Preeclampsia has two phenotypes which require different treatment strategies

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The opinion on the mechanisms underlying the pathogenesis of preeclampsia still divides scientists and clinicians. This common complication of pregnancy has long been viewed as a disorder linked primarily to placental dysfunction, which is caused by abnormal trophoblast invasion, however, evidence from the previous two decades has triggered and supported a major shift in viewing preeclampsia as a condition that is caused by inherent maternal cardiovascular dysfunction, perhaps entirely independent of the placenta. In fact, abnormalities in the arterial and cardiac functions are evident from the early subclinical stages of preeclampsia and even before conception. Moving away from simply observing the peripheral blood pressure changes, studies on the central hemodynamics reveal two different mechanisms of cardiovascular dysfunction thought to be reflective of the early-onset and late-onset phenotypes of preeclampsia. More recent evidence identified that the underlying cardiovascular dysfunction in these phenotypes can be categorized according to the presence of coexisting fetal growth restriction instead of according to the gestational period at onset, the former being far more common at early gestational ages. The purpose of this review is to summarize the hemodynamic research observations for the two phenotypes of preeclampsia. We delineate the physiological hemodynamic changes that occur in normal pregnancy and those that are observed with the pathologic processes associated with preeclampsia. From this, we propose how the two phenotypes of preeclampsia could be managed to mitigate or redress the hemodynamic dysfunction, and we consider the implications for future research based on the current evidence. Maternal hemodynamic modifications throughout pregnancy can be recorded with simple-to-use, noninvasive devices in obstetrical settings, which require only basic training. This review includes a brief overview of the methodologies and techniques used to study hemodynamics and arterial function, specifically the noninvasive techniques that have been utilized in preeclampsia research.

Key words: arterial function, blood pressure, cardiac output, cardiovascular function, fetal growth restriction, hemodynamics, hypertensive disease of pregnancy, preeclampsia, vascular resistance

Introduction

Classical obstetrical teaching characterizes preeclampsia as a single pathophysiological entity with the defining features of hypertension in association with proteinuria, however, more recent definitions also include presentation with acute maternal kidney damage, abnormal liver function, neurologic impairment, pulmonary edema, hemolysis, thrombocytopenia, or fetal growth restriction (FGR). The goal of therapy is to reduce the blood pressure with vasodilator drugs and in severe preeclampsia, in which there is a risk of pulmonary edema because of endothelial dysfunction, to prevent intravascular fluid overload by limiting fluid intake. This approach presupposes that preeclampsia is associated with both vasoconstriction and increased intravascular volume. From a
mechanistic or physiological point of view, these two abnormalities are unlikely to coexist in the same person: it is more likely that a vasoconstricted state would exist with a depleted intravascular volume, and that increased intravascular fluid would exist with a relative state of vasodilatation. In fact, emerging evidence since the early 2000s suggests that preeclampsia may be caused by two opposing mechanisms that are represented by these two extremes.

Early-onset preeclampsia is associated with a low cardiac output and high vascular resistance,⁷ and women with this condition are at risk of cardiovascular dysfunction categorized as heart failure many months after delivery.⁴ These findings are in contrast with those of Easterling et al.⁵ who found that women with preeclampsia had a higher cardiac output than healthy women in a longitudinal study. These apparently contradictory findings have been explained by the gestational age at the onset of preeclampsia, with the early-onset (before 34 weeks of gestation) condition being attributed to a low cardiac output, high vascular resistance, and a depleted intravascular fluid state and late-onset preeclampsia being associated with a high cardiac output, normal or low vascular resistance, and an intravascular fluid overload. More recently, work conducted by our group in women who were studied between 24 and 40 weeks of gestation, in which all of the cardiovascular measurements were adjusted for conditions being attributed to a low cardiac output, high vascular resistance, and a depleted intravascular fluid state and late-onset preeclampsia being associated with a high cardiac output, normal or low vascular resistance, and an intravascular fluid overload. More recently, work conducted by our group in women who were studied between 24 and 40 weeks of gestation, in which all of the cardiovascular measurements were adjusted for

| Figure 1 |

Schematic representation of changes in the cardiac parameters and arterial function in PE, FGR, or the combination of both complications⁵

<table>
<thead>
<tr>
<th>Cardiac Output</th>
<th>FGR</th>
<th>PE</th>
<th>PE + FGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Peripheral Resistance</td>
<td>▲</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Maternal Pulse</td>
<td>▲</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Augmentation Index</td>
<td>▲</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Pulse Wave Velocity</td>
<td>▲</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

FGR, fetal growth restriction; PE, preeclampsia.
low-output cardiac state. Data from a study by Lund-Johansen,13 many years before, support this transitional hypothesis. It also raises the possibility that intervention during the high-output stages of hypertension may prevent resistance vessel remodeling, and thus the development of fixed hypertension, which requires life-long therapy.

In contrast to the observations in younger hypertensives, the main hemodynamic abnormality in older individuals with isolated systolic hypertension is increased aortic stiffness14 rather than an elevated resistance or cardiac output. The human aorta contains a large proportion of elastin, which allows it to buffer the cyclical changes in pressure caused by the intermittent left ventricular ejection of blood into the arterial tree. This phenomenon makes the cardiovascular system more efficient, minimizes peak (systolic) pressure, and maintains a diastolic pressure. Pulse pressure (the difference between the systolic and diastolic pressures) is related to the aortic stiffness and stroke volume as follows:

Pulse pressure ≡ aortic stiffness × stroke volume

The aorta progressively stiffens with age15 owing to the mechanical degeneration of the elastin fibers and other processes such as calcium deposition. For reasons that are not fully understood, this seems to be exaggerated or accelerated in some individuals and gives rise to a widened pulse pressure and thus systolic hypertension.16

A Possible Latent Phase in Preeclampsia

Pregnancy is a condition of physiological expansion in the volume of noncirculating and circulating body fluid. This expansion in volume is a potential stressor for the maternal cardiovascular system, as illustrated by those women who show cardiac signs of volume overload during an uncomplicated third trimester. This is associated with a rise in the cardiac output from the second trimester to a plateau at term and with a decrease in the peripheral vascular resistance to a nadir in the early third trimester. The change in cardiac output during gestation has recently been shown to be a strong determinant of birthweight,19 with a higher cardiac output being associated with larger babies, and the converse also being true. In the latent phase of preeclampsia, longitudinal observations from the first trimester to term have shown 3 different patterns of evolutions of the cardiac output and peripheral vascular resistance. Early-onset preeclampsia with FGR presents with high peripheral vascular resistance from the first trimester onward,20 which is associated with a failure to adequately increase the cardiac output from the first to the second trimester.20,21 The latter is most likely caused by extravasation of the intravascular fluids into the interstitium, as is illustrated by the high volume of extracellular water that is already present in the first trimester of early-onset preeclampsia.22 It is important to mention that women who develop this type of preeclampsia already show low cardiac output and high peripheral vascular resistance before conception.20,23 Some women who develop a low cardiac output with high vascular resistance phenotype of preeclampsia in the late third trimester initially showed a high cardiac output and low peripheral vascular resistance in the first trimester, which subsequently converted to the low output with high vascular resistance circulation state during the course of the pregnancy.24 During this crossover, a short temporary state of “apparently normal” cardiovascular function is present. One explanation for this evolution is an endothelial dysfunction triggered by an intravascular overload with a subsequent increase in the vascular tone (peripheral vascular resistance) and a decrease in the cardiac output, as observed in pregnant women with obesity during an uncomplicated third trimester pregnancy.25 Endothelial dysfunction caused by intravascular volume overload has been documented in nonpregnant individuals during hemodialysis26 and acute heart failure.27 For late-onset preeclampsia, frequently seen in women with obesity, high-output circulation is seen throughout all the stages of pregnancy, including the clinical stage of late-onset preeclampsia, during delivery, and postpartum (Figure 2). The dual etiology of preeclampsia suggested by these two
different evolutions of cardiovascular function in the latent phases of the disease is supported by the observation of bimodal skewing in the distribution of birthweight, with a higher prevalence of neonates who are either small or large for gestational age in women with preeclampsia.

**Cardiovascular Physiology in Pregnancy**

To understand the different patterns of pathologic modifications in the maternal cardiovascular function in complicated pregnancies, it is useful to summarize the expected changes in a healthy pregnancy. From the very early stages of gestation, the maternal cardiovascular system experiences major changes in the different parameters, and these modifications are the key for a successful and uncomplicated pregnancy. Different parameters can show an increase or decrease, which varies in magnitude depending on the parameter itself and the gestational age. The most important changes to consider involve blood volume expansion, central hemodynamics, modifications in the cardiac mass, and arterial vascular function.

As has been mentioned, pregnancy, above all, is a condition of prolonged maternal blood volume overload, particularly in the third trimester. Compared with prepregnancy, the blood volume increases by 40% at term, mainly because of a 45% to 55% increase in the plasma volume and a 20% to 30% increase in the erythrocyte mass. Modification to the central hemodynamics and in the cardiac structure are strongly connected with these changes.

Arguably the most informative hemodynamic parameter is cardiac output, which reflects the growing demand of the cardiovascular system during gestation, and, as such, it starts to increase soon after the beginning of pregnancy. The magnitude and trend of this increase have been described recently in a meta-analysis by Meah et al who showed that the cardiac output increases by 15% in the first trimester when compared with the prepregnancy value, then peaks in the early third trimester to 31% higher than the prepregnancy value (+1.5 L/min), and then decreases by 6% in the late third trimester. These results were obtained from the analysis of both cross-sectional and longitudinal studies, but most of them lacked prepregnancy measurements of the same subjects and not all of them were performed using the same technique. Studies in which women were recruited before pregnancy and subsequently followed throughout pregnancy generally included only a few subjects (8–69), and reported contrasting results about the magnitude of change (17%–49% above the prepregnancy value) and the gestational age at the peak of cardiac output (12–38 weeks of gestation). Our group, using different methodologies, recently reported that a rise in the peak cardiac output occurred earlier and more modestly than previously thought (+1.05 L/min or 17.5% above the prepregnancy value at 15.2 weeks’ gestation) as measured using the inert gas rebreathing technique; +0.47 L/min or 7.7% above the prepregnancy value at 10.4 weeks’ gestation as measured using the pulse wave velocity. As the product of stroke volume and heart rate, the cardiac output increase is driven more by the progressive rise in the heart rate, which peaks in the third trimester (20%
24% higher than the prepregnancy value), than stroke volume (13% increase from the prepregnancy value in the second trimester).\(^3\,04,\,43\)

The decrease in the peripheral vascular resistance with gestational age is associated with a reduction in the uterine artery and fetal umbilical Doppler impedance.\(^4\,44,\,45\) This is detectable from the early stages of pregnancy and is driven by vasodilatory mediators. The peripheral vascular resistance inversely reflects the changes in the cardiac output, progressively decreasing until the third trimester when the lowest value of 30% below the prepregnancy level is reached and then showing a slight increase until term.\(^3\,2,\,36,\,40,\,46,\,47\) (Figure 3).

As a consequence of these considerable hemodynamic changes during the course of gestation, the maternal heart experiences profound remodeling. A progressive increase in the left ventricular mass has been reported widely, most markedly in the third trimester (34% above the prepregnancy values).\(^3\,2,\,36,\,40,\,47\) The left ventricular cavity dimension is increased proportionally to the left ventricular wall thickness, leading to eccentric myocardial hypertrophy, which reflects the increase in the preload (owing to the maternal relative blood volume overload).\(^4\,8\) These changes are comparable with the physiological hypertrophy of an athlete who shares several common characteristics such as increased myocardial angiogenesis, the absence of fibrosis, and reversibility.\(^4\,9\)

Changes in the large artery function are predictors of cardiovascular risk in nonpregnant subjects.\(^4\,0\) The loss of the elastic properties of the aorta and the consequent rise in arterial stiffness cause an increase in blood pressure, as previously discussed.\(^5\,1\) In a normal pregnancy, the pulse wave velocity, which is a measurement of the blood flow velocity in the aorta, and augmentation index, a parameter that provides a measure of the pressure wave reflection through the muscular arterial tree, decrease from the first weeks of pregnancy and reach the lowest value in the second trimester, followed by a rise during the third trimester.\(^4\,0,\,42,\,46,\,52,\,53\)

A gradual return to the prepregnancy cardiovascular profile occurs postpartum, with different parameters restoring at different rates. The cardiac output remains significantly higher than the prepregnancy value for up to 1 year postpartum (+12% from the prepregnancy values) and a similar behavior is observed for the left ventricular mass, whereas the peripheral vascular resistance is reported to be lower than or similar to the prepregnancy value depending on the study.\(^3\,2,\,36,\,40\) This observation could explain the more marked changes in the hemodynamic profile observed in parous women who have previously experienced a low-risk pregnancy. These women, in fact, show a more rapid rise in the cardiac output, an increase in the cardiac volume, and a fall in the peripheral vascular resistance during gestation, with all of these changes being of a greater magnitude when compared with the observations in nulliparous women.\(^3\,6,\,54\)

**Hemodynamic Measurements in Pregnancy**

Assessment of the cardiovascular function in pregnancy has become more relevant in the previous few decades because of the body of work reporting significant links between the maternal cardiovascular function and disorders such as preeclampsia, FGR, and gestational diabetes. Studies on cardiovascular function in association with preeclampsia have largely focused on the

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**FIGURE 4**

Assessment of the carotid-femoral arterial pulse wave velocity calculated as the time delay between the pressure waveforms (\(\Delta t\)) and divided by the distance (\(\Delta d\)) measured between the carotid and femoral arteries.

arterial function and circulatory hemodynamics. These are described below.

**Arterial function**

Arterial function differs significantly in cases of preeclampsia when compared with gestational age-matched normotensive controls. Arterial function is quantified by studying the stiffening of large vessels; vessel stiffness increases with age, genetic predisposition, or disease processes such as arteriosclerosis. Indices of arterial stiffness include the velocity of the blood flow (pulse wave velocity), the amplitude of the blood waveform (augmentation index), or endothelial function studies (flow-mediated dilatation or forearm blood flow). In the case of pulse wave velocity, the velocity of the pressure wave is inversely related to the vessel elasticity and compliance and is an independent predictor of cardiovascular mortality and morbidity. There are no reported normal limits for the pulse wave velocity in pregnancy, although a value of <10 m/s is within the range for healthy, nonpregnant women. The pulse wave velocity increases with maternal weight and age, but it is not influenced by parity. In women with a high risk for preeclampsia, an increased pulse wave velocity provided a detection rate of 82% with a 10% false-positive rate in predicting early-onset preeclampsia, but only a 20% detection rate in predicting late-onset preeclampsia.

The aortic pulse wave velocity is considered the gold standard when determining arterial function, but the carotid-femoral arterial pulse wave velocity is commonly used as a pragmatic surrogate, because it covers the region that exhibits the greatest age-related stiffening (Figure 4). A variety of noninvasive devices utilizing computerized oscillometry, applanation tonometry, or Doppler have been utilized to study the pulse wave velocity in pregnancy, because most devices have been validated against invasive testing in nonpregnant cohorts.

The augmentation index is a measure of the arterial pressure waveform and is quantified as the ratio of the pressure difference in relation to the pulse pressure and is expressed as a percentage (Figure 5). Significantly higher augmentation index levels have been observed in the subclinical stage of preeclampsia, and the augmentation index is proposed to be a useful predictive marker for risk modeling when combined with other variables such as the central systolic blood pressure. The augmentation index is commonly estimated from either the radial or the brachial artery waveform, using approaches such as tonometry or oscillometric devices to assess the upper limb waveform (Table 1). This is then transformed using an algorithm to derive the aortic augmentation index.

**Endothelial function**

The endothelial function is most commonly assessed by studying upper-arm, flow-mediated dilatation or forearm blood flow. Normal arteries dilate by 10% to 15% in response to blood flow. By definition, vasodilation measurements of <5% from the resting tone measurement indicate overt endothelial dysfunction. A reduced flow-mediated dilatation has been found in the first half of pregnancy in high-risk women who subsequently develop preeclampsia when compared with controls, and an increase in the flow-mediated dilatation has been observed in the postpartum period of preeclampsia cases, suggesting a reversal of the endothelial dysfunction once preeclampsia has resolved. The devices and techniques to measure the arterial function in pregnancy is summarized in a consensus statement from the International Working Group of Maternal Hemodynamics (Foo et al).

**Cardiac output**

Early pregnancy is associated with significant increases in the cardiac output, and a corresponding decrease in the peripheral vascular resistance (Figure 3). The magnitude of these changes during pregnancy varies enormously among different studies and is probably reflective of the different measurement
techniques, cohort designs, and reference points for the baseline and pregnancy data that were used. The cardiac output can be assessed using invasive techniques (eg, pulmonary artery catheterization either with direct Fick’s or thermodilution adjunct methods) but these are mostly utilized in an intensive care setting in critically unwell women. Most commonly, and universally undertaken in obstetrical research settings, minimally invasive (eg, pulse-contour or transesophageal Doppler) or noninvasive (eg, cardiac magnetic resonance imaging, transthoracic echocardiography, and inert gas nonrebreathing) techniques are utilized. The measurement methodology and devices are summarized in a consensus statement by Bijl et al.63 Table 2 also summarizes some of these methods. Once the cardiac output and blood pressure are measured, the peripheral vascular resistance can be calculated by dividing the mean arterial blood pressure by the cardiac output.

Cardiovascular Function Before Conception

There is growing evidence that the pre pregnancy blood pressure values and early gestational changes relate to the risk of developing new-onset gestational hypertension disorders 64,65 and other complications such as fetal loss66 or placental malperfusion.67 This is true not only for women diagnosed with chronic hypertension, but also for those with so-called prehypertension, defined either as systolic values between 130 and 140 mm Hg or diastolic values between 80 and 90 mm Hg.68 In the latter group, low cardiac output and high vascular resistance reflect temporary poor hemodynamic function already before conception.23 Importantly, the relationship between prehypertension and gestational hypertension exists with or without the use of aspirin65 and accounts for all subtypes of gestational hypertension disorders.69 Physical exercise restores the plasma volume and venous compliance to near normal in formerly preeclamptic women,70 improves arterial function, and reduces elevated blood pressure before conception.71,72 These effects are associated with improvements...
<table>
<thead>
<tr>
<th>Methodology</th>
<th>Minimal intraobserver variability, but expensive and requires ongoing consumable costs</th>
<th>No ongoing cost and validated against echocardiogram</th>
<th>Can be performed in the supine position and easy to operate</th>
<th>Machines and operators widely available; findings operator dependent</th>
</tr>
</thead>
</table>

in the cardiac output and peripheral vascular resistance and are observed in healthy or diseased individuals at all ages. These effects are most efficient when physical exercise is embedded in a program of patient education, stress management, and lifestyle interventions. Despite good evidence from mechanistic studies, none were sufficiently powered to show a reduction in preeclampsia or the severity of pre-eclampsia in a subsequent pregnancy. It remains unclear whether pharmacologic interventions that tightly control blood pressure before conception or during pregnancy improves the gestational outcome.

**Therapeutic Implications of Different Preeclampsia Phenotypes**

The concept of different phenotypes of preeclampsia, detectable by noninvasive technologies in the latent subclinical stage of the disease, opens perspectives about targeted management and prolonged gestation in preeclampsia. This does, of course, require knowledge of not only the blood pressure but the cardiac output and vascular resistance as well. These parameters can be obtained in real time using a variety of relatively inexpensive Doppler tools or whole-body impedance devices as we have described earlier. These devices are commonly used in operating theaters, critical care units, and emergency departments.

In cases with a low blood volume, low cardiac output, and high resistance circulation characteristically associated with FGR, the use of nitric oxide (NO) donors, which is associated with plasma volume expansion, has shown improvements in the end diastolic blood flow velocity in the umbilical artery in parallel with a reduction in the maternal peripheral arterial resistance and a beneficial effect on the maternal and neonatal outcomes. In the cases with a high blood volume, high cardiac output, and low vascular resistance that are characteristic of preeclampsia without FGR, reduction of the cardiac output and the systolic and diastolic blood pressures have been reported after the administration of the loop diuretic, furosemide. Diuretics are rarely used in the management of preeclampsia; their use in a woman with depleted intravascular volume could be dangerous. In contrast, the use of furosemide and hydrochlorothiazide in pregnancies complicated by heart failure has shown no teratogenic effects and only minor adverse effects such as neonatal jaundice, thrombocytopenia, imbalanced electrolytes, or clotting factors. This has stimulated international societies such as the European Society of Hypertension/European Cardiology Society and the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy to openly question the general recommendation of discouraging diuretic use during pregnancy.

The reduced cardiac output and increased vascular resistance linked to the heart rate changes now consistently found in clinical series studies on early preeclampsia, allow for pharmacologic intervention to be directed toward restoring the maternal cardiovascular status to optimal and to perfuse the peripheral tissues and placenta. The possibility of identifying a personalized targeted therapy on the basis of the hemodynamic profile of a patient to improve placental perfusion and fetal growth has been investigated in early stage studies. Reducing the vascular resistance and increasing the plasma volume so as to try and restore the maternal cardiovascular status by increasing the cardiac output is the main goal of the treatment. It is important to differentiate this intervention from the intervention required to treat late preeclampsia or, more correctly, preeclampsia that is not associated with FGR, which usually present with elevated cardiac output and low vascular resistances, mandating a different pharmacologic approach.

### TABLE 3

**Examples of pharmacologic treatment choices based on the maternal hemodynamic findings**

<table>
<thead>
<tr>
<th>Cardiovascular parameter</th>
<th>Low cardiac output and high vascular resistance phenotype</th>
<th>High cardiac output and low vascular resistance phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal heart rate</td>
<td>&lt;70 bpm</td>
<td>&gt;90 bpm</td>
</tr>
<tr>
<td>Calcium channel blockers (eg, nifedipine), NO donors, and fluids</td>
<td>Alpha- and beta-blockers</td>
<td>Alpha- and beta-blockers</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>&lt;5 L/min</td>
<td>&gt;8 L/min</td>
</tr>
<tr>
<td>Calcium channel blockers (eg, nifedipine), NO donors, and fluids</td>
<td>Alpha- and beta-blockers</td>
<td>Alpha- and beta-blockers</td>
</tr>
<tr>
<td>Peripheral vascular resistance</td>
<td>&gt;1400 dynes s cm⁻⁵</td>
<td>&lt;900 dynes s cm⁻⁵</td>
</tr>
<tr>
<td>Calcium channel blockers (eg, nifedipine), NO donors, and fluids</td>
<td>Alpha- and beta-blockers</td>
<td>Alpha- and beta-blockers</td>
</tr>
</tbody>
</table>

Late preeclampsia, or that without FGR, is usually characterized by high cardiac output and low vascular resistances, whereas early preeclampsia, or preeclampsia associated with FGR, frequently shows low cardiac output and elevated peripheral vascular resistances.

bpm, beats per minute; FGR, fetal growth restriction; NO, nitric oxide.

Adapted from Vasapollo et al.

Treatment of hypertension
There is no consensus on the relative efficacy and safety of the medications used to treat severe hypertension in pregnancy, and the most recent Cochrane review found insufficient data to recommend a specific drug. The current drug choice in the obstetrical practice is empirical and simplistic and often linked to the experience and familiarity of the clinician with the drug, and it is therefore not based on the cardiovascular profile of the patient. Pharmacologic agents have different mechanisms of action, but they are often used interchangeably. The major categories are alpha- and beta-blockers (labetalol), which have a negative effect on the cardiac output, calcium channel blockers, which have a predominantly vasodilator mode of action, and centrally acting antihypertensive agents as alpha-methyldopa. The gold standard aim of the medical treatment is to achieve blood pressure control, but this is usually administered “blindly” without considering the maternal hemodynamic profile.

Therefore, a possible “intelligent” therapeutic approach to treat hypertensive disorders in pregnancy based on the maternal cardiovascular hemodynamic parameters is presented in Table 3. To optimize rational antihypertensive therapy without jeopardizing the uteroplacental circulation for cases in which hemodynamic assessments can be undertaken, the following steps could be followed: (1) evaluate the blood pressure values to classify patients according to the following hemodynamic parameters: maternal heart rate, cardiac output, and peripheral vascular resistance; (2) choose the appropriate treatment on the basis of the hemodynamic profile (Table 4), considering the pharmacologic effects of the antihypertensive drug; and (3) verify the response to the drug treatment after a time interval of 4 to 7 days by performing a hemodynamic evaluation.

Treatment of fetal growth restriction
The findings that the maternal cardiac adaptation in cases of isolated FGR is linked with reduced ventricular mass, a reduction in the increase in the maternal heart rate, a reduced cardiac output, and an increased vascular resistance have been confirmed in several studies after the first results appeared almost 20 years ago (Table 4, Figure 6), and opens potential therapeutic approaches that can be used to reduce the vascular resistance and increase the intravascular volume.

Implications for Research
Personalized treatments have been shown to reduce the risk of severe hypertension and allows for the identification of the low cardiac output and high vascular resistance phenotype of preeclampsia. However, clinically impactful therapeutic studies in which the antihypertensive therapy and management has been chosen based on the following steps could be followed: (1) evaluate the blood pressure values to classify patients according to the following hemodynamic parameters: maternal heart rate, cardiac output, and peripheral vascular resistance; (2) choose the appropriate treatment on the basis of the hemodynamic profile (Table 4), considering the pharmacologic effects of the antihypertensive drug; and (3) verify the response to the drug treatment after a time interval of 4 to 7 days by performing a hemodynamic evaluation.

| TABLE 4
<p>| Summary of the principal hemodynamic findings of the maternal cardiovascular adaptation in a normal pregnancy and in FGR |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal fetal growth</th>
<th>FGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↑ ↑</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>Vascular resistance</td>
<td>↓ ↓</td>
<td>↑ ↑</td>
</tr>
<tr>
<td>Ventricular mass</td>
<td>↑ ↑</td>
<td>↓ ↓</td>
</tr>
</tbody>
</table>

FGR, fetal growth restriction; ↑, increased; ↓, decreased.

maternal hemodynamic profile in pre-eclampsia have not yet been undertaken. This is a priority research area, especially given the abundance of lightweight, noninvasive devices, which makes studies of this type feasible.

A combined approach to restore the optimal maternal cardiovascular performance has shown promise both in FGR without end diastolic flow in the umbilical artery and in fetuses with less severe features of growth restriction. The approach for future therapeutic studies is to use an NO donor (e.g., in transdermal patches) to reduce the vascular resistance and to modify the capacity of the venous system by increasing the heart rate and contractility of the myocardium. Transdermal glyceryl trinitrate patches that release NO are effective in increasing the availability of NO at the level of the tissues, which leads to vasodilatation. The increase in the plasma volume with oral or intravenous hydration adds to the pharmacologic effect, potentially restoring the cardiac output. Though these proof of principle studies show positive results, they are yet to be reported in larger phase 2 randomized studies.

Conclusion
There exists incontrovertible evidence that preeclampsia exists as two phenotypes, and that these have opposite presentations with respect to the cardiac output, vascular resistance, and intravascular volume. Although they are not entirely inaccurate, the terms early and late preeclampsia should be consigned in the future as the key discriminators of the two phenotypes, and it should be emphasized that the key discriminator is the absence or presence of FGR. FGR can occur at any gestational age although it is far more frequent in combination with preeclampsia that develops at an early gestational age.

The “blind” management of hypertension in women with preeclampsia may achieve blood pressure control, but it ignores the effects on the maternal cardiovascular system and, more crucially, on the utero-placental circulation with the associated downstream effects on the fetus. Comprehensive hemodynamic assessment of women with preeclampsia in addition to ultrasound and Doppler investigations of the fetus can guide a rational choice of antihypertensive and fluid management strategies in preeclampsia. The investigation and management of adult hypertension outside pregnancy has moved toward personalized management based on hemodynamic assessments. It is high time that obstetricians and physicians involved in obstetrical care reappraised their approach to preeclampsia management.

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metabolic rate in early human pregnancy.


