Gestational hypertensive disorders show unique patterns of circulatory deterioration with ongoing pregnancy

Peer-reviewed author version

GYSELAERS, Wilfried; VONCK, Sharona; STAELENS, Anneleen; LANSSENS, Dorien; TOMSIN, Kathleen; OBEN, Jolien; DREESEN, Pauline & BRUCKERS, Liesbeth (2019) Gestational hypertensive disorders show unique patterns of circulatory deterioration with ongoing pregnancy. In: AMERICAN JOURNAL OF PHYSIOLOGY-REGULATORY INTEGRATIVE AND COMPARATIVE PHYSIOLOGY, 316(3), p. R210-R221.

DOI: 10.1152/ajpregu.00075.2018
Handle: http://hdl.handle.net/1942/30226

TITLE: Gestational hypertensive disorders show unique patterns of circulatory deterioration with ongoing pregnancy.

Brief title: Pathophysiology of GHD

Authors: Wilfried Gyselaers[1-3*], Sharona Vonck[1,2], Anneleen Simone Staelens[2], Dorien Lanssens[1,2], Kathleen Tomsin[2], Jolien Oben[2], Pauline Dreesen[1,2], Liesbeth Bruckers[4].

Affiliations: [1] Faculty of Medicine and Life Sciences, Hasselt University, Agoralaan, 3590 Diepenbeek, Belgium

[2] Department of Obstetrics & Gynaecology, Ziekenhuis Oost-Limburg, Schiepse Bos 6, 3600 Genk, Belgium

[3] Department Physiology, Hasselt University, Agoralaan, 3590 Diepenbeek, Belgium

[4] Interuniversity Institute for Biostatistics and statistical Bioinformatics, Hasselt University, Agoralaan, 3590 Diepenbeek, Belgium

*Corresponding Author:

Wilfried Gyselaers, Ziekenhuis Oost-Limburg, Department of Obstetrics & Gynaecology, Schiepse Bos 6, 3600 Genk, Belgium

E-mail: wilfried.gyselaers@zol.be

Tel.: +32 89 32 75 24

Contribution of each author to the study:

WG + SV: study design, patient inclusion, data management, writing of the article

LB: statistics

ASS, DL, KT, JO: patient inclusion

Abstract (1 paragraph, 250w max)

A combined assessment of heart, arteries, veins and body fluid content throughout pregnancy has not yet been reported. We hypothesized that a gradual aggravation of circulatory dysfunction exists from latent to clinical phase of gestational hypertensive disease (GHD), and that pathways are unique for preeclampsia with early-onset < 34w (EPE), late-onset ≥ 34w (LPE) and gestational hypertension (GH). Women with singleton pregnancy and no known diseases were invited for a prospective, observational study and had standardized sphygmomanometric blood pressure measurement, bioimpedance body water spectrum analysis, impedance cardiography for cardiac and arterial assessment and combined Doppler-ECG of hepatic and renal interlobar veins and uterine arteries. Outcome was categorized as uncomplicated (UP, n = 1700), EPE (n = 87), LPE (n = 218) or GH (n = 188). A linear mixed model for repeated measurements, corrected for age, parity and body mass index, was employed in SAS 9.4 to analyze trimestral changes within and between groups. From 1st to 3rd trimester, body water increased in all groups, and an increasing number of abnormal parameters relative to UP occurred in all GHD. First trimester blood pressure and peripheral resistance were higher in GHD than UP, together with increased uterine flow resistance and extracellular water in EPE, and with lower heart rate and aorta flow velocity in LPE. An overall gestational rise of body water volumes co-exists with a gradual worsening of cardiovascular dysfunction in GHD, of which pathophysiologic pathways are unique for EPE, LPE and GH respectively.

Keywords: Maternal hemodynamics, gestational hypertensive disease, gestational hypertension, preeclampsia, pathophysiology

Introduction

The human systemic circulation is a closed circuit containing different components, each with specific physiologic functions and properties. The heart as a pump creates positive propulsive forces to forward the blood in the arterial system, but also negative suction forces to maintain venous return. The central arterial hemodynamic function of aorta flow serves the distribution of blood between central organs (heart and brain) and the periphery, but also the progressive amplification of arterial pulse waves and pulse wave velocity. Blood pressure and peripheral resistance are the key determinating factors for the volume of circulating systemic blood, interrelating according to Ohm's equation: mean blood pressure = cardiac output x peripheral resistance. Most human body organ systems, including the uterine circulation, are connected in parallel circuits, regulated by both central and local control mechanisms. Intrarenal veins not only drain the blood from the kidneys, but also control intrarenal hemodynamics and tubular function, which is necessary to protect the kidney against failure from renal congestion (57). The hepatic veins, together with the splanchnic venous system, serve as a volume reservoir of non-circulating blood. Whenever necessary, this reserve blood volume can be shifted into the circulation via an auto-transfusion mechanism, as such contributing to the control of cardiac output (67). Several other physiologic components and functions exist in the circuit, which are not further discussed here because they are not relevant for this paper's discussion. It is important to recognize however that the functioning of all components of the circulation is interdependent, and that a suboptimal function of one component will automatically influence the functioning of the others (9, 42, 45).

Pregnancy is a specific physiological condition in a woman's life requiring major adaptations of the cardiovascular system, starting already very soon after conception

(66). It is generally accepted that these changes are triggered by a uniform vasodilatation and relative hypovolemia, with subsequent activation of volume restoring mechanisms, eventually leading to an expanded intravascular volume (15). The increase of circulating volume and cardiac output are needed for an adequate blood supply to the pregnant uterus and its contents, without compromising the perfusion of other organs. A large proportion of women with uncomplicated term pregnancies however show echocardiographic signs of chronic volume overload (34). This illustrates that the gestational volume expansion is an important stressor for a pregnant woman's cardiovascular system. Inadequate plasma volume expansion has been reported in pregnancies complicated with hypertension and/or poor fetal growth (11, 48, 49). Although plasma volume, as a fraction of total body water content, is in constant equilibrium with other body fluid compartments, very few research has been done on gestational changes of intra- and extracellular body water compartments (31, 55, 62).

Between 5 – 10 % of pregnancies worldwide are complicated with hypertension, involving both chronic hypertension and new onset gestational hypertensive disease (GHD), depending on presentation before or after 20 weeks of gestation respectively. GHD are classified as (a) early onset (EPE) or (b) late onset preeclampsia (LPE) when maternal renal, hepatic and/or other organ dysfunctions present already before or after 34 weeks of gestation respectively, or (c) gestational hypertension (GH) when no maternal organ dysfunctions are present (7). The two types of preeclampsia have also been labeled placental (early onset) or maternal (late onset) preeclampsia (18, 39, 43, 50, 56), or high output and low output preeclampsia (58). Today, the circulatory pathophysiologic pathways explaining the different clinical presentations of EPE, LPE and GH in both latent and clinical stage are unknown. Different

characteristics of cardiac and arterial function and of intravascular filling state in the latent and clinical phase of EPE and LPE have been reported (33, 61). Next to this, GH differs from preeclampsia by lack of venous hemodynamic dysfunction (27, 28). No studies have been published on the global functioning of the maternal circulation, serving as a closed circuit with interdependent components.

For this study, we hypothesized that (a) expansion of body water volume occurs in every pregnancy, including those complicated with GHD, (b) already in the first trimester, functioning of major components of the maternal circulation - including heart, central and peripheral arteries, central veins and body fluid content - is different between normal pregnancies and those complicated with GHD, (c) there is a gradual worsening of overall maternal hemodynamic dysfunction from latent to clinical phase of GHD, and the sequence of this process is unique for EPE, LPE and GH respectively.

Methods

Patients

Approval of the Ethical Committee was obtained before study onset (MEC ZOL, reference: 06/043, 08/049, 13/090U) and informed consent was obtained before inclusion. Women with apparently normotensive singleton pregnancies, at random gestational ages, presenting at the obstetric ultrasound scanning clinic Ziekenhuis Oost-Limburg Genk, as well as women with suspected new-onset hypertension in ambulatory or hospital setting, were invited to participate in an observational study on maternal cardiovascular functioning between 2011-2017, as part of the ongoing Hasselt University Research Project of Maternal Venous Hemodynamics. When included in first or second trimester, women were asked for follow-up measurements and 48% eventually did so. Three periods of assessment were considered for the statistical analysis: women included in the first trimester (< 15 weeks), second trimester (15+0 to 27+6 weeks) and third trimester (≥ 28 weeks). At birth, data on gestational outcome was categorized according to the criteria revised by the International Society for Studies of Hypertension in Pregnancy (6, 7). Preeclampsia was defined as new-onset hypertension with proteinuria ≥300mg/24h, other organ dysfunction or fetal growth restriction, labelled as early-onset at clinical presentation <34 weeks (EPE) and late-onset at presentation ≥34 weeks (LPE). Gestational hypertension (GH) was defined as new-onset hypertension without proteinuria, other organ dysfunction or fetal growth restriction. Women with GHD giving birth to neonates small for gestational age (SGA) - defined as birth weight < 10th percentile (22) - were included, as poor fetal growth was considered a clinical feature of GHD. Multiplet pregnancies, women with essential hypertension or with chronic cardiovascular, renal, endocrine, hematologic or auto-immune diseases and

normotensive women with SGA neonates were excluded (Figure 1). Demographic details were maternal age (years), pregestational BMI, gestational age at assessment and at delivery, parity, medication, smoking, neonatal birth weight and percentile. To evaluate the effect of smoking, average measurements per group and per trimester were compared between non-smokers and the study population.

Cardiovascular profile

A maternal cardiovascular profile was assessed in every pregnant woman combining three non-invasive techniques to obtain information about arteries, veins, heart and body fluid content (Table 1). A standardized protocol was used as reported in previous studies (27).

Blood pressure measurement

Blood pressures were measured twice in each participant, once in supine and once in standing position, in order to evaluate the cardiovascular orthostatic reflex response of which results have been reported elsewhere (54, 65). Arterial blood pressure was measured from the right brachial artery using an appropriate cuff size of the automated sphygmomanometer incorporated in the impedance cardiography monitoring device (~~see further).~~ Measurements in the upright position were recorded after two minutes of adaptation following the postural change (Figure 2), which is reported to be representative for long lasting effects after posture change (5, 12). For this study, only standing values were considered of systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP), as defined in Table 1.

Bio-impedance spectrum analysis

The body composition and fluid balance were measured by a multiple frequency bioelectrical impedance analyser (Maltron Bioscan 920-II, Maltron International LTD,

Essex, UK) in supine position with stretched arms and legs, without socks or shoes (Figure 2) (55). Two electrodes, receiving the electrical signal, were placed on the dorsal surfaces of the wrist and ankle at the level of the process of the radial and ulnar resp. fibular and tibial bones. Two other electrodes, sending the electrical signal, were attached to the third metacarpal bone of the right hand and right foot. The applied current was 0.6 mA with a frequency of 5, 50, 100 and 200 kHz during 5 seconds. Total Body Water (TBW) is estimated by bio-impedance as explained briefly in Table 1. TBW totals intracellular water (ICW) and extracellular water (ECW), which in turn is considered the sum of interstitial, transcellular water and plasma volume.

Impedance Cardiography (ICG)

The Non-Invasive Continuous Cardiac Output Monitor (NICCOMO, Medis Medizinische Messtechnik GmbH, Ilmenau, Germany) was used for impedance cardiography assessment with four skin-resistance-eliminating electrodes, two on the axillary line under the thorax and two in the neck. The examination was performed after 3-minute stabilization of cardiovascular function in standing position (Figure 2). Parameters were classified into three groups. (a) Cardiac function parameters are heart rate (HR) in beats per minute and stroke volume (SV), as calculated from the ICG measurements using the formula of Bernstein (2). Cardiac output (CO) in L/min is calculated as HR x SV. (b) Characteristics of Aorta flow velocities are represented by Velocity index (VI), defined as the peak systolic flow expressed in 1/1000/s, and acceleration index (ACI), defined as maximum acceleration of systolic flow expressed in 1/100/s². (c) Total Peripheral Resistance (TPR) is calculated as MAP x 80/CO and expressed in dyn.sec/cm^5 (21).

Uterine Artery Doppler

As reported elsewhere, the automated algorithm of the Doppler ultrasound scanner was used to measure Resistivity index (RI = [Peak systolic velocity – minimal diastolic velocity]/Peak systolic velocity) and Pulsatility Index (PI = [Peak systolic velocity – minimal diastolic velocity]/Mean velocity) in the uterine arcuate arteries, at < 2cm of the insertion of the intra-uterine branching of the uterine artery (27, 40) . RI is a proxy for arterial wall counteraction against forward blood flow, altered by a combination of vascular compliance and resistance (8). PI merely reflects the intra-cycle variability of blood flow velocities in a vessel. Both parameters were measured three consecutive times at each side, and averaged as part of a standardized protocol (52).

Hepatic and Renal venous ECG-Doppler Ultrasound

An electrocardiogram was used to assist Doppler ultrasonography of the maternal renal interlobar and hepatic veins using a 3.5 MHz transabdominal probe during interrupted breathing in supine position (Aplio Mx, Toshiba Medical Systems nv, Sint-Stevens-Woluwe, Belgium). Each parameter was measured three consecutive times and averaged as part of a standardized protocol, reducing intra-and inter-variability (52). Parameters were classified into 2 groups: heart rate corrected pulse transit and impedance indices.

The heart rate corrected venous pulse transit (VPT) is the time interval between the P-top from the ECG-wave and the A-wave of the Doppler pulse wave, and expressed in ms. The atrial contraction is responsible for a retrograde rebounce of blood into the venous system (13). This rebound can be observed by Doppler sonography up to the level of the renal interlobar veins in pregnancies complicated with early onset preeclampsia (27). The P-A time interval, labeled as venous pulse transit (VPT) is a measure for the velocity at which this rebouncing A-wave propagates through the

213 venous system. As heart rate varies during the course of gestation, VPT is expressed
214 as a fraction of heart rate, measured as the time interval in msec between the
215 consecutive ECG R-waves of the corresponding heart cycle. As such, VPT is without
216 units. VPT is considered the venous equivalent of arterial pulse transit time (or pulse
217 wave velocity), and is inversely related to vascular wall stiffness: the shorter this time
218 interval, the faster and more distant the rebound of atrial contraction travels in
219 retrograde direction through the central veins (27, 66). Venous vascular stiffness
220 depends on vaso-activity from autonomic nervous system induced or endothelium
221 dependent smooth muscle contraction, as well as on (micro-) structural composition
222 of the different layers of the vascular walls (19).
223 At the venous side, the maximum and minimum flow velocity is measured at the level
224 of the renal interlobar and hepatic veins as explained elsewhere (25, 26). Venous
225 flow velocities depend on the pressure gradient relative to the right atrium,
226 intravascular filling, vascular tone and external compression (20). A venous
227 impedance index is calculated using the formula [(Maximum Velocity-Minimum
228 Velocity)/Maximum velocity] (26). Venous impedance index is the venous Doppler
229 equivalent arterial PI, representing the intra-cycle variability of blood flow velocities in
230 the veins.
231
232 **Statistics**
233 An independent t-test at 5% significance level was used for intergroup comparison of
234 continuous demographic data. Chi-square test was used for categorical demographic
235 variables. Normality was checked via Shapiro-Wilk. Data were presented as mean ±
236 SD or n (%).

Linear Mixed Models for repeated measurements were used to examine differences between UP and all types of GHD. A random patient effect was used to correct for the correlation between trimestrial measurements of a pregnancy, as multiple measurements were performed in 48% of the patients. Fixed effects of trimester and group, as well as their interaction term were specified. The fixed effects structure was simplified by using a significance level of 5%. Analyses were done in SAS (SAS 9.4, Institute Inc., Cary, NC, USA). A correction for demographical influences (BMI, nulliparity and age) on the cardiovascular parameters was implemented in the linear mixed model. Corrections for multiple testing were not implemented.

Interpretation of measured values (summarized in Table 1).

Hypertension is defined according to ISSHP criteria as systolic and/or diastolic pressure repeatedly ≥ 140 or 90 mm Hg respectively (7). As discussed elsewhere (65), blood pressures in GHD can be significantly higher than in UP, without meeting the criteria of hypertension.

Body water volumes

To allow comparison within and between groups, all measurements of TBW, ECW and ICW are corrected for age, parity and BMI with mean values estimated for a 30 year old primigravid with BMI 23.

Cardiac function parameters

Similar to body water volumes, all measurements of SV, HR, VI and ACI are standardized for age, parity and BMI, as such representing the values obtained in a 30 year old primigravid with BMI 23, which allows for intra- and intergroup comparison. CO is the product of SV and HR, which indicates that opposite abnormal trends of SV and HR can present with normal CO.

Aorta flow velocities

Reduced VI and/or AI reflect abnormal central arterial function. The latter relates to cardiac systolic function, aorta or peripheral arterial pressure, intravascular filling and aorta compliance (41).

Total peripheral resistance

TPR represents the overall arterial resistance in the systemic circulation.

Uterine arterial flow

Uterine artery PI and RI relate directly to vascular wall resistance against uterine blood flow. Increased PI and RI are reported in GHD and/or poor fetal growth (10). Unilateral abnormal values in left or right uterine arteries are very common, and therefore some authors recommend averaging (30). For this study, we preferred to present unilateral left and right values, similar to the venous Doppler values of renal interlobar veins (~~see further~~).

Hepatic venous flow

In non-pregnant individuals, hepatic venous flow shows a triphasic waveform (Venous impedance index > 1), and this turns to a completely flat pattern in uncomplicated third trimester pregnancy (Venous Impedance Index = 0) (25). This shift is associated with increase of intra-abdominal pressure (60), a physiologic feature of uncomplicated pregnancy (53), and also with increase of VPT (59). In the clinical stage of early onset preeclampsia, triphasic HV patterns are frequently observed, together with short VPT (24, 59). The same is true for late onset preeclampsia, but to a much lesser degree (37).

Renal interlobar vein Doppler

During the course of uncomplicated pregnancy, VPT increases (59) and renal interlobar venous impedance index decreases (26). In early onset PE, VPT is short

and rebound of atrial contraction is responsible for the so-called venous pre-acceleration nadir (23), with subsequent increase of Impedance Index in one or both kidneys. This can be observed already weeks before clinical onset of disease (37). In late onset PE, borderline reduced VPT and increased RIVI are reported, usually unilaterally and presenting only at onset of disease (37). Gestational hypertension presents without abnormalities of VPT and Impedance Index (27, 28).

Results

A total of 2193 assessments were done in 1459 women, of which 1700 (77.5%) in UP, 87 (4.0%) in EPE, 218 (9.9%) in LPE and 188 (8.6%) in GH. Numbers of pregnancies assessed per group per trimester are presented in the flow chart (Figure 1). As explained, 674 (46.2%) of the women had measurements in more than 1 trimester. Patient demographics are shown in Table 2: GHD groups had more women with high BMI, nulliparity and antihypertensive medication. Smoking was less in LPE. For all parameters in this study, the average measurements per group and per trimester differed less than 15% when comparing all women and smokers only, except for 16.5% HVI difference in third trimester GH. Birth weight percentile was lower in EPE only.

Figure 3 shows the inter-trimestrial differences of (age-, BMI- and parity- corrected) least square mean values of systolic, diastolic and mean arterial pressure. For all GHD groups, SBP, DBP and MAP are higher than UP from the first trimester onward.

Figure 4 shows for each group the (age-, BMI- and parity- corrected) intertrimestrial differences of volume homeostasis parameters TBW, ECW, ICW and ECW/ICW. In all pregnancies, every least square mean value is higher ($p < 0.05$) in each consecutive trimester, except for ECW/ICW between 1st and 2nd trimester EPE ($p =$

312 0.075) and for ICW between 1st and 2nd trimester LPE (p = 0.054). In 2nd trimester
313 EPE, all parameters are higher than in every other group (Table 4), and ECW is
314 higher than UP already from the first trimester onward (Tables 3-5). In LPE and GH,
315 significant differences relative to UP only exist in the third trimester (Table 5).

316 Tables 3-5 show the trimestrial values of blood pressures (DBP, MAP), cardiac
317 function (SV, HR, CO), central arterial function (VI, ACI), TPR, uterine artery Doppler
318 parameters (PI, RI), hepatic venous flow parameters (HVI, HVPT) and renal
319 interlobar venous flow parameters (RIVI and RVPT).

320 As is shown in Table 3, every GHD group in the first trimester presents with different
321 sets of abnormal parameters relative to UP: high pressures and TPR are present in
322 each GHD group, and this is associated with abnormal uterine flow, ECW and central
323 arterial function in EPE, and with abnormal cardiac and central arterial function in
324 LPE. Tables 3, 4 and 5 shows that the number of abnormal parameters increases per
325 trimester in every GHD group. Third trimester cardiovascular dysfunctions are similar
326 in EPE and LPE, but the magnitude of abnormal values of most arterial and venous
327 Doppler parameters and of ECW/ICW is higher in EPE.

328 Figure 5 presents visually the abnormal functioning of different circulatory
329 components per trimester in each type of GHD. As is show, EPE presents in the first
330 trimester with higher values than UP for blood pressure, total peripheral resistance,
331 uterine artery resistance and extracellular water volume, and this is associated with
332 reduced Aorta flow velocities. In the second trimester, reduced cardiac output and
333 hepatic vein pulse transit are added, as well as increased hepatic vein impedance
334 index. Finally, in the third trimester, also left and right renal impedance index are
335 higher and venous pulse transits are lower.

LPE differs from UP in the first trimester by higher blood pressure and total peripheral resistance, together with lower heart rate and aorta flow acceleration index. In the second trimester, abnormal renal interlobar vein Doppler values are added and in the third trimester, also hepatic vein Doppler values are abnormal.

GH differs from EPE and LPE by a lack of abnormal venous Doppler flow measurements. In the first trimester, blood pressure and total peripheral resistance are higher than UP. In the second trimester, unilateral left uterine artery Doppler PI and RI are higher, but is not observed anymore in the third trimester at which stage cardiac output, stroke volume and aorta flow velocities are lower and body water volumes are higher than UP.

Discussion

The key findings of this study are that (1) intracellular and extracellular water volume expansion is a feature of gestational physiology in uncomplicated pregnancies, but also in those complicated with different types of gestational hypertensive disease, (2) circulatory dysfunctions relative to UP are different between GHD groups already from the first trimester onward, and (3) the evolution of circulatory dysfunction from 1st to 3th trimester GHD is unique for EPE, LPE and GH respectively.

Our study is the first to assess all major circulatory components as one integrated functional circuit: volumes, heart, arterial and venous hemodynamics. A standardized protocol of non-invasive techniques with reported inter- and intra-observer correlations is used (26, 52, 59). All statistical analyses comparing groups or inter-trimestrial changes within a group are corrected for age, parity and BMI, which allows comparing the pathophysiologic processes within and between GHD groups. The bio-impedance technique used to be criticized as being less valid than

echocardiography, dye dilution plasma volume measurements or other so-called gold standard technologies, however clinically relevant associations between bio-impedance measurements in pregnant women with parameters of maternal and neonatal outcome have clearly illustrated the usefulness of this non-invasive technique for application during pregnancy. Next to this, the reported and current results observed by our research team have always been in line with these so-called golden standard methods (51). We acknowledge the large difference in number of included patients per group, and some patient groups containing a low number of inclusions. This is anticipated by the statistical model, using trend lines based upon the behavior of second and third trimester values. Another weakness is the significantly difference between gestations at assessment in the study groups (Table 2). Our numbers of longitudinal assessments in each trimester is low, and need confirmation from a systematic longitudinal observation with or without inclusion of more clinical or physical parameters as reported by others (44, 64). Ideally, for the type of study as presented here, smoking and medication use should be excluded; in our study however, this would reduce the number of inclusions in some patient groups to below the statistically acceptable level. However, for all parameters in this study apart from one exception, the average measurements per group and per trimester differed less than 15% when comparing all women and smokers only.

Our analysis sheds a new light on the circulatory pathophysiology of GHD. It is generally accepted that in uncomplicated pregnancy, an early postconceptional vasodilatation is responsible for a condition of intravascular underfilling (16), triggering volume expansion mechanisms (15, 16). The intravascular refill leads to a state of chronic volume overload, pushing the pregnant woman's cardiovascular system at the maximum possible performance, close to the edge of decompensation

(34). To meet the increased cardiac workload needed to circulate large volumes of blood, cardiac functional and structural changes occur, supporting systolic function but hampering diastolic properties (35). This in turn troubles venous return and predisposes to organ congestion (38). In order to maintain optimal control of CO, the venous compartment responds with autonomic nervous induced mobilization of stored blood volumes mainly from the splanchnic bed (32). Our observations in uncomplicated pregnancies are consistent with reported data of gestational physiology: a reduction of diastolic pressure, mean arterial pressure and peripheral resistance from first to second trimester, with a subsequent rise in third trimester, as well as an increase of cardiac output and stroke volume from first to second trimester with subsequent stabilization (46). The latter, combined with reduced Aorta flow velocities and increased total body water from second to third trimester, is consistent with increased intravascular volume load in UP. In addition, we added to this knowledge by demonstrating and explaining the difference in circulatory (dys-)function in EPE, LPE and GH at different stages of gestation. Our observations support the theorized concept of preeclampsia occurring as a result of abnormal maternal cardiovascular adaptation and volume intolerance has already been published 20 years ago by Bernstein *et al*. (3). During the last decade, it has become more and more evident that the type of GHD and subsequent maternal and neonatal outcome not only relate to the degree of placental dysfunction, but also to the adaptive capabilities of the maternal cardiovascular system (36). Some cardiovascular functions are reported to differ between gestational hypertension, early onset and late onset preeclampsia already before conception (17), during pregnancy (27) and in postpartum (63), but these studies were always limited to an incomplete assessment of the circulatory circuit. We built upon this gap, and present

411 simultaneously obtained data of the most relevant components of the cardiovascular
412 circuit in each trimester. This clearly illustrates typical features of circulatory
413 dysfunctions within each GHD group, which are type-specific already from the first
414 trimester onward. The process of volume expansion, as explained above, is
415 superimposed on these subclinical abnormal conditions in early gestation, and this is
416 accompanied with a gradual aggravation of overall circulatory dysfunction in GHD.
417 We cannot conclude from our data whether this association is causal or co-existing.
418 Apart from the differences already reported for CO and TPR (61), cardiac function
419 and morphology (4, 61), central arterial (29) and uterine arterial function (47), we
420 specifically want to highlight in this paper our reported finding concerning the
421 differences in venous hemodynamic function between EPE and LPE on the one
422 hand, and GH and UP on the other hand (Tables 3-5, Figure 4). In the second
423 trimester, venous hemodynamic dysfunctions are also different between EPE and
424 LPE, with Hepatic vein Doppler abnormalities presenting in EPE and renal interlobar
425 vein abnormalities in LPE (Table 4). These observations not only indicate that
426 venous hemodynamic dysfunction is a typical feature of preeclampsia but not
427 gestational hypertension, but also that the pathways of developing venous
428 hemodynamic dysfunction are different between EPE and LPE. We already reported
429 elsewhere that venous dysfunction is a typical preeclampsia feature (27), but now we
430 highlight that this is already present from the second trimester onwards. We
431 hypothesize that the process of gestational volume expansion is responsible for a
432 chronic volume overload in every pregnant woman, which may eventually lead to
433 signs of subclinical diastolic failure in a proportion of uncomplicated pregnancies (34).
434 Similar to the reported pathophysiologic process of cardiac failure with preserved
435 ejection fraction (1), the deleterious effects of volume overload are transmitted into

retrograde direction to the venous compartment (Figure 4). When venous compensatory mechanisms fail, congestion induced organ failure may occur (14). In non-pregnant individuals, the so-called cardio-hepatic and cardio-renal syndromes are examples of this pathophysiologic process. From the concepts explained, the gestational process of volume expansion and overloading can be considered a two-step process: the evolution from normal to a preclinical abnormal stage occurs in normal pregnancy, and from preclinical abnormal to symptomatic gestational hypertensive disease occurs in pathologic pregnancy. This type specific evolution depends on the first trimester functional status of the cardiovascular circuit.

We conclude from the data presented that body water volume expansion is a normal feature of gestational physiology in both uncomplicated pregnancies and those complicated with GHD. In GHD, this volume expansion is associated with a gradual aggravation of circulatory dysfunctions from first to third trimester, a process that is type-specific already from the first trimester onward. Our study illustrates that, to understand in full the pathophysiologic processes of GHD for both diagnosis and therapy, a multiple functions evaluation of the maternal circulation is required.

Perspectives and significance

The results presented in this paper shed a new light on the pathophysiologic background mechanisms of gestational hypertensive diseases (GHD), by describing them as processes of gradual circulatory decompensation in co-existence with increasing body water volumes. The circulatory pathways from first to third trimester are unique for early onset preeclampsia(EPE), late onset preeclampsia (LPE) and gestational hypertension (GH). This view helps filling some of the gaps in the current knowledge of the etiology of preeclampsia, and illustrates the relevance of exploring the maternal cardiovascular system as a closed circuit with interdependently functioning components. The non-invasive nature of the applied technologies, easy to be performed by both clinicians and paramedics, opens perspectives towards a rationalized implementation of the biophysical assessment of circulatory function in (a) the prediction and screening for GHD at early stages of pregnancy, (b) the diagnosis of and discrimination between EPE, LPE and GH and (c) the type-specific management in preclinical and clinical stages of EPE, LPE and GH.

Acknowledgements

All authors acknowledge the support by the Limburg Clinical Research Program (LCRP) at Hasselt University, Belgium.

Sources of Funding

The first author SV is funded by a Ph.D. grant of the Agency for Innovation by Science and Technology (IWT) in Brussels, Belgium.

Conflicts of Interest/Disclosures

Other authors declare no conflict of interest.

References

1. **Beale AL, Meyer P, Marwick TH, Lam CSP, and Kaye DM**. Sex Differences in Cardiovascular Pathophysiology: Why Women Are Overrepresented in Heart Failure With Preserved Ejection Fraction. *Circulation* 138: 198-205, 2018.

2. **Bernstein DP, and Lemmens HJ**. Stroke volume equation for impedance cardiography. *Medical & biological engineering & computing* 43: 443-450, 2005.

3. **Bernstein IM, Meyer MC, Osol G, and Ward K**. Intolerance to volume expansion: a theorized mechanism for the development of preeclampsia. *Obstetrics and gynecology* 92: 306-308, 1998.

4. **Borges VTM, Zanati SG, PeraColi MTS, Poiati JR, Romao-Veiga M, PeraColi JC, and Thilaganathan B**. Maternal hypertrophy and diastolic disfunction and brain natriuretic peptide concentration in early and late Pre-Eclampsia. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2017.

5. **Borst C, van Brederode JF, Wieling W, van Montfrans GA, and Dunning AJ**. Mechanisms of initial blood pressure response to postural change. *Clinical science (London, England : 1979)* 67: 321-327, 1984.

6. **Brown MA, Lindheimer MD, de Swiet M, Van Assche A, and Moutquin JM**. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertension in pregnancy* 20: IX-XIV, 2001.

7. **Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, Hall DR, Warren CE, Adoyi G, and Ishaku S**. Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. *Hypertension (Dallas, Tex : 1979)* 72: 24-43, 2018.

8. **Bude RO, and Rubin JM**. Relationship between the resistive index and vascular compliance and resistance. *Radiology* 211: 411-417, 1999.

9. **Chmielewski J, Lewandowski RJ, and Maddur H**. Hepatorenal Syndrome: Physiology, Diagnosis and Management. *Seminars in interventional radiology* 35: 194-197, 2018.

10. **Cnossen JS, Morris RK, ter Riet G, Mol BW, van der Post JA, Coomarasamy A, Zwinderman AH, Robson SC, Bindels PJ, Kleijnen J, and Khan KS**. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 178: 701-711, 2008.

11. **de Haas S, Ghossein-Doha C, van Kuijk SM, van Drongelen J, and Spaanderman ME**. Physiological adaptation of maternal plasma volume during pregnancy: a systematic review and meta-analysis. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 49: 177-187, 2017.

12. **Del Bene R, Barletta G, Mello G, Lazzeri C, Mecacci F, Parretti E, Martini E, Vecchiarino S, Franchi F, and La Villa G**. Cardiovascular function in pregnancy: effects of posture. *BJOG : an international journal of obstetrics and gynaecology* 108: 344-352, 2001.

13. **Devine PJ, Sullenberger LE, Bellin DA, and Atwood JE**. Jugular venous pulse: window into the right heart. *Southern medical journal* 100: 1022-1027; quiz 1004, 2007.

14. **Dupont M, Mullens W, and Tang WH**. Impact of systemic venous congestion in heart failure. *Curr Heart Fail Rep* 8: 233-241, 2011.

15. **Duvekot JJ, Cheriex EC, Pieters FA, Menheere PP, and Peeters LH**. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. *American journal of obstetrics and gynecology* 169: 1382-1392, 1993.

16. **Duvekot JJ, and Peeters LL**. Renal hemodynamics and volume homeostasis in pregnancy. *Obstet Gynecol Surv* 49: 830-839, 1994.

17. **Egeland GM, Klungsoyr K, Oyen N, Tell GS, Naess O, and Skjaerven R**. Preconception Cardiovascular Risk Factor Differences Between Gestational Hypertension

535 and Preeclampsia: Cohort Norway Study. *Hypertension (Dallas, Tex : 1979)* 67: 1173-1180,
536 2016.
537 18. **Ferrazzi E, Stampalija T, Monasta L, Di Martino D, Vonck S, and Gyselaers W**.
538 Maternal hemodynamics: a method to classify hypertensive disorders of pregnancy.
539 *American journal of obstetrics and gynecology* 218: 124.e121-124.e111, 2018.
540 19. **Fleenor BS, and Berrones AJ**. Arterial Stiffness. In: *Implications and*
541 *Interventions*Springer International Publishing, 2015, p. 61.
542 20. **Gelman S**. Venous function and central venous pressure: a physiologic story.
543 *Anesthesiology* 108: 735-748, 2008.
544 21. **GmbH mMM**. IMPEDANCE CARDIOGRAPHY WITH ACM TECHNOLOGY. Medis.
545 22. **Guidelines QC**. Term small for gestation age baby. edited by Committee QCGS, and
546 (Queensland) SMaNCN2016.
547 23. **Gyselaers W**. Hemodynamics of the maternal venous compartment: a new area to
548 explore in obstetric ultrasound imaging. *Ultrasound in obstetrics & gynecology : the official*
549 *journal of the International Society of Ultrasound in Obstetrics and Gynecology* 32: 716-717,
550 2008.
551 24. **Gyselaers W, Mesens T, Tomsin K, Molenberghs G, and Peeters L**. Maternal
552 renal interlobar vein impedance index is higher in early- than in late-onset pre-eclampsia.
553 *Ultrasound in obstetrics & gynecology : the official journal of the International Society of*
554 *Ultrasound in Obstetrics and Gynecology* 36: 69-75, 2010.
555 25. **Gyselaers W, Molenberghs G, Mesens T, and Peeters L**. Maternal hepatic vein
556 Doppler velocimetry during uncomplicated pregnancy and pre-eclampsia. *Ultrasound in*
557 *medicine & biology* 35: 1278-1283, 2009.
558 26. **Gyselaers W, Molenberghs G, Van Mieghem W, and Ombelet W**. Doppler
559 measurement of renal interlobar vein impedance index in uncomplicated and preeclamptic
560 pregnancies. *Hypertension in pregnancy* 28: 23-33, 2009.
561 27. **Gyselaers W, Staelens A, Mesens T, Tomsin K, Oben J, Vonck S, Verresen L,**
562 **and Molenberghs G**. Maternal venous Doppler characteristics are abnormal in pre-

563 eclampsia but not in gestational hypertension. *Ultrasound in obstetrics & gynecology : the*
564 *official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 45:
565 421-426, 2015.
566 28. **Gyselaers W, Tomsin K, Staelens A, Mesens T, Oben J, and Molenberghs G**.
567 Maternal venous hemodynamics in gestational hypertension and preeclampsia. *BMC*
568 *pregnancy and childbirth* 14: 212, 2014.
569 29. **Khalil A, Garcia-Mandujano R, Maiz N, Elkhouli M, and Nicolaides KH**.
570 Longitudinal changes in maternal hemodynamics in a population at risk for pre-eclampsia.
571 *Ultrasound in obstetrics & gynecology : the official journal of the International Society of*
572 *Ultrasound in Obstetrics and Gynecology* 44: 197-204, 2014.
573 30. **Kofinas AD, Penry M, Swain M, and Hatjis CG**. Effect of placental laterality on
574 uterine artery resistance and development of preeclampsia and intrauterine growth
575 retardation. *American journal of obstetrics and gynecology* 161: 1536-1539, 1989.
576 31. **Larciprete G, Valensise H, Vasapollo B, Altomare F, Sorge R, Casalino B, De**
577 **Lorenzo A, and Arduini D**. Body composition during normal pregnancy: reference ranges.
578 *Acta diabetologica* 40 Suppl 1: S225-232, 2003.
579 32. **Marik PE, Baram M, and Vahid B**. Does central venous pressure predict fluid
580 responsiveness? A systematic review of the literature and the tale of seven mares. *Chest*
581 134: 172-178, 2008.
582 33. **McLaughlin K, Zhang J, Lye SJ, Parker JD, and Kingdom JC**. Phenotypes of
583 Pregnant Women Who Subsequently Develop Hypertension in Pregnancy. *Journal of the*
584 *American Heart Association* 7: 2018.
585 34. **Melchiorre K, Sharma R, Khalil A, and Thilaganathan B**. Maternal Cardiovascular
586 Function in Normal Pregnancy: Evidence of Maladaptation to Chronic Volume Overload.
587 *Hypertension (Dallas, Tex : 1979)* 67: 754-762, 2016.
588 35. **Melchiorre K, Sharma R, and Thilaganathan B**. Cardiac structure and function in
589 normal pregnancy. *Curr Opin Obstet Gynecol* 24: 413-421, 2012.

590 36. **Melchiorre K, Sharma R, and Thilaganathan B**. Cardiovascular implications in
591 preeclampsia: an overview. *Circulation* 130: 703-714, 2014.
592 37. **Mesens T, Tomsin K, Oben J, Staelens A, and Gyselaers W**. Maternal venous
593 hemodynamics assessment for prediction of preeclampsia should be longitudinal. *The*
594 *journal of maternal-fetal & neonatal medicine : the official journal of the European*
595 *Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies,*
596 *the International Society of Perinatal Obstet* 28: 311-315, 2015.
597 38. **Miller WL**. Assessment and Management of Volume Overload and Congestion in
598 Chronic Heart Failure: Can Measuring Blood Volume Provide New Insights? *Kidney Dis*
599 *(Basel)* 2: 164-169, 2017.
600 39. **Myatt L, and Roberts JM**. Preeclampsia: Syndrome or Disease? *Current*
601 *hypertension reports* 17: 83, 2015.
602 40. **Nelson TR, and Pretorius DH**. The Doppler signal: where does it come from and
603 what does it mean? *AJR American journal of roentgenology* 151: 439-447, 1988.
604 41. **O'Rourke MF, and Adji A**. Noninvasive studies of central aortic pressure. *Current*
605 *hypertension reports* 14: 8-20, 2012.
606 42. **Poelzl G, and Auer J**. Cardiohepatic syndrome. *Current heart failure reports* 12: 68-
607 78, 2015.
608 43. **Redman CW, and Sargent IL**. Latest advances in understanding preeclampsia.
609 *Science (New York, NY)* 308: 1592-1594, 2005.
610 44. **Reslan OM, and Khalil RA**. Molecular and vascular targets in the pathogenesis and
611 management of the hypertension associated with preeclampsia. *Cardiovasc Hematol Agents*
612 *Med Chem* 8: 204-226, 2010.
613 45. **Ronco C, and Di Lullo L**. Cardiorenal syndrome. *Heart failure clinics* 10: 251-280,
614 2014.
615 46. **Sanghavi M, and Rutherford JD**. Cardiovascular physiology of pregnancy.
616 *Circulation* 130: 1003-1008, 2014.

47. **Scandiuzzi RM, Prado CA, Araujo Junior E, Duarte G, Quintana SM, da Silva Costa F, Tonni G, Cavalli Rde C, and Marcolin AC**. Maternal uterine artery Doppler in the first and second trimesters as screening method for hypertensive disorders and adverse perinatal outcomes in low-risk pregnancies. *Obstet Gynecol Sci* 59: 347-356, 2016.

48. **Scholten RR, Lotgering FK, Hopman MT, Van Dijk A, Van de Vlugt M, Janssen MC, and Spaanderman ME**. Low Plasma Volume in Normotensive Formerly Preeclamptic Women Predisposes to Hypertension. *Hypertension (Dallas, Tex : 1979)* 66: 1066-1072, 2015.

49. **Scholten RR, Oyen WJ, Van der Vlugt MJ, Van Dijk AP, Hopman MT, Lotgering FK, and Spaanderman ME**. Impaired fetal growth and low plasma volume in adult life. *Obstetrics and gynecology* 118: 1314-1322, 2011.

50. **Sibai B, Dekker G, and Kupferminc M**. Pre-eclampsia. *Lancet (London, England)* 365: 785-799, 2005.

51. **Staelens A, Tomsin K, Grieten L, Oben J, Mesens T, Spaanderman M, Jacquemyn Y, and Gyselaers W**. Non-invasive assessment of gestational hemodynamics: benefits and limitations of impedance cardiography versus other techniques. *Expert review of medical devices* 10: 765-779, 2013.

52. **Staelens AS, Tomsin K, Oben J, Mesens T, Grieten L, and Gyselaers W**. Improving the reliability of venous Doppler flow measurements: relevance of combined ECG, training and repeated measures. *Ultrasound in medicine & biology* 40: 1722-1728, 2014.

53. **Staelens AS, Van Cauwelaert S, Tomsin K, Mesens T, Malbrain ML, and Gyselaers W**. Intra-abdominal pressure measurements in term pregnancy and postpartum: an observational study. *PloS one* 9: e104782, 2014.

54. **Staelens AS, Vonck S, Mesens T, Tomsin K, Molenberghs G, and Gyselaers W**. Type-specific orthostatic hemodynamic response of hypertensive diseases in pregnancy. *Clinical and experimental pharmacology & physiology* 42: 1036-1044, 2015.

55. **Staelens AS, Vonck S, Molenberghs G, Malbrain ML, and Gyselaers W**. Maternal body fluid composition in uncomplicated pregnancies and preeclampsia: a bioelectrical

impedance analysis. *European journal of obstetrics, gynecology, and reproductive biology* 204: 69-73, 2016.

56. **Steegers EA, von Dadelszen P, Duvekot JJ, and Pijnenborg R**. Pre-eclampsia. *Lancet (London, England)* 376: 631-644, 2010.

57. **Tang WH, and Kitai T**. Intrarenal Venous Flow: A Window Into the Congestive Kidney Failure Phenotype of Heart Failure? *JACC Heart failure* 4: 683-686, 2016.

58. **Tay J, Foo L, Masini G, Bennett PR, McEniery CM, Wilkinson IB, and Lees CC**. 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. *American journal of obstetrics and gynecology* 218: 517.e511-517.e512, 2018.

59. **Tomsin K, Mesens T, Molenberghs G, and Gyselaers W**. Venous pulse transit time in normal pregnancy and preeclampsia. *Reproductive sciences (Thousand Oaks, Calif)* 19: 431-436, 2012.

60. **Tomsin K, Vriens A, Mesens T, and Gyselaers W**. Non-invasive cardiovascular profiling using combined electrocardiogram-Doppler ultrasonography and impedance cardiography: An experimental approach. *Clinical and experimental pharmacology & physiology* 40: 438-442, 2013.

61. **Valensise H, Vasapollo B, Gagliardi G, and Novelli GP**. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. *Hypertension (Dallas, Tex : 1979)* 52: 873-880, 2008.

62. **Valensise H, Vasapollo B, Novelli GP, Larciprete G, Andreoli A, Altomare F, Di Pierro G, Galante A, Arduini D, De Lorenzo A, and Caserta D**. Maternal cardiac systolic function and total body water estimation in normal and gestational hypertensive women. *Acta diabetologica* 40 Suppl 1: S216-221, 2003.

63. **Veerbeek JH, Hermes W, Breimer AY, van Rijn BB, Koenen SV, Mol BW, Franx A, de Groot CJ, and Koster MP**. Cardiovascular disease risk factors after early-onset preeclampsia, late-onset preeclampsia, and pregnancy-induced hypertension. *Hypertension (Dallas, Tex : 1979)* 65: 600-606, 2015.

673 64. **Verlohren S, Perschel FH, Thilaganathan B, Droge LA, Henrich W, Busjahn A,**
674 **and Khalil A**. Angiogenic Markers and Cardiovascular Indices in the Prediction of
675 Hypertensive Disorders of Pregnancy. *Hypertension (Dallas, Tex : 1979)* 69: 1192-1197,
676 2017.
677 65. **Vonck S OJ, Staelens AS, Lanssens D, Molenberghs G, Gyselaers W**.
678 Optimization of Simple Sphygmomanometric Blood Pressure Measurement in Routine
679 Prenatal Care. *Health Care Current Reviews* 5: 2017.
680 66. **Vonck S, Staelens AS, Bollen I, Broekx L, and Gyselaers W**. Why non-invasive
681 maternal hemodynamics assessment is clinically relevant in early pregnancy: a literature
682 review. *BMC pregnancy and childbirth* 16: 302, 2016.
683 67. **Vonck S, Staelens AS, Mesens T, Tomsin K, and Gyselaers W**. Hepatic
684 hemodynamics and fetal growth: a relationship of interest for further research. *PloS one* 9:
685 e115594, 2014.

686

Figure Legends

Figure 1: Flowchart from pregnancies included in the observational study as part of the Hasselt University Study Project on Maternal Venous Hemodynamics. The grey colored parts are used for this study's analysis. In 1326 pregnant women, 2022 assessments were performed. After birth, patients were classified into uncomplicated pregnancy (UP), gestational hypertension (GH), late-onset (LPE) and early-onset (EPE) preeclampsia. Assessments per patient were done in the first, second or third trimester (1T, 2T, 3T resp.), ranging between 1 and 3 assessments per pregnancy.

Figure 2: Study protocol of the combined assessment of body volumes, cardiac function, central & peripheral arterial function, uterine arterial flow, hepatic and renal venous flow, as performed since 2011 in the ongoing Hasselt University Research Project of Maternal Venous Hemodynamics. In consecutive order (from left to right): Doppler ultrasound and bio-impedance spectrum analysis in supine position, sphyngomanometric blood pressure measurement after 2 min stabilization in standing position, with another 1 min interval before impedance cardiographic assessment.

Figure 3: *S*ystolic, diastolic, mean arterial and pulse pressure in first (1T), second (2T) and third trimester (3T) in uncomplicated pregnancies (UP) and those complicated with early onset preeclampsia (EPE), late onset preeclampsia (LPE) and gestational hypertension (GH). Data are presented as Least Square Mean of BMI-, age and parity-corrected values, inside the interquartile ranges of raw data.

Figure 4: Least Square Mean values of total body water (TBW), extracellular water (ECW), intracellular water (ICW) and ECW/ICW in first (1T), second (2T) and third trimester (3T) in uncomplicated pregnancies (UP) and those complicated with

711 early onset preeclampsia (EPE), late onset preeclampsia (LPE) and gestational
712 hypertension (GH).
713 Figure 5: Presentation of the maternal circulation as a circuit. The parameters of
714 the different cardiovascular function systems, as assessed in this study, are
715 explained in the legend. The first, second and third trimester circuits of early onset
716 preeclampsia (EPE), late onset preeclampsia (LPE) and gestational hypertension
717 (GH), only contain icons of those organ systems with abnormal function relative to
718 uncomplicated pregnancy (UP) (Tables 3-5). As is shown, already in the first
719 trimester, the combinations of components that function abnormally relative to UP are
720 different between EPE, LPE and GH. There is a gradual increase in abnormal
721 hemodynamic functions from first to third trimester in each group, and this
722 aggravating sequence is unique for EPE, LPE and GH respectively.
723
724
725

Table 1: Summary of technological principles of the devices used in the Hasselt University Study Project on Maternal Venous Hemodynamics.

Parameter	Technology	Units	Thresholds, range	Interpretation
Pressures				
Systolic BP	Automated Sphyngomanometer	mm Hg	cut off 140	> 140 mm Hg = hypertension > UP = abnormal
Diastolic BP		mm Hg	cut off 90	> 90 mm Hg = hypertension >UP = abnormal
Mean Art BP		mmm Hg	DBP + (SBP-DBP)/3	> UP = abnormal
Volumes				
Total Body Water	Bioimpedance Spectrum Analysis	Liter	Table 3-5	> UP = abnormal
Extracellular water		Liter	Table 3-5	> UP = abnormal
Intracellular water		Liter	Table 3-5	> UP = abnormal
ECW/ICW			Table 3-5	> UP = abnormal

Cardiac function				
Stroke Volume	Impedance Cardiography	mL	Table 3-5	< UP = abnormal
Heart rate		Beats/min	Table 3-5	< or > UP = abnormal
Cardiac output		L/min	Table 3-5	< or > UP = abnormal
Central Arterial function				
Velocity Index	Impedance Cardiography	1/1000/s	Table 3-5	< UP = abnormal
Acceleration Index		1/100/s²	Table 3-5	< UP = abnormal
Total Peripheral Resistance				
	Impedance Cardiography	dyn.s/cm^5	Table 3-5	> UP = abnormal
Uterine Artery Flow				
Pulsatility Index	Doppler Sonography	/	Table 3-5	> UP = abnormal
Resistivity Index		/	Table 3-5	> UP = abnormal

Hepatic Venous Flow

Impedance Index	ECG-Doppler Sonography	/	Table 3-5	> UP = abnormal
Pulse Transit		/	Table 3-5	< UP = abnormal

Renal Interlobar Venous flow

Impedance Index	ECG-Doppler Sonography	/	Table 3-5	> UP = abnormal
Pulse Transit		/	Table 3-5	< UP = abnormal

Legend: BP: Blood Pressure, SBP: Systolic blood pressure, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure, > UP: significantly higher than in uncomplicated pregnancies, < UP: significantly lower than in uncomplicated pregnancies, ECG: Electrocardiogram,

804 Table 2: Patient and outcome characteristics of women with an uncomplicated
805 pregnancy (UP), early onset preeclampsia (EPE), late onset preeclampsia (LPE) and
806 gestational hypertension (GH).

	UP (n=1068)	EPE (n=75)	LPE (n=177)	GH (n=139)
Characteristics at inclusion				
Maternal age (years)	30.4±5.9	30.3±5.3	30.0±5.2	30.2±4.4
Gestational age at assessment (weeks)				
First trimester	12.2±0.8	12.9±0.5*	11.8±0.8*	12.2±0.7
Second trimester	20.7±1.6	25.2±2.3*	22.0±2.3*	21.5±2.7*
Third trimester	33.4±3.2	31.5±1.5*	36.7±2.4*	36.8±2.7*
Pre-pregnancy BMI (kg/m²)	24.6±4.9	26.9±6.2*	26.1±5.7*	26.4±6.0*
Nulliparity (n,% women)	502 (47)	51 (68)*	129 (73)*	88 (63)*
Cigarette smoker (n,% women)	203 (19)	7 (10)	12 (7)*	21 (15)
Medication (n, % assessments)				
non-cardiovascular	201 (12)	8 (9)	15 (7)	16 (9)
antihypertens/anticoag	69 (4)	22 (25)*	60 (28)*	47 (25)*
Outcome characteristics				
Birth weight, g	3380±535	1280±536*	2915±652*	3069±744*
Birth weight, percentile	55±27	27±26*	43±31	45±32
Gestational age at delivery (weeks)	39.2±1.8	30.4±2.8*	37.7±1.8*	38.4±2.6*

807

808 Data are presented as mean ± SD or n (%). *p<0,05 indicates significantly different
809 from UP.

Table 3: Haemodynamic differences in first trimester of uncomplicated pregnancies compared with early (EPE) preeclampsia, late (LPE) and gestational hypertension (GH). Data for UP are presented as least-square means of BMI-, age- and parity-corrected values, together with Inter-Quartile Range of raw data (IQR), and for EPE, LPE and GH as a difference relative to UP (ΔUP)

		UP		EPE			LPE			GH		Legend		
		LSMean	IQR	Δ UP	P (UP)	P (GHD)	Δ UP	P	P (GHD)	Δ UP	P	Symbol	Comparison	P
SBP	*mm Hg*	114	108-124	16,395	**<0,001**	□ ○	8,383	**<0,001**	▫▫	9,89	**< 0,001**	▪	**EPE-LPE**	**< 0,05**
DBP	*mm Hg*	74	71 -81	13,973	**< 0,001**	▪ ●	7,499	**< 0,001**	▫▫	8,628	**< 0,001**	□	EPE-LPE	NS
MAP	*mm Hg*	84	80-91	14,382	**< 0,001**	▪ ●	7,811	**< 0,001**	▫▫	8,439	**< 0,001**	●	**EPE-GH**	**< 0,05**
TBW	*L*	32,9	31,2-35,8	1,735	0,101	□ ○	-0,095	0,876	▫▫	-0,031	0,957	○	EPE-GH	NS
ECW	*L*	14,1	13,1-15,7	1,273	**0,021**	▪ ○	0,045	0,917	▫▫	0,091	0,775	*	**LPE-GH**	**< 0,05**
ICW	*L*	18,8	18,1-20,2	0,638	0,125	□ ○	-0,193	0,434	▫▫	0,025	0,917	▫▫	LPE-GH	NS
ECW/ICW		0,75	0,72-0,79	0,032	0,056	□ ○	0,007	0,43	▫▫	0,004	0,698			
SV	*mL*	74	65-85	-1,193	0,77	□ ○	4,04	0,076	*	-2,642	0,22			
HR	*bpm*	96	88-103	-3,769	0,279	□ ○	-5,469	**0,003**	▫▫	-1,057	0,555			
CO	*L/min*	7	6,3-7,9	-0,399	0,212	□ ○	-0,091	0,61	▫▫	-0,242	0,155			
VI	*1/1000/s*	80	64-88	-10,871	**0,015**	□ ○	-3,859	0,114	▫▫	-2,828	0,22			
ACI	*1/100/s²*	173	125-198	-24,233	**0,034**	□ ○	-12,683	**0,046**	▫▫	-2,165	0,719			
TPR	*dyn.s/cm5*	993	856-1084	223,9	**< 0,001**	□ ○	107,3	**< 0,001**	▫▫	142,2	**< 0,001**			
L Aut PI		0,97	0,74-1,19	0,267	**0,007**	▪ ●	-0,068	0,139	*	0,058	0,181			
L AUt RI		0,64	0,54-0,75	0,115	**0,017**	▪ ○	-0,036	0,11	*	0,028	0,193			
R Aut PI		0,90	0,67-1,11	0,155	0,112	□ ○	-0,009	0,828	▫▫	0,061	0,159			
R Aut RI		0,61	0,50-0,71	0,074	0,129	□ ○	-0,007	0,767	▫▫	0,026	0,228			
HVI		1,24	0,75-1,56	-0,031	0,837	□ ○	0,051	0,524	▫▫	0,072	0,352			
HVPT		0,18	0,13-0,23	-0,005	0,877	□ ○	-0,016	0,346	▫▫	-0,002	0,897			
L RIVI		0,45	0,39-0,50	-0,006	0,854	□ ○	-0,029	0,063	▫▫	-0,019	0,201			
L RVPT		0,30	0,25-0,35	0,007	0,775	□ ○	0,018	0,139	▫▫	0,004	0,756			
R RIVI		0,46	0,40-0,51	-0,003	0,923	□ ○	-0,01	0,487	▫▫	0,005	0,747			
R RVPT		0,27	0,21-0,34	0,024	0,374	□ ○	-0,001	0,937	▫▫	0,006	0,68			

Legend UP: Uncomplicated pregnancy, EPE: Early Onset Preeclampsia, LPE : Late onset Preeclampsia, GH: Gestational Hypertension, GHD: Gestational Hypertension Diseases,LSMean: Least Square Mean of age, parity and BMI corrected values, IQR: Interquartile Range of raw data, ΔUP: mean numeric difference relative to UP, P(UP): significance level when compared with UP, P(GHD): significantly or not-significantly different from other GHD, labelled as: ▪: EPE-LPE difference, P<0.05; □: EPE-LPE difference not significant; ●: EPE-GH difference,p<0.05; ○: EPE-GH difference not significant, *: LPE-GH difference,p<0.05; ∞: LPE-GH difference not significant, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure, TBW: total body water volume, ECW:extracellular water volume, ICW: intracellular water volume, SV: Stroke Volume, HR: Heart Rate, CO: Cardiac Output, VI: Aorta Flow Velocity Index, ACI: Aorta Flow Acceleration Index, TPR: Total peripheral Resistance, L Aut PI: Left Uterine Artery Doppler Pulsatility Index, L AUt RI: Left Uterine Artery Doppler Resistivity Index, R Aut PI: Right Uterine Artery Doppler Pulsatility Index, R AUt RI: Right Uterine Artery Doppler Resistivity Index, HVI: Hepatic Vein Impedance Index, HVPT: Hepatic Vein Pulse Transit, L RIVI: Left Renal Interlobar Vein Impedance Index, L RVPT: Left Renal Interlobar Vein Pulse Transit, R RIVI: Right Renal Interlobar Vein Impedance Index, R RVPT: Right Renal Interlobar Vein Pulse Transit.

Table 4: Haemodynamic differences in second trimester of uncomplicated pregnancies compared with early (EPE) preeclampsia, late (LPE) and gestational hypertension (GH). Data for UP are presented as least-square means of BMI-, age- and parity-corrected values together with Inter-Quartile Range of raw data (IQR), and for EPE, LPE and GH as a difference relative to UP (ΔUP).

		UP		EPE			LPE			GH		Legend		
		LSMean	IQR	Δ UP	P (UP)	P (GHD)	Δ UP	P	P (GHD)	Δ UP	P	Symbol	Comparison	P
SBP	*mm Hg*	112	106-122	36,383	**<0,001**	▪ ●	13,038	**<0,001**	▫▫	11,406	**<0,001**	▪	**EPE-LPE**	**< 0,05**
DBP	*mm Hg*	72	69-79	18,087	**<0,001**	▪ ●	10,435	**<0,001**	▫▫	10,084	**<0,001**	□	EPE-LPE	NS
MAP	*mm Hg*	82	78-89	25,758	**<0,001**	▪ ●	11,064	**<0,001**	▫▫	10,198	**<0,001**	●	**EPE-GH**	**< 0,05**
TBW	*L*	33,9	32,1-36,9	3,006	**<0,001**	▪ ●	-0,007	0,991	▫▫	-0,032	0,955	○	EPE-GH	NS
ECW	*L*	14,7	13,8-16,3	1,797	**<0,001**	▪ ●	0,139	0,656	▫▫	0,082	0,793	*	**LPE-GH**	**< 0,05**
ICW	*L*	19,1	18,3-20,5	1,226	**<0,001**	▪ ●	-0,163	0,495	▫▫	0,081	0,737	▫▫	LPE-GH	NS
ECW/ICW		0,77	0,74-0,81	0,036	**0,005**	▪ ○	0,01	0,272	▫▫	0,009	0,46			
SV	*mL*	81	72-93	-8,322	**0,002**	□ ●	-4,319	0,073	▫▫	-1,609	0,467			
HR	*bpm*	97	89-105	-5,385	**0,012**	□ ○	-1,7	0,396	▫▫	-0,869	0,637			
CO	*L/min*	7,7	7,1-8,7	-1,259	**<0,001**	▪ ●	-0,581	**0,002**	▫▫	-0,189	0,279			
VI	*1/1000/s*	85	66-96	-27,562	**<0,001**	▪ ●	-13,288	**<0,001**	*	-4,409	0,065			
ACI	*1/100/s²*	177	131-209	-51,432	**<0,001**	▪ ●	-29,603	**<0,001**	*	-7,026	0,25			
TPR	*dyn.s/cm5*	876	759-951	464,9	**<0,001**	▪ ●	198,9	**<0,001**	▫▫	152,2	**<0,001**			
L Aut PI		0,72	0,55-0,87	0,374	**<0,001**	▪ ●	0,057	0,234	▫▫	0,113	**0,012**			
L AUt RI		0,52	0,43-0,60	0,184	**<0,001**	▪ ●	0,02	0,383	▫▫	0,056	**0,011**			
R Aut PI		0,68	0,51-0,81	0,407	**<0,001**	▪ ●	0,009	0,853	▫▫	0,072	0,104			
R Aut RI		0,49	0,40-0,58	0,202	**<0,001**	▪ ●	-0,001	0,965	▫▫	0,031	0,165			
HVI		0,85	0,24-1,39	0,4	**<0,001**	▪ ●	-0,078	0,368	▫▫	0,031	0,697			
HVPT		0,24	0,16-0,30	-0,063	**0,002**	▪ ●	0,006	0,734	▫▫	-0,007	0,683			
L RIVI		0,43	0,36-0,49	0,029	0,096	▪ ●	-0,029	0,084	▫▫	-0,029	0,051			
L RVPT		0,31	0,27-0,36	-0,018	0,201	▪ ●	0,037	**0,005**	▫▫	0,02	0,103			
R RIVI		0,42	0,35-0,48	0,017	0,326	▪ ○	-0,04	**0,011**	▫▫	-0,005	0,764			
R RVPT		0,31	0,26-0,37	0,007	0,679	□ ○	0,023	0,132	▫▫	-0,003	0,86			

Legend UP: Uncomplicated pregnancy, EPE: Early Onset Preeclampsia, LPE : Late onset Preeclampsia, GH: Gestational Hypertension, GHD: Gestational Hypertension Diseases,LSMean: Least Square Mean of age, parity and BMI corrected values, IQR: Interquartile Range of raw data, ΔUP: mean numeric difference relative to UP, P(UP): significance level when compared with UP, P(GHD): significantly or not-significantly different from other GHD, labelled as: ▪: EPE-LPE difference, P<0.05; □: EPE-LPE difference not significant; ●: EPE-GH difference,p<0.05; ○: EPE-GH difference not significant, *: LPE-GH difference,p<0.05; ∞: LPE-GH difference not significant, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure, TBW: total body water volume, ECW:extracellular water volume, ICW: intracellular water volume, SV: Stroke Volume, HR: Heart Rate, CO: Cardiac Output, VI: Aorta Flow Velocity Index, ACI: Aorta Flow Acceleration Index, TPR: Total peripheral Resistance, L Aut PI: Left Uterine Artery Doppler Pulsatility Index, L AUt RI: Left Uterine Artery Doppler Resistivity Index, R Aut PI: Right Uterine Artery Doppler Pulsatility Index, R AUt RI: Right Uterine Artery Doppler Resistivity Index, HVI: Hepatic Vein Impedance Index, HVPT: Hepatic Vein Pulse Transit, L RIVI: Left Renal Interlobar Vein Impedance Index, L RVPT: Left Renal Interlobar Vein Pulse Transit, R RIVI: Right Renal Interlobar Vein Impedance Index, R RVPT: Right Renal Interlobar Vein Pulse Transit.

Table 5: Haemodynamic differences in third trimester of uncomplicated pregnancies compared with early (EPE) preeclampsia, late (LPE) and gestational hypertension (GH). Data for UP are presented as least-square means of BMI-, age- and parity-corrected values, together with Inter-Quartile Range of raw data (IQR), and for EPE, LPE and GH as a difference relative to UP (ΔUP).

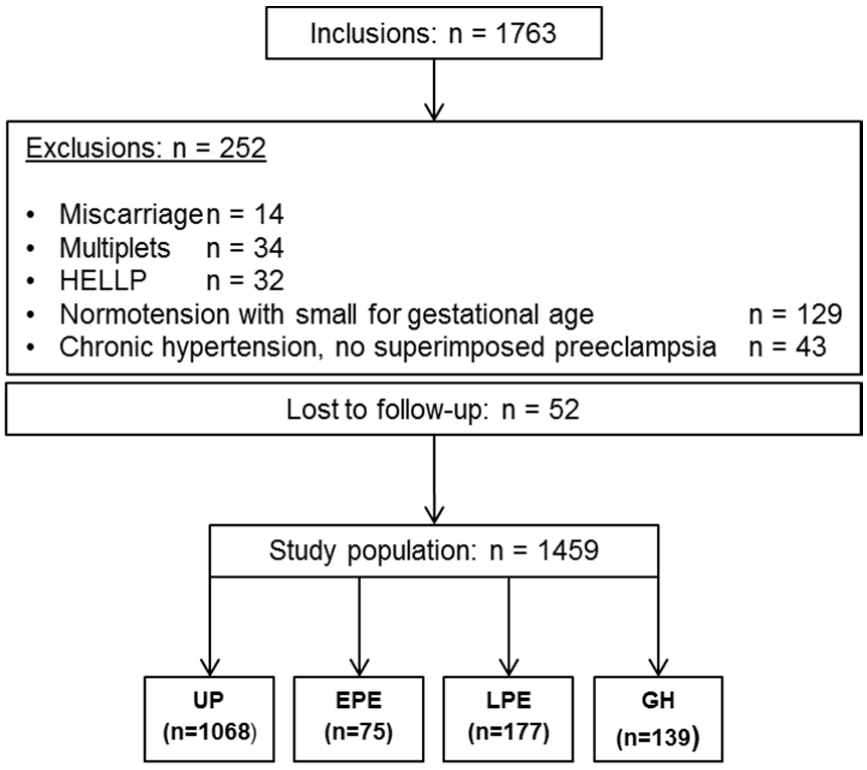
		UP		EPE			LPE			GH		Legend		
		LSMean	IQR	Δ UP	P (UP)	P (GHD)	Δ UP	P	P (GHD)	Δ UP	P	Symbol	Comparison	P
SBP	*mm Hg*	121	116-135	24,84	**<0,001**	□ ●	22,954	**<0,001**	*	16,27	**<0,001**	▪	**EPE-LPE**	**< 0,05**
DBP	*mm Hg*	79	74-88	18,087	**<0,001**	□ ●	16,869	**<0,001**	*	13,615	**<0,001**	□	EPE-LPE	NS
MAP	*mm Hg*	89	85-98	20,245	**<0,001**	□ ●	18,785	**<0,001**	*	14,742	**<0,001**	●	**EPE-GH**	**< 0,05**
TBW	*L*	35,0	34,0-39,4	5,614	**<0,001**	□ ●	4,94	**<0,001**	*	1,86	**0,001**	○	EPE-GH	NS
ECW	*L*	15,8	14,9-17,9	4,149	**<0,001**	□ ●	3,259	**<0,001**	*	0,932	**0,002**	*	**LPE-GH**	**< 0,05**
ICW	*L*	19,6	18,9-21,5	1,44	**<0,001**	□ ●	1,56	**<0,001**	*	0,611	**0,009**	▫▫	LPE-GH	NS
ECW/ICW		0,80	0,77-0,85	0,128	**<0,001**	▪ ●	0,094	**<0,001**	*	0,026	**0,003**			
SV	*mL*	80	70-93	-4,279	0,087	□ ○	-2,29	0,165	▫▫	-4,587	**0,011**			
HR	*bpm*	97	89-107	-3,952	**0,049**	□ ●	-3,898	**0,004**	*	0,392	0,789			
CO	*L/min*	7,7	6,9-8,9	-0,733	**<0,001**	□ ○	-0,528	**<0,001**	▫▫	-0,406	**0,005**			
VI	*1/1000/s*	75	52-81	-19,401	**<0,001**	□ ○	-18,562	**<0,001**	*	-14,32	**<0,001**			
ACI	*1/100/s²*	157	97-166	-43,231	**<0,001**	□ ○	-36,467	**<0,001**	▫▫	-30,918	**<0,001**			
TPR	*dyn.s/cm5*	960	822-1070	355,8	**<0,001**	□ ●	292,1	**<0,001**	*	219,6	**<0,001**			
L Aut PI		0,68	0,51-0,83	0,349	**<0,001**	▪ ●	0,093	**0,003**	▫▫	0,032	0,345			
L AUt RI		0,49	0,41-0,58	0,179	**<0,001**	▪ ●	0,048	**0,002**	▫▫	0,019	0,269			
R Aut PI		0,61	0,46-0,74	0,232	**<0,001**	▪ ●	0,087	**0,005**	▫▫	0,027	0,428			
R Aut RI		0,46	0,37-0,54	0,125	**<0,001**	▪ ●	0,044	**0,004**	*	0,005	0,759			
HVI		0,43	0,13-0,42	0,514	**<0,001**	▪ ●	0,245	**<0,001**	*	0,05	0,437			
HVPT		0,35	0,27-0,44	-0,074	**<0,001**	□ ●	-0,053	**<0,001**	*	-0,023	0,095			
L RIVI		0,37	0,30-0,40	0,063	**<0,001**	□ ●	0,327	**0,003**	*	-0,003	0,793			
L RVPT		0,39	0,34-0,45	-0,051	**<0,001**	▪ ●	-0,017	0,059	*	0,009	0,351			
R RIVI		0,33	0,27-0,36	0,092	**<0,001**	▪ ●	0,047	**<0,001**	*	-0,002	0,829			
R RVPT		0,38	0,33-0,45	-0,057	**<0,001**	▪ ●	-0,017	0,08	*	0,008	0,447			

Legend UP: Uncomplicated pregnancy, EPE: Early Onset Preeclampsia, LPE : Late onset Preeclampsia, GH: Gestational Hypertension, GHD: Gestational Hypertension Diseases,LSMean: Least Square Mean of age, parity and BMI corrected values, IQR: Interquartile Range of raw data, ΔUP: mean numeric difference relative to UP, P(UP): significance level when compared with UP, P(GHD): significantly or not-significantly different from other GHD, labelled as: ▪: EPE-LPE difference, P<0.05; □: EPE-LPE difference not significant; ●: EPE-GH difference,p<0.05; ○: EPE-GH difference not significant, *: LPE-GH difference,p<0.05; ∞: LPE-GH difference not significant, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure, TBW: total body water volume, ECW:extracellular water volume, ICW: intracellular water volume, SV: Stroke Volume, HR: Heart Rate, CO: Cardiac Output, VI: Aorta Flow Velocity Index, ACI: Aorta Flow Acceleration Index, TPR: Total peripheral Resistance, L Aut PI: Left Uterine Artery Doppler Pulsatility Index, L AUt RI: Left Uterine Artery Doppler Resistivity Index, R Aut PI: Right Uterine Artery Doppler Pulsatility Index, R AUt RI: Right Uterine Artery Doppler Resistivity Index, HVI: Hepatic Vein Impedance Index, HVPT: Hepatic Vein Pulse Transit, L RIVI: Left Renal Interlobar Vein Impedance Index, L RVPT: Left Renal Interlobar Vein Pulse Transit, R RIVI: Right Renal Interlobar Vein Impedance Index, R RVPT: Right Renal Interlobar Vein Pulse Transit.

862 **Figure 1**

863 Flowchart from pregnancies included in the observational study as part of the Hasselt
864 University Study Project on Maternal Venous Hemodynamics. 1620 pregnant women were
865 classified based upon diagnosis in gestational hypertension (GH), late preeclampsia (LPE),
866 early preeclampsia (EPE), essential hypertension (EH), uncomplicated pregnancy (UP) with
867 or without small for gestational age (SGA) neonates. Assessments per patient were done in
868 the first, second or third trimester (1T, 2T, 3T resp.) alone or in multiple trimesters.

869

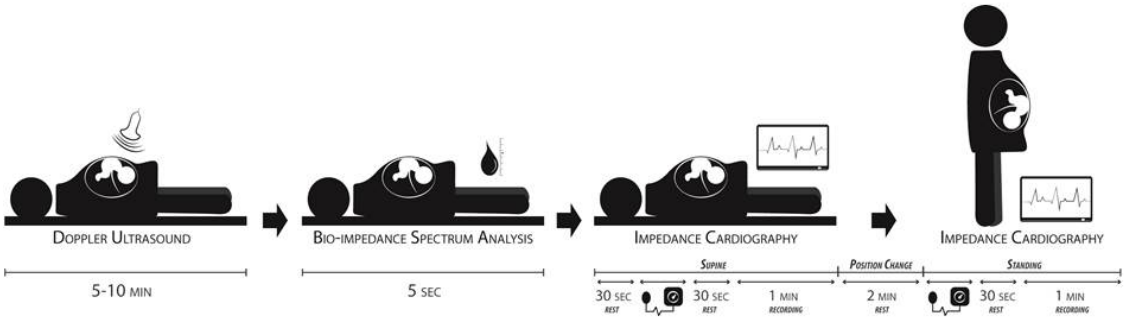


N assessments	1700	87	218	188
T1 only	333	0	12	6
T2 only	27	23	5	7
T3 only	113	42	131	86
T1+T2	537	6	12	21
T1+T3	3	1	2	5
T2+T3	18	1	3	5
T1+T2+T3	37	2	12	9

870

871

872 **Figure 2**



- Obstetric scan
- Uterine Arcuate Arteries
  - Pulsatility Index
  - Resistivity Index
- Hepatic Vein
  - Impedance Index
  - Pulse transit
- Renal Interlobar Vein
  - Impedance Index
  - Pulse transit

- Total Body Water
- Extracellular Water
- Intracellular Water
- Extra-/Intracellur Water

- Data not presented

- Blood Pressure
  - Systolic
  - Diastolic
  - Mean Arterial
- Cardiac function
  - Cardiac output
  - Heart rate
  - Stroke volume
- Central arterial function (aorta flow)
  - Velocity Index
  - Acceleration Index
- Total Peripheral Resistance

873

874

875

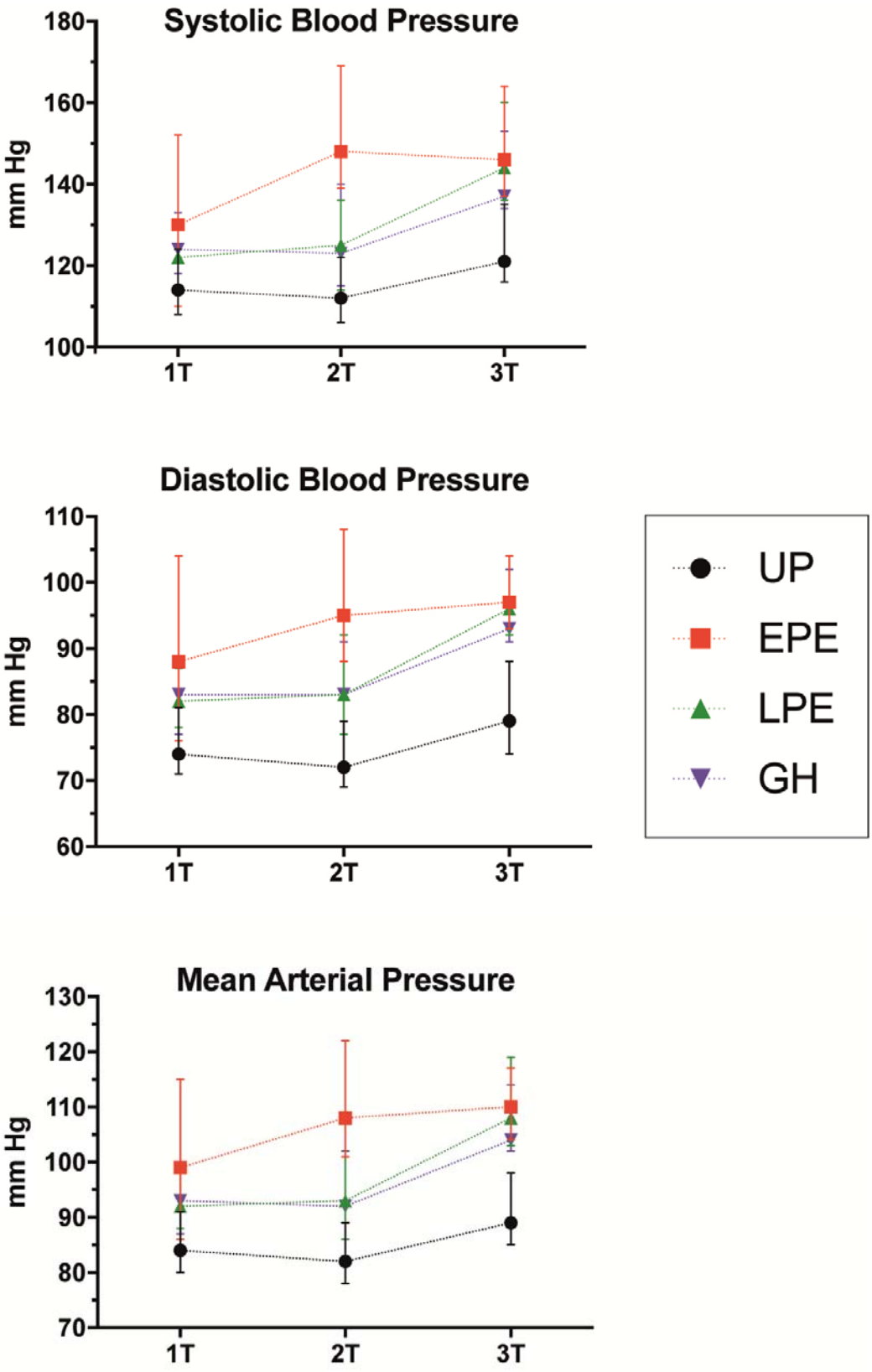
876

877

878

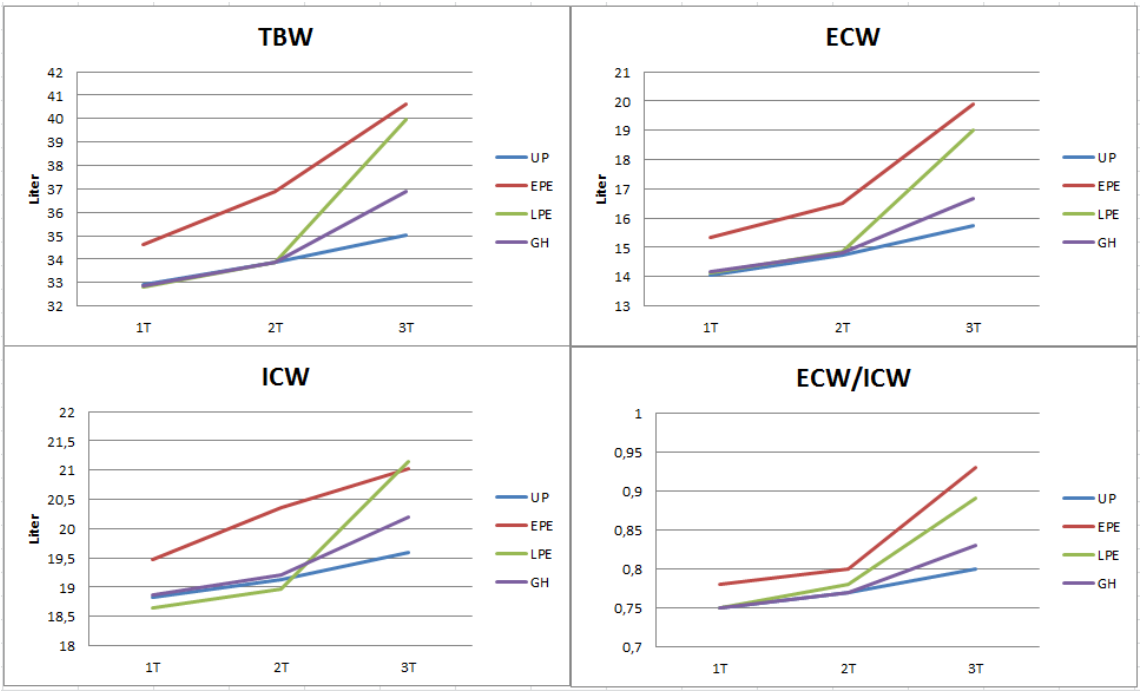
879

880 **Figure 3**



881

882 **Figure 4**



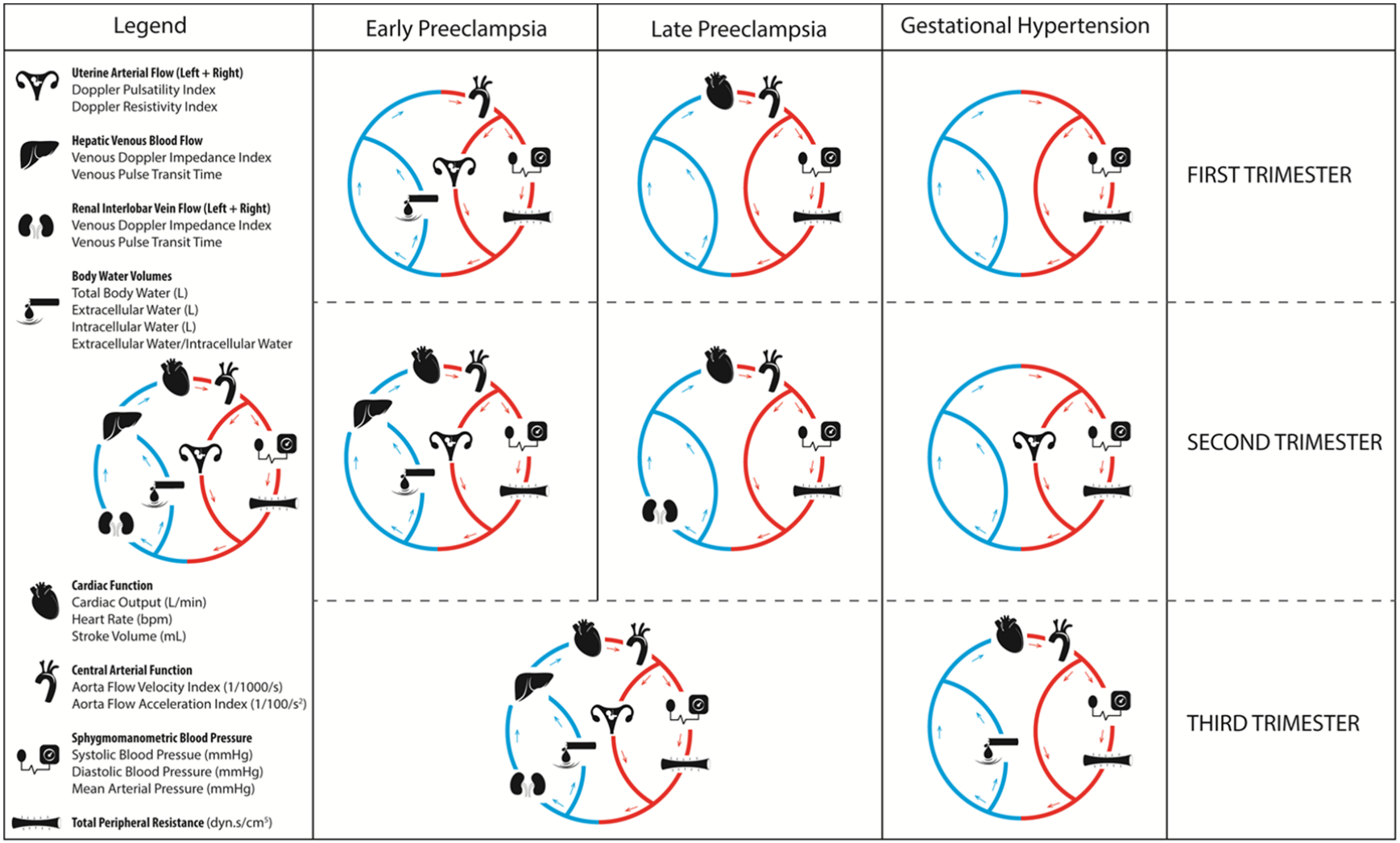
883

884

885

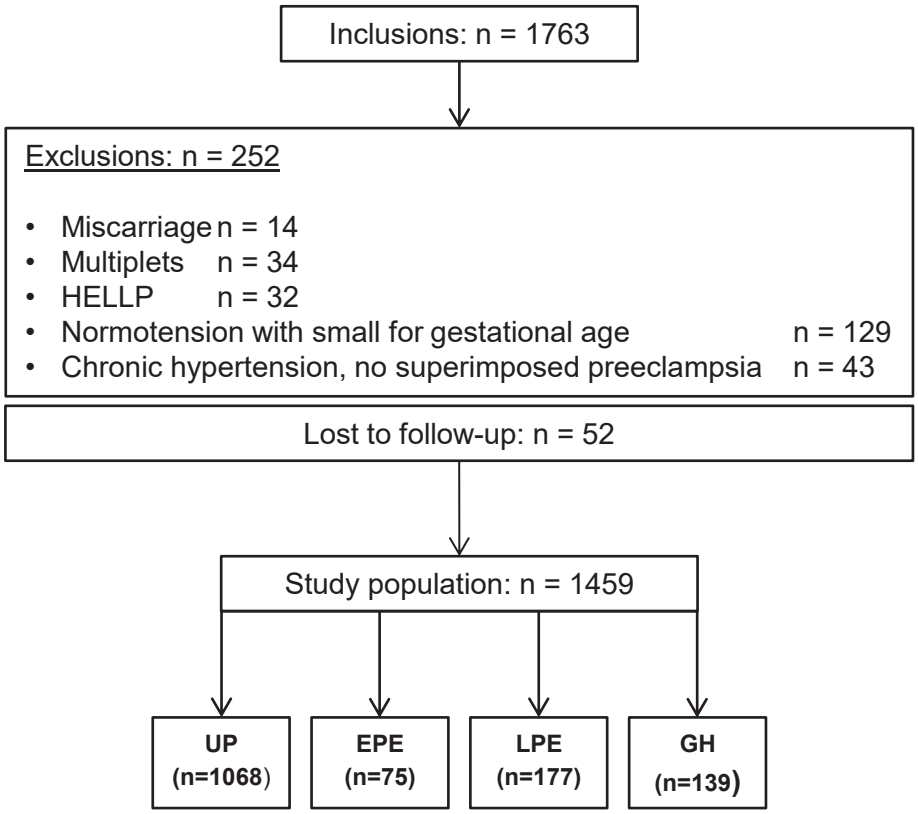
886

887 **Figure 5**

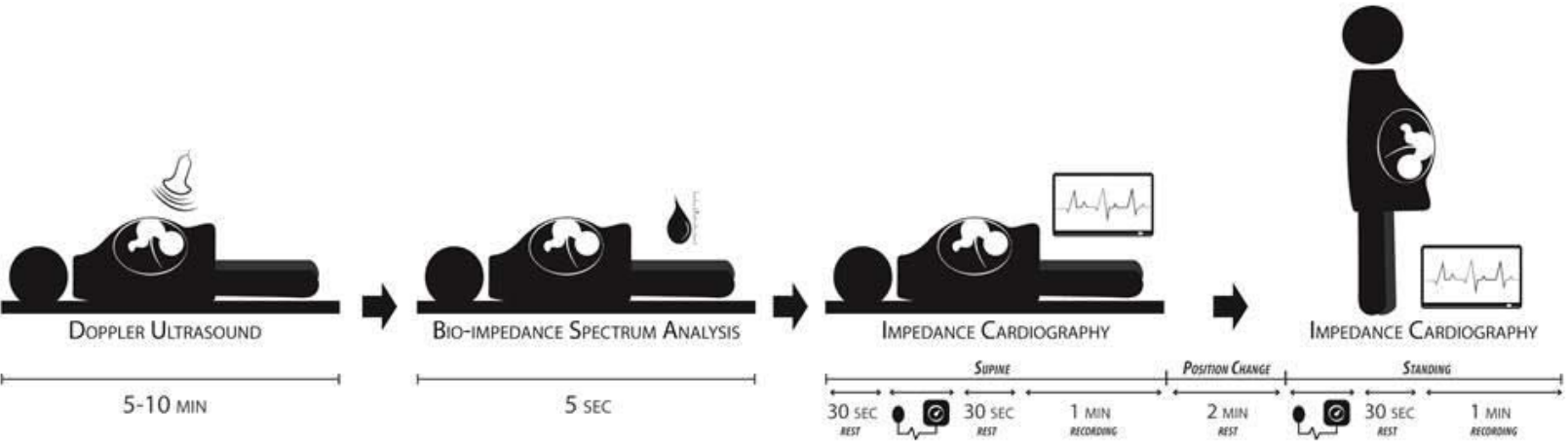


888

889



N assessments	1700	87	218	188
T1 only	333	0	12	6
T2 only	27	23	5	7
T3 only	113	42	131	86
T1+T2	537	6	12	21
T1+T3	3	1	2	5
T2+T3	18	1	3	5
T1+T2+T3	37	2	12	9



- Obstetric scan
- Uterine Arcuate Arteries
  - Pulsatility Index
  - Resistivity Index
- Hepatic Vein
  - Impedance Index
  - Pulse transit
- Renal Interlobar Vein
  - Impedance Index
  - Pulse transit

- Total Body Water
- Extracellular Water
- Intracellular Water
- Extra-/Intracellur Water

- Data not presented

- Blood Pressure
  - Systolic
  - Diastolic
  - Mean Arterial
- Cardiac function
  - Cardiac output
  - Heart rate
  - Stroke volume
- Central arterial function (aorta flow)
  - Velocity Index
  - Acceleration Index
- Total Peripheral Resistance