increases until term[57] or decreases late in pregnancy[58]; inconsistencies in results between studies can be explained by differences in their design and/or methodology, population and other factors. CO returns to prepregnancy values from 2 weeks postpartum[1].

Plasma volume

PV starts to increase early in pregnancy, peaks during the second trimester and changes minimally throughout the third trimester, returning to normal levels after 6 weeks postpartum[4]. Around one-third of the PV is contained in the arterial compartment, while two-thirds are located in the venous compartment and represent a hemodynamically inactive intravascular volume[59].

Systemic vascular resistance

SVR decreases, with an overall 30% decrease early in pregnancy[55] and nadir in the late second trimester[56].

Mean arterial pressure

MAP decreases during pregnancy until 24 weeks of gestation, because the increase in CO is not sufficient to balance the fall in SVR. Both systolic and diastolic BP decrease; however, the reduction in diastolic BP is greater than that in central and brachial systolic BP[49]. There is also a significant fall in AIx (i.e. arterial stiffness), which explains the reduced central systolic BP. Central systolic BP reflects better than brachial systolic BP the uterine artery pressure, which contributes to the uteroplacental perfusion[49]. The BP returns to baseline levels during the third trimester[55,56].

Maternal heart

Increased preload and concomitant decreased afterload have a positive effect on maternal cardiac function in the first trimester of pregnancy. The change in left ventricular diastolic function in the first trimester appears to be determined by an increased contribution of passive left ventricular filling[4]. In advanced gestation, left ventricular diastolic function seems to worsen progressively, as reflected by a decreased E-wave to A-wave (E/A) ratio[4].

Morphological changes start in the first trimester and continue throughout pregnancy, peaking around 30 weeks. The left ventricular mass increases by approximately 50%[55]. Myocardial eccentric hypertrophy observed during healthy pregnancy represents a reversible and uncomplicated phenomenon that has usually resolved by 6 months postpartum[60,61].

Key points

- Important maternal hemodynamic changes occur in the first weeks of pregnancy.
- Placentation is not necessary for maternal hemodynamic changes to occur in early healthy pregnancy.
- Maternal hemodynamic changes are important for adequate uterine and placental perfusion and adequate nutrient and oxygen supply to the placenta and fetus.
- Maternal hemodynamic changes represent a reversible process in healthy pregnancy, which reverts in the postpartum period.
- It is crucial to understand the physiological maternal hemodynamic changes that take place in healthy pregnancy, in order to understand their role in pathological conditions.

MATERNAL HEMODYNAMIC ADAPTATION TO MULTIPLE PREGNANCY

More profound maternal hemodynamic changes have been reported in uncomplicated multiple compared with singleton pregnancies, including higher CO and lower SVR across gestation[62–64]. The greater increase of circulating blood volume and the higher concentrations of vasodilating hormones, such as prostaglandins and progesterone, are thought to drive these changes[65].

In uncomplicated twin gestation, changes in maternal systolic and diastolic function have been documented from the first to the third trimester[66–68]. In particular, diastolic and mean BP show a U-shaped trend through gestation, reaching their nadir at midgestation. Based on serial echocardiograms, left ventricular systolic function, expressed either by classical parameters (ejection fraction or fractional shortening) or by tissue Doppler parameters (longitudinal contractility, quantified by S′ (myocardial velocity during isovolumetric longitudinal contraction)) worsens progressively during pregnancy[62,67]. Moreover, relative diastolic dysfunction is observed, as evidenced by a progressive reduction in the mitral E-wave and an increase in the A-wave velocities, together with consistent modifications of the tissue Doppler parameters (reduction in E′ and increase in A′)[67]. These findings indicate that the maternal heart is subjected to profound adjustments during the course of a twin gestation, regardless of whether there are cardiovascular complications.

The progressive decrease of ventricular performance may depend on the volume overload[65], and, in the late stages of apparently uneventful twin gestation, may lead to increased end-systolic residual volumes in the ventricle, thus contrasting with the early diastolic phase and promoting active atrial contribution to left ventricular filling across the atrioventricular valves. In other words, the late stages of an uncomplicated twin pregnancy at the level of the maternal heart may mimic diastolic dysfunction as observed in the early stages of chronic cardiac insufficiency. It is noteworthy that similar findings, suggestive of early diastolic dysfunction, have been described at postpartum echocardiography in women who developed preterm or severe pre-eclampsia (PE) in a singleton gestation[17,69].

At second-trimester maternal echocardiography, the left ventricular mass is increased in twin pregnancies compared with singletons, but there are only subtle differences in systolic and diastolic left ventricular functional indices[70]. The pattern of cardiac changes is similar between monochorionic and dichorionic twin pregnancies. These cardiovascular changes resemble those seen in singletons in late gestation and suggest physiological remodeling in response to the increase

in volume loading rather than decompensation of the maternal cardiovascular system.

Changes in maternal cardiac function in uncomplicated twin gestation, from early to late pregnancy, include an increase in CO and a parallel decrease in SVR. It is unclear how these cardiac findings differ with respect to chorionicity. Using serial transthoracic echocardiography, one study reported lower maternal CO in second-trimester monochorionic *vs* dichorionic twin pregnancies, possibly because of the smaller increase in the circulating blood volume[66]. In contrast, another study recently showed a higher CO in the second trimester in monochorionic compared to dichorionic twin pregnancies[68]. Most cardiac parameters revert towards the values of early pregnancy soon after delivery, with the exception of some indices of systolic function, such as fractional shortening, ejection fraction and tissue Doppler S′, which have been reported to remain significantly below those observed in the first trimester[67]. This may indicate that the workload caused to the maternal heart by the increased circulating volumes may still affect the ventricular contractility in the early postpartum period and that complete recovery is delayed.

Key points

- Uncomplicated twin pregnancy is associated with more profound maternal hemodynamic changes than those seen in singleton pregnancy, and the maternal heart is exposed to more profound adjustments, most likely due to volume overload.
- Maternal left ventricular systolic function shows progressive worsening during uncomplicated twin pregnancy.
- In the late stages of uncomplicated twin pregnancy, there may be signs of maternal diastolic dysfunction.

MATERNAL HEMODYNAMICS IN HYPERTENSIVE DISORDERS OF PREGNANCY

Maternal hemodynamics in pre-eclampsia phenotypes

The first classification of PE phenotypes was based on the timing of clinical disease onset, before ('early-onset') or after ('late-onset') 34 weeks of gestation[71,72]. Early-onset PE typically follows a more aggressive course, presenting with severe symptoms of maternal organ dysfunction or with poor fetal growth that precedes the development of maternal hypertension, in association with serum markers of immune and endothelium activation[73]. The maternal hemodynamic characteristics are markedly different between the two phenotypes, both in the clinical[14] and in the latent[14,74] phase of the disease[15]. A new classification system has been proposed that is based on maternal hemodynamics and fetal growth[14,15,75,76]. PE associated with FGR is characterized by low CO and high SVR, in both preclinical and overt phases of the disease. PE associated with normal fetal growth is not characterized by low CO, while the SVR in the preclinical phase of the disease is low and may increase in the overt phase. This classification allows discrimination between two PE phenotypes, one characterized by vascular-resistance-induced hypertension ('resistance-dominant HDP') and the other by intravascular-volume-induced hypertension ('volume-dominant HDP') (Figure 3). As such, the fundamental physiological definition of BP as the product of CO and SVR (Ohm's law) is pertinent: hypertension is the result of either increased SVR, increased CO or both[6,77].

The theory that the placenta is the main etiological driver of PE is challenged by the observation of subclinical abnormal hemodynamic function already present in the preconception stage in women who subsequently developed PE[47,78]. An increasing number of clinical, epidemiological and experimental observations support that the abnormal placentation process associated with PE is a result of, rather than a cause of, abnormal maternal hemodynamic function[7]. Latent suboptimal hemodynamic function before conception predisposes not only to gestational complications, but also to early-onset cardiovascular disease in later life[79–81]. Moreover, abnormal intrauterine hemodynamics may be a direct link between poor fetal growth and early-onset adult cardiovascular and renal disease[82]. While impaired maternal cardiovascular performance plays a role in the poor development of placentation, we should not overlook the contribution of immune-system dysfunction, which is observed when defective trophoblast invasion occurs in early gestation[83]. The association between confirmed poor maternal hemodynamics and the immune system should be a focus of future research[84].

The classification of PE into resistance-dominant or volume-dominant phenotypes challenges the reported longitudinal hemodynamic evolution from early pregnancy until term in women who eventually develop PE[6]. In all studies reported since 1990, a hemodynamic imbalance between CO and SVR was present at all stages of pregnancy in women who developed PE[8,78,85]. Early-onset PE typically presents with first-trimester increased SVR and a blunted rise of CO[85]. Late-onset PE, on the other hand, starts with high CO and normal SVR[8]. This imbalance can remain unchanged[8,57], or convert from a high-CO circulation to a high-resistance circulation with advancing gestation[8], probably due to endothelial damage and intravascular overload[86], thereby establishing a 'vicious circle' that, in association with hypoalbuminemia and impaired cerebral blood flow autoregulation, strongly predisposes to eclampsia[87].

Gestational hypertension

Gestational hypertension (GH) also presents with both volume-dominant and resistance-dominant phenotypes[8,85]. Contrary to HDP associated with renal damage, abnormal maternal venous Doppler characteristics are absent in GH[6], raising the question as to whether PE-related symptoms of organ dysfunction may relate to venous congestion induced by increased intravenous

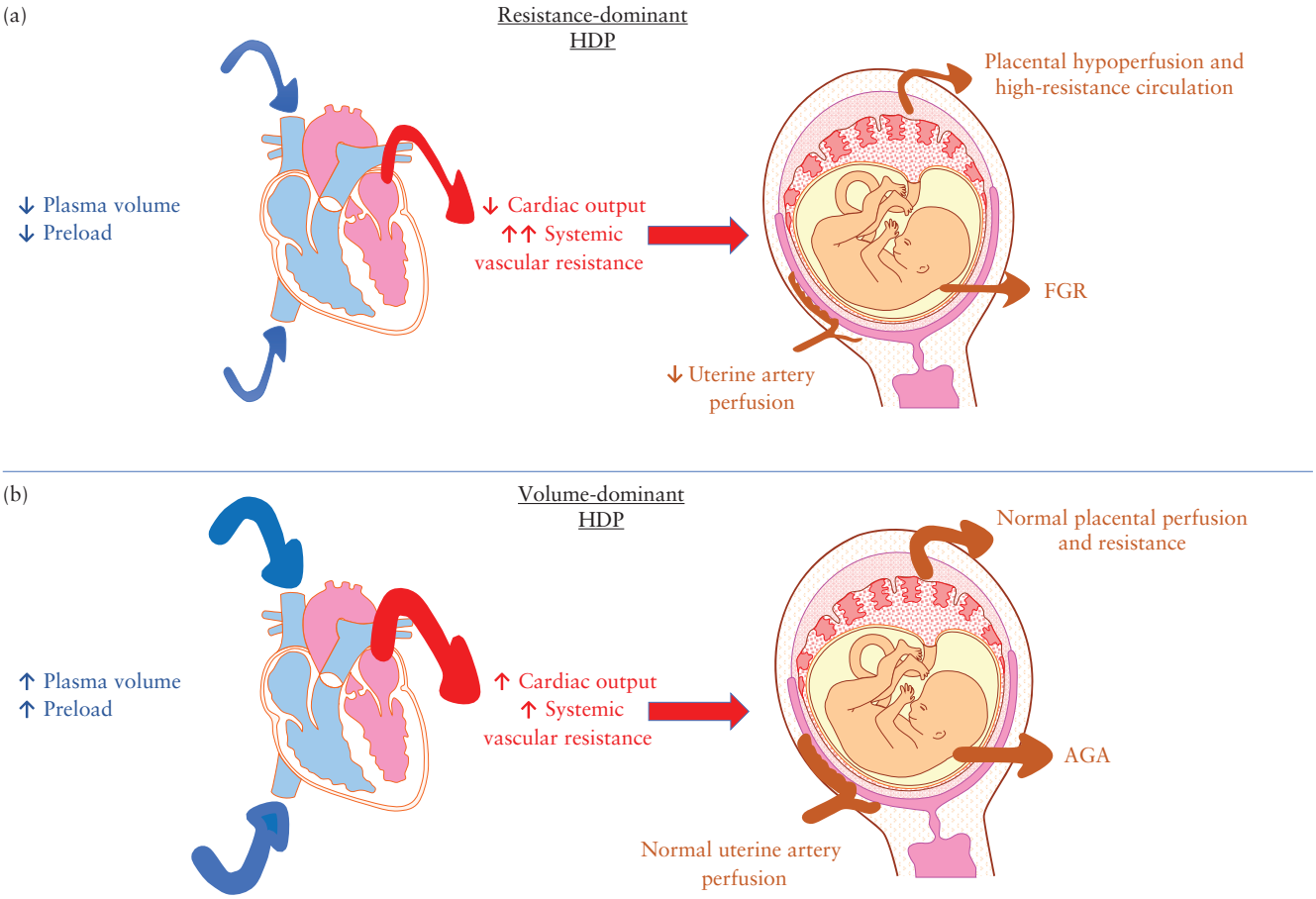

Figure 3 Diagram representing two phenotypes of hypertensive disorders of pregnancy (HDP): (a) resistance-dominant HDP and (b) volume-dominant HDP. FGR, fetal growth restriction; AGA, appropriate-for-gestational age.

pressure, reduced venous capacitance or external venous compression due to raised intra-abdominal pressure[88].

Overall, this evidence supports the abandonment of two traditional concepts of obstetrics. Firstly, the mechanistic time-dependent classification into early-onset and late-onset PE has no clinical relevance, and is meaningful only from an epidemiological perspective. Secondly, the very term 'pre-eclampsia' no longer bears any clinical meaning once we recognize the truly different pathophysiological pathways, which simply share similar downstream symptoms. Thus, PE and GH should be considered under the same umbrella, that is, HDP, with different clinical facets. Accordingly, herein, we use the broader term, 'HDP', unless otherwise indicated (e.g. when discussing studies focused only on PE).

Key points

- Maternal hemodynamic assessment differentiates two HDP phenotypes: resistance-dominant and volume-dominant (CO-dominant).
- These phenotypes are linked though not invariably to the gestational age at onset of HDP.
- The most important clinical factor that discriminates between the two HDP phenotypes is the presence of FGR.
- Abnormal maternal hemodynamic function is present in preconception and preclinical stages of HDP.

MATERNAL HEMODYNAMICS IN FETAL GROWTH RESTRICTION

Throughout healthy pregnancy, maternal CO correlates positively with fetal growth velocity and birth weight, and the physiological reduction in SVR is associated with increased birth weight. This is in line with the observation of an interaction between maternal cardiac and placental function[89]; the decrease in SVR coincides with the reduction of resistance in the uteroplacental circulation. Moreover, there is a significant correlation between fetal Doppler indices and maternal hemodynamics. Maternal SVR, CO, heart contractility and dynamicity of circulation all seem to influence the blood flow rate in the umbilical vein[90]. The evidence of a correlation between maternal, placental and fetal circulations[91] highlights the importance of hemodynamic assessment in cases of inadequate fetal growth.

The most common cause of FGR is so-called uteroplacental insufficiency, resulting from defective placentation, and, traditionally, FGR has been defined as a 'placental syndrome'[92,93]. The poorly functioning placenta restricts nutrient supply to the fetus and prevents

normal fetal growth. This condition is characterized by defective trophoblast invasion, abnormal uterine artery adaptation and increased placental vascular resistance.

A new interpretation of the pathophysiology of FGR has stemmed from the premise that placental function is dependent on its perfusion[15,93]. Thus, adequate systemic cardiovascular adaptation in pregnancy is crucial to ensure optimal placental function. Large population studies have identified the occurrence of FGR as an important risk factor for the development of cardiovascular disease later in a woman's life, with the highest risk in cases of the most severe and early FGR[94,95], regardless of the simultaneous presence of PE.

The definition of FGR is based on fetal biometry and Doppler evaluation, and it is classified as early or late according to whether it presents before or after 32 weeks of pregnancy, respectively[96].

Early fetal growth restriction

Early FGR has low incidence (0.5%) and is characterized by high-impedance uterine circulation, frequent association with HDP, high risk of perinatal mortality and morbidity, and poor neonatal outcome due to prematurity[97]. While it is known that defective trophoblast invasion with subsequent failure of spiral artery adaptation is associated with early FGR[92], maternal hemodynamic assessment provides further insight, linking evidence of uteroplacental dysfunction with signs of maternal cardiovascular impairment in pregnancies with early FGR.

Women with a prepregnancy or early-pregnancy abnormal maternal hemodynamic profile, with low CO, high SVR and a hypovolemic state, have an increased risk of developing FGR[47,98], and this hemodynamic profile is maintained during the pregnancy. These hemodynamic alterations can be identified in apparently healthy women at different preclinical stages before manifestation of the disease, and SVR seems to be the most important predictive factor[99,100]. The fact that in patients with chronic hypertension there is an increased risk of FGR further supports the hypothesis that the maternal cardiovascular system plays a crucial role in the pathogenesis of abnormal placental function[99,101].

Late fetal growth restriction

Compared with early FGR, late FGR is less closely associated with HDP, abnormal placental development and spiral artery remodeling. The main clinical challenge is its correct identification and diagnosis, firstly, due to the subtle clinical manifestations and, secondly, due to the fact that FGR might also exist in fetuses with size (abdominal circumference (AC) or estimated fetal weight (EFW)) $> 10^{th}$ percentile[97,102,103]. However, late FGR, with a prevalence of around 5–10%, is much more common than early FGR and thus has an important clinical impact[97].

The association between late FGR and placental histopathological lesions is less evident than that in early FGR, and the differences compared with healthy pregnancy are often very subtle[104]. Late FGR, compared with early FGR, shows less pronounced changes in uterine artery impedance[92]. In about one-third of all pregnancies, there is a worsening of uterine artery Doppler in the late third trimester[105], suggesting that this late variation in uterine vascular resistance is not related to trophoblast invasion but is an effect of changes that involve the maternal cardiovascular system[106]. In these cases, there is a higher risk of low birth-weight percentile[105]. This observation explains the low predictive capacity of uterine artery Doppler velocimetry to identify late FGR and suggests the importance of maternal hemodynamic assessment in these cases. The second trimester may be optimal for maternal cardiovascular assessment for identification of patients at risk of developing late FGR[13].

In pregnancies complicated by late FGR, maternal hemodynamic parameters do not show physiological cardiovascular adaptation, but show a flat, static pattern, with low CO and high SVR[106].

Small-for-gestational age

When fetal size (AC or EFW) is below the 10^{th} percentile, a priority is to differentiate between small-for-gestational age (SGA) and FGR. Some SGA fetuses might be constitutionally small but otherwise healthy and, consequently, at lower risk of adverse outcome. Identification of these pregnancies is important for their correct management and to avoid maternal anxiety and overtreatment. Thus, biophysical parameters other than size are required to differentiate SGA from FGR (e.g. fetal growth velocity, fetoplacental Doppler velocimetry, biomarkers)[97,103,107]. Maternal hemodynamics could play an important role in differentiating FGR from SGA. A normotensive pregnancy complicated by FGR is characterized by lower maternal HR, lower CO and higher SVR, while a pregnancy with a SGA fetus is characterized by a maternal hemodynamic profile similar to that of a healthy pregnancy[13,108]. Assessment of umbilical vein blood flow might provide even more detailed insights into the imbalance between fetal demand and maternal cardiovascular and placental availability[90,91,109,110].

Key points

- Maternal hemodynamic parameters, such as CO and SVR, are associated with fetal growth and birth weight.
- Women with a hypodynamic circulation before and early in pregnancy are at higher risk of their pregnancy being affected by FGR.
- Early FGR is characterized by profound maternal hemodynamic changes, similar to those present in HDP with FGR.
- Late FGR is characterized by less pronounced maternal hemodynamic alterations, suggesting late maternal hemodynamic maladaptation to fetoplacental requirements.
- Maternal hemodynamics, biomarkers and umbilical vein blood flow evaluation might provide additional

information to differentiate SGA from FGR, but further research is needed.

MATERNAL HEMODYNAMICS AND CARDIOVASCULAR DISEASE LATER IN LIFE

There is growing evidence that the abnormal hemodynamic and echocardiographic findings that are common in women with HDP do not resolve following delivery. Many women continue to be hypertensive in the immediate postnatal period, with some exhibiting signs of cardiac dysfunction[16,17,111], and some are at risk of cardiovascular disease later in life[112]. Data from a recent randomized controlled trial (RCT) suggest that long-term cardiovascular health may be improved by close monitoring and effective control of BP in the immediate postnatal period[113]. Given these findings, increasingly, the hemodynamic assessment and management of women following HDP is considered important.

Risk of cardiovascular disease after HDP

The development of chronic hypertension after pregnancy complicated by HDP largely explains the increased risk of developing cardiovascular disease[111,112]. A meta-analysis showed that postpartum hypertension occurred five times more frequently in the first year following delivery in women affected by HDP[112]. The risk of HDP and/or chronic hypertension is related to obesity[114], social deprivation[115] and pre-existing or gestational diabetes[115]. The association of cardiovascular disease with specific risk factors after an episode of HDP remains subject to diverse interpretation. Dyslipidemia[116], metabolic syndrome[18] and accelerated rate of systematic atherosclerosis have been discussed regarding their possible link with an increased incidence of cardiovascular disease[117]. It seems likely that a cardiovascular system with subclinical impairment might be stressed by the demands during pregnancy, and/or that the endothelial stress of HDP accelerates damage of a dysfunctional cardiovascular system[118].

The use of cardiovascular risk scoring does not improve prediction of postpartum cardiovascular complications, but, recently, a prediction model including maternal demographic characteristics, BP and echocardiographic parameters in the peripartum period identified women at risk of postpartum hypertension[119,120].

Understanding factors that influence HDP for tailored proactive prevention later in life

HDP during pregnancy is a critical event affecting future cardiovascular health. Understanding the origin of HDP in pregnancy could help in proactively suggesting tailored preventive measures for the postpartum period and later in life. For instance, HDP associated with high placental oxidative stress, i.e. a high ratio between soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF), are more frequently associated with FGR[118]. In the postpartum period, women who had HDP with lower values of PlGF showed worse cardiac structure, increased BP levels and higher lipid levels[121]. A recent meta-analysis confirmed that women who had early-onset PE, which is more frequently associated with FGR, had even higher risk of cardiovascular disease later in life[122].

Whatever the cause and clinical phenotype of the disease, there is a dose-dependent effect between severity of HDP and likelihood of adverse cardiovascular outcome[16]. Preventive measures should be guided by a better understanding of the most likely cause of the HDP[7].

Peripartum and postpartum echocardiographic assessment

Profound echocardiographic changes are seen in most women with HDP, including increased left ventricular mass, cardiac remodeling and diastolic dysfunction[113,123]. Women with a history of PE also have altered cardiac structure and evidence of diastolic and myocardial dysfunction in the early years after delivery[124,125]. Despite this evidence, there are no recommendations regarding cardiac evaluation after HDP. However, women presenting with symptoms of dyspnea or signs of intravascular volume overload require echocardiographic evaluation[123].

Compared to women with HDP and normal echocardiograpy, those with HDP with severe left ventricular remodeling and diastolic dysfunction at echocardiography are more likely to develop chronic hypertension in the next decade[126].

Optimal method and frequency of blood pressure measurement postpartum

According to a Norwegian population-based study, BP life-course trajectories remained higher in a HDP cohort compared to controls[127]. This study supports the interpretation of HDP not as causal, but rather as a marker of a pre-existing subclinical disease, and that diastolic BP does not return to 'normal' levels during the postpartum period following HDP. Whatever the interpretation, longitudinal BP measurements should be undertaken in the postpartum period, as either home or scheduled ambulatory BP monitoring. One trial proved that postpartum BP telemonitoring is effective, achieving 8-fold fewer hypertension-related readmissions[128]. It is well-tolerated by patients, is a better predictor of end organ damage than clinical measurement[129] and may also reduce ethnic health disparities in postpartum care related to compliance.

Severe hypertension can occur postpartum, with the average latency period between delivery and BP levels that necessitate treatment being approximately 6 days[130]. These findings suggest that it is sensible to measure BP for at least the first 10 days postpartum[130]. Given the significant diurnal variation in BP in women with HDP, with BP climbing in the afternoon and evening in approximately 50% of women, twice-daily readings would seem appropriate[131].

A trial of postpartum BP self-monitoring and self-management via remote medication advice and feedback in women who experienced HDP demonstrated high acceptability, adherence and accuracy, and a significant improvement in BP control[132]. BP control was better whilst on treatment, but, more importantly, the diastolic BP was on average 4.5 mmHg lower 6 months postpartum, approximately 3 months after stopping medication. A follow-up study 4 years postpartum demonstrated that the diastolic BP was more than 7 mmHg lower in those originally randomized to postpartum BP self-management *vs* those treated with standard care[133]. This is highly suggestive of a window of opportunity to optimize long-term cardiovascular health by optimal monitoring and management of BP postpartum.

Optimal antihypertensive medication

Optimal management strategies once hypertension and/or cardiovascular dysfunction has been confirmed postpartum remain largely undetermined. It is likely that the findings from a furosemide RCT could be adopted to treat women with hypervolemic hyperdynamic late preterm or term HDP, using a 5-day course of 20-mg oral furosemide[134]. However, no specific guidelines are available for long-term prevention or therapeutic intervention, except for the American Heart Association's recommendation regarding HDP as an additional risk factor to guide prescription of statins as a risk-reduction measure[135].

Angiotensin-converting enzyme (ACE) inhibitors were tested in a double-blind randomized placebo-controlled trial in the postpartum period in patients who had early-onset PE[136]. This trial fell short of proving a reduction in SVR, yet patients in the treated arm showed lower diastolic BP, better diastolic function and improved left ventricular remodeling at 6 months postpartum. Obstetrician-gynecologists, physicians and primary-care doctors should exploit the 'fourth trimester' to help improve the future cardiovascular health of women who have been exposed to HDP.

Key points

- Maternal hemodynamic alterations present during HDP may persist in the postpartum period and predispose women to increased cardiovascular risk later in life.
- Women with a history of HDP and symptoms of dyspnea or signs of volume overload should undergo an echocardiographic evaluation.
- Longitudinal BP measurements, obtained by either home or ambulatory monitoring, should be carried out in the postpartum period in women with a history of HDP.
- In women with a history of HDP, postpartum monitoring of BP should continue for at least the first 10 days and should be performed at least twice per day.
- Women who experienced HDP should be counseled proactively regarding life-style changes (e.g. diet, smoking habit, exercise).

IMPLICATIONS FOR PREDICTION, PREVENTION AND MANAGEMENT

The association between HDP and FGR and maternal changes in cardiovascular function, both before and after development of the clinical syndrome, presents an opportunity for using assessment of maternal hemodynamics in the clinical setting.

Potential for prediction

Despite evidence of maternal cardiovascular maladaptation in pregnancies destined to develop HDP and FGR, prediction of these conditions in early pregnancy is not feasible given the wide overlap between physiological and pathological changes. The performance of first-trimester prediction of PE using biomarkers (PlGF), uterine artery Doppler and maternal characteristics (BP and body mass index (BMI)) presents a promising 'proof-of-principle' algorithm, and assessment of second-trimester uterine artery Doppler has been well described[137].

Prevention

Given the relationship between high SVR prior to pregnancy[47] and risk factors such as high BMI and low PV[138,139], it is tempting to consider that optimizing maternal cardiovascular function prior to pregnancy might reduce the risk of HDP and FGR. Exercise in women with previous PE improves cardiovascular function, returning it to that of a sedentary woman[140], and results from a meta-analysis suggest that exercise prior to pregnancy reduces the incidence of placental syndromes[141]. Non-pharmacological vasoactive dietary nitrates might reduce BP in hypertensive pregnant women[136]. No study has examined the potential for nitrates and exercise in reducing the risk of HDP or PE in high-risk women, though the rationale for this is compelling. Other treatments, such as low-dose aspirin[142], have been proposed for the prevention of PE; however, with the relationship to maternal hemodynamic parameters being unclear, their description is beyond the scope of this document.

Management of established HDP and/or fetal growth restriction

Despite major pharmacological advances in the treatment of hypertension in the non-pregnant population, treatments for hypertension in HDP and PE have remained largely unchanged over the last 50 years. Adrenoceptor antagonists (such as labetalol) and the competitive alpha-adrenoceptor blocker, doxazosin, calcium channel antagonists (such as nifedipine), vasodilators (such as hydralazine) and centrally acting dopamine antagonists (such as alpha-methyldopa) are the mainstay of antihypertensive therapy during pregnancy. The definitive treatment for HDP and PE is delivery; hence, iatrogenic preterm birth is common, usually indicated because of

uncontrolled maternal hypertension, organ dysfunction or risk of seizures.

Therapy for HDP principally involves strategies to lower BP. This can be achieved by one or both of two mechanisms: by causing vasodilation and, thus, decreasing SVR, or by decreasing CO. Currently, these treatments are used variably with respect to the timing of onset of HDP and the presence of FGR. Knowledge of the two phenotypes of HDP, resistance-dominant and volume-dominant, could provide a potential opportunity for targeted antihypertensive therapy that seeks to compensate for the underlying cardiovascular deficit, although it is important to note that targeting BP in PE may compromise a growth-restricted fetus[15]. As FGR frequently coexists with PE, especially at earlier gestational ages, at least theoretically, it is important for CO and BP to be maintained in order not to compromise the uteroplacental circulation.

The pathophysiological concept of a bimodal hemodynamic pattern of HDP has important clinical implications. The BP-lowering pharmacological mechanisms of different antihypertensive drugs differ, offering opportunities for phenotype-specific treatment of hypertension in pregnancy[143–145]. Calcium channel blockers predominantly reduce arteriolar hypertonia, resulting in lower SVR with a subsequent rise in CO[146,147]. Beta-blocking agents are less active in vascular resistance-dominant HDP and, for this reason, clinical management protocols have been reported proposing the replacement of beta blockers by calcium channel blockers after 24 h in non-responsive cases[148]. Treatment of women with HDP with beta blockers, including labetalol, has been associated with lower neonatal birth weight[149]; therefore, their use should be considered carefully in cases of HDP with poor fetal growth. RCTs are currently running to evaluate the gestational and neonatal outcome of targeted antihypertensive treatment in resistance-dominant or volume-dominant HDP[143,150].

Discrimination between resistance-dominant HDP and volume-dominant HDP also challenges general guidelines recommending a 'one-for-all' pharmacological treatment[151] and stimulates further exploration of the role of targeted pharmacological treatment in both latent and clinical stages of disease. New and currently unexplored management options include treatment with diuretics in cases of volume-dominant HDP[152] and/or NO donors targeting the activated endothelium of arterial, microcirculatory and venous parts of the circulation[153,154]. A previous observational study suggests that vasodilator therapy improves birth weight and growth velocity in FGR[155]. More studies are required to identify whether targeting therapy in HDP in this way achieves better BP control or improved obstetric outcome.

Additional preventive and therapeutic approaches include the possible immune-modulation impact of low-molecular-weight heparin in HDP associated with FGR[156].

Sildenafil prolonged gestation by a non-significant 4 days[157] and its use in clinical practice has been curtailed due to findings of increased neonatal death due to pulmonary hypertension in trials in pregnancies affected by severe early-onset FGR[158,159]. No benefit in terms of prolongation of gestation has been reported from the use of esomeprazole, pravastatin[160,161] or antithrombin[162]. There is evidence to support the prolongation of gestation in expectantly managed PE with administration of metformin, although more studies are needed[163]. NO donor S-nitrosoglutathione has demonstrated efficacy in improving proteinuria and arterial and platelet function in women with severe early-onset PE, suggesting a potential disease-modifying mechanism of action[153,164,165].

Key points

- Maternal hemodynamic changes precede the development of clinical symptoms in pregnancies with PE and FGR, opening a window of opportunity for prediction and prevention.
- Exercise, dietary nitrates and control of BP prior to and in early pregnancy may improve hemodynamic indices but have not been shown to reduce the incidence of PE and FGR in women at high risk.
- Knowledge of the two cardiovascular phenotypes of HDP could provide a potential opportunity for targeted antihypertensive therapy to replace a 'one-size-fits-all' pharmacological approach to HDP.
- Calcium channel blockers are preferred in women with high SVR and low CO (usually PE/HDP associated with FGR, i.e. the resistance-dominant phenotype).
- Beta-blocking agents should be used with care in cases of HDP associated with FGR.

AREAS FOR RESEARCH

From the evidence outlined above, it is clear that the assessment of maternal hemodynamics adds information to current knowledge on the pathophysiology of gestational complications. However, it is unclear to what extent these assessments are clinically useful and cost-efficient. Further research is required to address the following areas.

Applicability in clinical practice

Future research should focus on identifying the most effective techniques and maternal hemodynamic parameters, used either individually or in combination, and on establishing their normal reference ranges[27]. The potential value of assessing the currently unexplored pathophysiological mechanism of the maternal venous system and body water volumes, independently or in combination with cardiac and arterial function, should be investigated[85]. Whether hemodynamic testing is better limited to a selected high-risk population or offered to all pregnant women should also be explored.

Screening for gestational complications

Prospective longitudinal studies that include preconceptional data are required to improve our understanding of changes in maternal hemodynamics and to clarify whether, in pregnancies affected by HDP, the cardiovascular profile is altered due to maladaptation in the index pregnancy, or pre-existing pathology in the cardiovascular system is unmasked by pregnancy[78,166]. The feasibility and relevance of preconceptional screening remains to be explored.

Little is known regarding changes in maternal hemodynamics in the preclinical phase, among pregnant women at risk of developing PE who are taking low-dose aspirin, calcium supplements and/or vitamin C. Furthermore, newly emerging screening strategies using biophysical parameters only should be evaluated[167]. Future prognostic studies are required to evaluate the optimum structure and timing of a screening program that could help to identify women at risk of developing HDP and pregnancy complications. The program should use current available reference ranges for both maternal cardiac function[32] and arterial stiffness[22]. They should report parameters appropriately adjusted for confounding factors and identify optimum timing of, and parameters for, screening.

PE is a risk factor for short- and long-term cardiovascular disease. Research is required to identify the optimum postpartum screening program that could identify women at risk of long-term cardiovascular dysfunction and guide future management in subsequent pregnancies[12,16,18].

Few studies have examined changes in maternal hemodynamics among pregnant women with multiple pregnancy or reduced fetal movements, those undergoing induction of labor and those who require regional anesthetics at the time of delivery. Future studies should provide guidance regarding the benefits of maternal hemodynamic assessment in the clinical setting in these cases.

Diagnosis of medical disorders

Assessment of maternal hemodynamics, including venous function and volume homeostasis, is useful to discriminate between GH, PE and normotensive FGR[6,85]. This approach can also help distinguish volume-dominant from resistance-dominant GH[6]. However, the feasibility and applicability of these methodologies require further evaluation.

The use of point-of-care/near-patient testing and continuous monitoring is increasing, revolutionizing maternal healthcare. Future investigators should report maternal hemodynamic parameters appropriately adjusted for confounding factors and identify optimum timing of, and parameters for, screening.

Gestational diabetes is noted to be associated with maladaptation of the cardiovascular system in pregnancy. Future studies are required to evaluate the optimum timing for screening, correlate findings to clinical outcomes and critically evaluate the role of metformin therapy and modulation of arterial stiffness[22,168–172].

Management of HDP

Volume-dominant and resistance-dominant HDP are two different pathophysiological phenotypes[76,106,173]. It remains to be determined whether targeted antihypertensive treatment may improve obstetric and neonatal outcome[150]. Large RCTs are needed to evaluate the potential therapeutic benefit of targeting variable components of the maternal hemodynamic maladaptation syndrome observed in pregnant women with HDP. The algorithmic model that combines the *Z*-score of multiple parameters of maternal hemodynamics will need further validation to assess whether it could guide treatment and assess the treatment response[174,175]. Hemodynamics-assisted monitoring of gestational complications might be useful to improve obstetric and neonatal outcome, but this approach has yet to be validated[106,176]. The implementation of maternal hemodynamic assessment is an opportunity to explore the application and effectiveness of currently unexplored antihypertensive treatments, such as diuretics[176–178] and nitrates[179–181].

Prevention

As the subpopulation of younger parturients with morbidities is on the rise, hemodynamic assessment provides opportunities to initiate prevention strategies with the aim of improving maternal cardiovascular function before conception[182]. The same applies to women with a history of PE, in whom prevention strategies could potentially be initiated during the interpregnancy interval[140]. The clinical relevance of these interventions remains to be explored.

Obesity is associated with low-grade chronic inflammation in adipose tissue, diastolic dysfunction and arterial stiffness[183]; studies should examine how this contributes in general to vascular dysfunction and, more specifically, to the pathogenesis of hypertension and vascular stiffening[184,185].

CONCLUSION

Maternal hemodynamic assessment provides additional clinical information that is useful for management of pregnancies complicated by HDP and/or FGR. Moreover, it opens a window of opportunity for prediction and prevention of maternal hemodynamic maladaptation, which may benefit both the index pregnancy and future maternal cardiovascular health.

CONSENSUS STATEMENTS

- After 20 weeks of gestation, assessment of maternal hemodynamics should be performed with the woman in a left lateral position.
- Different techniques of maternal hemodynamic evaluation cannot be used interchangeably.

- Maternal hemodynamics differentiates two HDP phenotypes: resistance-dominant and volume-dominant.
- Women with resistance-dominant HDP (usually HDP associated with FGR) should be treated with a vasodilator, such as calcium channel blockers.
- Women with volume-dominant HDP (usually HDP with appropriate-for-gestational-age fetal growth) should be treated with beta-blocking agents.
- Maternal hemodynamic evaluation might be useful in preconception and preclinical stages of HDP as an opportunity for prediction and prevention, but further research is required.
- An echocardiographic assessment should be performed in women with a history of HDP and symptoms of dyspnea or volume overload.
- Maternal hemodynamics should be evaluated in the postpartum period in women with a history of HDP, to identify those at increased risk of cardiovascular disease later in life.
- In women with a history of HDP, longitudinal BP measurements are recommended in the postpartum period.
- Women with a history of HDP should be counseled proactively regarding life-style changes.

AUTHORS

T. Stampalija,Unit of Fetal Medicine and Prenatal Diagnosis, Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy; and Department of Medical, Surgical and Health Science, University of Trieste, Trieste, Italy
C. Lees, Centre for Fetal Care, Department of Obstetrics and Gynaecology, Queen Charlotte's and Chelsea Hospital, Imperial College Healthcare NHS Trust, London, UK; and Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK
T. Ghi, Catholic University of Sacred Heart Rome, Department of Women and Child Health, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
J. Cornette, Department of Obstetrics and Gynecology, Division Obstetrics and Fetal Medicine, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
W. Gyselaers, Faculty of Medicine and Life Sciences, Limburg Clinical Research Center, Hasselt University, Diepenbeek, Belgium; and Department of Obstetrics & Gynecology, Ziekenhuis Oost-Limburg, Genk, Belgium
E. Ferrazzi, Obstetrics Unit, Department of Woman Child and Newborn, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy; and Department of Community and Health Sciences, University of Milan, Milan, Italy
T. Mousa, Maternal and Fetal Medicine Unit, University of Leicester, Leicester, UK
M. Spaanderman, Department of Obstetrics and Gynecology, Maastricht University Medical Center, The Netherlands; and Department of Gynaecology and Obstetrics, Radboud University Medical Centre, Nijmegen, The Netherlands
B. Thilaganathan, Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust, University of London, London, UK; and Molecular and Clinical Sciences Research Institute, St. George's University of London, London, UK
H. Valensise, Department of Surgical Sciences, University of Rome Tor Vergata, Rome, Italy; and Department of Obstetrics and Gynecology, Policlinico Casilino, Rome, Italy

Collaborators

We would like to thank the following members of the International Maternal Hemodynamic Group for their critical revision and contribution to this document:
J. J. Duvekot, Department of Obstetrics and Gynecology, Erasmus MC University Medical Center, Rotterdam, the Netherlands
C. Ghossein-Doha, Department of Obstetrics and Gynecology, Maastricht University Medical Centre, Maastricht, the Netherlands; and Research School GROW, University of Maastricht, Maastricht, the Netherlands
C. McEniery, Division of Experimental Medicine and Immunotherapeutics, University of Cambridge, Cambridge, UK
F. Mecacci, Department of Obstetrics and Gynecology, Department of Experimental, Clinical and Biomedical Sciences, Careggi University Hospital, University of Florence, Florence, Italy
G. P. Novelli, Division of Cardiology, Depatment of Medicine, Tor Vergata Polyclinic, Rome, Italy
B. Vasopollo, Department of Surgical Sciences, Tor Vergata University, Rome, Italy; and Department of Obstetrics and Gynecology, Policlinico Casilino Hospital, Rome, Italy
I. Wilkinson, Division of Experimental Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

CITATION

This Consensus Statement should be cited as: 'Stampalija T, Lees C, Ghi T, Cornette J, Gyselaers W, Ferrazzi E, Mousa T, Spaanderman M, Thilaganathan B, Valensise H and Collaborators. ISUOG Consensus Statement on maternal hemodynamic assessment in hypertensive disorders of pregnancy and fetal growth restriction. *Ultrasound Obstet Gynecol* 2025. doi:10.1002/uog.70040.

REFERENCES

1. Capeless EL, Clapp JF. Cardiovascular changes in early phase of pregnancy. *Am J Obstet Gynecol*. 1989;161:1449-1453.
2. Clapp JF, Capeless E. Cardiovascular function before, during, and after the first and subsequent pregnancies. *Am J Cardiol*. 1997;80:1469-1473.
3. Cornette J, Roos-Hesselink JW. Normal cardiovascular adaptation to pregnancy. *Evidence-Based Cardiology Consult*. Springer; 2014:423-432. doi:10.1007/978-1-4471-4441-0˙29

4. de Haas S, Ghossein-Doha C, van Kuijk SMJ, van Drongelen J, Spaanderman MEA. Physiological adaptation of maternal plasma volume during pregnancy: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2017;49:177-187.
5. Duvekot JJ, Cheriex EC, Pieters FA, Menheere PP, Peeters LH. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. *Am J Obstet Gynecol*. 1993;169:1382-1392.
6. Gyselaers W. Hemodynamic pathways of gestational hypertension and preeclampsia. *Am J Obstet Gynecol*. 2022;226:S988-S1005.
7. Melchiorre K, Giorgione V, Thilaganathan B. The placenta and preeclampsia: villain or victim? *Am J Obstet Gynecol*. 2022;226:S954-S962.
8. Bosio PM, McKenna PJ, Conroy R, O'Herlihy C. Maternal central hemodynamics in hypertensive disorders of pregnancy. *Obstet Gynecol*. 1999;94:978-984.
9. Bamfo JEAK, Kametas NA, Chambers JB, Nicolaides KH. Maternal cardiac function in fetal growth-restricted and non-growth-restricted small-for-gestational age pregnancies. *Ultrasound Obstet Gynecol*. 2007;29:51-57.
10. Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. *Hypertension*. 2018;72:24-43.
11. Stott D, Bolten M, Salman M, et al. Maternal demographics and hemodynamics for the prediction of fetal growth restriction at booking, in pregnancies at high risk for placental insufficiency. *Acta Obstet Gynecol Scand*. 2016;95:329-338.
12. Mulder EG, Ghossein-Doha C, Cauffman E, et al. Preventing recurrent preeclampsia by tailored treatment of nonphysiologic hemodynamic adjustments to pregnancy. *Hypertension*. 2021;77:2045-2053.
13. Vasapollo B, Valensise H, Novelli GP, et al. Abnormal maternal cardiac function precedes the clinical manifestation of fetal growth restriction. *Ultrasound Obstet Gynecol*. 2004;24:23-29.
14. Tay J, Foo L, Masini G, et al. Early and late preeclampsia are characterized by high cardiac output, but in the presence of fetal growth restriction, cardiac output is low: insights from a prospective study. *Am J Obstet Gynecol*. 2018;218:517.e1-517.e12.
15. Vasapollo B, Zullino S, Novelli GP, et al. Maternal hemodynamics from preconception to delivery: research and potential diagnostic and therapeutic implications: position statement by Italian association of preeclampsia and Italian society of perinatal medicine. *Am J Perinatol*. 2024;41:1999-2013.
16. Melchiorre K, Thilaganathan B, Giorgione V, et al. Hypertensive disorders of pregnancy and future cardiovascular health. *Front Cardiovasc Med*. 2020;7:59.
17. Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension*. 2011;58:709-715.
18. Ghossein-Doha C, van Neer J, Wissink B, et al. Pre-eclampsia: an important risk factor for asymptomatic heart failure. *Ultrasound Obstet Gynecol*. 2017;49:143-149.
19. Brouwers L, van Neer J, Wissink B, et al. Recurrence of pre-eclampsia and the risk of future hypertension and cardiovascular disease: a systematic review and meta-analysis. *BJOG*. 2018;125:1642-1654.
20. Sharman JE, Avolio AP, Baulmann J, et al. Validation of non-invasive central blood pressure devices: ARTERY Society task force consensus statement on protocol standardization. *Eur Heart J*. 2017;38:2805-2812.
21. Aldridge E, Mollen J, Verburg PE, et al. Agreement of aneroid and oscillometric blood pressure devices used in pregnancy. *Pregnancy Hypertens*. 2019;17:43-48.
22. Anness AR, Nath M, Melhuish K, et al. Arterial stiffness throughout pregnancy: arteriograph device-specific reference ranges based on a low-risk population. *J Hypertens*. 2022;40:870-877.
23. Foo FL, McEniery CM, Lees C, Khalil A, International Working Group on Maternal Hemodynamics. Assessment of arterial function in pregnancy: recommendations of the International Working Group on Maternal Hemodynamics. *Ultrasound Obstet Gynecol*. 2017;50:324-331.
24. Di Martino DD, Stampalija T, Rosti E, et al. Bedside cardiovascular maternal interrogation in the first trimester to predict different phenotypes of hypertensive disorders in pregnancy. *Pregnancy Hypertens*. 2016;6:300-305.
25. Perry H, Gutierrez J, Binder J, Thilaganathan B, Khalil A. Maternal arterial stiffness in hypertensive pregnancies with and without small-for-gestational-age neonate. *Ultrasound Obstet Gynecol*. 2020;56:44-50.
26. Hausvater A, Giannone T, Sandoval Y-HG, et al. The association between preeclampsia and arterial stiffness. *J Hypertens*. 2012;30:17-33.
27. Bijl RC, Valensise H, Novelli GP, et al. Methods and considerations concerning cardiac output measurement in pregnant women: recommendations of the International Working Group on Maternal Hemodynamics. *Ultrasound Obstet Gynecol*. 2019;54:35-50.
28. Rossi A, Cornette J, Johnson MR, et al. Quantitative cardiovascular magnetic resonance in pregnant women: cross-sectional analysis of physiological parameters throughout pregnancy and the impact of the supine position. *J Cardiovasc Magn Reson*. 2011;13:31.
29. Humphries A, Mirjalili SA, Tarr GP, Thompson JMD, Stone P. The effect of supine positioning on maternal hemodynamics during late pregnancy. *J Matern Fetal Neonatal Med*. 2019;32:3923-3930.
30. van Oppen AC, van der Tweel I, Duvekot JJ, Bruinse HW. Use of cardiac index in pregnancy: is it justified? *Am J Obstet Gynecol*. 1995;173:923-928.
31. Chantler PD, Clements RE, Sharp L, George KP, et al. The influence of body size on measurements of overall cardiac function. *Am J Physiol Heart Circ Physiol*. 2005;289:H2059-H2065.
32. Vinayagam D, Thilaganathan B, Stirrup O, Mantovani E, Khalil A. Maternal hemodynamics in normal pregnancy: reference ranges and role of maternal characteristics. *Ultrasound Obstet Gynecol*. 2018;51:665-671.
33. Dyer RA, Piercy JL, Reed AR, et al. Comparison between pulse waveform analysis and thermodilution cardiac output determination in patients with severe pre-eclampsia. *Br J Anaesth*. 2011;106:77-81.
34. Brogly N, Schiraldi R, Puertas L, et al. Pulse contour analysis calibrated by Trans-pulmonar thermodilution (Picco Plus®) for the perioperative management of a caesarean section in a patient with severe cardiomyopathy. *Braz J Anesthesiol*. 2016;66:329-332.
35. Romagano M, Louis-Jacques A, Quinones J, et al. Is there a role for cardiac magnetic resonance imaging during pregnancy? *J Matern Fetal Neonatal Med*. 2020;33:558-563.
36. Belfort MA, Rokey R, Saade GR, Moise KJ. Rapid echocardiographic assessment of left and right heart hemodynamics in critically ill obstetric patients. *Am J Obstet Gynecol*. 1994;171:884-892.
37. Cornette J, Laker S, Jeffery B, et al. Validation of maternal cardiac output assessed by transthoracic echocardiography against pulmonary artery catheterization in severely ill pregnant women: prospective comparative study and systematic review. *Ultrasound Obstet Gynecol*. 2017;49:25-31.
38. Mesa A, Jessurun C, Hernandez A, et al. Left ventricular diastolic function in normal human pregnancy. *Circulation*. 1999;99:511-517.
39. Griffiths SE, Waight G, Dennis AT. Focused transthoracic echocardiography in obstetrics. *BJA Educ*. 2018;18:271-276.
40. Kager CCM, Dekker GA, Stam MC. Measurement of cardiac output in normal pregnancy by a non-invasive two-dimensional independent Doppler device. *Aust N Z J Obstet Gynaecol*. 2009;49:142-144.
41. Farina S, Teruzzi G, Cattadori G, et al. Noninvasive cardiac output measurement by inert gas rebreathing in suspected pulmonary hypertension. *Am J Cardiol*. 2014;113:546-551.
42. Mahendru AA, Everett TR, Wilkinson IB, Lees CC, McEniery CM. A longitudinal study of maternal cardiovascular function from preconception to the postpartum period. *J Hypertens*. 2014;32:849-856.
43. Scardo JA, Ellings J, Vermillion ST, Chauhan SP. Validation of bioimpedance estimates of cardiac output in preeclampsia. *Am J Obstet Gynecol*. 2000;183:911-913.
44. Vinayagam D, Bowe S, Sheehan E, Thilaganathan B, Khalil A. Non-invasive haemodynamic monitoring in pregnancy: a comparative study using ultrasound and bioreactance. *Fetal Diagn Ther*. 2017;41:273-282.
45. Auler JOC, Torres MLA, Cardoso MM, et al. Clinical evaluation of the flotrac/Vigileo system for continuous cardiac output monitoring in patients undergoing regional anesthesia for elective cesarean section: a pilot study. *Clinics (Sao Paulo)*. 2010;65:793-798.
46. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1:307-310.
47. Foo FL, Collins A, McEniery CM, et al. Preconception and early pregnancy maternal haemodynamic changes in healthy women in relation to pregnancy viability. *Hum Reprod*. 2017;32:985-992.
48. Vonck S, Staelens AS, Bollen I, Broekx L, Gyselaers W. Why non-invasive maternal hemodynamics assessment is clinically relevant in early pregnancy: a literature review. *BMC Pregnancy Childbirth*. 2016;16:302.
49. Mahendru AA, Everett TR, Wilkinson IB, Lees CC, McEniery CM. Maternal cardiovascular changes from pre-pregnancy to very early pregnancy. *J Hypertens*. 2012;30:2168-2172.
50. Spaanderman ME, Willekes C, Hoeks AP, Ekhart TH, Peeters LL. The effect of pregnancy on the compliance of large arteries and veins in healthy parous control subjects and women with a history of preeclampsia. *Am J Obstet Gynecol*. 2000;183:1278-1286.
51. Chapman AB, Zamudio S, Woodmansee W, et al. Systemic and renal hemodynamic changes in the luteal phase of the menstrual cycle mimic early pregnancy. *Am J Phys*. 1997;273:F777-F782.
52. Chapman AB, Abraham WT, Zamudio S, et al. Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. *Kidney Int*. 1998;54:2056-2063.
53. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Phys*. 1989;256:H1060-H1065.
54. Poppas A, Shroff SG, Korcarz CE, et al. Serial assessment of the cardiovascular system in normal pregnancy. Role of arterial compliance and pulsatile arterial load. *Circulation*. 1997;95:2407-2415.
55. Liu LX, Arany Z. Maternal cardiac metabolism in pregnancy. *Cardiovasc Res*. 2014;101:545-553.
56. Mulder E, de Haas S, Mohseni Z, et al. Cardiac output and peripheral vascular resistance during normotensive and hypertensive pregnancy – a systematic review and meta-analysis. *BJOG*. 2022;129:696-707.
57. Easterling TR, Benedetti TJ, Schmucker BC, Millard SP. Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study. *Obstet Gynecol*. 1990;76:1061-1069.
58. Masini G, Foo LF, Cornette J, et al. Cardiac output changes from prior to pregnancy to post partum using two non-invasive techniques. *Heart*. 2019;105:715-720.
59. Krabbendam I, Janssen BJ, Van Dijk APJ, et al. The relation between venous reserve capacity and low plasma volume. *Reprod Sci*. 2008;15:604-612.
60. Estensen ME, Beitnes JO, Grindheim G, et al. Altered maternal left ventricular contractility and function during normal pregnancy. *Ultrasound Obstet Gynecol*. 2013;41:659-666.
61. Savu O, Jurcuţ R, Giuşcă S, et al. Morphological and functional adaptation of the maternal heart during pregnancy. *Circ Cardiovasc Imaging*. 2012;5:289-297.
62. Kuleva M, Youssef A, Maroni E, et al. Maternal cardiac function in normal twin pregnancy: a longitudinal study. *Ultrasound Obstet Gynecol*. 2011;38:575-580.
63. Kametas NA, McAuliffe F, Krampl E, Chambers J, Nicolaides KH. Maternal cardiac function in twin pregnancy. *Obstet Gynecol*. 2003;102:806-815.

64. Robson SC, Hunter S, Boys RJ, Dunlop W. Hemodynamic changes during twin pregnancy. A Doppler and M-mode echocardiographic study. *Am J Obstet Gynecol*. 1989;161:1273-1278.
65. Thomsen JK, Fogh-Andersen N, Jaszczak P. Atrial natriuretic peptide, blood volume, aldosterone, and sodium excretion during twin pregnancy. *Acta Obstet Gynecol Scand*. 1994;73:14-20.
66. Ghi T, Dall'Asta A, Franchi L, et al. The effect of chorionicity on maternal cardiac adaptation to uncomplicated twin pregnancy: a prospective longitudinal study. *Fetal Diagn Ther*. 2019;45:394-402.
67. Ghi T, Esposti DD, Montaguti E, et al. Maternal cardiac evaluation during uncomplicated twin pregnancy with emphasis on the diastolic function. *Am J Obstet Gynecol*. 2015;213:376.e1-376.e8.
68. Farsetti D, Pometti F, Novelli GP, et al. Longitudinal hemodynamic evaluation of uncomplicated twin pregnancies according to chorionicity: physiological cardiovascular dysfunction in monochorionic twin pregnancy. *Ultrasound Obstet Gynecol*. 2024;63(2):198-205.
69. Ghi T, Esposti DD, Montaguti E, et al. Post-partum evaluation of maternal cardiac function after severe preeclampsia. *J Matern Fetal Neonatal Med*. 2014;27:696-701.
70. Nunez E, Huluta I, Arozena MG, et al. Maternal cardiac function in twin pregnancy at 19-23 weeks' gestation. *Ultrasound Obstet Gynecol*. 2022;59:627-632.
71. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. *Science*. 2005;308:1592-1594.
72. Steegers EAP, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet*. 2010;376:631-644.
73. Raymond D, Peterson E. A critical review of early-onset and late-onset preeclampsia. *Obstet Gynecol Surv*. 2011;66:497-506.
74. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. *Hypertension*. 2008;52:873-880.
75. Ferrazzi E, Zullino S, Stampalija T, et al. Bedside diagnosis of two major clinical phenotypes of hypertensive disorders of pregnancy. *Ultrasound Obstet Gynecol*. 2016;48:224-231.
76. Ferrazzi E, Stampalija T, Monasta L, et al. Maternal hemodynamics: a method to classify hypertensive disorders of pregnancy. *Am J Obstet Gynecol*. 2018;218(1):124.e1-124.e11.
77. Wieling W, Jardine DL, de Lange FJ, et al. Cardiac output and vasodilation in the vasovagal response: An analysis of the classic papers. *Heart Rhythm*. 2016;13:798-805.
78. Rang S, van Montfrans GA, Wolf H. Serial hemodynamic measurement in normal pregnancy, preeclampsia, and intrauterine growth restriction. *Am J Obstet Gynecol*. 2008;198(519):e1-e9.
79. Amaral LM, Cunningham MW, Cornelius DC, LaMarca B. Preeclampsia: long-term consequences for vascular health. *Vasc Health Risk Manag*. 2015;11:403-415.
80. Ogunwole SM, Mwinnyaa G, Wang X, et al. Preeclampsia across pregnancies and associated risk factors: findings from a high-risk US birth cohort. *J Am Heart Assoc*. 2021;10:e019612.
81. Ogunwole SM, Chen X, Mitta S, et al. Interconception care for primary care providers: consensus recommendations on preconception and postpartum management of reproductive-age patients with medical comorbidities. *Mayo Clin Proc Innov Qual Outcomes*. 2021;5:872-890.
82. Menendez-Castro C, Rascher W, Hartner A. Intrauterine growth restriction - impact on cardiovascular diseases later in life. *Mol Cell Pediatr*. 2018;5:4.
83. James JL, Whitley GS, Cartwright JE. Pre-eclampsia: fitting together the placental, immune and cardiovascular pieces. *J Pathol*. 2010;221:363-378.
84. Mor G, Aldo P, Alvero AB. The unique immunological and microbial aspects of pregnancy. *Nat Rev Immunol*. 2017;17:469-482.
85. Gyselaers W, Vonck S, Staelens AS, et al. Gestational hypertensive disorders show unique patterns of circulatory deterioration with ongoing pregnancy. *Am J Physiol Regul Integr Comp Physiol*. 2019;316:R210-R221.
86. Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med*. 2013;369:1243-1251.
87. McDermott M, Miller EC, Rundek T, Hurn PD, Bushnell CD. Preeclampsia: association with posterior reversible encephalopathy syndrome and stroke. *Stroke*. 2018;49:524-530.
88. Gyselaers W. Maternal venous hemodynamic dysfunction in proteinuric gestational hypertension: evidence and implications. *J Clin Med*. 2019;8(3):335.
89. Perry H, Lehmann H, Mantovani E, Thilaganathan B, Khalil A. Correlation between central and uterine hemodynamics in hypertensive disorders of pregnancy. *Ultrasound Obstet Gynecol*. 2019;54:58-63.
90. Valensise H, Farsetti D, Pometti F, et al. The cardiac-fetal-placental unit: fetal umbilical vein flow rate is linked to the maternal cardiac profile in fetal growth restriction. *Am J Obstet Gynecol*. 2023;228(222):e1-222.e12.
91. Barbieri M, Di Martino DD, Ferrazzi EM, Stampalija T. Umbilical vein blood flow: State-of-the-art. *J Clin Ultrasound*. 2023;51:318-325.
92. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. *Am J Obstet Gynecol*. 2011;204:193-201.
93. Mecacci F, Avagliano L, Lisi F, et al. Fetal growth restriction: does an integrated maternal hemodynamic-placental model fit better? *Reprod Sci*. 2021;28:2422-2435.
94. Bonamy A-KE, Parikh NI, Cnattingius S, Ludvigsson JF, Ingelsson E. Birth characteristics and subsequent risks of maternal cardiovascular disease. *Circulation*. 2011;124:2839-2846.
95. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. *Lancet*. 2005;366:1797-1803.
96. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol*. 2016;48:333-339.
97. Lees CC, Stampalija T, Baschat A, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol*. 2020;56:298-312.
98. Duvekot JJ, Cheriex EC, Pieters FA, et al. Maternal volume homeostasis in early pregnancy in relation to fetal growth restriction. *Obstet Gynecol*. 1995;85:361-367.
99. Vasapollo B, Novelli GP, Farsetti D, Valensise H. Maternal peripheral vascular resistance at mid gestation in chronic hypertension as a predictor of fetal growth restriction. *J Matern Fetal Neonatal Med*. 2022;35:9834-9836.
100. Farsetti D, Vasapollo B, Pometti F, et al. Maternal hemodynamics for the identification of early fetal growth restriction in normotensive pregnancies. *Placenta*. 2022;129:12-14.
101. Vasapollo B, Novelli GP, Gagliardi G, Farsetti D, Valensise H. Pregnancy complications in chronic hypertensive patients are linked to pre-pregnancy maternal cardiac function and structure. *Am J Obstet Gynecol*. 2020;223(425):e1-425.e13.
102. Lees C, Stampalija T, Hecher K. Diagnosis and management of fetal growth restriction: the ISUOG guideline and comparison with the SMFM guideline. *Ultrasound Obstet Gynecol*. 2021;57:884-887.
103. Lees CC, Romero R, Stampalija T, et al. Clinical Opinion: the diagnosis and management of suspected fetal growth restriction: an evidence-based approach. *Am J Obstet Gynecol*. 2022;226(3):336-378.
104. Pathak S, Lees CC, Hackett G, Jessop F, Sebire NJ. Frequency and clinical significance of placental histological lesions in an unselected population at or near term. *Virchows Arch*. 2011;459:565-572.
105. Binder J, Monaghan C, Thilaganathan B, Carta S, Khalil A. De-novo abnormal uteroplacental circulation in third trimester: pregnancy outcome and pathological implications. *Ultrasound Obstet Gynecol*. 2018;52:60-65.
106. Stott D, Papastefanou I, Paraschiv D, Clark K, Kametas NA. Longitudinal maternal hemodynamics in pregnancies affected by fetal growth restriction. *Ultrasound Obstet Gynecol*. 2017;49:761-768.
107. Stampalija T, Wolf H, Mylrea-Foley B, et al. Reduced fetal growth velocity and weight loss are associated with adverse perinatal outcome in fetuses at risk of growth restriction. *Am J Obstet Gynecol*. 2023;228:71.e1-71.e10.
108. Perry H, Lehmann H, Mantovani E, Thilaganathan B, Khalil A. Are maternal hemodynamic indices markers of fetal growth restriction in pregnancies with a small-for-gestational-age fetus? *Ultrasound Obstet Gynecol*. 2020;55:210-216.
109. Stampalija T, Monasta L, Barbieri M, et al. Late-term fetuses with reduced umbilical vein blood flow volume: an under-recognized population at increased risk of growth restriction. *Eur J Obstet Gynecol Reprod Biol*. 2022;272:182-187.
110. Hamidi OP, Driver C, Steller JG, et al. Umbilical venous volume flow in late-onset fetal growth restriction. *J Ultrasound Med*. 2023;42:173-183.
111. Giorgione V, Ridder A, Kalafat E, Khalil A, Thilaganathan B. Incidence of postpartum hypertension within 2 years of a pregnancy complicated by pre-eclampsia: a systematic review and meta-analysis. *BJOG*. 2021;128:495-503.
112. Honigberg MC, Zekavat SM, Aragam K, et al. Long-term cardiovascular risk in women with hypertension during pregnancy. *J Am Coll Cardiol*. 2019;74:2743-2754.
113. McCarthy FP, O'Driscoll J, Seed P, et al. Planned delivery to improve postpartum cardiac function in women with preterm pre-eclampsia: the PHOEBE mechanisms of action study within the PHOENIX RCT. Southampton (UK): NIHR Journals Library; 2021 Sep. (Efficacy and Mechanism Evaluation, No. 8.12).
114. Heida KY, Franx A, van Rijn BB, et al. Earlier age of onset of chronic hypertension and type 2 diabetes mellitus after a hypertensive disorder of pregnancy or gestational diabetes mellitus. *Hypertension*. 2015;66:1116-1122.
115. Boucheron P, Lailler G, Moutengou E, et al. Hypertensive disorders of pregnancy and onset of chronic hypertension in France: the nationwide CONCEPTION study. *Eur Heart J*. 2022;43:3352-3361.
116. Stuart JJ, Tanz LJ, Missmer SA, et al. Hypertensive disorders of pregnancy and maternal cardiovascular disease risk factor development. *Ann Intern Med*. 2018;169:224.
117. Sharma S, Skog J, Timpka S, Ignell C. Preeclampsia and high blood pressure in early pregnancy as risk factors of severe maternal cardiovascular disease during 50-years of follow-up. *Pregnancy Hypertens*. 2021;26:79-85.
118. Anne Cathrine Staff,Redman CWG, Williams D, et al. Pregnancy and long-term maternal cardiovascular health: progress through harmonization of research cohorts and biobanks. *Hypertension*. 2016;67:251-260.
119. Giorgione V, Khalil A, O'Driscoll J, Thilaganathan B. Peripartum screening for postpartum hypertension in women with hypertensive disorders of pregnancy. *J Am Coll Cardiol*. 2022;80:1465-1476.
120. Markovitz AR, Stuart JJ, Horn J, et al. Does pregnancy complication history improve cardiovascular disease risk prediction? Findings from the HUNT study in Norway. *Eur Heart J*. 2019;40:1113-1120.
121. Benschop L, Schalekamp-Timmermans S, Broere-Brown ZA, et al. Placental growth factor as an indicator of maternal cardiovascular risk after pregnancy. *Circulation*. 2019;139:1698-1709.
122. Dall'Asta A, D'Antonio F, Saccone G, et al. Cardiovascular events following pregnancy complicated by pre-eclampsia with emphasis on comparison between early- and late-onset forms: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2021;57:698-709.
123. Castleman JS, Ganapathy R, Taki F, et al. Echocardiographic structure and function in hypertensive disorders of pregnancy: a systematic review. *Circ Cardiovasc Imaging*. 2016;9(9):e004888.
124. Reddy M, Wright L, Rolnik DL, et al. Evaluation of cardiac function in women with a history of preeclampsia: a systematic review and meta-analysis. *J Am Heart Assoc*. 2019;8:e013545.

125. Bokslag A, Franssen C, Alma LJ, et al. Early-onset preeclampsia predisposes to preclinical diastolic left ventricular dysfunction in the fifth decade of life: an observational study. *PLoS One*. 2018;13:e0198908.
126. Countouris ME, Villanueva FS, Berlacher KL, et al. Association of hypertensive disorders of pregnancy with left ventricular remodeling later in life. *J Am Coll Cardiol*. 2021;77:1057-1068.
127. Haug EB, Horn J, Markovitz AR, et al. Life course trajectories of cardiovascular risk factors in women with and without hypertensive disorders in first pregnancy: the hunt study in Norway. *J Am Heart Assoc*. 2018;7(15):e009250.
128. Hoppe KK, Thomas N, Zernick M, et al. Telehealth with remote blood pressure monitoring compared with standard care for postpartum hypertension. *Am J Obstet Gynecol*. 2020;223:585-588.
129. Tucker KL, Sheppard JP, Stevens R, et al. Self-monitoring of blood pressure in hypertension: a systematic review and individual patient data meta-analysis. *PLoS Med*. 2017;14:e1002389.
130. Magee L, Sadeghi S. Prevention and treatment of postpartum hypertension. *Cochrane Database Syst Rev*. 2005;(1):CD004351. doi:10.1002/14651858.CD004351.pub2
131. Ayala DE, Hermida RC, Mojón A, Fernández JR, Iglesias M. Circadian blood pressure variability in healthy and complicated pregnancies. *Hypertension*. 1997;30:603-610.
132. Cairns AE, Tucker KL, Leeson P, et al. Self-management of postnatal hypertension: the SNAP-HT trial. *Hypertension*. 2018;72:425-432.
133. Kitt JA, Fox RL, Cairns AE, et al. Short-term postpartum blood pressure self-management and long-term blood pressure control: a randomized controlled trial. *Hypertension*. 2021;78:469-479.
134. Lopes Perdigao J, Lewey J, Hirshberg A, et al. Furosemide for accelerated recovery of blood pressure postpartum in women with a hypertensive disorder of pregnancy: a randomized controlled trial. *Hypertension*. 2021;77:1517-1524.
135. Arnett DK, Khera A, Blumenthal RS. 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease: part 1, lifestyle and behavioral factors. *JAMA Cardiol*. 2019;4:1043.
136. Ormesher L, Higson S, Luckie M, et al. Postnatal enalapril to improve cardiovascular function following preterm preeclampsia (pick-up):: a randomized double-blind placebo-controlled feasibility trial. *Hypertension*. 2020;76:1828-1837.
137. Albaiges G. One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. *Obstet Gynecol*. 2000;96:559-564.
138. Scholten RR, Sep S, Peeters L, et al. Prepregnancy low-plasma volume and predisposition to preeclampsia and fetal growth restriction. *Obstet Gynecol*. 2011;117:1085-1093.
139. Scholten RR, Lotgering FK, Hopman MT, et al. Low plasma volume in normotensive formerly preeclamptic women predisposes to hypertension. *Hypertension*. 2015;66:1066-1072.
140. Scholten RR, Thijssen DJH, Lotgering FK, Hopman MTE, Spaanderman MEA. Cardiovascular effects of aerobic exercise training in formerly preeclamptic women and healthy parous control subjects. *Am J Obstet Gynecol*. 2014;211:516.e1-516.e11.
141. Davenport MH, Ruchat S-M, Poitras VJ, et al. Prenatal exercise for the prevention of gestational diabetes mellitus and hypertensive disorders of pregnancy: a systematic review and meta-analysis. *Br J Sports Med*. 2018;52:1367-1375.
142. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med*. 2017;377:613-622.
143. McLaughlin K, Snelgrove JW, Sienas LE, et al. Phenotype-directed management of hypertension in pregnancy. *J Am Heart Assoc*. 2022;11:e023694.
144. Novelli GP, Vasapollo B, Valensise H. Hemodynamic prediction and stratification of hypertensive disorders of pregnancy: a dream that is coming true? *J Am Heart Assoc*. 2018;7(14):e010084.
145. Lees C, Ferrazzi E. Relevance of haemodynamics in treating pre-eclampsia. *Curr Hypertens Rep*. 2017;19:76.
146. Cornette J, Buijs EAB, Duvekot JJ, et al. Hemodynamic effects of intravenous nicardipine in severely pre-eclamptic women with a hypertensive crisis. *Ultrasound Obstet Gynecol*. 2016;47:89-95.
147. Cornette J, Duvekot JJ, Roos-Hesselink JW, Hop WCJ, Steegers EAP. Maternal and fetal haemodynamic effects of nifedipine in normotensive pregnant women. *BJOG*. 2011;118:510-540.
148. Stott D, Stott D, Bolten M, et al. Longitudinal hemodynamics in acute phase of treatment with labetalol in hypertensive pregnant women to predict need for vasodilatory therapy. *Ultrasound Obstet Gynecol*. 2017;49:85-94.
149. Duan L, Ng A, Chen W, Spencer HT, Lee M-S. Beta-blocker subtypes and risk of low birth weight in newborns. *J Clin Hypertens (Greenwich)*. 2018;20:1603-1609.
150. Lanssens D, Thijs IM, Gyselaers W, PREMOM II – consortium. Design of the Pregnancy REmote MOnitoring II study (PREMOM II): a multicenter, randomized controlled trial of remote monitoring for gestational hypertensive disorders. *BMC Pregnancy Childbirth*. 2020;20:626.
151. Hypertension in Pregnancy. *Diagnosis and Management*. National Institute for Health and Care Excellence (NICE); 2019.
152. Tamás P, Hantosi E, Farkas B, et al. Preliminary study of the effects of furosemide on blood pressure during late-onset pre-eclampsia in patients with high cardiac output. *Int J Gynaecol Obstet*. 2017;136:87-90.
153. Everett TR, Wilkinson IB, Mahendru AA, et al. S-Nitrosoglutathione improves haemodynamics in early-onset pre-eclampsia. *Br J Clin Pharmacol*. 2014;78:660-669.
154. Lang NN, Ahmad FA, Cleland JG, et al. Haemodynamic effects of the nitroxyl donor cimlanod (BMS-986231) in chronic heart failure: a randomized trial. *Eur J Heart Fail*. 2021;23:1147-1155.
155. Kubo M, Umekawa T, Maekawa Y, et al. Retrospective study of tadalafil for fetal growth restriction: Impact on maternal and perinatal outcomes. *J Obstet Gynaecol Res*. 2017;43:291-297.
156. McLaughlin K, Hobson SR, Chandran AR, et al. Circulating maternal placental growth factor responses to low-molecular-weight heparin in pregnant patients at risk of placental dysfunction. *Am J Obstet Gynecol*. 2022;226:S1145-S1156.e1.
157. Trapani A, Gonçalves LF, Trapani TF, et al. Perinatal and hemodynamic evaluation of sildenafil citrate for preeclampsia treatment: a randomized controlled trial. *Obstet Gynecol*. 2016;128:253-259.
158. Pels A, Onland W, Berger RMF, et al. Neonatal pulmonary hypertension after severe early-onset fetal growth restriction: post hoc reflections on the Dutch STRIDER study. *Eur J Pediatr*. 2022;181:1709-1718.
159. Pels A, Derks J, Elvan-Taspinar A, et al. Maternal sildenafil vs placebo in pregnant women with severe early-onset fetal growth restriction: a randomized clinical trial. *JAMA Netw Open*. 2020;3:e205323.
160. Ahmed A, Williams DJ, Cheed V, et al. Pravastatin for early-onset pre-eclampsia: a randomised, blinded, placebo-controlled trial. *BJOG*. 2020;127:478-488.
161. Brownfoot FC, Tong S, Hannan NJ, et al. Effects of pravastatin on human placenta, endothelium, and women with severe preeclampsia. *Hypertension*. 2015;66:687-697.
162. Paidas MJ, Tita ATN, Macones GA, et al. Prospective, randomized, double-blind, placebo-controlled evaluation of the pharmacokinetics, safety and efficacy of recombinant antithrombin versus placebo in preterm preeclampsia. *Am J Obstet Gynecol*. 2020;223:739.e1-739.e13.
163. Cluver CA, Hiscock R, Decloedt EH, et al. Use of metformin to prolong gestation in preterm pre-eclampsia: randomised, double blind, placebo controlled trial. *BMJ*. 2021;374:n2103.
164. de Belder A, Lees C, Martin J, Moncada S, Campbell S. Treatment of HELLP syndrome with nitric oxide donor. *Lancet*. 1995;345:124-125.
165. Lees C, Langford E, Brown AS, et al. The effects of S-nitrosoglutathione on platelet activation, hypertension, and uterine and fetal Doppler in severe preeclampsia. *Obstet Gynecol*. 1996;88:14-19.
166. Foo FL, Mahendru AA, Masini G, et al. Association between prepregnancy cardiovascular function and subsequent preeclampsia or fetal growth restriction. *Hypertension*. 2018;72:442-450.
167. Vonck S, Staelens AS, Lanssens D, et al. Development of a biophysical screening model for gestational hypertensive diseases. *J Biomed Sci*. 2019;26:38.
168. Osman MW, Nath M, Khalil A, et al. Haemodynamic differences amongst women who were screened for gestational diabetes in comparison to healthy controls. *Pregnancy Hypertens*. 2018;14:23-28.
169. Osman MW, Nath M, Khalil A, et al. The effects of metformin on maternal haemodynamics in gestational diabetes mellitus: a pilot study. *Diabetes Res Clin Pract*. 2018;139:170-178.
170. Anness AR, Nath M, Osman MW, et al. Does treatment modality affect measures of arterial stiffness in women with gestational diabetes? *Ultrasound Obstet Gynecol*. 2023;62:422-429.
171. Anness AR, Clark A, Melhuish K, et al. Maternal hemodynamics and neonatal birth weight in pregnancies complicated by gestational diabetes: new insights from novel causal inference analysis modeling. *Ultrasound Obstet Gynecol*. 2022;60:215-222.
172. Mecacci F, Ottanelli S, Vannuccini S, et al. Maternal hemodynamic changes in gestational diabetes: a prospective case-control study. *Arch Gynecol Obstet*. 2022;306:357-363.
173. Masini G, Foo LF, Tay J, et al. Preeclampsia has two phenotypes which require different treatment strategies. *Am J Obstet Gynecol*. 2022;226:S1006-S1018.
174. Vasapollo B, Novelli GP, Valensise H. Hemodynamic guided treatment of hypertensive disorders in pregnancy: is it time to change our mind? *J Matern Fetal Neonatal Med*. 2021;34:3830-3831.
175. Valensise H, Farsetti D, Pisani I, et al. Friendly help for clinical use of maternal hemodynamics. *J Matern Fetal Neonatal Med*. 2021;34:3075-3079.
176. McLaughlin K, Scholten RR, Kingdom JC, Floras JS, Parker JD. Should maternal hemodynamics guide antihypertensive therapy in preeclampsia? *Hypertension*. 2018;71:550-556.
177. Report of the national high blood pressure education program working group on high blood pressure in pregnancy. *Am J Obstet Gynecol*. 2000;183:S1-S22.
178. Brown CM, Garovic VD. Drug treatment of hypertension in pregnancy. *Drugs*. 2014;74:283-296.
179. Massimiani M, Tiralongo GM, Salvi S, et al. Treatment of pregnancies complicated by intrauterine growth restriction with nitric oxide donors increases placental expression of epidermal growth factor-like domain 7 and improves fetal growth: a pilot study. *Transl Res*. 2021;228:28-41.
180. Vasapollo B, Novelli GP, Gagliardi G, et al. Medical treatment of early-onset mild gestational hypertension reduces total peripheral vascular resistance and influences maternal and fetal complications. *Ultrasound Obstet Gynecol*. 2012;40:325-331.
181. Valensise H, Vasapollo B, Novelli GP, et al. Maternal and fetal hemodynamic effects induced by nitric oxide donors and plasma volume expansion in pregnancies with gestational hypertension complicated by intrauterine growth restriction with absent end-diastolic flow in the umbilical artery. *Ultrasound Obstet Gynecol*. 2008;31:55-64.
182. Thakkar A, Hailu T, Blumenthal RS, et al. Cardio-obstetrics: the next frontier in cardiovascular disease prevention. *Curr Atheroscler Rep*. 2022;24:493-507.
183. Buddeberg BS, Sharma R, O'Driscoll JM, et al. Cardiac maladaptation in obese pregnant women at term. *Ultrasound Obstet Gynecol*. 2019;54:344-349.
184. Koenen M, Hill MA, Cohen P, Sowers JR. Obesity, adipose tissue and vascular dysfunction. *Circ Res*. 2021;128:951-968.
185. Golinska-Grzybala K, Wiechec M, Golinski B, et al. Subclinical cardiac performance in obese and overweight women as a potential risk factor of preeclampsia. *Pregnancy Hypertens*. 2021;23:131-135.