

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

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

**Brief title:** Pathophysiology of GHD

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**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

25 **Abstract (1 paragraph, 250w max)**

26 A combined assessment of heart, arteries, veins and body fluid content throughout  
27 pregnancy has not yet been reported. We hypothesized that a gradual aggravation of  
28 circulatory dysfunction exists from latent to clinical phase of gestational hypertensive  
29 disease (GHD), and that pathways are unique for preeclampsia with early-onset <  
30 34w (EPE), late-onset  $\geq$  34w (LPE) and gestational hypertension (GH). Women with  
31 singleton pregnancy and no known diseases were invited for a prospective,  
32 observational study and had standardized sphygmomanometric blood pressure  
33 measurement, bioimpedance body water spectrum analysis, impedance  
34 cardiography for cardiac and arterial assessment and combined Doppler-ECG of  
35 hepatic and renal interlobar veins and uterine arteries. Outcome was categorized as  
36 uncomplicated (UP, n = 1700), EPE (n = 87), LPE (n = 218) or GH (n = 188). A linear  
37 mixed model for repeated measurements, corrected for age, parity and body mass  
38 index, was employed in SAS 9.4 to analyze trimestral changes within and between  
39 groups. From 1<sup>st</sup> to 3<sup>rd</sup> trimester, body water increased in all groups, and an  
40 increasing number of abnormal parameters relative to UP occurred in all GHD. First  
41 trimester blood pressure and peripheral resistance were higher in GHD than UP,  
42 together with increased uterine flow resistance and extracellular water in EPE, and  
43 with lower heart rate and aorta flow velocity in LPE. An overall gestational rise of  
44 body water volumes co-exists with a gradual worsening of cardiovascular dysfunction  
45 in GHD, of which pathophysiologic pathways are unique for EPE, LPE and GH  
46 respectively.

47 **Keywords:** Maternal hemodynamics, gestational hypertensive disease, gestational  
48 hypertension, preeclampsia, pathophysiology

49

## 50 **Introduction**

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

75 (66). It is generally accepted that these changes are triggered by a uniform  
76 vasodilatation and relative hypovolemia, with subsequent activation of volume  
77 restoring mechanisms, eventually leading to an expanded intravascular volume (15).  
78 The increase of circulating volume and cardiac output are needed for an adequate  
79 blood supply to the pregnant uterus and its contents, without compromising the  
80 perfusion of other organs. A large proportion of women with uncomplicated term  
81 pregnancies however show echocardiographic signs of chronic volume overload (34).  
82 This illustrates that the gestational volume expansion is an important stressor for a  
83 pregnant woman's cardiovascular system. Inadequate plasma volume expansion has  
84 been reported in pregnancies complicated with hypertension and/or poor fetal growth  
85 (11, 48, 49). Although plasma volume, as a fraction of total body water content, is in  
86 constant equilibrium with other body fluid compartments, very few research has been  
87 done on gestational changes of intra- and extracellular body water compartments  
88 (31, 55, 62).

89 Between 5 – 10 % of pregnancies worldwide are complicated with hypertension,  
90 involving both chronic hypertension and new onset gestational hypertensive disease  
91 (GHD), depending on presentation before or after 20 weeks of gestation respectively.  
92 GHD are classified as (a) early onset (EPE) or (b) late onset preeclampsia (LPE)  
93 when maternal renal, hepatic and/or other organ dysfunctions present already before  
94 or after 34 weeks of gestation respectively, or (c) gestational hypertension (GH) when  
95 no maternal organ dysfunctions are present (7). The two types of preeclampsia have  
96 also been labeled placental (early onset) or maternal (late onset) preeclampsia (18,  
97 39, 43, 50, 56), or high output and low output preeclampsia (58). Today, the  
98 circulatory pathophysiologic pathways explaining the different clinical presentations of  
99 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 ( $\geq 28$  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  $\geq 300\text{mg}/24\text{h}$ , other organ dysfunction or fetal growth restriction, labelled as early-onset at clinical presentation  $< 34$  weeks (EPE) and late-onset at presentation  $\geq 34$  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  $< 10\text{th}$  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  $HR \times SV$ . (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  $1/100/s^2$ . (c) Total Peripheral Resistance (TPR) is calculated as  $MAP \times 80/CO$  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 rebound 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 rebounding A-wave propagates through the

venous system. As heart rate varies during the course of gestation, VPT is expressed as a fraction of heart rate, measured as the time interval in msec between the consecutive ECG R-waves of the corresponding heart cycle. As such, VPT is without units. VPT is considered the venous equivalent of arterial pulse transit time (or pulse wave velocity), and is inversely related to vascular wall stiffness: the shorter this time interval, the faster and more distant the rebound of atrial contraction travels in retrograde direction through the central veins (27, 66). Venous vascular stiffness depends on vaso-activity from autonomic nervous system induced or endothelium dependent smooth muscle contraction, as well as on (micro-) structural composition of the different layers of the vascular walls (19).

At the venous side, the maximum and minimum flow velocity is measured at the level of the renal interlobar and hepatic veins as explained elsewhere (25, 26). Venous flow velocities depend on the pressure gradient relative to the right atrium, intravascular filling, vascular tone and external compression (20). A venous impedance index is calculated using the formula  $[(\text{Maximum Velocity} - \text{Minimum Velocity}) / \text{Maximum velocity}]$  (26). Venous impedance index is the venous Doppler equivalent arterial PI, representing the intra-cycle variability of blood flow velocities in the veins.

## **Statistics**

An independent t-test at 5% significance level was used for intergroup comparison of continuous demographic data. Chi-square test was used for categorical demographic variables. Normality was checked via Shapiro-Wilk. Data were presented as mean  $\pm$  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  $\geq 140$  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 1<sup>st</sup> and 2<sup>nd</sup> trimester EPE ( $p =$

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

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

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

Figure 5 presents visually the abnormal functioning of different circulatory components per trimester in each type of GHD. As is show, EPE presents in the first trimester with higher values than UP for blood pressure, total peripheral resistance, uterine artery resistance and extracellular water volume, and this is associated with reduced Aorta flow velocities. In the second trimester, reduced cardiac output and hepatic vein pulse transit are added, as well as increased hepatic vein impedance index. Finally, in the third trimester, also left and right renal impedance index are 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 1<sup>st</sup> 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



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

380 Our analysis sheds a new light on the circulatory pathophysiology of GHD. It is  
381 generally accepted that in uncomplicated pregnancy, an early postconceptional  
382 vasodilatation is responsible for a condition of intravascular underfilling (16),  
383 triggering volume expansion mechanisms (15, 16). The intravascular refill leads to a  
384 state of chronic volume overload, pushing the pregnant woman's cardiovascular  
385 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

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

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

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## **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.

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477 **Conflicts of Interest/Disclosures**

478 Other authors declare no conflict of interest.

479

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## 687 **Figure Legends**

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

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

703 Figure 3: Systolic, diastolic, mean arterial and pulse pressure in first (1T), second  
704 (2T) and third trimester (3T) in uncomplicated pregnancies (UP) and those  
705 complicated with early onset preeclampsia (EPE), late onset preeclampsia (LPE) and  
706 gestational hypertension (GH). Data are presented as Least Square Mean of BMI-,  
707 age and parity-corrected values, inside the interquartile ranges of raw data.

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

early onset preeclampsia (EPE), late onset preeclampsia (LPE) and gestational hypertension (GH).

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



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

728	Parameter	Technology	Units	Thresholds, range	Interpretation
729	<b><u>Pressures</u></b>				
730					
731	Systolic BP	Automated Sphyngomanometer	mm Hg	cut off 140	> 140 mm Hg = hypertension > UP = abnormal
732					
733					
734	Diastolic BP		mm Hg	cut off 90	> 90 mm Hg = hypertension >UP = abnormal
735					
736					
737	Mean Art BP		mmm Hg	DBP + (SBP-DBP)/3	> UP = abnormal
738					
739	<b><u>Volumes</u></b>				
740					
741	Total Body Water	Bioimpedance Spectrum Analysis	Liter	Table 3-5	> UP = abnormal
742					
743	Extracellular water		Liter	Table 3-5	> UP = abnormal
744					
745	Intracellular water		Liter	Table 3-5	> UP = abnormal
746					
747	ECW/ICW			Table 3-5	> UP = abnormal
748					
749					

750

751	<b><u>Cardiac function</u></b>				
752					
753	Stroke Volume	Impedance	mL	Table 3-5	< UP = abnormal
754		Cardiography			
755	Heart rate		Beats/min	Table 3-5	< or > UP = abnormal
756					
757	Cardiac output		L/min	Table 3-5	< or > UP = abnormal
758					
759					
760	<b><u>Central Arterial function</u></b>				
761					
762	Velocity Index	Impedance	1/1000/s	Table 3-5	< UP = abnormal
763		Cardiography			
764	Acceleration Index		1/100/s <sup>2</sup>	Table 3-5	< UP = abnormal
765					
766					
767	<b><u>Total Peripheral Resistance</u></b>				
768					
769		Impedance	dyn.s/cm <sup>5</sup>	Table 3-5	> UP = abnormal
770		Cardiography			
771					
772					
773	<b><u>Uterine Artery Flow</u></b>				
774					
775	Pulsatility Index	Doppler	/	Table 3-5	> UP = abnormal
776		Sonography			
777	Resistivity Index		/	Table 3-5	> UP = abnormal
778					
779					
780					

781	<b><u>Hepatic Venous Flow</u></b>				
782					
783	Impedance Index	ECG-Doppler	/	Table 3-5	> UP = abnormal
784		Sonography			
785	Pulse Transit		/	Table 3-5	< UP = abnormal
786					
787					
788					
789					
790					
791	<b><u>Renal Interlobar Venous flow</u></b>				
792					
793	Impedance Index	ECG-Doppler	/	Table 3-5	> UP = abnormal
794		Sonography			
795	Pulse Transit		/	Table 3-5	< UP = abnormal
796					
797					
798					
799					

800

801 Legend: BP: Blood Pressure, SBP: Systolic blood pressure, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure, > UP: significantly higher  
802 than in uncomplicated pregnancies, < UP: significantly lower than in uncomplicated pregnancies, ECG: Electrocardiogram,  
803

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)
<b>Characteristics at inclusion</b>				
Maternal age (years)	30.4±5.9	30.3±5.3	30.0±5.2	30.2±4.4
Gestational age at assessment (weeks)				
<i>First trimester</i>	12.2±0.8	12.9±0.5*	11.8±0.8*	12.2±0.7
<i>Second trimester</i>	20.7±1.6	25.2±2.3*	22.0±2.3*	21.5±2.7*
<i>Third trimester</i>	33.4±3.2	31.5±1.5*	36.7±2.4*	36.8±2.7*
Pre-pregnancy BMI (kg/m <sup>2</sup> )	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)*
<b>Outcome characteristics</b>				
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 ( $\Delta$ UP)

		UP		EPE			LPE			GH		Legend		
		LSMean	IQR	$\Delta$ UP	P (UP)	P (GHD)	$\Delta$ UP	P	P (GHD)	$\Delta$ 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/s <sup>2</sup>	173	125-198	-24,233	0,034	□ ○	-12,683	0,046	∞	-2,165	0,719			
TPR	dyn.s/cm <sup>5</sup>	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			

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

		UP		EPE			LPE			GH		Legend		
		LSMean	IQR	$\Delta$ UP	P (UP)	P (GHD)	$\Delta$ UP	P	P (GHD)	$\Delta$ 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/s <sup>2</sup>	177	131-209	-51,432	<0,001	•●	-29,603	<0,001	*	-7,026	0,25			
TPR	dyn.s/cm <sup>5</sup>	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			

835 Legend UP: Uncomplicated pregnancy, EPE: Early Onset Preeclampsia, LPE : Late onset Preeclampsia, GH: Gestational Hypertension, GHD: Gestational  
836 Hypertension Diseases,LSMean: Least Square Mean of age, parity and BMI corrected values, IQR: Interquartile Range of raw data,  $\Delta$ UP: mean numeric difference relative to  
837 UP, P(UP): significance level when compared with UP, P(GHD): significantly or not-significantly different from other GHD, labelled as:  $\blacktriangle$ : EPE-LPE difference,  $P<0.05$ ;  $\square$ :  
838 EPE-LPE difference not significant;  $\bullet$ : EPE-GH difference, $p<0.05$ ;  $\circ$ : EPE-GH difference not significant,  $*$ : LPE-GH difference, $p<0.05$ ;  $\infty$ : LPE-GH difference not significant,  
839 DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure, TBW: total body water volume, ECW:extracellular water volume, ICW: intracellular water volume, SV: Stroke  
840 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  
841 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  
842 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  
843 Interlobar Vein Pulse Transit, R RIVI: Right Renal Interlobar Vein Impedance Index, R RVPT: Right Renal Interlobar Vein Pulse Transit.  
844



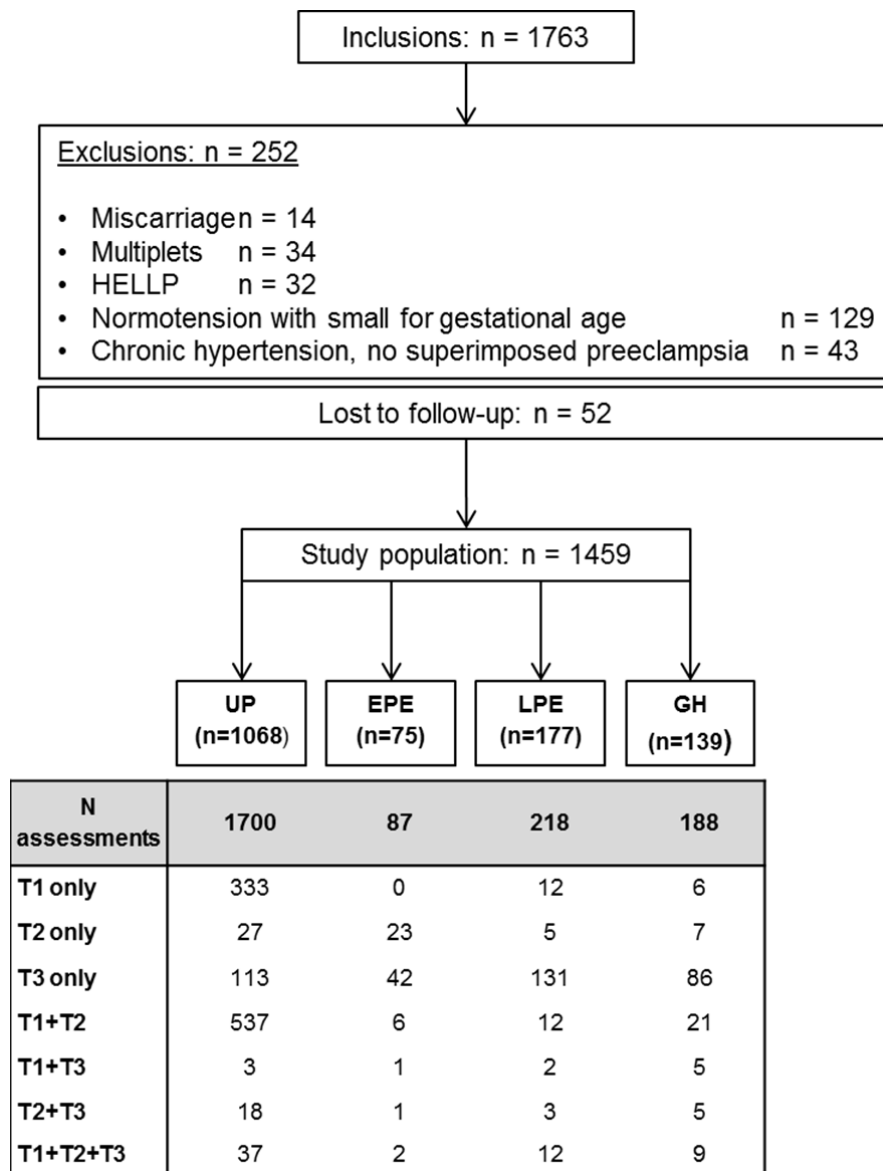
Table 5: Haemodynamic differences in third trimester of uncomplicated pregnancies compared with early (EPE) preeclampsia, late (LPE) and gestational hypertension (GH). Data for UP are presented as least-square means of BMI-, age- and parity-corrected values, together with Inter-Quartile Range of raw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

		UP		EPE			LPE			GH		Legend		
		LSMean	IQR	$\Delta$ UP	P (UP)	P (GHD)	$\Delta$ UP	P	P (GHD)	$\Delta$ 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/s <sup>2</sup>	157	97-166	-43,231	<0,001	□ ○	-36,467	<0,001	∞	-30,918	<0,001			
TPR	dyn.s/cm <sup>5</sup>	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			

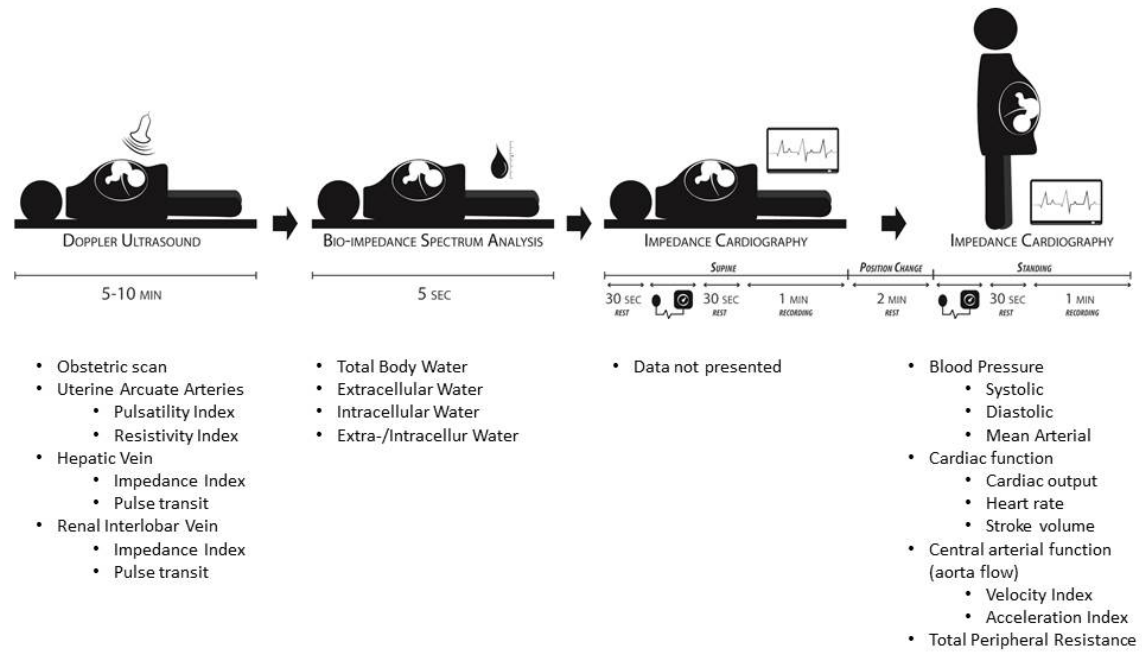
851 Legend UP: Uncomplicated pregnancy, EPE: Early Onset Preeclampsia, LPE : Late onset Preeclampsia, GH: Gestational Hypertension, GHD: Gestational  
 852 Hypertension Diseases,LSMean: Least Square Mean of age, parity and BMI corrected values, IQR: Interquartile Range of raw data,  $\Delta$ UP: mean numeric  
 853 difference relative to UP, P(UP): significance level when compared with UP, P(GHD): significantly or not-significantly different from other GHD, labelled as:  $\square$ :  
 854 EPE-LPE difference,  $P<0.05$ ;  $\square$ : EPE-LPE difference not significant;  $\bullet$ : EPE-GH difference,  $p<0.05$ ;  $\circ$ : EPE-GH difference not significant,  $*$ : LPE-GH  
 855 difference,  $p<0.05$ ;  $\infty$ : LPE-GH difference not significant, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure, TBW: total body water volume,  
 856 ECW:extracellular water volume, ICW: intracellular water volume, SV: Stroke Volume, HR: Heart Rate, CO: Cardiac Output, VI: Aorta Flow Velocity Index,  
 857 ACI: Aorta Flow Acceleration Index, TPR: Total peripheral Resistance, L Aut PI: Left Uterine Artery Doppler Pulsatility Index, L AUt RI: Left Uterine Artery  
 858 Doppler Resistivity Index, R Aut PI: Right Uterine Artery Doppler Pulsatility Index, R AUt RI: Right Uterine Artery Doppler Resistivity Index, HVI: Hepatic Vein  
 859 Impedance Index, HVPT: Hepatic Vein Pulse Transit, L RIVI: Left Renal Interlobar Vein Impedance Index, L RVPT: Left Renal Interlobar Vein Pulse Transit, R  
 860 RIVI: Right Renal Interlobar Vein Impedance Index, R RVPT: Right Renal Interlobar Vein Pulse Transit.  
 861

## Figure 1

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



872 **Figure 2**



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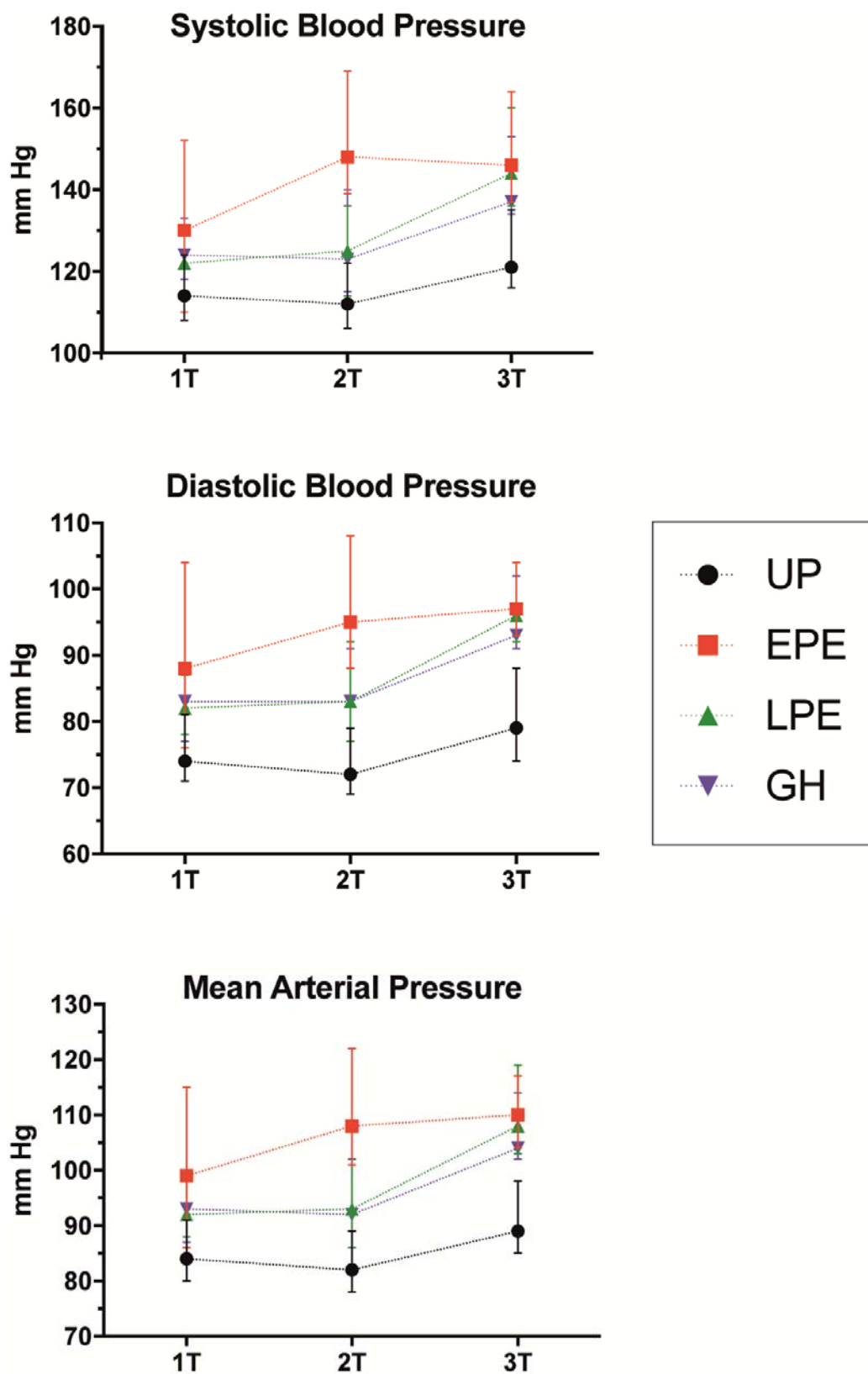
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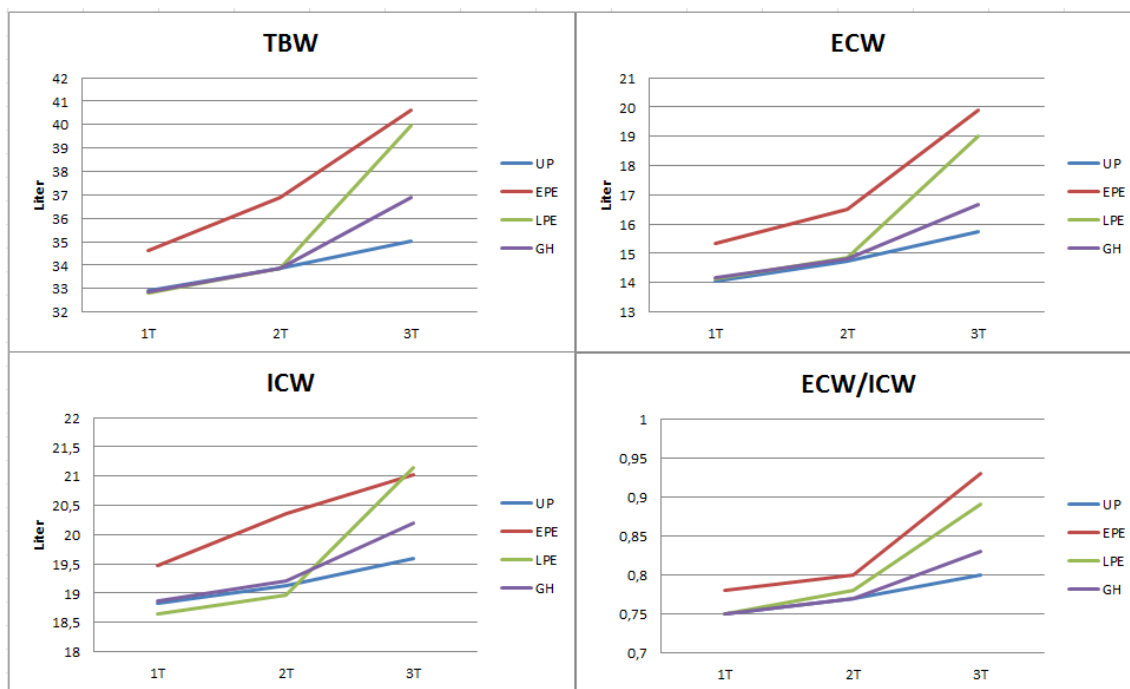
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880 **Figure 3**

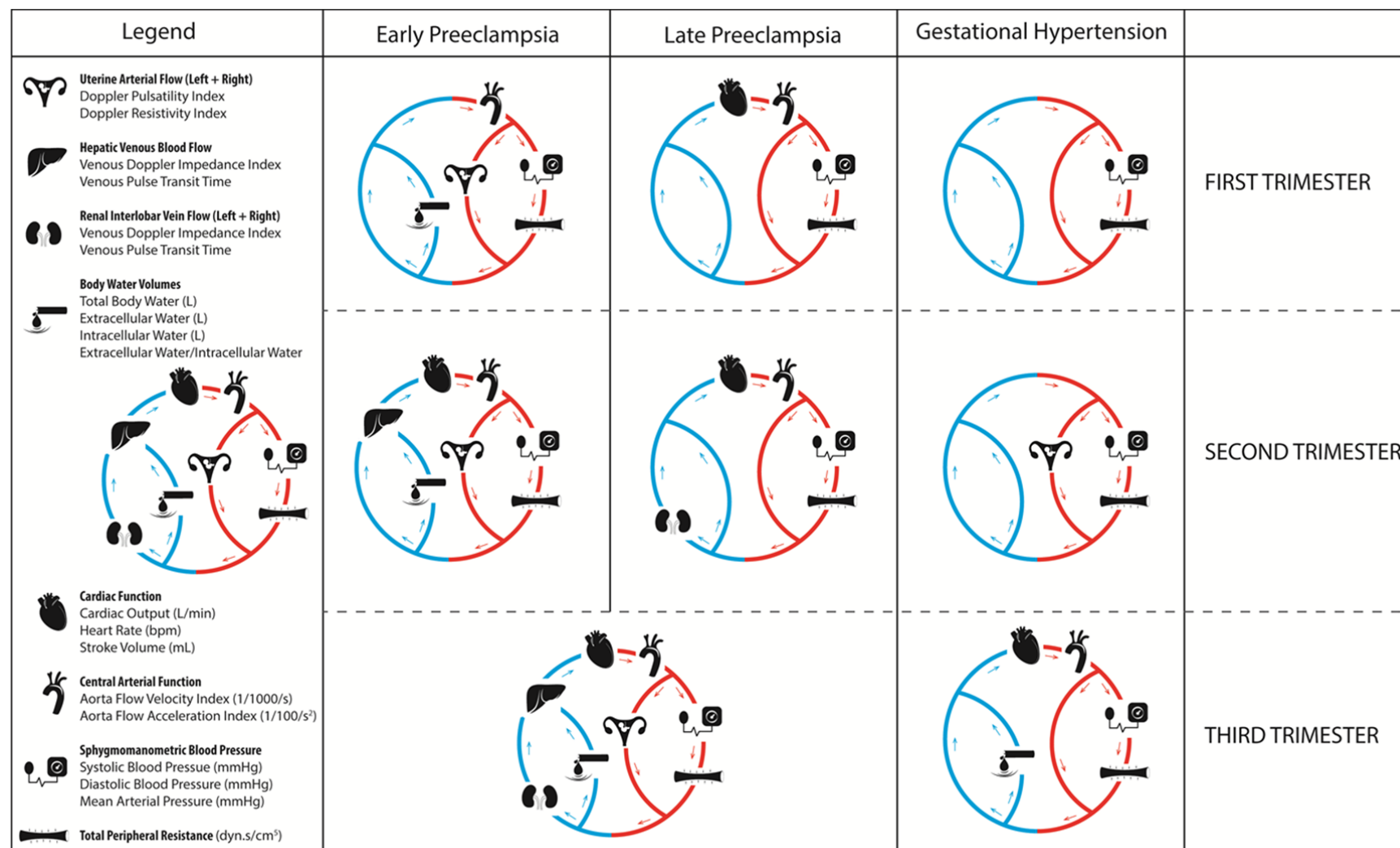


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882 **Figure 4**

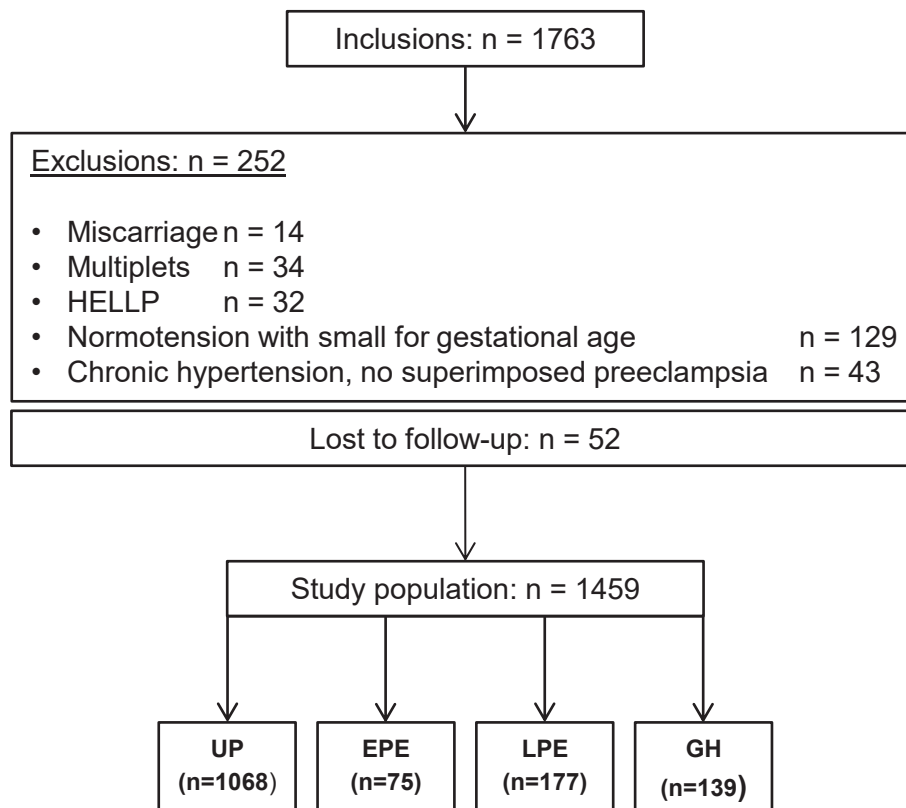


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**Figure 5**

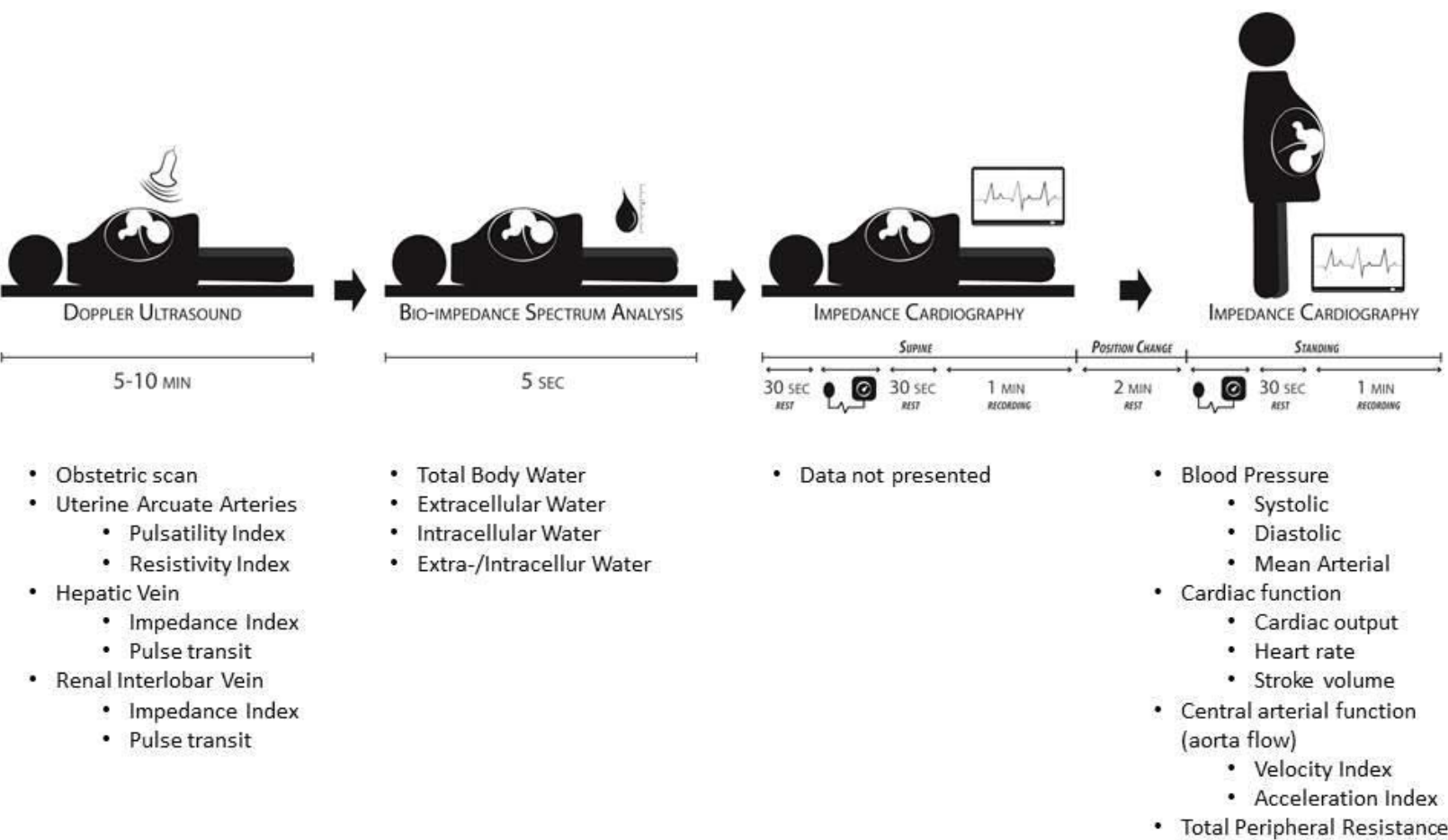
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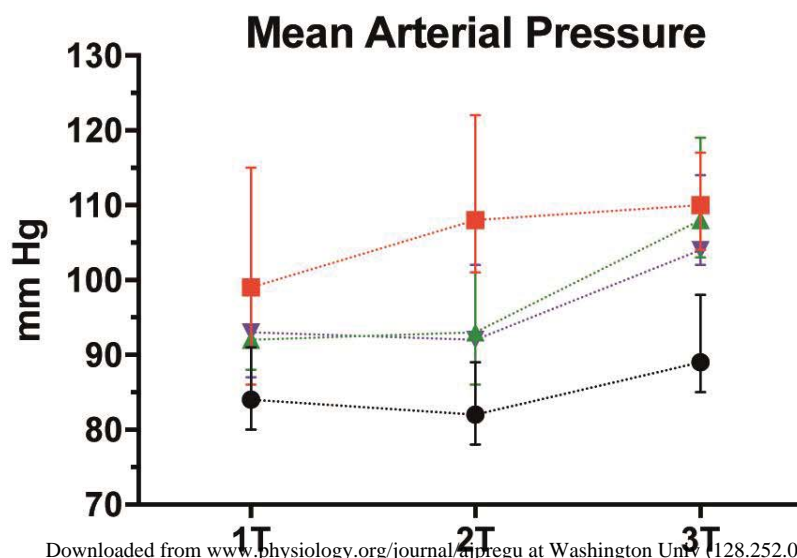
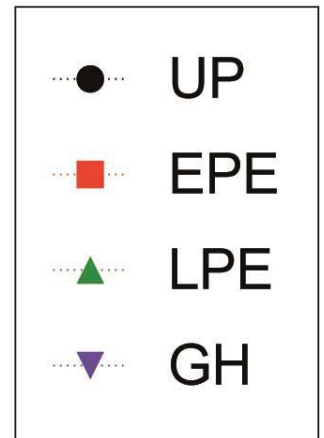
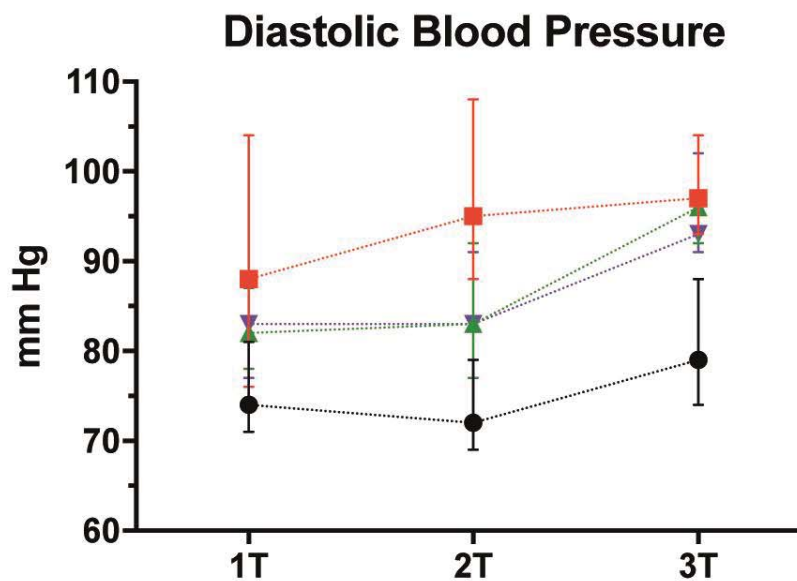
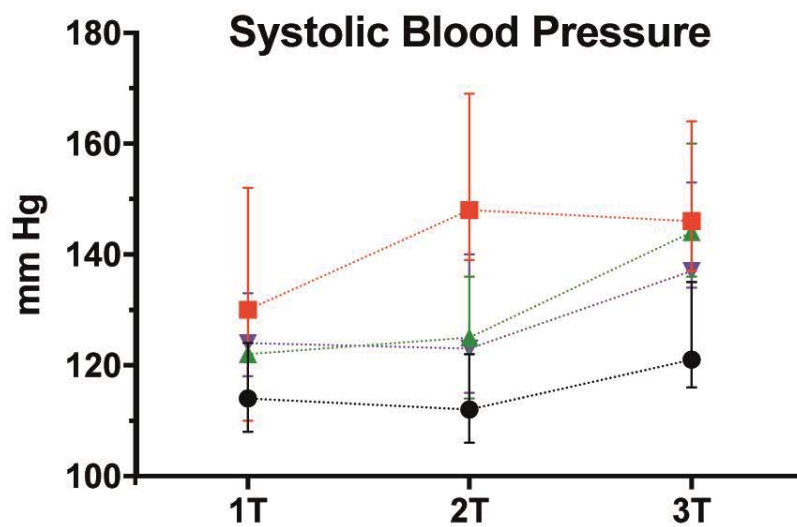
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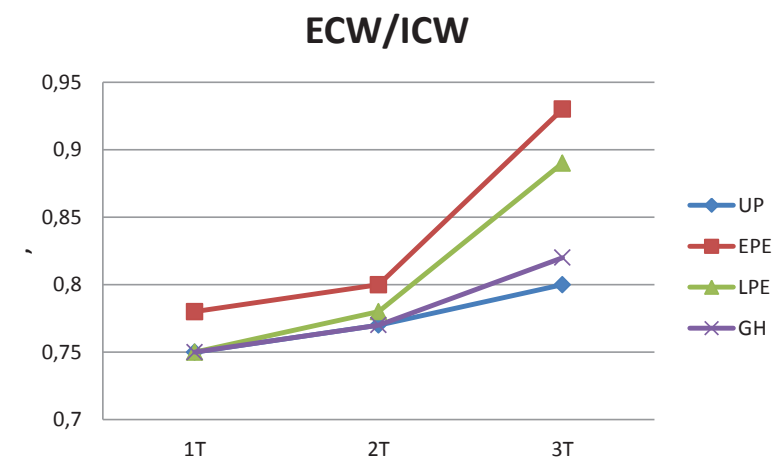
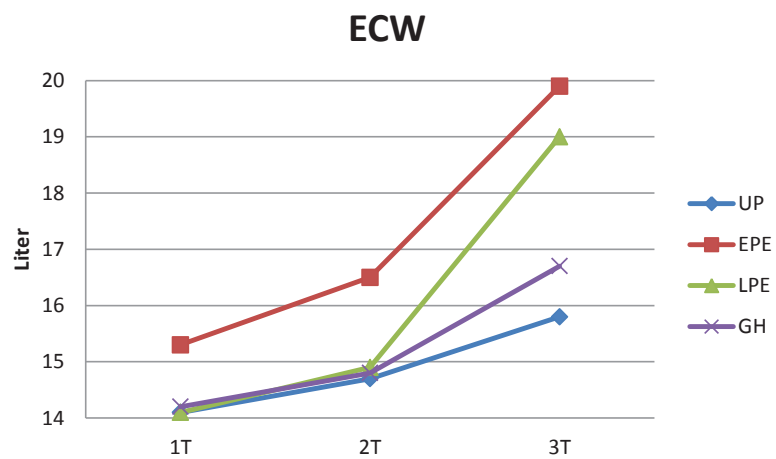
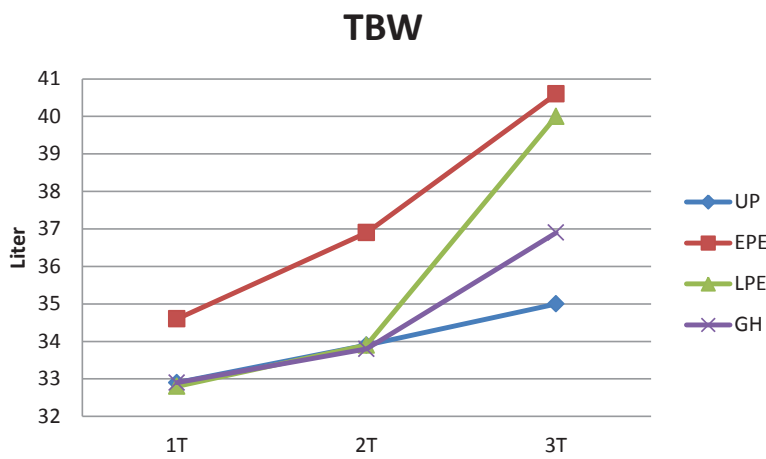










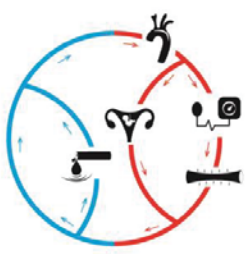
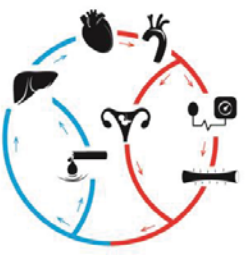
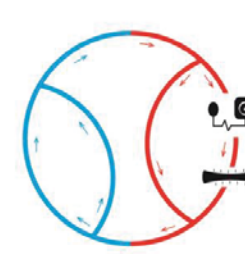
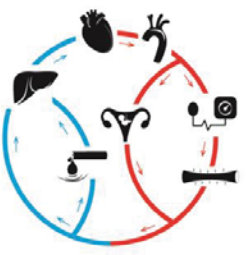
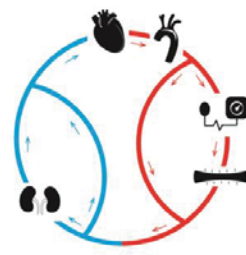
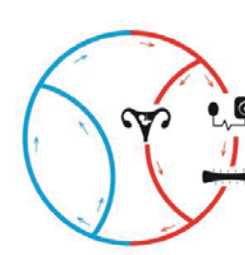
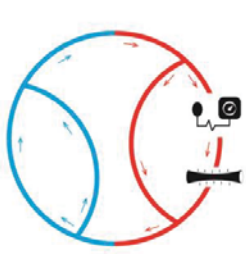
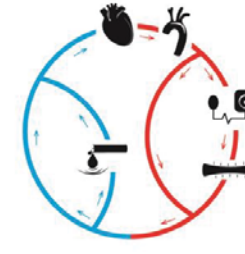
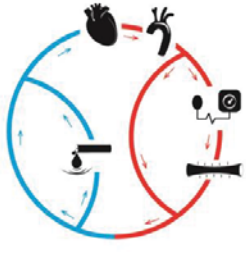
N assessments	1700	87	218	188
T1 only	333	0	12	6
T2 only	27	23	5	7
T3 only	113	42	131	86
T1+T2	537	6	12	21
T1+T3	3	1	2	5
T2+T3	18	1	3	5
T1+T2+T3	37	2	12	9









Legend	Early Preeclampsia	Late Preeclampsia	Gestational Hypertension	
 <b>Uterine Arterial Flow (Left + Right)</b> Doppler Pulsatility Index Doppler Resistivity Index   <b>Hepatic Venous Blood Flow</b> Venous Doppler Impedance Index Venous Pulse Transit Time   <b>Renal Interlobar Vein Flow (Left + Right)</b> Venous Doppler Impedance Index Venous Pulse Transit Time   <b>Body Water Volumes</b> Total Body Water (L) Extracellular Water (L) Intracellular Water (L) Extracellular Water/Intracellular Water   <b>Cardiac Function</b> Cardiac Output (L/min) Heart Rate (bpm) Stroke Volume (mL)   <b>Central Arterial Function</b> Aorta Flow Velocity Index (1/1000/s) Aorta Flow Acceleration Index (1/100/s²)   <b>Sphygmomanometric Blood Pressure</b> Systolic Blood Pressure (mmHg) Diastolic Blood Pressure (mmHg) Mean Arterial Pressure (mmHg)   <b>Total Peripheral Resistance (dyn.s/cm⁵)</b>	  	  	  	<p>FIRST TRIMESTER</p> <p>SECOND TRIMESTER</p> <p>THIRD TRIMESTER</p>