Hemodynamic pathways of gestational hypertension and preeclampsia

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Gestational hypertension and preeclampsia are the 2 main types of hypertensive disorders in pregnancy. Noninvasive maternal cardiovascular function assessment, which helps obtain information from all the components of circulation, has shown that venous hemodynamic dysfunction is a feature of preeclampsia but not of gestational hypertension. Venous congestion is a known cause of organ dysfunction, but its potential role in the pathophysiology of preeclampsia is currently poorly investigated. Body water volume expansion occurs in both gestational hypertension and preeclampsia, and this is associated with the common feature of new-onset hypertension after 20 weeks of gestation. Blood pressure, by definition, is the product of intravascular volume load and vascular resistance (Ohm’s law). Fundamentally, hypertension may present as a spectrum of cardiovascular states varying between 2 extremes: one with a predominance of raised cardiac output and the other with a predominance of increased total peripheral resistance. In clinical practice, however, this bipolar nature of hypertension is rarely considered, despite the important implications for screening, prevention, management, and monitoring of disease. This review summarizes the evidence of type-specific hemodynamic profiles in the latent and clinical stages of hypertensive disorders in pregnancy. Gestational volume expansion superimposed on an early gestational closed circulatory circuit in a pressure- or volume-overloaded condition predisposes a patient to the gradual deterioration of overall circulatory function, finally presenting as gestational hypertension or preeclampsia—the latter when venous dysfunction is involved. The eventual phenotype of hypertensive disorder is already predictable from early gestation onward, on the condition of including information from all the major components of circulation into the maternal cardiovascular assessment: the heart, central and peripheral arteries, conductive and capacitance veins, and body water content. The relevance of this approach, outlined in this review, openly invites for more in-depth research into the fundamental hemodynamics of gestational hypertensive disorders, not only from the perspective of the physiologist or the scientist, but also in assistance of clinicians toward understanding and managing effectively these severe complications of pregnancy.

Key words: abdominal compartment, bioimpedance spectrum analysis, capacitance, capillary dysfunction, cardiac output, cardiovascular, congestion, Doppler waveform, early-onset preeclampsia, gestational hypertension, gestational physiology, heart rate, hepatic circulation, hepatic veins, impedance cardiography, impedance index, inflammation, intraabdominal pressure, intravenous pressure, late-onset preeclampsia, maternal hemodynamics, peripheral vascular resistance, preeclampsia, renal interlobar veins, splanchnic circulation, stroke volume, total body water, venoconstriction, venous congestion, venous hemodynamics, venous return, venous system

Introduction

Normal pregnancy is known as a physiological state of generalized vasodilatation, triggering volume expansion mechanisms to increase the circulating blood volume and cardiac output to maintain uterine perfusion constant relative to the needs of the growing fetus. Evidence has demonstrated that cardiovascular maladaptation is present in a large subset of women with preeclampsia (PE) or gestational hypertension (GH). Although human circulation is a closed-loop circuit with different components coupled in series, most studies on hemodynamic changes during pregnancy mainly focus on the heart and the arterial vascular tree, neglecting the microcirculation, venous system, and volume load. As such, many important aspects of gestational cardiovascular physiology are overlooked or remain unexplored, and this contributes to an incomplete understanding of the pathophysiological processes of gestational hypertensive disorders. The venous compartment is generally considered a rather passive organ, despite its active cooperation with the heart in the control of cardiac output. This function is gender-specific, as the modulation of cardiac output in males is predominantly systole-driven, whereas...
in females, this is mainly achieved by increased venous return during diastole. This explains why cardiac failure at an advanced age in men presents with a reduced ejection fraction because of a loss of contraction force, whereas in females, the ejection fraction is preserved, and failure merely relates to diastolic dysfunction. The venous blood volume nearly doubles compared with the volume in the arterial tree, as a large fraction of blood is stored in the venous capacitance bed, which is mainly located in the liver and the splanchic veins. Emptying of the capacitance reservoir can occur via orthosympathic induced venoconstriction, but it also depends on the intraabdominal pressure. During normal pregnancy, the intraabdominal pressure rises up to the pathologic range of intraabdominal hypertension in nonpregnant individuals, returning to normal values immediately after birth. The clinical signs of an increased intraabdominal pressure in pregnancy are the development of varicose veins associated with an increased pressure in the femoral veins and the supine hypotension syndrome. Figure 1 shows an example of the change of hepatic vein Doppler waveform in nonpregnant individuals during Valsalva and pneumoperitoneum (horizontal arrow), illustrating that the normal change of hepatic Doppler wave patterns from the first to the third trimester during normal pregnancy (semicircular arrow) is related to an overall rise of intraabdominal pressure. Intraabdominal hypertension is responsible for reduced drainage of venous blood from the internal organs with a subsequent congestion of the functional parenchyma, leading to organ dysfunction, and eventually, failure. The latter is a dangerous clinical situation known as the intraabdominal compartment syndrome. In the earliest stages of pregnancy, the trophoblast cells invade the venous and lymphatic vessels before they start remodeling the spiral arteries, and this allows for cardiovascular and immunologic signaling of the maternal organism about the presence of the conceptus before the activation of uteroplacental circulation. Global malfunctioning of the closed-loop circulatory circuit can result as part of a systemic inflammatory response syndrome, with overall endothelial activation in both the arterial and the venous vasculature; it can also gradually grow from interorgan signaling during the process of increasing intravascular volume load and/or intra-abdominal pressure. All the above arguments clearly illustrate the involvement of the venous compartment, body water homeostasis, and intraabdominal pressure in the normal physiology of pregnancy and their contribution to the development and/or clinical presentation of hypertensive disorders in pregnancy. To understand their role in the pathophysiology of GH and PE, it is mandatory to obtain a global helicopter view of all the major components of circulation simultaneously, when it comes to interpreting maternal cardiovascular studies in normal or complicated pregnancies.

Noninvasive Cardiovascular Assessment Tools

Today, many technologies exist to assess maternal hemodynamics noninvasively. Methods to measure cardiac output and arterial function have been reviewed recently. Measurements from different devices are not interchangeable,
Cardiac function is evaluated by an impedance cardiography measurement of the stroke volume in mL, the heart rate in beats per min, and the cardiac output in L/min, using the formula of Bernstein. Many other parameters, such as the left ventricular ejection time (msec), the preejection period (msec), and the systolic and ejection time ratios are also available, but these are currently not included in the maternal cardiovascular assessment.

The central arterial function is assessed by an impedance cardiography measurement of the aorta flow velocity index in 1/1000/s and acceleration index in 1/100/s². The peripheral arterial function is measured calculating the total peripheral resistance as the mean arterial pressure*80/cardiac output, expressed in dyn*s/cm⁵. Again, more parameters such as the arterial pulse transit time and the total arterial compliance are available, but these are currently not included in the protocol. Blood pressure is measured by automated sphygmomanometry after 2 mins of adaptation following the postural change, as is reported representative for long-lasting effects after posture change (Figure 2).

Bioimpedance spectrum analysis is used for the estimation of the total body water volume in liters, which totals the intracellular and extracellular water, the latter in turn being the sum of the interstitial, transcellular water, and plasma volume. A bioimpedance spectrum analysis does not allow to obtain information of the circulatory volume or intravascular filling, for which other technologies exist. The measurements are performed in the supine position immediately after the Doppler sonography assessment (Figure 2). Four electrodes are placed, 2 on the right hand and 2 on the right bare foot: the receiving electrodes are attached at the dorsal side of the right wrist and the ankle, and the sending electrodes are placed at the distal end of the metacarpal and metatarsal bones (Figure 2). The applied current is 0.6 mA, transmitted in 4 different frequencies (5, 50, 100, and 200 kHz), during 5 seconds. The following 3 fluid parameters are recorded: 1) the total body water volume, respectively.

The practical aspects of the technical principles, application, and methodology are reported elsewhere and are briefly summarized here for the purpose of this review. Figure 2 shows the standardized protocol as installed in 2012 and maintained unchanged ever since and an illustration of the technical equipment used. Figure 2 also illustrates the placement of the electrodes in the neck and the lower thorax for impedance cardiography (right panel), and at the hand and the foot for bioimpedance spectrum analysis (lower left panel). For each of the parameters discussed, the acceptable inter- and/or intraobserver correlations have been confirmed before study onset. The normal reference ranges per trimester of pregnancy are set from a subset of 1000 uncomplicated pregnancies and are reported as interquartile ranges. Figure 3 shows the gestational evolution from the first to the third trimester of the normal reference interquartile range for the most important functional parameters of the heart, central arteries, peripheral arteries, body water volume, and venous Doppler flow, as reported.
body water (TBW), which is the sum of 2) the extracellular water (ECW) and 3) the intracellular water (ICW).

The methods to study venous hemodynamic functions are much more complex and difficult to perform than arterial function assessments, particularly during pregnancy. Many of these methods target the peripheral venous vasculature in the limbs or the skin; however, these veins differ from the conductive venous return system or the venous capacitance bed in the liver and the splanchnic veins by their physiological role in thermoregulation and the anatomic presence of intraluminal valves. Doppler sonography is one method to assess maternal venous hemodynamics at the level of the inferior vena cava, liver, and kidneys; however, it has higher intra- and interobserver variability than Doppler flow assessments at the arterial site. Technical assistance from electrocardiographic signaling, operator training, and repeated measures are required to achieve acceptable reproducibility. Doppler ultrasonography of the maternal renal interlobar and hepatic veins is performed using a 3.5 MHz transabdominal probe during interrupted breathing in the supine position (Aplio Mx, Toshiba Medical Systems bv, Sint-Stevens-Woluwe, Belgium). Examinations are performed at random occasions throughout the day, irrespective of food intake. All women are examined in the supine position, despite the potential risk for compression of the vena cava with a subsequent reduction of the cardiac output and the supine hypotension syndrome (Figure 2). This is because central veins play a fundamental role in the control of cardiac output, and sensitivity for compression of these veins is an important physiological variable in the evaluation of the venous contribution to the maternal circulation and uteroplacental-fetal blood supply in normal and pathologic pregnancies. Obviously, women who show signs of hypotension during the procedure are allowed to remain in a semirecumbent position, but this was only necessary in <2% of assessments.

The liver is scanned intercostally in a transverse plane. The right, left, and middle branches of the hepatovenous tree are identified using color Doppler flow mapping and are differentiated from the hepatic arteries and the portal system (Figure 4, A and B). The impact of breathing movements on the ultrasound image is demonstrated to every patient, and the relevance of holding the breath during Doppler measurements is explained and demonstrated. Doppler signals are sampled at 3 different locations from the craniocaudal midportion in the liver, preferably 1 sample of each of the main branches (Figure 4, B). The real-time ultrasonic B-image and Doppler signal are visualized simultaneously, and the scanning image is frozen after visualization of at least 2–3 similar Doppler waveforms during interrupted breathing. As the direction

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**FIGURE 3**
Gestational evolution of cardiovascular assessments

<table>
<thead>
<tr>
<th>Diastolic blood pressure</th>
<th>Mean arterial pressure</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Mm Hg</td>
</tr>
<tr>
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<td>100</td>
</tr>
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<td>Dyn.s.cm⁻²</td>
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<tr>
<td>9</td>
<td>1000</td>
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<tr>
<td>7</td>
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<table>
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<tr>
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<table>
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<tr>
<td>ml</td>
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<tr>
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<table>
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<tr>
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<td>2nd trim</td>
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<td>0,4</td>
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Obtained from a set of 1000 pregnancies with normal outcome, presented as mean and interquartile range.²⁹

²⁹ 1̅st trim, first trimester; 2̅nd trim, second trimester; 3̅rd trim, third trimester; accel, acceleration; Ao, aorta; BMI, body mass index; Hepatic V, hepatic vein; Imped index, impedance index; Periph, peripheral; RIV, renal interlobar vein.

of the Doppler beam is mostly parallel with the examined vessels, Doppler angle correction is rarely needed. If so, the axis of adjustment normally does not exceed 30°. The velocities of the hepatic vein (HV) Doppler wave characteristics A and X are measured (Figure 4, B). For the monophasic or flat Doppler waveforms, where the Doppler wave characteristics cannot be easily identified, the venous maximum velocity and minimum velocity are used. For every woman, each of 3 consecutive Duplex images is stored for offline analysis. After the scan, the mean values of the 3 measured values of A and X velocities are calculated, and the HV Impedance Index is calculated as (A−X)/X. This result is registered in the database. The venous impedance index is considered as the venous Doppler equivalent of arterial pulsatility index (PI), representing the intracycle variation of blood flow velocities in the veins.

Both the kidneys are scanned in a transverse or longitudinal plane, as illustrated in Figure 2. The interlobar arteries and veins are identified using color Doppler flow mapping in the area between the intrarenal pyelon and renal cortex (Figure 4, C and D). Again, the impact of breathing movements on the ultrasound image is demonstrated and the woman is instructed. Once the patient is familiar with the instructions of the ultrasonographer, the real-time ultrasound image in the combined B-D mode is frozen after the visualization of at least 2 to 3 similar Doppler flow patterns during interrupted breathing. The direction of the Doppler beam is adjusted according to the axis of the examined vessel, when necessary, which normally should not exceed 30°. The venous maximum velocity X and minimum velocity A are measured consecutively at 3 different locations within the area of interest, and the mean values are calculated. The renal interlobar vein impedance index is calculated as (A−X)/X and registered in the database.

The reproducibility of the methodology is evaluated by performing the sequence of measurements twice in the same individual by 2 or more investigators and calculating the inter- and intraclass correlation coefficient using maximum likelihood estimation for the linear mixed model. The impact of an increasing number of repeat samples per organ is evaluated by calculating the means, standard deviations, and the intraclass correlations of 2, 3, 4, 5, and 6 consecutive measurements per organ (MIXED procedure, SAS). It is concluded that the mean value of 3 consecutive measurements combined with electrocardiogram (ECG)-assisted interpretation of the Doppler wave deflection by trained sonographers allows obtaining reproducible Doppler flow indices at the level of the renal interlobar and hepatic veins.

The automated algorithm of the Doppler ultrasound scanner is used to
measure the resistivity index \( \text{RI} = \frac{\text{Peak systolic velocity} - \text{minimal diastolic velocity}}{\text{peak systolic velocity}} \) and the PI \( \text{PI} = \frac{\text{Peak systolic velocity} - \text{minimal diastolic velocity}}{\text{mean velocity}} \) in the uterine arcuate arteries at < 2 cm of the insertion of the intrauterine branching of the uterine artery.\(^{28}\)

**Maternal cardiovascular profile**
The combination of all the parameters mentioned above and presented in Figure 3 offers information from all the following major components of maternal circulation in one assessment session: the heart, the central arteries, peripheral arteries, uterine arteries, body water volume, and the intrarenal and hepatic venous hemodynamics. This allows to evaluate the interactions between the different sites of circulation under conditions of increased circulatory stress, such as pregnancy. With this methodology, unique patterns of circulatory deterioration with increasing body water expansion during the course of pregnancy are observed for different types of hypertensive disorders in pregnancy.\(^{28}\)

**Gestational Volume Expansion: A Stressor for the Maternal Cardiovascular System**
Irrespective of the pregnancy outcome, the TBW volume—including circulatory\(^{43}\) and noncirculatory volumes\(^{44}\)—increases in all women during pregnancy. However, the degree of increase differs among the types of hypertensive disorders (Figure 5).\(^{45}\) The expansion of the intravascular volume is an important stressor of the maternal cardiovascular system, as illustrated by the observation of volume-dependent diastolic dysfunction and impaired myocardial relaxation with preserved myocardial contractility in 17.9% and 28.4% of women, respectively, during an uncomplicated third trimester pregnancy.\(^{46}\) This observation is particularly evident in obese women, whose body water volume and cardiac output are constitutionally larger than those of normal-weight women.\(^{47,48}\) The latter is considered to result from an increased intraabdominal pressure and external renal vein compression, leading to an increased glomerular capillary pressure with the activation of the juxtaglomerular apparatus and the renin-angiotensin-aldosterone system with subsequent sodium and water retention.\(^{49}\) Gestational volume expansion superimposed on the constitutionally high intravascular volume of obese women is associated with a reduction of the cardiac output and an increase in the total vascular resistance during an uncomplicated third trimester pregnancy, an observation untrue for normal-weight pregnant women.\(^{46}\) It can be hypothesized that the increased intravascular volume load with a reduced expandability of the venous compartment observed in women with obesity and in those with increased intraabdominal pressure can induce the production of inflammatory mediators and oxidative stress.\(^{50}\) This process is also found in endothelitis-like syndromes, such as in acute heart failure.\(^{51}\) Acute endothelitis results from increased shear stress, triggering the endothelial production of mediators of oxidative stress interfering with nitric-oxide-induced vasodilatation.\(^{52}\) This enhanced endothelial activation presents initially in the veins at the time of clinical decompensation, subsequently spreading to the arterial tree.\(^{51}\) When this condition persists for a longer period of time, a systemic inflammatory response syndrome occurs with generalized endothelial dysfunction and activation of the immune system. The latter presents with increased production, release, and transport of proinflammatory cytokines as interleukin 1β,
vascular signs of volume overload in such, the presentation of cardiac and interstitial events are well-known features of PE. As the body water volume increases from the second trimester onward (Figure 2), the cardiac output rises and the peripheral vascular resistance decreases (Figure 7). The net result is that blood pressure passes the threshold of 140/90 mm Hg near term and becomes hypertension.

Figure 7 also shows the reported data of the Genk/Hasselt GH population, where the first trimester normotension presents with a higher peripheral vascular resistance from the first trimester onward (blue area = hypertension vs gray area = normal). As associated with gestational volume expansion, the blood pressure crosses the threshold of 140/90 mm Hg during the course of pregnancy and becomes gestation-induced hypertension.

Essentially, the graphs presented in Figure 7 represent the 2 extremes of the spectrum of GH varying between volume- and resistance dominance, a spectrum also observed and reported for PE.

Gestational Hypertension
GH is defined as new-onset hypertension at >20 weeks of gestation without associated signs of organ dysfunction. It should be emphasized that in perinatal medicine today, the thresholds to discriminate normo- from hypertension are still 140 mm Hg systolic and 90 mm Hg diastolic pressure, despite the fact that during the last decade, many international societies of cardiovascular medicine have lowered these thresholds to 130/80 mm Hg, allowing the identification of an intermediate sub-hypertensive risk group.

There are 2 types of hypertension on the basis of the hemodynamic profile (Figure 6). The first type is characterized by a high peripheral resistance, and the second type is characterized by a high cardiac output. Blood pressure relates to the cardiac output and the total vascular resistance as mean arterial pressure = cardiac output × total peripheral resistance (Ohm’s law). This equation defines that blood pressure varies according to a spectrum ranging between high cardiac output and low vascular resistance (volume dominance) to low cardiac output and high vascular resistance (resistance dominance). By definition, hypertension can result from either a high cardiac output, high vascular resistance, or both.

Gestational Hypertension and Preeclampsia
The question that arises is why is this blood pressure spectrum in GH not associated with symptoms of organ dysfunction, as is the case for PE? It is generally accepted that PE is associated with a systemic endothelial activation and inflammatory response (or endothelitis as mentioned above). The profile...
Early-onset PE is generally defined as new-onset hypertension with clinical signs of organ dysfunction presenting at gestational age <34 weeks, and this is often associated with poor fetal growth. As shown in Figure 8, early-onset PE, compared with normal pregnancies, presents from the first trimester onward with high vascular resistance and from the second trimester onward with a low cardiac output in combination with a high TBW volume. For women destined to develop GH or PE disorders with fetal growth restriction, it has been found that a low cardiac output and high total peripheral resistance are already present before conception. Whereas the normal gestational rise of cardiac output is maintained until the early second trimester, this stabilizes already from 6 weeks onwards in hypertensive women with fetal growth restriction. Next to this, early-onset PE with fetal growth restriction is known with a reduced plasma volume expansion than normal. Early-onset PE also presents with abnormal venous Doppler flow characteristics, which is suggestive of a state of venoconstriction and a low volume capacity. Increased body water volume, associated with a poor increase of both the cardiac output and the plasma volume together with a constricted venous system suggests the extravasation of intravascular fluids already from early pregnancy onward. Early-onset PE is also known with the first trimester presence of biochemical markers of endothelium dysfunction, such as placental growth factor/soluble fms-like tyrosine kinase 1, endoglin, vascular endothelial growth factor (VEGF), and many others. In obstetrics literature, the origin of these markers is mostly considered placental; however, it should be recognized that most of these markers are also produced by nonpregnant males and females with chronic cardiovascular and/or renal disease. This questions whether the placenta is the sole source of reactive oxygen species.
inflammatory cytokines, and markers of endothelium dysfunction in early-onset PE.

Another very important but under-recognized issue in early gestational physiology is that a successful placentation requires a state of inflammation. To ensure this, both the embryo and the maternal decidua produce pro-inflammatory cytokines, whereas at the same time, immune tolerance for the conceptus is programmed in the maternal immune system. This is achieved by signaling the mother’s system from the site of implantation via trophoblast invasion of the venous and lymphatic vasculature weeks before spiral artery remodeling has been initiated (Figure 9). An overshoot of pro-inflammatory over protolerance mediators may cause early-onset endothelial damage, which target the veins before the arteries get involved, even though the trophoblast plugs still block the lumina of spiral arteries. Animal experiments showed altered venous wall permeability by VEGF in animal studies, observed as a product of placentation altering venoarterial communication and the local short-loop control of uteroplacental perfusion. Abnormal signaling from the venous site may interfere with arterial remodeling, as shallow dilatation of the spiral arteries reduces congestion at the level of the intervillous space in conditions of abnormal venous drainage from the uterus.

An overshoot of inflammatory signals at placentation allows understanding the role of paternal PE, primipaternity, and maternal immune disorders as important predisposing factors for early-onset PE. Constitutionally, subclinical maternal cardiovascular dysfunctions, already present before conception, are likely to interfere with the inflammatory placentation process. The production of the markers of endothelium dysfunction by organs other than the placenta allows explaining chronic organ diseases as predisposing factors for PE.

Late-Onset Preeclampsia
Evidence for 2 types of late-onset PE comes from 3 sources: (1) the

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**FIGURE 8**
Cardiac output, peripheral resistance and body water volume in early onset preeclampsia

Expressed as MoM, in pregnancies complicated with early-onset preeclampsia (brown area) compared with normal pregnancies (gray area). Values that are significantly different between normal (gray) and early-onset preeclampsia (brown) are marked by an asterisk. Data adapted from Gyselaers et al, and Gyselaers et al. The asterisk represents significant difference from the normal.

MoM, multiples of the mean; NS, not significantly different from normal.


**FIGURE 9**
Fetal-maternal communication during early placentation between 4 and 8 weeks

This is done when the arterial flow is blocked by spiral trophoblast plugs in the spiral arteries. This situation exists approximately 1 month before the start of spiral arteries remodeling. Arteriovenous flow is maintained via arteriovenous anastomoses. There is maternal-fetal interchange of immunologic signals, inducing both a stage of inflammation and of mother-fetus immune tolerance. The trophoblast cells invade the endometrial veins and lymphatic vessels before the trophoblast plugs are resolved. Implantation-induced Vascular Endothelial Growth Factor production alters the venous vascular wall permeability, a mechanism with potential impact on local venoarterial signaling and remodeling of uterine spiral arteries.

observation of the bimodal skewed distribution of the birthweight in neonates born from women with late-onset PE,65 (2) the placenta histology after late-onset PE mostly shows signs of underperfusion; however, these lesions are absent in a quarter of cases,66 and (3) the longitudinal observations in primigravid women developing late-onset PE by Easterling in 199067 and by Bosio in 1999,61 showing different evolutions for cardiac output and total peripheral resistance in the 2 populations. Both reports are reproduced in MoM-values in Figure 10 and show a high cardiac output from early pregnancy until the third trimester for the 2 populations. Although the cardiac output remains high and the total peripheral resistance remains low in the Easterling study,61 the Bosio data clearly show a radical cross over from volume dominance to resistance dominance in the late third trimester.61 The latter evolution is likely the result of shear stress on the vascular wall by gestation-induced high intravascular volume, combined with an increased intraabdominal pressure. In the veins,88 this combination induces oxidative stress in the endothelial cells and interferes with the nitric oxide pathway of vascular relaxation.89 This results in a state of overall vasocostriction at both the arterial and the venous sites.51 This will not only cause an increase of cardiac afterload with a subsequent reduction of cardiac output but also cause hampered organ drainage of venous blood with associated venous congestion, contributing to organ dysfunctions.90 On top of this, venous congestion can induce reflex constriction of the arteries, inducing hypertension.91 The Bosio report (Type 2 late-onset PE in Figure 10) is in line with this pathophysiological pathway.61

Of all the study groups presented in Table 1, the Easterling population has the highest body mass index (BMI).87 These women must also have had a constitutionally high intravascular volume and intraabdominal pressure. It is possible that the PE-like symptoms in these women relate to a high intraabdominal pressure, which in itself is a known predisposing factor for venous congestion and organ dysfunction.17 It was shown that pneumoperitoneum-induced intraabdominal hypertension during laparoscopy is associated with increased proteinuria, both during and in the first hours after the procedure.16 Intraabdominal hypertension in critically ill patients at intensive care units is associated with cardiovascular and organ dysfunctions that might trouble recovery and revalidation.92 The renal nutcracker syndrome is another known example of mechanically-induced proteinuria from external renal vein compression.93

The neonatal birthweight in the 2 discussed study populations with late-onset PE (Table 1) corroborate the explanations above, as the Bosio group presents with a low cardiac output in the clinical stage,61 whereas this is high at all stages in the Easterling population.87 Clearly, more clinical and experimental research is needed to explore the mechanisms discussed above.

Implications for clinical practice

It should be stressed firmly that the pathways outlined above and many of the related pathophysiological mechanisms need further exploration in clinical and experimental research. However, it is already clear now that a maternal cardiovascular assessment, including information of the body water volumes and venous hemodynamics, offers much more information than that based on assessments of the heart and the arteries only. This information even potentially could seem more informative for clinical practice than current strategies, both in terms of screening and the management of hypertensive disorders in pregnancy.

Lowering the thresholds to discriminate normo- from hypertension has
already been shown to be useful in screening for hypertensive disorders in pregnancy. At cutoff values of 79 mm Hg, the sensitivity of the standardized measurement of diastolic blood pressure at 12 wks in the standing position for the prediction of hypertension was 72%, with an area under the receiver operating characteristic curve of 74%.94 However, with an area under the receiver operating prediction of hypertension was 72%, at 12 wks in the standing position for the measurement of diastolic blood pressure Hg, the sensitivity of the standardized pregnancy. At cutoff values of 79 mm

### TABLE 1
Demographic characteristics of populations from published longitudinal studies on maternal hemodynamics in gestational hypertension and/or preeclampsia

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<tr>
<th>Author</th>
<th>Publication year</th>
<th>Group</th>
<th>Maternal age (y)</th>
<th>Nulliparity (%)</th>
<th>BMI (kg/m²)</th>
<th>BW (g)</th>
<th>Gestational age at birth (wk)</th>
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<tr>
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<td>1999</td>
<td>GH</td>
<td>27.9 (25.8—29.9)</td>
<td>100</td>
<td>28.0 (26.3—29.7)</td>
<td>3550 (3300—3780)</td>
<td>39.6 (39.3—40.1)</td>
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<td></td>
<td></td>
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<td>100</td>
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<td>2690 (2480—3260)</td>
<td>36.4 (36.1—37.5)</td>
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<td>Easterling et al</td>
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<td>3314 ± 309</td>
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<td>30.2 ± 4.4</td>
<td>63</td>
<td>26.4 ± 6.0</td>
<td>3069 ± 744</td>
<td>38.4 ± 2.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EPE</td>
<td>30.3 ± 5.3</td>
<td>60</td>
<td>26.9 ± 6.2</td>
<td>1280 ± 536</td>
<td>30.4 ± 2.8</td>
</tr>
</tbody>
</table>

BMI, body mass index; BW, birthweight; GH, gestational hypertension; LPE, late-onset preeclampsia.

a Mean (95% confidence interval); b Mean ± standard deviation.


### TABLE 2
Simplified schematic overview of the evolutions from the first to the third trimester in gestational hypertension and preeclampsia of cardiovascular parameters obtained from the most important components of the maternal closed-loop circulation: heart (cardiac output), central arterial hemodynamics (aorta flow velocity & acceleration), peripheral arteries (total peripheral resistance), total body water volume, capacitance veins (hepatic veins), conductive veins (renal interlobar veins), and uterine arterial flow

<table>
<thead>
<tr>
<th>Cardiovascular parameters</th>
<th>Gestational HT Type 1 (resistance)</th>
<th>Gestational HT Type 2 (volume)</th>
<th>Late PE Type 1 (output)</th>
<th>Late PE Type 2 (cross over)</th>
<th>Early PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressures (SBP/ DBP/ MAP)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Cardiac output (HR/SV)</td>
<td>=</td>
<td>=</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Total body water volume</td>
<td>=</td>
<td>=</td>
<td>↑</td>
<td>=</td>
<td>↑</td>
</tr>
<tr>
<td>Aorta flow (VI/ACI)</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Intrahepatic venous flow (HVI)</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Intrarenal venous flow (L/R RIVI)</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Uterine artery flow (P/VII)</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
</tbody>
</table>

The symbol “↑” indicates “and/or,” “=,” equal to normal pregnancy; ↑, higher than normal pregnancy; ↓, lower than normal pregnancy; ACI, aorta flow acceleration index; DBP, diastolic blood pressure; HR, heart rate; HT, hypertension; HV, hepatic vein impedance index; L/R, left and/or right; MAP, mean arterial pressure; PE, preeclampsia; PI, pulsatility index; RI, resistance index; RIVI, renal interlobar vein impedance index; SBP, systolic blood pressure; SV, stroke volume; T1, First trimester; T2, Second trimester; T3, Third trimester; VI, aorta flow velocity index.

peripheral resistance, and TBW volumes allows discriminating early-onset PE from other hypertensive disorders already in the first half of pregnancy, with detection rates of >80% at false-positive rates of <15% for all types of gestational hypertensive disorders. Likewise, hypertension can be categorized as volume-dominant, resistance-dominant, or both. Normal blood pressure can be classified as true or false normotension, the latter presenting as high volume antagonized by a low resistance, or vice versa (Figure 6).

Furthermore, the information obtained on venous hemodynamics might be very useful, particularly in the discrimination between GH and PE (Figure 11). Maternal venous Doppler sonography, however, is technically much more difficult than arterial Doppler sonography. The patterns of venous blood flow are more susceptible for external interfering factors such as breathing, muscle tone, and physical and psychological stress, and both standardization and training with ECG-equipped ultrasound scanners are mandatory to do these kinds of assessments. However, the presence or absence of flat (normal) vs bi- or triphasic (abnormal) HV Doppler flow patterns in the third trimester of pregnancy is a very simple method to get a qualitative, subjective impression when discriminating between the clinical stages of GH and PE. The clinical relevance of this is more or less similar to judging the presence or absence of uterine artery notching in the prediction of PE.

A maternal integral cardiovascular assessment also allows for a better understanding of the background mechanisms of PE, as illustrated in Figure 12. As explained above, early-onset PE presents with cardiovascular dysfunctions already from the first trimester onward. These dysfunctions can relate to fetal and maternal inflammation signaling and/or to pre-existing immunologic or organ dysfunctions (Figure 12, blue background). Therefore, feto-maternal miscommunication is responsible for oxidative stress and systemic inflammation, resulting in early-onset endothelium activation (Figure 12, yellow background). Late-onset PE with a crossover from high-output to high-resistance circulation (type 2 in Figure 10) can relate to endothelial activation from shear stress by high intravascular filling, with or without enhancement by pre-existing organ dysfunctions and/or a gestational increase of intraabdominal pressure (Figure 12, brown background).

**FIGURE 11**

Hepatic and intrarenal venous Doppler Impedance index in preeclampsia and gestational hypertension

As shown, an increased venous impedance index in the third trimester is an integral part of early-onset and late-onset preeclampsia but not of GH (Adapted from Gyselaers et al. The gray area represents the interquartile range of normal pregnancies. The brown area represents the interquartile range of early-onset preeclampsia. The green area represents the interquartile range of late-onset preeclampsia. The blue area represents the interquartile range of GH. The asterisk represents significant difference from the normal.

*1* trim, first trimester; *2* trim, second trimester; *3* trim, third trimester; GH, gestational hypertension.

Early-onset preeclampsia presents with cardiovascular dysfunctions already from the first trimester onward, relating to fetal and maternal inflammation signaling and/or preexisting immunologic, cardiovascular or organ dysfunctions (blue background). Subsequent oxidative stress and systemic inflammation cause early-onset endothelium activation (yellow background). Late-onset preeclampsia with a crossover from high-output to high-resistance circulation (type 2 in Figure 10) relates to endothelial activation from shear stress by high intravascular filling, with or without preexisting organ dysfunctions and/or increased intraabdominal pressure (brown background). This process also requires oxidative stress and systemic inflammation. Late-onset preeclampsia with a persistently high cardiac output (type 1 in Figure 10) can result from primary organ congestion induced by gestational increase of the intraabdominal pressure, a process not necessarily requiring oxidative stress or systemic inflammation (Figure 12, red background). The net result from these 3 different pathways on the venous system is a state of organ congestion by hampered drainage of venous blood, which, next to other vasoconstriction-inducing mediators, is known as an inductor of systemic arterial constriction and microcirculatory dysfunction.91

The venous capacitance function is located mainly in the splanchnic veins and in the liver. In obesity, a larger volume of blood is present, both in the capacitance bed as in the circulation, because of which there is reduced reserve storage capacity during pregnancy.

Activation of venous hemodynamics can be active or passive. Active venoconstriction is achieved by orthosympathic stimulation or endothelium activation via the nitric oxide-pathway. Passive activation is caused by external compression, such as the muscle pump or organic masses. This can also result from an increased intra-abdominal pressure or cardiac diastolic dysfunction.

In the short term, activation of venous hemodynamics will cause an increase of venous return and cardiac output (blue arrows). In the long term, however, increased venous pressure (with or without cardiac diastolic dysfunction) will result in the hampered drainage of venous blood from the microcirculation in different organs, finally resulting in capillary dysfunction because of organ congestion (purple arrows). Interstitial edema, proteinuria, abnormal serum concentration of liver enzymes, and others are among the clinical symptoms of organ congestion.

In early-onset preeclampsia, there is activation of venous hemodynamics via orthosympathic stimulation and endothelium activation, resulting in an increased venous Doppler impedance index already from the second trimester onward (Fig 8 & 12). Late-onset preeclampsia type 2 shows signs of activated venous endothelium and venoconstriction (Fig 10 & 12). Late-onset preeclampsia type 1 presents with organ congestion from external compression because of increased intraabdominal pressure (Fig 10 & 12). Because of the close functional relation between veins and the heart, abnormal venous hemodynamics is often associated with cardiac diastolic dysfunction.

has been shown in animal experiments to induce systemic arterial constriction and microcirculatory dysfunction. Venous hemodynamic dysfunction and organ congestion as potential etiological factors in the clinical presentation or symptoms of PE offer a new target for exploration by researchers and potentially also for clinical management.

In the management of PE, it might be important to consider the 2 clinical phenotypes of GH and PE, as antihypertensive drugs do not act via the same pharmacologic pathways. Calcium channel blockers in both normotensive and hypertensive pregnant women have been shown to reduce the arterial peripheral resistance with an increase of cardiac output, and these effects might be particularly useful in low cardiac output hypertensive patients. The maternal cardiac output is an important determinant of neonatal birthweight. Next to this, approximately one-quarter of pregnant women with hypertension do not respond to the beta-blocking agent Labetolol, which is the first-choice treatment for women who are not already on antihypertensives following the most recent National Institute for Health and Care Excellence guidelines. The pretreatment cardiovascular function of these women is characterized by a low cardiac output and high vascular resistance, a condition easily detectable by noninvasive technologies. As such, nonresponse to antihypertensive treatment can be avoided by simple cardiovascular profiling before the initiation of pharmacologic treatment, whereas response can be monitored longitudinally. Finally, as shown in figures 7 and 10, the subtypes of GH and late-onset PE can present with a low vascular resistance and high cardiac output or vice versa during both the latent and clinical phases of disease. Currently, there are no reports yet on the comparative results between the effects of either calcium- or beta-blocking agents on maternal hemodynamics and gestational outcome.

In nonpregnant individuals, there is not the slightest doubt about the use of diuretics in individuals with clinical signs of volume overload. The acknowledgment of high intravascular volume as one mechanism of hypertension in the latent and/or clinical stage of hypertension in pregnancy should stimulate to reconsider the use of diuretics in pregnancy. This reconsideration has already been suggested by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy in 2000 and repeated afterwards. Publications on diuretic use in hypertensive pregnancies are scarce and report a suboptimal response and reduction of plasma volume in chronic hypertensives; however, they clearly induce a decrease of the cardiac output with an increase of peripheral resistance. Essentially, diuretics used in a selected group of women with high cardiac output might perhaps prevent or even treat volume-dominant hypertension or PE. Next to this, as PE-related symptoms relate to activation of the endothelium in which the nitric oxide pathway is involved, nitric oxide donors might be useful in high-resistance PE. Nitric oxide donors in hypertension with poor fetal growth were reported to reduce gestational complications and reduce the clinical symptoms of disease and the prolongation of gestation.

Conclusions
The pathophysiology of different types of gestational hypertensive diseases can be narrowed to 2 different fundamental ground mechanisms following Ohm’s law in hemodynamics: volume- and/or resistance-dominant hypertension. In normotensive individuals, a dominance in either direction can be present before conception or develops during the process of implantation. Gestational volume expansion superimposed on this early gestational cardiovascular condition is responsible for a gradual deterioration of overall circulatory function. GH discriminates from PE by a different systemic inflammatory response, with the absence of venous hemodynamic dysfunction. Venous congestion as a pathway to explain organ dysfunction in PE is an interesting unifying theory but requires confirmation from further clinical and experimental research.

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