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LIST OF ABBREVIATIONS

ACI	acceleration index
ACOG	American congress of obstetricians and gynecologists
AGA	appropriate for gestational age
Aix	augmentation index
APTT	arterial pulse transit time
AUC	area under the curve
BMI	body mass index
BW%	birth weight percentile
CO	cardiac output
DBP	diastolic blood pressure
ECG	electrocardiogram
ECG-D	electrocardiogram-Doppler
ECW	extracellular water
EDD	end-diastolic dimension
EH	essential hypertension
EPE	early preeclampsia
ESD	end-systolic dimension
FPR	false positive ratio
GFR	glomerular filtration rate
GH	gestational hypertension
GHD	gestational hypertensive disorders
hCG	human chorionic gonadotropin
HELLP	haemolysis elevated liver enzymes and low platelets
HI	heather index
HP	hypertensive pregnancies
HR	heart rate
HVI	hepatic vein impedance index
ICG	impedance cardiography
ICW	intracellular water
IQR	interquartile range
ISSHP	International Society for Studies of Hypertension in Pregnancy
IUGR	intra-uterine growth restriction
LAD	left atrial dimension
LPE	late preeclampsia
LR	likelihood ratio
LVET	left ventricular ejection time
MAP	mean arterial pressure
MVAS	mitral valve annulus shortening
NGA	non-SGA
NICCOMO	non-invasive continuous cardiac output monitor
NP	normotensive pregnancies
PAPP-A	pregnancy-associated plasma protein A
PA/RR	venous pulse transit time
PE	preeclampsia
PEP	pre-ejection period
PI	pulsatility index
PlGF	placental growth factor
PP	pulse pressure
PWV	pulse wave velocity

QD/RR	arterial pulse transit time
RAAS	renin-angiotensin-aldosterone system
RFXP1	relaxin/insulin-like family peptide 1 receptor
RI	resistivity index
RIVI	renal interlobar vein impedance index
ROC	receiver operator curves
RPF	renal plasma flow
SBP	systolic blood pressure
sFlt-1	soluble FMs-like tyrosine kinase-1
SGA	small for gestational age
SV	stroke volume
TAC	total arterial compliance
TBW	total body water
TFC	thoracic fluid content
TPR	total peripheral resistance
UFP	uterine flow promoting
UP	uncomplicated pregnancy
UFPPR	uterine flow promoting peripheral resistance
VI	velocity index
VPTT	venous pulse transit time
ZOL	ziekenhuis oost-limburg

GENERAL INTRODUCTION

GENERAL INTRODUCTION

In 2015, approximately 65,000 deliveries occurred in Flanders, from which 4.6% were complicated by hypertension during pregnancy[1]. Hypertension in pregnancy involves important maternal consequences on the one hand, such as transient hypertension, risk of cardiac arrest and stroke, risk of renal failure or liver failure. On the other hand, it causes neonatal consequences, including preterm birth, low birth weight, respiratory distress syndrome or brain disorders. In later life, those children are prone to heart diseases, diabetes, metabolic syndrome, and in case of female offspring: their future pregnancies could also be complicated with hypertension or foetal growth restrictions. When untreated, this might lead to perinatal or maternal death[2,3].

Hypertension in pregnancy covers 3 types: essential/chronic hypertension (EH), gestational hypertension (GH) and preeclampsia (PE). According to the criteria revised by the International Society for Studies of Hypertension in Pregnancy (ISSHP), EH is defined as high blood pressure (>140/90 mmHg) detected before conception or developed in the first 20 weeks of gestation. GH is a condition wherein blood pressures are elevated above 140/90 mmHg, measured twice with 6h in between, after 20 weeks of gestation. Both conditions are sensitive to evolve to PE, which is a disease wherein hypertension is accompanied with protein loss (>300mg/24h)[4,5]. Preeclampsia diagnosed before 34 weeks is defined as early preeclampsia (EPE), thereafter it is defined as late preeclampsia (LPE)[5]. EPE is commonly known as the 'placental' type, triggered by a problem of trophoblast implantation and placentation, and is often associated with intra uterine growth restriction (IUGR, birth weight percentile $\leq$10)[6-8], contrary to the 'maternal' type (LPE) which is triggered by pre-existing maternal constitutional factors (obesity, age, diabetes, etc.), and has generally no foetal growth involvement[7].

A pregnancy initiates a physiological cascade where maternal cardiovascular adaptations play a prominent role. These events are initiated shortly after embryo implantation and are especially important in the first weeks of gestation, laying the fundaments for the second half of pregnancy[9]. Gestational hypertensive disorders are the consequence of cardiovascular maladaptations

occurring in the first trimester. The maternal hemodynamics differ in each pregnancy trimester from the normal cardiovascular system and aberrations become more prominent when disease onset approaches[10-17]. The exact trigger for those maladaptations is however not exactly known. Currently, the most appreciated hypothesis is that endothelium dysfunction is generated by a defective trophoblastic invasion which leads to oxidative stress and inflammation. This event provokes an increased vascular resistance in the first weeks of gestation, and thus already subclinical higher blood pressures. During pregnancy, multiple deficits could be measured at the level of arteries, veins and heart which is an indistinguishable circuit influencing each other constantly. Unfortunately, there are still too many question marks in this physiological process[18-20].

General cardiovascular assessments, as used in the field of cardiology, are usually executed with validated standard techniques, which are either invasive (pulmonary artery catheterization or Fick technique) or need high-level intensive training (pulmonary artery catheterization, echocardiography) and are therefore not completely appropriate in a pregnant population, seen its risky character and lack of specific experience in obstetricians[21]. Still, measuring the maternal cardiovascular adaptations during pregnancy is necessary to understand its physiology, both in normal pregnancies and pathological pregnancies. It is best to seek and apply different non-invasive techniques, which are absolute safe for mother and foetus, and it should be able to measure multiple levels of the maternal circulation in order to understand the function of each compartment and its relation to each other. The last few decades, several research groups introduced and validated valuable and feasible techniques to apply in pregnant women. First, a combined exam of electrocardiogram (ECG) with Doppler ultrasonography, measuring the vascular compartment (arterial and venous function)[12,22,23]. Second, multiple parameters of the heart could be measured through Impedance Cardiography (ICG) or the gold-standard echocardiography[21,24,25]. At last, a notion of body composition and fluid balance could be derived through bio-impedance or plasma volume dilution[26,27]. The impedance techniques are subject to criticism as not being a suitable alternative for the more validated echocardiography or biomarker dilution, however the results are shown to be in line with these gold-standard methods[21,25,28].

Impedance techniques are simple, safe, cheap and not time-consuming, contrary to echocardiography or plasma volume dilution[29]. A main disadvantage of bio-impedance is the lack of an exact plasma volume assessment. Total body water is measured, which includes plasma volume together with interstitial and transcellular water, and gives only an assumed notion of plasma volume.

Currently, there are 2 major problems. First, a lot of cardiovascular research is done during pregnancy to elucidate the physiology of hypertension in pregnancy. However, no-one combines different techniques to assess the complete maternal circulation, or the research is only done in one or two trimesters, which leads only to partial explanations. To cover this problem, our research group uses a combination of 3 standardized and validated techniques (ECG-Doppler ultrasonography, impedance cardiography and bio-impedance) to assess the complete cardiovascular system. A protocol is used wherein measurements of first, second and/or third trimester are included. Second, multiple efforts are done to translate the cardiovascular research to clinic. A standard cardiovascular investigation in a pregnant woman should deserve more attention, but it still lacks standardized methods or the explanatory link with basic physiology. A validated screening method would reduce the risk for hypertension, but only a biomarker model is currently available. The performance has good results for detecting EPE, which is no solution for the other 2/3rd of the potential hypertensive cases. Seen all of them are burdened with cardiovascular maladaptations in some degree, it would be favourable to use these as fundaments for a predictive test. This knowledge has also benefit for therapeutic interventions, as a hemodynamics-tailored therapy is a direct advantage.

PROTOCOL

Over the past years, our research group has examined multiple non-invasive, easy applicable and safe cardiovascular techniques and its usefulness in the field of obstetrics. To cover the most important parts of the maternal circulation, we use (1) ECG-Doppler ultrasound for venous and arterial measurements, (2) Impedance Cardiography for heart function estimates and (3) Bio-impedance for fluid parameters in our current protocol.

(1) ECG-Doppler ultrasound

The maternal renal interlobar veins (above the hilus), hepatic veins of the cranio-caudal part and arcuate branches of uterine arteries were evaluated using a 3.5 MHz transabdominal probe in supine position. Three consecutive measurements per organ were done during interrupted breathing and averaged afterwards. The derived parameters could be divided in two groups (Figure 0.1):

1. Pulse transit times (PTT)
   - **Venous** PTT (VPTT): Time interval between the P-top of the ECG and the A-wave of the pulse wave (PA), corrected for heart rate (RR). *Formula:* $\frac{PA}{RR}$
     This represents the atrial contraction.
   - **Arterial** PTT (APTT): Time interval between the Q-wave of the ECG and the end-diastolic point (QD), corrected for heart rate (RR). *Formula:* $\frac{QD}{RR}$
     This represents the start of systole.

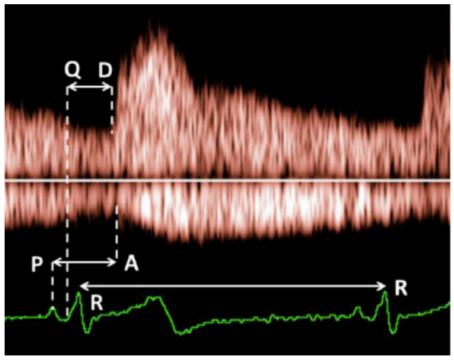

Figure 0.1: Combined ECG-Doppler ultrasound. PA: venous pulse transit time, i.e. the time interval between points P and A of the ECG and Doppler waves resp., both representing atrial contraction. QD: arterial pulse transit time, i.e. time interval between points Q and D of the ECG and Doppler resp., both representing start of systole. RR: ECG wave duration, i.e. time interval corresponding to heart rate.

2. Impedance indices

- **Vein** index (Renal interlobar vein index (RIVI), hepatic vein index (HVI)) *Formula:* $\frac{(Maximum\ Velocity - Minimum\ Velocity)}{Maximum\ Velocity}$

This represents the venous resistance to blood flow.

- **Arterial** index (Pulsatility index (PI), resistivity index (RI))

Formula PI: $\frac{(Peak\ Systolic\ Velocity - Minimum\ Diastolic\ Velocity)}{Mean\ Velocity}$

Formula RI: $\frac{(Peak\ Systolic\ Velocity - End\ Diastolic\ Velocity)}{Peak\ Systolic\ Velocity}$

These represent both the arterial resistance to blood flow.

(2) Impedance Cardiography (ICG)

Automated blood pressure measurements during supine and standing position were combined with continuous ICG registrations. Four electrodes were attached to the thorax (two on the axillary line under the thorax and two in the neck). Parameters were classified into five categories (Figure 0.2):

1. Blood pressures

Systolic blood pressure (SBP, mmHg) and Diastolic blood pressure (DBP, mmHg) are measured automatically. Pulse pressure (PP, mmHg) and Mean arterial pressure (MAP, mmHg) are calculated as (SBP-DBP) and (DBP+PP/3) respectively.

2. Flow parameters

Heart rate (HR, beats/minute) is measured as the RR-interval of the ECG-signal. Stroke volume (SV, ml) is calculated automatically using the Sramek-Bernstein formula, which estimates the electrically participating chest tissue from the height, weight, age and gender of the patient. SV represents the blood volume pumped by the left ventricle each beat. Cardiac output (CO, l/min) is the calculation of HR x SV, and represents the total amount of blood pumped by the heart during one minute.

3. Contractility parameters

The Pre-ejection period (PEP, ms) is the phase of isovolumetric ventricular contraction, defined as the time interval between the Q-wave

of the ECG and the B-point on the ICG. This is the time necessary to exceed the aortic pressure and start ejection. Left ventricular ejection time (LVET, ms) represents the ejection duration, defined as the time interval between opening (B) and closing (X) of the aortic valve on the ICG signal. Velocity index (VI, 1/1000/s) is the equivalent to the maximum velocity of the systolic wave (C at ICG signal). Acceleration index (ACI, $1/100/s^2$) is the maximum acceleration of the aortic blood flow. The heather index (HI, Ω/s^2) is a sensitive parameter for cardiac contractility.

4. Thoracic fluid parameters

Thoracic fluid content (TFC, $1/k\Omega$) is the amount of conducting fluid within the thorax.

5. Vascular parameters

Total arterial compliance (TAC, ml/mmHg) is the distensibility of the aorta, calculated as SV/PP. Total peripheral resistance (TPR, $dyn.s/cm^5$) is the resistance of the systemic blood vessels, calculated as (MAPx80)/CO.

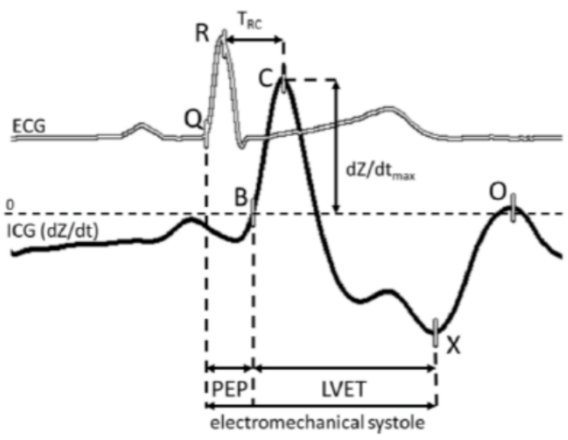

Figure 0.2: The corresponding signals of the electrocardiogram (ECG) and the impedance cardiogram (ICG). ICG (dZ/dt) is the first mathematical derivative of the change in impedance over time (Z) to an alternating current with a high frequency (60-100 kHz) and a very low amplitude (1 mA) transmitted through the maternal thorax by a four-electrode arrangement eliminating skin resistance. Q: start of ventricular depolarization, R: peak ventricular depolarisation, B: opening of the aortic valve, C: peak systolic flow, X: closure of the aortic valve, O: opening of the mitral valve: PEP: pre-ejection period, LVET: left ventricular ejection time, and TRC: time from point R to point C.

(3) Bio-impedance

A multiple frequency bioelectrical impedance analyser can measure different fluid contents. A current of 0.6 mA with a frequency of 5, 50, 100 and 200 kHz was used in supine position with stretched arms and legs. 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. Total body water (TBW, l) could be estimated, as a total of intracellular water (ICW, l) and extracellular water (ECW, l).

The cardiovascular profile of each participating patient was measured via these three methods. Patients were randomly included in diverse pregnancy trimesters (first, second or third) and some patients had multiple measurements during pregnancy. No initial exclusion criteria were taken into account. After birth, a diagnose was given to each patient based upon the presence of hypertension (GH, EPE, LPE, EH) and/or the presence of low birth weight (small for gestational age (SGA). With no presence of hypertension nor low neonatal birth weight, the diagnose 'uncomplicated pregnancy (UP)' was given. The majority of SGA neonates were constitutionally small, rather than pathological (IUGR) (Figure 0.3). For each described study done in this doctoral dissertation, the cardiovascular parameters of certain groups were compared.

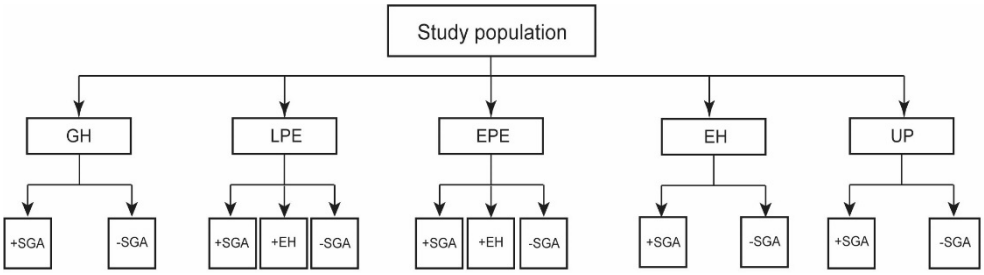

Figure 0.3: After birth, five main diagnoses were considered: gestational hypertension (GH), late preeclampsia (LPE), early preeclampsia (EPE), essential hypertension (EH) or uncomplicated pregnancy (UP). A subdivision was made, based upon the presence of low neonatal birth weight (+ or – SGA, small for gestational age) or pre-existing essential hypertension (+EH).

AIMS

The aim of this doctoral thesis is to unravel the contribution of the different components of the maternal circulation during different trimesters in uncomplicated pregnancies (part II) and pregnancies complicated with gestational hypertensive disorders (GHD, Part III). This is achieved by a standardized protocol of non-invasive, functional assessments of the central and peripheral arteries, central veins, heart and body fluid[30]. Consequently, this might shed new light upon predictive, diagnostic or therapeutic strategies for pregnant, hypertensive patients (Part IV).

This is achieved by following topics:

Part I A general overview on what is known so far about the hemodynamical changes and pathophysiological features during early pregnancy and the different techniques to assess these. Chapter based on a review article (Chapter 1.1).

Part II To explore the physiology in uncomplicated pregnancies with different approaches:
(1) the relation between liver function and neonatal growth (Chapter 2.1), (2) the influence of obesity on maternal hemodynamics (Chapter 2.2) and (3) the influence of hemodynamics in mothers with constitutionally small neonates (Chapter 2.3).

Part III To explore the physiology in pregnancies complicated with gestational hypertensive disorders (Chapter 3.1).

Part IV To explore the clinical relevance and the application of early gestational non-invasive maternal hemodynamics assessments (Chapter 4.1 and 4.2).

PART I

MATERNAL HEMODYNAMICS: GENERAL ASPECTS

OBJECTIVE | General overview on what is known about the hemodynamical changes and pathophysiological features during early pregnancy and the different techniques to assess these.

CHAPTER 1.1

Why non-invasive maternal hemodynamics assessment is clinically relevant in early pregnancy: a literature review

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ABSTRACT

Background: The maternal cardiovascular system adapts quickly when embryo implantation is recognized by the body. Those adaptations play an important role, as a normal cardiovascular adaptation is a requirement for a normal course of pregnancy. Disturbed adaptations predispose to potential hypertensive disorders further in pregnancy[9,31,32]. This report aims to briefly inform the obstetricians, general practitioners and midwives, who are the key players in detecting and treating hypertensive disorders during pregnancy.

Methods: The PubMed database was used as main tool to find studies involving clearly defined first trimester hemodynamic changes in normal pregnancies and hypertensive pregnancies. In addition, the bibliographies of these studies were investigated for further relevant literature.

Results: A comprehensive overview is given concerning the normal adaptations in the cardiovascular tree in a first trimester pregnancy. Additionally, signs of abnormal cardiovascular changes observed in first trimester are described together with the normal reference range for each non-invasive, easily applicable technique for maternal hemodynamics assessment.

Conclusions: With a combination of techniques, it is possible to integrate and evaluate the maternal heart, veins and arteries at 12 weeks of pregnancy. Applying those techniques into the daily clinic opens perspectives to prevention and prophylactic treatment, aiming for a reduction of the risk for hypertension during pregnancy.

BACKGROUND

A normal pregnancy is characterized by multiple cardiovascular adaptations to provide optimal conditions for foetal growth and development. Most of these changes are induced shortly after embryo implantation and thus well before the exponential increase of the foetal and placental demands for oxygen and nutrients, predominantly occurring in the second half of pregnancy. Most circulatory functions have changed significantly by the end of the first trimester[9].

A maladaptation in any step of the process changes the structural, physiological or metabolic environment of the foetus. The genetic program of the foetus induces phenotypic adaptions to the current environment, which influences the foetus' cardiovascular system in later life[31]. Additionally, those disturbed physiological processes predispose to pregnancy complications, such as pre-eclampsia and foetal growth restriction[32].

This review provides a summary of the most relevant cardiovascular changes in the first trimester of a normal pregnancy, as reported in diverse studies done in early pregnancy. Adaptations are presented and discussed at each part of the cardiovascular tree, the arteries, veins and heart. Additionally, a comprehensive overview is given about the pathology-specific features of hypertensive disorders, measurable in the first trimester, together with the normal values of each non-invasive, easily applicable technique.

PRE-PREGNANCY CARDIOVASCULAR FUNCTION

The cardiovascular function in women varies with the menstrual cycle. In the luteal phase, heart rate, plasma volume, cardiac output (CO), central and peripheral arterial compliance and distensibility have increased relative to the follicular phase. Meanwhile, mean arterial pressure (MAP) has decreased together with the vascular resistance. Chapman suggests that the fall in peripheral vascular resistance is the primary event in the luteal phase. Afterwards, the MAP decrease initiates a hemodynamic compensation through a rise in CO. Due to a dilated vascular system, the renal plasma flow and

glomerular filtration rate increase and an activation of the renin-angiotensin-aldosterone system (RAAS) during the luteal phase is seen[33,34].
This cyclic pattern resembles roughly to the simultaneous hormonal variations occurring during the menstrual cycle, which suggests prudently a role for oestrogen in modulating the vascular smooth muscle tone. Oestrogen has been shown to enhance [1] endothelial function, [2] dilate arterioles, [3] vascular smooth muscle cell proliferation, [4] inhibit fibroblast and [5] collagen accumulation in the aortic wall[35]. The exact mechanism by which oestrogens modulates arterial function has been explored in animal studies: vascular smooth muscle cells have oestrogen receptors[36] and oestrogen administration induces vasodilatation[37]. It is however difficult to postulate a direct relation between oestrogen and cardiovascular events, as other factors (like nitric oxide, relaxin, vascular endothelial growth factor, prostanoid metabolites, adhesion molecules, etc.) also vary during the menstrual cycle. It is probably a complex cascade of events which initiates the primary vasodilation[38].

Early pregnancy is characterized by vascular relaxation along with increased arterial compliance and distensibility. The pattern of cardiovascular changes in the luteal phase relative to the follicular phase of the menstrual cycle resemble those in early pregnancy. From conception until the 7th week of pregnancy, the maternal endocrine environment is dominated by the extended function of the corpus luteum, which is activated through the release of large amounts of human chorionic gonadotropin (hCG). Consequently, the hemodynamic and hormonal changes seen in the first weeks of gestation are independent of a functioning foetal-maternal-placental unit[34].

CARDIOVASCULAR CHANGES

5 WEEKS OF GESTATION

Doppler echography at the level of the pulmonary, mitral and aortic valves at 5 weeks pregnancy showed consistently higher values for heart rate and cardiac output relative to the prepregnant state (luteal phase)[39,40], whereas others reported a rise in cardiac output occurring later on in the first trimester[41] or not at all[42]. This discrepancy might be explained by the absence of a pre-pregnancy baseline[41] or the different measuring time points and design of the

study[42]. Both heart rate and cardiac output increase steadily in the course of the first trimester[39,41]. Cardiac output depends on heart rate, contractility, preload and afterload. Consequently, the initial increase in cardiac output is achieved by a rise in a higher heart frequency[39,43], simultaneously with the reduction in peripheral vascular resistance[39-41]. Peripheral vascular resistance decreases abruptly by 20-25% at 5 weeks compared to the beginning of the menstrual cycle[40], most likely in concert with an abrupt fall in plasma osmolality[44]. Also stroke volume and plasma volume are reported to be increased at week 5, indicating that all these adaptive changes contribute to the prolonged institution of a high cardiac output and low peripheral resistance circulation[39,45].

6 WEEKS OF GESTATION

At 6 weeks pregnancy, the magnitude of systemic vasodilatation had increased relative to 5 weeks[46] with lower blood pressures (systolic + diastolic, brachial and central) than before conception, occurring secondary to the peripheral vasodilation. This event arises together with an additional fall in pulse wave velocity, a parameter correlating with aortic stiffness[9,41,47]. Systolic and diastolic blood pressure continue to decrease until 24 weeks of gestation, because the CO incline is not sufficient to prevent the blood pressure fall as blood pressure is the product of cardiac output and total peripheral vascular resistance[46].

Shortly after implantation, the corpus luteum releases plasma relaxin, which is 3-4-fold higher at 6 weeks than during the menstrual cycle. Relaxin circulates in the maternal blood and rapidly reaches a plateau at the end of the first trimester. It is suggested to play a role in the vasodilation pathway, but the exact pathway is still unclear. The vasodilatory response of relaxin is mediated by its major receptor (relaxin/insulin-like family peptide 1 receptor, RFXP1) and depends on duration of hormone exposure. The rapid vasodilatory responses are performed through the activation of the pathway stimulating nitric oxide synthase. The sustained vasodilatory response relies on vascular endothelial and placental growth factors and the arterial gelatinase activity[48].

Renal hemodynamics are also characterized by a marked fall in renal vascular resistance, giving rise to a correspondingly increase in renal perfusion[49]. The latter induces a ≈ 50% rise in glomerular filtration rate (GFR) accompanied by a small decline in filtration fraction. Meanwhile, the low blood pressures activate renin-angiotensin-aldosterone system (RAAS), which increases plasma renin activity and plasma aldosterone. Angiotensin II induces constriction of the renal blood vessels, excretion of the vasopressin hormone and aldosterone/adrenaline/noradrenaline production. This mechanism, together with the higher aldosterone production, leads to sodium and water reabsorption. The vasopressin hormone prevents re-excretion of the water[50]. This causes the expansion of plasma volume, hemodilution, a higher renal plasma flow and a higher cardiac output[47,51]. Cardiac preload (i.e. venous return) increases in concert with the plasma volume expansion. This improves cardiac filling during diastole, which raises the efficiency of the Frank-Starling mechanism. Due to concomitant fall in cardiac afterload, a higher stroke volume arises and the elevated cardiac output is preserved, which anticipates an adequate foetal and placental supply of oxygen and nutrients throughout the course of pregnancy. These changes occur long before the uteroplacental circulation has become an important part of the systemic circulation[47,52,53].

7 WEEKS OF GESTATION

At 7 weeks of gestation an increasing distensibility and compliance of the arterial and venous compartment has been observed[40,54,55]. It is suggested that the arterial compliance increases due to relaxation of the muscular wall of the vessels[40,55]. The decrease in peripheral vascular resistance causes a decrease in diastolic pressure, but the presence of a higher arterial compliance counterbalances this event, assuring normalized perfusion pressure to coronaries and vital organs[55,56]. Both events may play a role in enhancing the left ventricular performance[54]. A higher venous compliance increases the capacity of the venous compartment to accommodate a larger reserve volume in the splanchnic system, which is also necessary to preserve the cardiac output during pregnancy[57]. The venous compliance keeps on rising by advancing pregnancy[58].

8 WEEKS OF GESTATION

Due to the increasing cardiac preload together with the lower afterload early in pregnancy, stroke volume and cardiac output keep on rising during the first trimester[39]. The continuous increase of cardiac output is from this moment not only caused by a higher heart rate, but is supported by the increase in stroke volume together with the observed anatomic increase of the heart surface area[41,43]. The left atrial diameter increases together with the left ventricular diastolic dimension, which is a measurement of the preload[41]. The systolic dimension of the left ventricle and the ventricle wall thickness were also significantly increased[39,43]. These changes enhance the performance of the total left ventricle[41]. The aortic, pulmonary and mitral velocities increase steadily and become significantly higher in week 8 as compared to pre-pregnancy values[39]. The onset of intervillous perfusion with maternal blood, starting to develop at ≈8 weeks, is not only associated with a rise in the intervillous oxygen tension, but also with a rise in the circulating levels of a number of placental biochemical markers for oxidative stress[59].

9 TO 12 WEEKS OF GESTATION

At 8 weeks, the first morphological changes have been reported in multiple studies. At 12 weeks, Doppler echocardiography indicated more advanced changes in the heart surface area: the mitral, aortic and pulmonary valve areas increase, together with diastolic dimensions, left atrial dimensions, total left ventricle wall thickness and left ventricle mass[39]. Left ventricular diastolic and systolic volumes are both increased comparing to pre-pregnancy, but not yet significant according to the first trimester study of Del Bene[42]. The increase of the cardiac dimensions are probably a consequence of the persistent increase of venous return and cardiac filling pressure, which can be expected to improve the cardiac performance continuously[39]. Cardiac output, blood volume and plasma volume are highest at 12 weeks in the first trimester, which might explain why most morphological heart changes only become significant around 12 weeks[47]. The progressive enlargement of the heart surface area represents the typical gestational phenomenon 'myocardial eccentric hypertrophy'. This is a reversible hypertrophy without any long term cardiac consequences[39,60]. Interestingly, all these pregnancy-related cardiac changes are identical to patients with a chronic

volume overload state and in isotonic-exercising athletes (swimming, running) 10 to 12 weeks after the start of the training program: higher left ventricle volume, left ventricle mass and ventricular performance[61].

In the first trimester, renal plasma flow (RPF) reaches a peak at 12 weeks. Afterwards RPF decreases. Glomerular filtration rate had increased steadily in the first trimester, continues to increase in the second trimester but tends to decline again in the third trimester. Atrial natriuretic peptide (α-ANP) is significantly raised at week 12, and keeps increasing even more afterwards. It has diuretic, natriuretic and vasodilator properties and might play an important role in volume homeostasis[47]. α-ANP is considered not active in early pregnancy because plasma concentrations remain low during the first weeks, but increase by 35% in the second trimester in association with the plasma volume increase. This suggests that plasma α-ANP changes are secondary to the plasma volume increase, rather than playing a primary role in the hemodynamic changes[41,47].

In the second half of the first trimester, retrograde trophoblast invasion into the spiral artery together with a lower responsiveness to vasoconstrictor agents may explain the further rise in uteroplacental vascular compliance, as the resistance index (RI) and pulsatility index (PI) of the uterine artery decrease when gestational age increases. RI and PI are representative for the resistance in the uterine arteries. There exists an inverse relation between RI or PI with ongoing trophoblastic invasion into the spiral arteries[62,63] Intervillous blood flow becomes only detectable from 12 weeks onwards, because trophoblastic migration is only observed from week 10, and a consecutive formation into the myometrium of the spiral arteries starts from week 14. This implies that physiological changes are completed and heart/vessels are adapted morphologically. Spiral arteries remodelling induces the change from high-resistance flow to low-resistance flow[59]. Also, further studies have shown a continuous decrease of resistance and pulsatility indices between 12 and 16 weeks[64-66].

Table 1.1.1: Overview of all early cardiovascular changes in normal pregnancy *(See also Appendix 1.1.1)*

		Early first trimester			Late first trimester
		5 weeks	6 weeks	7 weeks	8–12 weeks
Arteries	Total Peripheral Resistance (TPR)	↓			
	Pulse Wave Velocity (PWV)		↓		
	Aorta Compliance			↑	
	Blood Pressure		↓		
	Blood Velocity				↑
Heart	Heart Rate (HR)	↑			
	Stroke Volume (SV)	↑			
	Cardiac Output (CO)	↑			
	Cardiac Filling Pressure		↑		
	Inotropy				↑
	Heart Surface Area				↑
	Atrial-Ventricular Dimensions				↑
	Ventricular Wall				↑
Veins	Venous Return		↑		
	Distensibility			↑	
	Capacitance			↑	
Hematology	Plasma Volume	↑			
	Plasma Osmolality	↓			
	Relaxin		↑		
Kidney	Glomerular Filtration Rate (GFR)		↑		
	Renal Plasma Flow (RPF)		↑		
	Renal Vascular Dilatation		↓		
	Filtration Fraction		↓		
	Renin Angiotensin Aldosterone System (RAAS)		↑		

PATHOLOGICAL SIGNS IN THE FIRST TRIMESTER

The cardiovascular system in patients with hypertensive disorders differs from the normal maternal cardiovascular system. Focusing on hemodynamic characteristics could help to understand the physiological maladaptations in the first trimester.

ARTERIES

Peripheral arteries

Higher uterine pulsatility indices in early preeclampsia than uncomplicated pregnancies have been reported in the early pregnancy (2.35 vs. 1.79), which is a measurement for impaired placentation and arterial stiffness[67]. Additionally, placental volume was shown to be smaller too in (early) preeclamptic patients (60 vs. 43 cm^3)[67]. In patients developing late preeclampsia however no

aberrant uterine pulsatility indices or placental volume were found[67]. There is a direct relation between resistance, arterial stiffness and endothelial dysfunction, which clinically presents in high blood pressures. This is in congruence with measurements for total vascular resistance, which was shown to be higher in the late preeclamptic group (1,105 dyne*sec*cm^{-5} versus 1,260 dyne*sec*cm^{-5}), measured as [MAP (mmHg)/CO (L/min) x 80][16]. Another measurement for arterial stiffness is the pulse wave velocity (PWV) and augmentation index (AIx). Already at the end of the first trimester, the pulse wave velocity and augmentation index in the brachial artery is significantly higher in the hypertensive group (7.47 m/s vs. 6.55 m/s (PWV); 13.2% vs. 10.6% (AIx))[68]. Peripheral higher blood pressures (diastolic, systolic, mean arterial pressure) could be measured (123 vs. 114 mmHg (SBP); 82 vs. 75 mmHg (DBP); 92 vs. 85 mmHg (MAP)) in an eventual late hypertensive group[69]. All those results indicate a stiffer peripheral arterial system already in the first trimester of pregnancies destined to develop pre-eclampsia.

Central arteries

Additionally, the early gestational central systolic blood pressure is also higher in the preeclamptic group (122 mmHg vs. 108 mmHg)[68]. First trimester aorta flow parameters (velocity index (VI), acceleration index (ACI) and heather index (HI)), which are directly related to systolic function and aorta compliance, are shown to be different between normal and pathological pregnancies (VI: 72 vs. 57 1/1000/s; ACI: 133 vs. 108 1/100/s²; HI: 23.1 vs. 17.3 Ω/s²). Lower values, as seen in the late hypertensive group, reflect a poor ventricular ejection and thus systolic dysfunction already present in the first trimester[69].

Heart

Khaw et al. investigated different cardiovascular functions at 11-14 weeks between uncomplicated pregnancies, eventual preeclamptic pregnancies with appropriate for gestational age babies (AGA) and preeclamptic patients with small for gestational age babies (SGA). Cardiac output, cardiac index and stroke volume were significantly higher in the preeclamptic group with AGA than the uncomplicated group (6.2 l/min, 3.3 l/min/m², 87.9 ml versus 4.9 l/min, 2.9 l/min/m², 67 ml resp.)[16,70]. A higher mitral valve annulus shortening is also

found in this pathological group (15.5 mm versus 17.8 mm), supporting this suggestion. Preeclampsia with SGA babies have no aberrant cardiac output, cardiac index or stroke volume parameters (4.9l/min, 2.8 l/min/m², 66.3 ml resp) compared to the uncomplicated group[16]. Further, higher values are observed for mitral valve E-wave velocity (82.4 mm/sec versus 95.7 mm/sec) in the late preeclamptic group. Mitral valve E-wave velocity measures the diastolic function, which is the passive filling of the ventricle. Khaw et al. also measured the mitral valve A-wave velocity (representation of the active filling during atrial systole), which did not differ significantly between the 2 groups in this study[16]. Both velocities are strongly dependent from physiological changes in heart rate, preload, left ventricular compliance and contractility. An initial rise in the E/A ratio is consistent with an initially impaired adaptation of cardiac diastolic function, which is already present in a first trimester measurement in the hypertensive group. An increase of more than 7% at 12 weeks indicates an important higher risk for pre-eclampsia[14].

Veins

Also, venous impedance is observed to be higher in pathological pregnancies than normal pregnancies. A high venous impedance is accompanied with a low venous distensibility, a higher venous pressure, a lower venous capacity and a smaller increase in plasma volume[71]. However, venous hemodynamic function is shown to be normal in the first trimester, but becomes abnormal during the second trimester in the pregnancies destined to develop preeclampsia[69].

Haematology

Plasma volume increase is very important for normal foetal development. Maladaptation of the cardiovascular system can obstruct a necessary increase in plasma volume. There is a correlation between maternal cardiac output and the growth of the foetus, already present in the first trimester[21]. The link between cardiac output and birth weight percentiles is associated with the grade of heart, vein and artery dysfunction because those are the driving forces of the cardiac output[21].

Kidney

A direct consequence of a high vascular resistance and high blood pressure is the decrease in renal perfusion and glomerular filtrate rate. The renal clearance will decrease, which leads to a higher plasma concentration of uric acid. Preeclampsia is characterized by proteinuria, which possibly relates to a higher capillary pressure in the glomerular filter. This induces a lower tubular absorption, contributing to glomerular endotheliosis. However, no studies are found concerning this topic in first trimester[72].

Aberrant hemodynamic characteristics may already be evident in the first trimester, however not always measurable. More and more researchers focus on well-defined subject groups, as the pathophysiology between gestational hypertension, early preeclampsia and late preeclampsia with and without intra uterine growth restriction have important hemodynamic differences.

TECHNIQUES: NORMAL VALUES

To assess abovementioned maternal cardiovascular adaptations, safe, easily accessible and non-invasive first trimester techniques are useful, which have the potential to evaluate the different compartments of the maternal cardiovascular system (Table 1.1.2).

A Doppler ultrasound of the uterine artery is a widely used, non-invasive technique to measure the pulsatility index (PI; [peak systolic flow – end diastolic flow / mean flow]) and the resistance index (RI; [peak systolic flow – end diastolic flow / peak systolic flow) from the flow velocity waveforms of the uterine arteries. Normal values vary between 0.56 and 0.76 for RI, and minimum 1.11 and maximum 2.08 for PI[16,62,64,68,69,73,74]. Low end-diastolic velocities and an early diastolic notch are typical waveforms in the first trimester pregnancy, indicating a high uterine resistance[73,75,76]. Other parameters reflecting arterial stiffness is the pulse wave velocity, measured from artery pulse waveforms in the brachial[68,77,78] or radial artery[79]. SphygmoCor (West Ryde, Australia), Complior (Vincennes, France) or Arteriograph (TensioMed, Budapest, Hungary) are the three techniques used for pulse wave analysis. The normal pulse wave velocity ranges between 6.13 and 8.13 m/sec. PI, measured with the artery pulse waveform technique, lies between 1.4 and 2.08[68,77]. In

preeclampsia, PI, RI and pulse wave velocity are considerably higher[16,67-69,79-81].

The combination of electrocardiogram and Doppler ultrasound is used to investigate the maternal venous system (renal interlobular veins and hepatic veins), using venous impedance indices and the 'venous pulse transit time' (VPTT). Tomsin et al. reported a gradual rise of the VPTT in normal pregnancy and a significantly shorter VPTT in preeclamptic patients, which illustrates a venous hemodynamic dysfunction in preeclampsia[22,82]. Also aberrant venous impedance indices (Hepatic Vein Index (HVI), Renal Interlobar Vein Index (RIVI)) are seen in the active phase of preeclampsia. Compared to normal pregnancies, in the preeclamptic group at 12 weeks, the venous function seems to be normal [VPTT kidney: 0.24-0.35 ms; VPTT liver: 0.13-0.23 ms; HVI: 0.7-1.6; RIVI: 0.38-0.56][69].

Aortic Doppler flow measurements estimate the aortic valve area, cardiac output and stroke volumes. The aortic area has a normal range from 3.85 to 3.94 cm^2. Stroke volume with this technique is reported between 81.5 – 84.1 ml, and cardiac output between 6.61 and 6.83 l/min[39]. In (late) preeclampsia, stroke volume and cardiac output are higher[16,70]. Aortic valve area uses calculations from the aortic diameter, which is reported to be higher in preeclampsia in the first trimester [83].

Echocardiography is the preferred technique to evaluate the systolic and diastolic function of the heart during the complete course of pregnancy. Cardiac output, stroke volume (systolic function); E-wave and A-wave (diastolic function) and mitral valve annulus shortening (MVAS) measurement are parameters measured with this technique. Diastolic function has an E-wave range from 68.8 - 96 mm/sec, and an A-wave range from 40.5 - 57.3 mm/sec. The mitral valve annulus is found to be normal between 13.5 and 17.5 mm[16]. Robson et al. measured also left ventricle End-Systolic Dimension (ESD), ranging from 2.85 – 2.91 cm, and End-Diastolic Dimension (EDD), ranging from 4.63 – 4.69 cm. The Left Atrial Dimension (LAD) ranges between 3.26 and 3.36 cm. Further, the thickness of the left ventricle wall is measured, as 1.56 – 1.62 cm, and the mass: 134 – 140 g. The ejection fraction is 75.7 – 76.9 %, all parameters measured around 12 weeks[39]. In preeclampsia, increased mitral

valve shortening and E-wave are reported, but significant differences in ESD, EDD, LAD, left ventricular wall thickness and mass were not observed[14].

Other systolic parameters can be measured by impedance cardiography, which monitors the cardiovascular changes by transmitting an electrical current with high frequency and low amplitude through the maternal thorax. Another non-invasive method is the USCOM (Sydney, Australia) device which measures the velocity of the aortic/pulmonary blood flow, used to calculate a time-velocity integral, and as such basically is a derived echocardiography technique. In these cases, cardiac output and stroke volume seem to have an overestimation with those two techniques relative to echocardiography measurements as the normal range for CO is reported around 6.48-7.89 l/min, and for SV 72.62-94.62 ml. Echo cardio measurements are lower: CO 4.3 - 5.5 l/min, and SV 55.3 - 78.7 ml. Non-Invasive Cardiac Output Monitor (NICOM, Cheetah Medical, USA) also measures HR, CO and SV. It is based on a thoracic bioreactance technology, but no published studies on patients in the first trimester of pregnancy were traced. It is still quite controversial using non-invasive techniques in clinics, as the reliability compared to the golden standard echocardiography is highly discussed in literature. However, using only one technique with its method-specific reference values eliminates possible over- or underestimation[16,69,81,84]. With the use of the formula: [(MAP(mmHg)/CO(L/min) x 80], total peripheral resistance (dyne*sec*cm^{-5}) can also be calculated (1,015-1,212)[16,39]. With the USCOM device, this parameter is automatically measured using a non-reported formula and the range is found to be slightly lower (940.87 – 1,118.53)[81]. Impedance cardiography additionally provides some important aorta flow parameters: aorta velocity index (1/1000/s), acceleration index (1/100/s²) and heather index (Ω/s²). In the first trimester, those parameters have an important implication. Normal values are seen between 62 and 82; 107 and 156; 19.2 and 26.9 respectively. In preeclampsia, aortic flow measurements are in a lower range[69].

Studies using echocardiography, impedance cardiography and USCOM additionally measured the blood pressures. Normal systolic blood pressures at 12 weeks vary from 107 to 122 mmHg, diastolic blood pressures range from 65 to 77 mmHg. The mean arterial pressure lies between 77 and 86 mmHg. Heart

rates range in the first trimester between 76 and 92[16,39,69,81]. In preeclampsia, first trimester blood pressures and heart rate are already slightly higher than normal[16,69,79-81].

APPLICATION OF TECHNIQUES

Together with gaining basic knowledge about the normal physiological cardiovascular changes in the first trimester of pregnancy, all techniques discussed above allow investigating a population of 12 week pregnant women non-invasively, which opens a window to screen for hypertensive disorders. With a combination of techniques, it is possible to integrate and evaluate the maternal heart, veins and arteries at 12 weeks of pregnancy[69]. In this review, normal values are summarized which opens easily future perspectives to search for aberrant cardiovascular signs in each part of the cardiovascular tree of the doctor's patients. Screening for hypertensive disorders is very useful as an early stratification into a high risk vs. a low risk group is possible. Possible follow-up or treatment strategies could be based on prescribing low-dose aspirin before 16 weeks of gestation, which is associated with a 50% reduction of PE risk and 80% of early PE[85,86], paying attention to regular physical activity during pregnancy[87] or remote blood pressure monitoring[88]. Applying those techniques into the daily clinic opens perspectives to prevention and prophylactic treatment, aiming for a reduction of the risk for hypertension during pregnancy. In the long run, it may reduce significantly the maternal and neonatal morbidity and mortality associated with hypertensive disorders[89,90]. It should however be emphasized that in this review all described hemodynamic changes with corresponding normal or hypertensive values reflect average values, which are subject to individual variability.

CONCLUSION

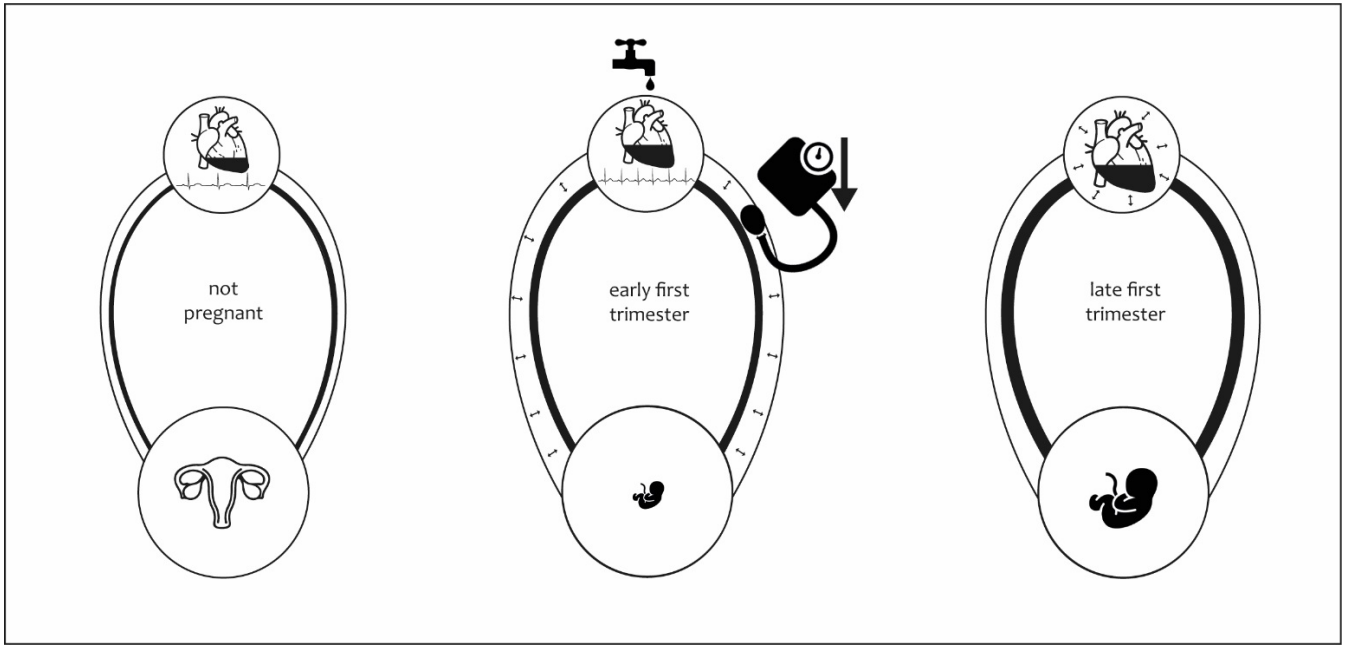
Many recent studies disclose the fact that initiation of placentation is not a necessary step for the normal or pathological hemodynamic alterations in a pregnancy, as placentation starts later than the very first maternal hemodynamic changes. This emphasizes the important role of the maternal cardiovascular system during gestation, with a normal hemodynamic adaptation as a requirement for a normal course of pregnancy. Today, many non-invasive

techniques allow a detailed assessment of maternal cardiovascular adaptations which opens perspectives to early postconceptional screening for gestational hypertensive disorders.

Table 1.2.1: Normal first trimester reference values of different non-invasive techniques

	Pulse Wave Doppler [10, 33, 35, 39–41, 47, 48]	Artery Pulse Waveforms [40, 51, 52]	Echocardiography [10, 39]	Impedance Cardiography [41]	USCOM [55]
Peripheral arteries	PI: 1.11–2.08 RI: 0.56–0.76	PI: 1.4–2.08 PWV (m/s): 6.13–8.13	MAP (mmHg): 73–83 SBP (mmHg): 102–113 DBP (mmHg): 58–67 TVR (dyne*sec*cm^{-5}): 1015–1212	MAP (mmHg): 81–90 SBP (mmHg): 106–123 DBP (mmHg): 71–81	SBP (mmHg): 114–130 DBP (mmHg): 67–82 TVR (dyne*sec*cm^{-5}): 941–1118
Central arteries	Aortic area (cm^2): 3.85–3.94	SBP (mmHg): 101–117		ACI (1/100/s^2): 107–156 VI (1/1000/s): 62–82 HI (/s^2): 19.2–26.9	
Heart	CO (l/min): 6.61–6.83 SV (ml): 81.5–84.1		CO (l/min): 4.3–5.5 SV (ml): 55.3–78.7 HR (bpm): 73–85 MVAS (mm): 13.5–17.5 E-wave (mm/s): 68.8–96 A-wave (mm/s): 40.5–57.3 ESD (cm): 2.85–2.91 EDD (cm): 4.63–4.69 LAD (cm): 3.26–3.36 LV wall thickness (cm): 1.56–1.62 LV mass (g): 134–140 EF (%): 75.7–76.9	CO (l/min): 6.2–8.2 SV (ml): 66–86 HR (bpm): 87–104	CO (l/min): 6.8–7.6 SV (ml): 79.23–103.23 HR (bpm): 69–89
Veins	RIVI: 0.38–0.56 HVI: 0.7–1.6 VPTT (kidneys) (ms): 0.24–0.35 VPTT (liver) (ms): 0.13–0.23				

MAP Mean Arterial Pressure, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *TVR* Total Vascular Resistance, *CO* Cardiac Output, *SV* Stroke Volume, *HR* Heart Rate, *MVAS* Mitral Valve Annulus Shortening, *E-wave* E-wave velocity, *A-wave* A-wave velocity, *ESD* End-Systolic Dimension, *EDD* End-Diastolic Dimension, *LAD* Left Atrial Dimension, *LV* Left Ventricle, *EF* Ejection Fraction, *ACI* Acceleration Index, *VI* Velocity Index, *HI* Heather Index, *PI* Pulsatility Index, *RI* Resistivity Index, *RIVI* Renal Interlobar Vein Index, *HVI* Hepatic Vein Index, *VPTT* Venous Pulse Transit Time, *PWV* Pulse Wave Velocity



Appendix 1.1.1: Simplified illustration of the physiological changes during the first trimester. In first instance, heart rate, stroke volume, cardiac output and blood volume rise immediately after implantation, together with vasodilation of the blood vessels. The blood pressure drops as consequence of the imbalance between vasodilation and rise in cardiac output, which activates the renin-angiotensin-aldosterone-system for a further blood volume increase. Consequently, morphological changes occur to the heart due to the continuous increase of blood volume.

PART II

MATERNAL HEMODYNAMICS IN NORMAL PREGNANCIES

Objective | To explore the physiology in uncomplicated pregnancies with different approaches: (1) the relation between liver function and neonatal growth (Chapter 2.1), (2) the influence of obesity on maternal hemodynamics (Chapter 2.2) and (3) the influence of hemodynamics in mothers with constitutionally small neonates (Chapter 2.3).

CHAPTER 2.1

Hepatic hemodynamics and foetal growth: a relationship of interest for further research.

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ABSTRACT

Background: It is well known that hepatic hemodynamics is an important physiologic mechanism in the regulation of cardiac output (CO). It has been reported that maternal cardiac output relates to neonatal weight at birth.

Aims: In this study, we assessed the correlation between maternal hepatic vein Doppler flow parameters, cardiac output and neonatal birth weight.

Methods: Healthy women with uncomplicated second or third trimester pregnancy attending the outpatient antenatal clinic of Ziekenhuis Oost-Limburg in Genk (Belgium), had a standardized combined electrocardiogram-Doppler ultrasound with Impedance Cardiography, for measurement of Hepatic Vein Impedance Index (HVI = [maximum velocity – minimum velocity]/maximum velocity), venous pulse transit time (VPTT = time interval between corresponding ECG and Doppler wave characteristics) and cardiac output (heart rate x stroke volume). After delivery, a population-specific birth weight chart, established from a cohort of 27,000 neonates born in the index hospital, was used to define customized birth weight percentiles (BW%). Correlations between HVI, VPTT, CO and BW% were calculated using Spearman's ρ, linear regression analysis and R^2 goodness of fit in SPSS 22.0.

Results: A total of 73 women were included. There was a negative correlation between HVI and VPTT ($\rho = -0.719$, $p<0.001$). Both HVI and VPTT correlated with CO ($\rho = -0.403$, $p<0.001$ and $\rho = 0.332$, $p<0.004$ resp.) and with BW% ($\rho = -0.341$, $p<0.003$ and $\rho = 0.296$, $p<0.011$ resp.)

Conclusion: Our data illustrate that the known contribution of hepatic hemodynamics in the regulation of cardiac output is also true for women with uncomplicated pregnancies. Our study is the first to illustrate a potential link between maternal hepatic hemodynamics and neonatal birth weight. Whether this link is purely associative or whether hepatic vascular physiology has a direct impact on foetal growth is to be evaluated in more extensive clinical and experimental research.

INTRODUCTION

One of the main functions of the venous system is the regulation of cardiac output. The cardiovascular circuit is a closed circulatory loop, implicating that in steady state conditions the venous flow back to the heart (i.e. preload) is equal to the arterial flow towards the organs (i.e. cardiac output). Due to the Frank-Starling mechanism, an increase in venous return will automatically lead to an increase in cardiac output and vice versa. Next to this, the venous compartment is also a capacitance reservoir: storage of non-circulating reserve blood occurs in the splanchnic bed and liver, from where this can be mobilised into the circulation whenever necessary. This mobilization occurs via the portal vein and the liver. As such, the hepatic circulation is actively involved in the regulation of cardiac output, both in a direct and indirect way[91].

Changes of maternal cardiac output start already in early gestation[41,92,93]. The physiologic increase of cardiac output during pregnancy is important for a normal course of pregnancy. Several studies have highlighted the important interaction between maternal cardiovascular maladaptation (i.e. low cardiac output) and intra-uterine growth restriction (IUGR) with or without maternal hypertension or organ-dysfunction[94-96]. Bamfo et al. suggests that cardiac output is reduced in the IUGR population due to a reduction in stroke volume, which is the consequence of a reduction in preload[97].

An integrated assessment of the cardiovascular loop can be done non-invasively by the use of impedance cardiography (ICG) and combined electrocardiogram – Doppler (ECG-D) sonography[11,22,98,99]. ICG is a safe and reproducible technique for an estimation of cardiac output and other hemodynamic parameters[21]. Changes in maternal arterial and central venous function can be evaluated reliably by ECG-Doppler assessments[82,100,101].

The aim of the study was to investigate whether a relation exists between maternal ICG and/or ECG-D parameters and neonatal birth weight percentiles. As hepatic hemodynamics has a physiological role in the regulation of CO and CO is known to correlate with BW%, we hypothesize that HVI correlates with BW%.

METHODS

ETHICS STATEMENT

The study protocol was approved by the local Ethics Committee of Hasselt University and Hospital Oost-Limburg (CME ZOL reference 08/049 and 09/050). Written informed consent was obtained.

PARTICIPANTS

Pregnant women in their second or third pregnancy trimester with or without gestational complications, attending the outpatient antenatal clinic, were invited to participate in this observational study. After written informed consent, a non-invasive cardiovascular assessment was performed according to a standardised protocol as reported elsewhere[98] using non-invasive impedance cardiography (ICG) and combined electrocardiogram-Doppler (ECG-D) ultrasound. Demographic details were recorded: maternal age (years), parity, pregestational BMI and gestational age at assessment. After delivery, outcome of pregnancy was evaluated, gestational age at birth and neonatal birth weight were also recorded. Only data from uncomplicated pregnancies with normal neonatal outcome were included in this study. Exclusion criteria were pre-existing maternal disease or medication use, diagnosis of preeclampsia, Haemolysis Elevated Liver enzymes and Low Platelets (HELLP), essential hypertension, gestational hypertension, multiplets and intra-uterine growth retardation (IUGR) (Figure 2.1.1).

BIRTH WEIGHT PERCENTILES

Customized birth weight charts were established from a cohort of 27,000 neonates, born as singletons without congenital anomalies in Ziekenhuis Oost-Limburg between 2001 and 2013. Charts were categorized into 4 groups: primiparous & baby girl, primiparous & baby boy, multiparous & baby girl, multiparous & baby boy. Birth weights were classified per week of gestation, and birth weight percentiles (BW%) were calculated with an interval of 2.5% between P2.5 and P97.5. According to these population-specific data, the weight at birth of each neonate in the study was expressed as a customized birth weight percentile.

Table 2.1.1: Demographic data, neonatal outcome and maternal cardiovascular characteristics in healthy pregnant women. Data are presented as median ± interquartile range.
HVI: hepatic vein index, CO: cardiac output, VPTT: venous pulse transit time.

	Uncomplicated Pregnancies (n=73)
DEMOGRAPHIC CHARACTERISTICS	
MATERNAL AGE, YEARS	29.74 ± 5.77
GESTATIONAL AGE AT INCLUSION, WEEKS	35w4d ± 5w4d
PRE-PREGNANCY BMI, KG/M²	23.38± 6.06
NULLIPARITY, %	47.94
NEONATAL OUTCOME	
BIRTH WEIGHT, G	3325 ± 725
BIRTH WEIGHT, PERCENTILE	50 ± 52.5
GESTATIONAL AGE AT DELIVERY, WEEKS	39w1d ± 2w5d
CARDIOVASCULAR CHARACTERISTICS	
HVI	0.24 ± 0.26
CO	7.8 ± 2.2
VPTT	0.39 ± 0.17

IMPEDANCE CARDIOGRAPHY

ICG examinations were performed in standing position using the Non-Invasive Continuous Cardiac Output Monitor (NICCOMO™, SonoSite, Medis Medizinische Messtechnik GmbH, Ilmenau, Germany), according to a standard protocol as described [24]. Technological principles, benefits, limitations and figures on reproducibility have been reported elsewhere[21,102]. Maternal cardiac output (mL/min) was calculated from the product of measured values of heart rate (beats/min) and stroke volume (mL).

VENOUS ECG-DOPPLER ULTRASOUND

The ECG-Doppler assessment was performed by four ultra-sonographers (SV, AS, TM and KT) with known intra- and interobserver correlation[101] according to the study protocol as reported[82] in supine position during interrupted breathing, using a 3.5 MHz transabdominal probe (Aplio Mx, Toshiba Medical Systems nv., Sint-Stevens-Woluwe, Belgium). The hepatic veins were evaluated at the cranio-caudal portion of the liver. Maximum en minimum velocities (V_{max}, V_{min}) were measured, and a hepatic venous impedance index (HVI) was calculated as [V_{max}-V_{min}/V_{max}]. Venous pulse transit times (VPTT) were measured as the time interval between the P-wave of the ECG and the corresponding A-wave of the venous Doppler wave, corrected for heart rate [PA/RR][82,100].

STATISTICS

Statistical analyses were done using SPSS 22.0. Shapiro Wilk was performed to assess normal distribution of VI, VPTT, CO and BW%. Data were recorded as median + interquartile range. Rank-based Spearman's ρ correlation coefficient was calculated to assess the relation between HVI, CO, VPTT and BW%. For each relation, linear regression analysis was performed with calculation of R^2 goodness of fit and p-value, which was considered significant at nominal level $\alpha < 0.05$.

RESULTS

From a total of 309 women, 236 pregnant women were excluded due to maternal, gestational or foetal problems[98], leaving 73 inclusions with a normal course of pregnancy and neonatal outcome (Figure 2.1.1). Data on participant demographics, neonatal outcome + BW% and maternal cardiovascular characteristics are shown in Table 2.1.1. Only CO and VPTT showed normal distribution.

Correlations between HVI, VPTT, CO and BW% are shown in Figure 2. All correlations were significant. There was a negative correlation between HVI and VPTT ($\rho = -0.719$, $p<0.001$). Both HVI and VPTT correlated with CO ($\rho = -0.403$, $p<0.001$ and $\rho = 0.332$, $p<0.004$ resp.) and with BW% ($\rho = -0.341$,

$p<0.003$ and $\rho = 0.296$, $p<0.011$ resp.). Linear equations, values of R^2 and p values are resented in Figure 2.1.2.

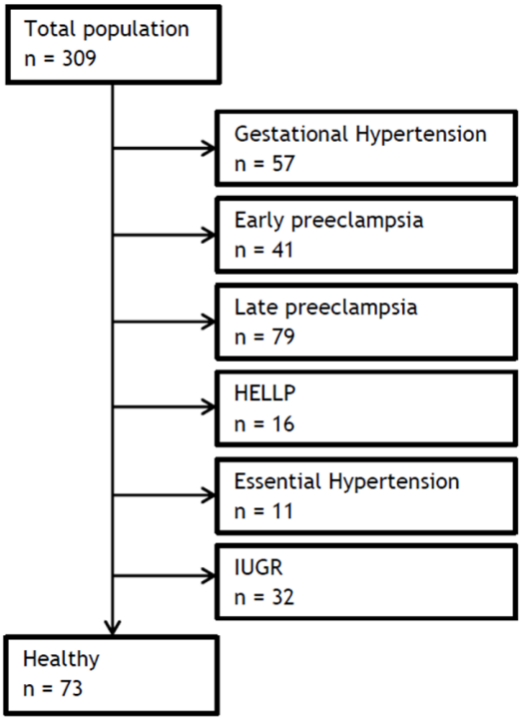

Figure 2.1.1: Structured record of the included and excluded participants.

DISCUSSION

This study aimed to investigate the relation between maternal cardiac output, maternal hepatic venous function and birth weight percentiles during healthy pregnancy. We observed that HVI and VPTT (hepatic venous parameters), both measured by ECG-Doppler, correlate with maternal CO as measured by ICG, which in turn correlates with birth weight percentiles. Moreover, the hepatic venous parameters also show a significant correlation with the birth weight percentiles.

This study's strengths are the use of rigid protocols for ICG and ECG-D assessment with reliable measurements and known inter- and intra-observer correlations, as well as customized population-specific birth weight charts. As all included women had antenatal care and delivery in the same hospital, all data on gestational, maternal and neonatal outcome are complete and directly available from the hospital records. The use of ICG for measuring maternal cardiac output during pregnancy may be subject of criticism[103,104], however this point of discussion has been dealt with in a recent review from our research team[21]. The current analysis does however not permit that hepatic circulation per se impacts on birth weight since there is an interdependency between CO and hepatic circulation. A different analysis is necessary to assess the contribution of CO and VPTT/HVI to variations in BW%.

An influence of the maternal CO on birth weight is already observed in other studies, supporting a physiological role of maternal cardiac output on foetal growth[97,105-107]. Already in the first trimester of pregnancy the relation between cardiac output and birth weights could be demonstrated[94,99]. The maternal cardiac output starts to increase very early in pregnancy and pregnancies which fail to achieve this increase often end up with growth restricted babies[108].

The venous compartment cooperates with the heart as one functional unit to regulate venous return and cardiac output[109,110]. This venous activity is far more important than the arterial resistance in this process[109]: experiments showed that changes of venous resistance affect the cardiac output eight times more than changes in arterial resistance[111]. A small change in vein diameter, compliance and intraluminal pressure has a tremendous impact on its blood content and flow, which can easily influence cardiac output[110]. Next to this, the venous compartment is a capacitance reservoir which contains approximately two thirds of the total blood volume, one third of this residing in the splanchnic bed[112]. The liver is considered the most important buffer system for acute intravascular volume changes: a sudden increase of blood volume is sequestered in the hepatic venous bed[113] whereas this stored volume can easily be mobilized into the systemic circulation in case of sudden blood loss[114]. As such, hepatic hemodynamics is an important physiologic system in the control and regulation of cardiac output. Our data are in line with this. On the

one hand, we observed a positive correlation between venous pulse transit time (VPTT) of the liver and cardiac output. Venous pulse transit time is considered a Doppler measure for venous tone or wall stiffness. A low VPTT value suggests a fast retrograde conduct into the central circulation of the venous A-wave, which is caused by the contraction of the right atrium. This suggest a more rigid state of the venous vascular wall[82]. In chronic conditions, this low compliance will hamper intraluminal storage of blood and venous drainage from the organs[115], and consequently venous return and cardiac output will be low[109]. On the other hand, we observed that the hepatic vein impedance index (HVI) is negatively correlated with the cardiac output. This index is the Doppler equivalent of Arterial Resistivity Index and is calculated from the maximum and minimum velocities of the venous pulse wave[22]. A large value for HVI indicates a strong intravenous rebound of atrial contraction, which counteracts venous drainage from the organs[115]. In healthy pregnancies, this index becomes gradually lower due to adaptational changes[116]. Our findings illustrate that a low venous impedance index is correlated with a high cardiac output and vice versa. Both correlations suggest that the physiologic function of the hepatic venous bed in the regulation of cardiac output, reported for non-pregnant individuals, is also present during pregnancy. The importance of hepatic hemodynamics in normal or abnormal changes of maternal cardiac output is to be examined in further clinical and experimental research.

A new and interesting observation from our study is the correlation between hepatic venous Doppler indices and neonatal birth weight percentile (Figure 2.1.2). From the arguments outlined above, this correlation in fact seems logical as hepatic hemodynamics is involved in control of cardiac output, and maternal cardiac output is known to correlate with birth weight percentiles. A significant correlation does not necessarily mean that a causal relation exists between hepatic venous flow and foetal growth, however our observation invites to further explore the role of hepatic hemodynamics in the process of maternal cardiovascular adaptation and in the pathophysiology of gestational complications such as foetal growth restriction, gestational hypertension and/or liver diseases.

From the data presented in this paper, we conclude that in healthy women with uncomplicated pregnancies a correlation exists between hepatic vein Doppler parameters, maternal cardiac output and foetal birth weight percentiles. The role of hepatic hemodynamics in the regulation of cardiac output of non-pregnant individuals, and the relevance of maternal cardiac output towards foetal growth are well known. However, our data show for the first time a potential link between maternal hepatic hemodynamics and neonatal weight at birth. Whether this link is purely associative or whether hepatic vascular physiology has a direct impact on foetal growth is to be evaluated in more extensive clinical and experimental research.

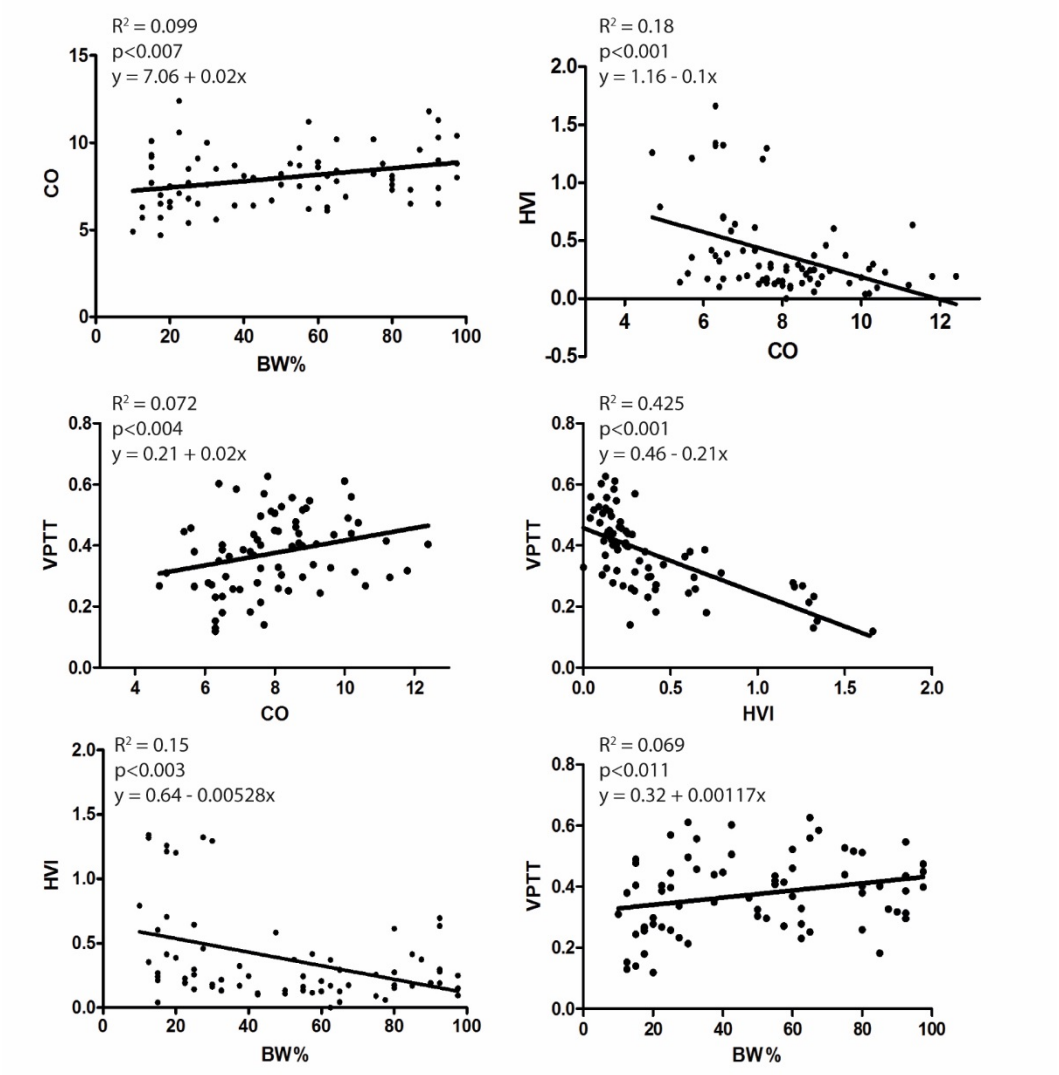

Figure 2.1.2: Scatterplots of the relations between maternal cardiac output (CO), hepatic vein impedance index (HVI), hepatic vein pulse transit time (VPTT) and customised birth weight percentile (BW%).

CHAPTER 2.2

Obesity in pregnancy causes a volume overload in third trimester

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ABSTRACT

Objectives

To investigate the maternal circulatory differences during pregnancy between obese and normal weight women.

Methods

An observational study was performed on 117, 83 & 32 pregnant, obese women (BMI ≥30 kg/m^2) and 506, 349 & 64 pregnant, normal weight women (BMI 20-25 kg/m^2) in resp. first, second and third trimester. The functioning of the maternal circulation (arteries, veins, heart and body fluid) was assessed by ECG-Doppler ultrasound, impedance cardiography and bio-impedance.

Results

Blood pressures, cardiac output and body fluid content were persistently higher in obese compared to non-obese patients ($p<0.001$). Central arterial function ($p<0.0001$) was reduced and peripheral veins and arteries were more compliant ($p<0.05$). In third trimester, a significant drop of cardiac output ($p<0.037$) was seen in obese but not in non-obese women.

Conclusion

The circulatory gestational adaptations between non-obese and obese women were generally similar. The findings suggest that pregnancy in obese women start as a state of high volume load, gradually shifting to a volume overload in third trimester, potentially predisposing to certain gestational complications.

INTRODUCTION

Obesity is a major risk factor for cardiovascular diseases, including systolic and diastolic dysfunction[117-119], left ventricular hypertrophy[117-119], increased blood pressures[120,121], impaired arterial[122] and/or venous function[123-125]. The aetiology of obesity related cardiovascular morbidity is however still not completely understood. The frequency of obese pregnant women is increasing worldwide and is known to be a risk factor for maternal complications, including gestational diabetes, hypertension, heart failure or thromboembolic complications[126,127], and for adverse neonatal outcomes, including foetal macrosomia, prematurity/stillbirth or congenital anomalies[127].

A normal pregnancy demands a profound adaptation of the maternal cardiovascular system to meet the oxygen and nutrient requirements of the foetus. A fall in peripheral vascular resistance occurs initially[39-41] and is followed by an increase of heart rate[39,43] and cardiac output[39,40] in association with cardiac morphologic changes[39,42,60]. The imbalance between vasodilation and cardiac output lowers maternal blood pressure until mid-gestation[46]. The blood pressure fall induces sodium and water reabsorption[128], thereby increasing the total maternal body water[47,52,53,129].

An obese woman starts pregnancy with a pre-existing chronical endothelial dysfunction and diverse haemodynamically aberrations which might influence the normal physiological changes occurring during pregnancy[130]. Higher heart rates[131,132] and blood pressures[132-134], but no differences in stroke volume, cardiac output or total peripheral resistance[132,135], were found in reported obesity studies with pregnant women. However, those studies are performed in pregnant, obese women to assess their cardiovascular function but they do not provide full information of all trimesters or consider the maternal circulation only partially[131-135]. At Hasselt University, a study project on Maternal Hemodynamics is ongoing where the global cardiovascular system is assessed according to a standard protocol in >1000 women. From this set of data, several analyses are being done, one of which is presented in this study. Here, we aim to investigate the maternal circulatory differences between uncomplicated obese and normal weight pregnancies by applying a combined assessment of the

important parts of the circulation (heart, central and peripheral arteries, central veins and body fluid) during first, second and third trimester, and hypothesize that the haemodynamic function is different in these two groups, both at start and during course of pregnancy.

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 normal singleton pregnancies presenting at the obstetric ultrasound scanning clinic at Ziekenhuis Oost-Limburg Genk were invited to participate in an observational study on maternal cardiovascular function, as part of the ongoing Hasselt University Study Project on Maternal Venous Hemodynamics (Figure 1, appendix). Patients with an uncomplicated pregnancy course and a pregestational body mass index (BMI) between 20-25 kg/m2 (non-obese group) and ≥30 kg/m2 (obese group) were selected for this analysis. Three periods of assessment were considered: women included in the first trimester (< 15 weeks), second trimester (15+0 to 27+6 weeks) and third trimester (≥ 28 weeks). All women were invited for longitudinal measurements, of which 56% eventually did partly (2 trimesters) and 3,2% completely (3 trimesters). BMI was based on pregestational weight and height (BMI = weight (kg)/length (m)²). Patients with any type of hypertension, HELLP, proteinuria or small for gestational age neonates were excluded, as well those with pregestational or early gestational cardiovascular disease, pregnancies with multiplets or with pregestational BMI <20 or between 25-30. Demographic details were maternal age (years), pregestational BMI, gestational age at assessment and at delivery, parity, smoking, neonatal birth weight and percentile.

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 volume content (Table 2.2.1), in a quiet environment after the routine obstetric ultrasound scan. All patients had all assessments in 1

session and at least once during pregnancy. A standardised protocol with known inter- and intra-observer correlations was used as reported in previous studies[24,136,137].

Impedance Cardiography (ICG)

The Non-Invasive Continuous Cardiac Output Monitor (NICCOMO, Medis Medizinische Messtechnik GmbH, Ilmenau, Germany) was used for automated blood pressure measurements on the right arm and with an appropriate cuff width (Medium for the non-obese group and Large for the obese group) at standard time points. ICG analysis was performed with four electrodes (two on the axillary line under the thorax and two in the neck) eliminating skin resistance. The examination was performed after stabilisation of cardiovascular function in standing position, as reported. Parameters were classified into five groups: blood pressures [systolic (SBP), diastolic (DBP), mean arterial pressure (MAP), pulse pressure (PP)], flow parameters [heart rate (HR), stroke volume (SV), cardiac output (CO)], contractility parameters [pre-ejection period (PEP), left ventricular ejection time (LVET), velocity index (VI), acceleration index (ACI), heather index (HI)], thoracic fluid parameters [thoracic fluid content (TFC)], vascular parameters [total arterial compliance (TAC), total peripheral resistance (TPR)]. The latter was calculated using the formula (MAP x 80) / CO [138,139].

Table 2.2.1: Overview of all parameters derived in one cardiovascular assessment session with the three techniques. ECG: electrocardiogram; ICG: impedance cardiography.

	ECG-DOPPLER	ICG	BIO-IMPEDANCE
HEART		Heart Rate (HR) Stroke Volume (SV) Cardiac Output (CO) Pre-ejection Period (PEP) Left Ventricular Ejection Time (LVET)	
ARTERIES	Arterial Pulse Transit Time (APTT) Pulsatility Index (PI) Resistivity Index (RI)	Velocity Index (VI) Acceleration Index (ACI) Heather Index (HI) Total Arterial Compliance (TAC) Total Peripheral Resistance (TPR) Systolic Blood Pressure (SBP) Diastolic Blood Pressure (DBP) Mean Arterial Pressure (MAP) Pulse Pressure (PP)	
VEINS	Hepatic Venous Pulse Transit Time (VPTT) Left and Right Renal VPTT Hepatic Vein Index (HVI) Renal Interlobal Vein Index (RIVI)		
FLUID		Thoracic Fluid Content (TFC)	Total Body Water (TBW) Extracellular Water (ECW) Intracellular Water (ICW)

ECG-Doppler Ultrasound

An electrocardiogram was combined with Doppler ultrasonography of the maternal renal interlobar veins, hepatic veins, and the arcuate uterine arteries 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-variability[101]. Parameters of arteries and veins were divided into 2 groups: pulse transit times and impedance indices.

The venous pulse transit time (VPTT) is the time interval between the P-top from the ECG-wave and the A-wave from the Doppler pulse wave (PA in ms). In the arteries (arterial pulse transit time, APTT), the time interval starts at the Q-wave on the ECG and ends at the start of the Doppler end-diastolic point D (QD in ms). The pulse transit times (APTT + VPTT) are adjusted for heart rate, which is variable due to advancing gestation, and thereby divided by RR (time interval between two consecutive R-waves of the ECG signal)[82].

At the venous side, the maximum and minimum flow velocity is measured from the renal and hepatic Doppler signal. An impedance index is calculated using the formula [(Maximum Velocity-Minimum Velocity)/Maximum velocity][136,140]. This renal interlobar vein index (RIVI) and hepatic vein index (HVI) are considered the venous equivalents of the arterial Resistive Index (RI) which is calculated by the formula (Peak systolic velocity – End diastolic velocity)/Peak systolic velocity. In the uterine arcuate arteries, RI and Pulsatility Index (PI, (Peak systolic velocity – minimal diastolic velocity)/Mean velocity) were measured as reported[12,141].

Bio-impedance

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 [26]. 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) could be estimated by bio-impedance, as the total of intracellular water (ICW) and extracellular water (ECW), including interstitial, transcellular water, and plasma volume.

STATISTICS

Normality was checked via Shapiro-Wilk. For the demographical variables, a Mann Whitney-U test at 5% significance level was used for continuous data to compare the obese group with the non-obese group. Chi-square test was used for categorical demographic variables. Data were presented as median with interquartile range or n (%). By use of a Mann Whitney-U test at 5% significance, the cardiovascular parameters were compared between the obese and non-obese patients in each trimester, even as the cross-trimestral changes within the obese and non-obese group. All analyses were done in SPSS (SPSS Inc., Chicago, Illinois, USA).

RESULTS

There were 117 measurements done in first trimester in the obese group, 83 in second trimester and 32 in third trimester. The non-obese group consisted of 506 measurements in first trimester, 349 in second trimester and 64 in third trimester. Baseline patient and outcome characteristics are enlisted in Table 2.2.2. In the obese group, mean birth weight, birth weight percentile and pregestational BMI were higher than the control group. Nulliparity was 39% in the obese group vs. 47% in the control group. There were no further demographical differences between both groups apart from a coincidental difference between gestational age at recruitment in second trimester.

Table 2.2.3 provides a detailed summary of all hemodynamical features. Blood pressures, CO and body fluids were consistently higher in obese compared to non-obese patients ($p<0.03$). Higher CO was due to a higher SV in first trimester ($p<0.0001$) and a higher HR in third trimester ($p<0.02$). Central arterial function, indicated by lower VI and ACI, was worse throughout pregnancy in obese patients ($p<0.001$). Veins and arteries in liver, kidneys and uterus, assessed by VPTT and APTT, were more compliant in obese patients in

each trimester ($p<0.05$). Compared to normal patients, TPR was significantly lower in first and second trimester in obese women.

Figure 2.2.1 presents visually the hemodynamic changes throughout pregnancy in the obese and non-obese patients. Non-obese patients showed a physiological blood pressure decrease in mid-gestation, which was not observed in the obese group where only a late gestational increase was present (Figure 2.2.1A). A remarkable decrease in CO was seen in the obese group between second and third trimester, which was not present in the non-obese group (Figure 2.2.1B). Its component HR and SV were found with diverse patterns too: HR remained stable in non-obese, whereas it increased in second trimester in obese (Figure 2.2.1C). SV increased until mid-gestation and stabilized in non-obese, whereas SV showed no difference between the trimesters in the obese group (Figure 2.2.1D). Arterial and venous pulse transit times showed a similar evolution in obese and non-obese (Figure 2.2.1E-F), but at another baseline level. Central arterial function, measured by VI and ACI, is shown in Figure 2.2.1G and values peaked in second trimester for non-obese but not obese, and both decreased in third trimester. Figure 2.2.1H shows TPR, which had a similar evolutionary pattern, although the decrease and increase of TPR was less pronounced in obese. Body fluids (TBW, ECW and ICW) were found to increase during early gestation in both controls and obese, but a further TBW rise in late gestation was only present in non-obese women (Figure 2.2.1I).

Table 2.2.2: Patient and outcome characteristics of the non-obese vs. the obese population. Data are presented as median (IQR) or n (%). p<0.05 was considered significant.

	NON-OBESE (N=919)	OBESE (N=232)	P-VALUE
CHARACTERISTICS AT INCLUSION			
MATERNAL AGE, YEARS	30 (28-34)	30 (28-34)	*0.74*
GESTATIONAL AGE AT ASSESSMENT, WEEKS+DAYS			
FIRST TRIMESTER	12w2d (11w5d-12w5d)	12w2d (11w5d-12w5d)	*0.675*
SECOND TRIMESTER	20w2d (19w6d-20w5d)	20w3d (20w-21w)	***0.041***
THIRD TRIMESTER	32w3d (30w3d-35w2d)	32w6d (30w2d-34w6d)	*0.929*
PREGESTATIONAL BMI, KG/M²			
FIRST TRIMESTER	22,57 (21.3-23.94)	33,12 (31.61-35.93)	***0.0001***
SECOND TRIMESTER	22,57 (21.3-24.11)	33,17 (31.64-35.67)	***0.0001***
THIRD TRIMESTER	23,26 (21.51-24.61)	33,58 (31.27-36.77)	***0.0001***
NULLIPARITY	434 (47%)	91 (39%)	***0.032***
CIGARETTE SMOKER	123 (18%)	22 (14%)	*0.202*
OUTCOME CHARACTERISTICS			
BIRTH WEIGHT, G	3,400 (3,145-3,675)	3,555 (3,237-3,862)	***0.0001***
BIRTH WEIGHT, PERCENTILE	57.5 (32.5-75)	67.5 (40-90)	***0.0001***
GESTATIONAL AGE AT DELIVERY, WEEKS + DAYS	39w5d (38w5d-40w3d)	39+4 (38w1d-40w4d)	*0.083*

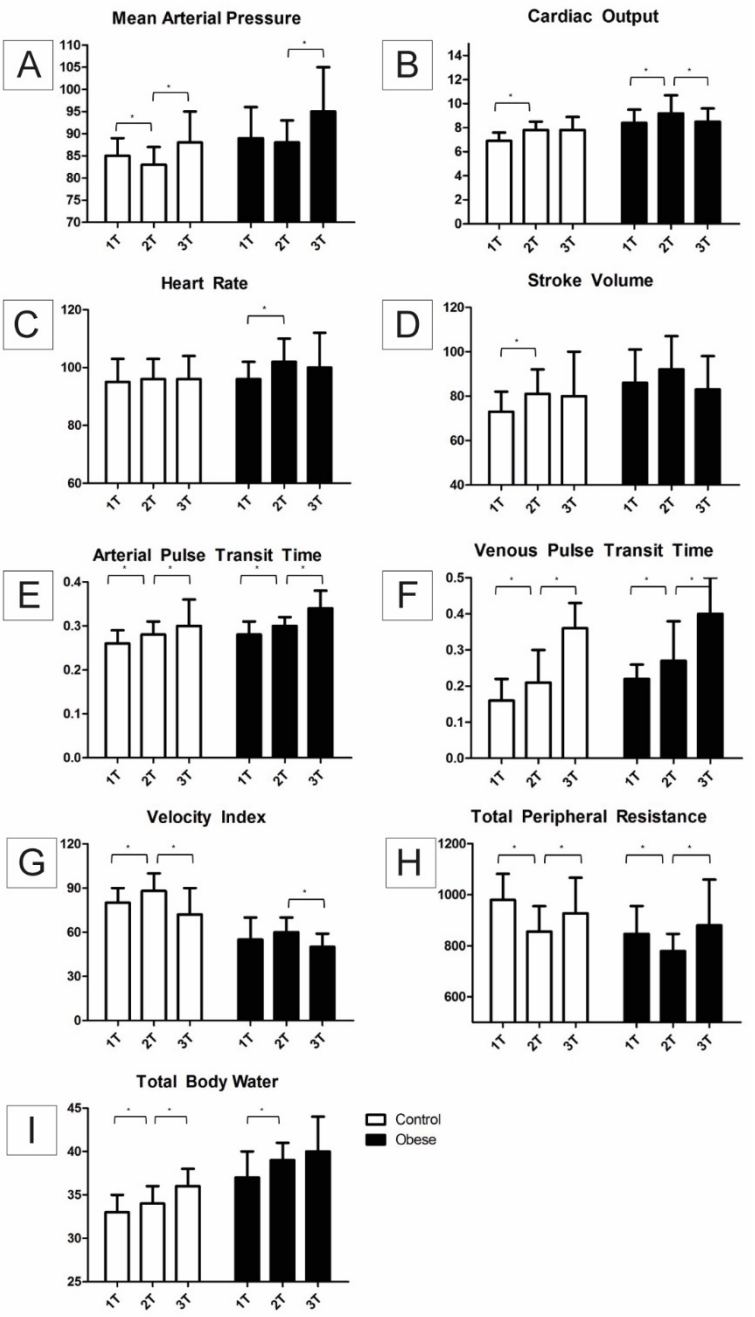

Figure 2.2.1: Graphical representation of the hemodynamic changes in obese (black) and non-obese (white) patients. The median with interquartile range is represented. 1T: first trimester; 2T: second trimester; 3T: third trimester. *Significant cross-trimestrial change in the obese or non-obese group at a 5% level of significance.

Table 2.2.3: Hemodynamic differences in each trimester between non-obese and obese patients. Data are shown as median (interquartile range). p<0.05 was considered significant.

	FIRST TRIMESTER			SECOND TRIMESTER			THIRD TRIMESTER		
	Non-obese	Obese	*p-value*	Non-obese	Obese	*p-value*	Non-obese	Obese	*p-value*
PRESSURES									
SYSTOLIC BLOOD PRESSURE (MMHG)	113 (106-122)	123 (115-132)	***0.0001***	111 (105-121)	122 (113-127)	***0.0001***	120 (111-130)	134 (123-142)	***0.0001***
DIASTOLIC BLOOD PRESSURE (MMHG)	75 (70-79)	80 (73-84)	***0.0001***	72 (68-77)	78 (73-82)	***0.0001***	78 (71-85)	84 (78-94)	***0.001***
MEAN ARTERIAL PRESSURE (MMHG)	85 (80-89)	89 (84-96)	***0.0001***	83 (78-87)	88 (83-93)	***0.0001***	88 (80-95)	95 (90-105)	***0.0001***
PULSE PRESSURE	37 (33-44)	45 (39-50)	***0.0001***	40 (34-47)	43 (37-50)	***0.005***	43 (37-47)	45 (39-59)	***0.0001***
FLOW									
CARDIAC OUTPUT (L/MIN)	6.9 (6.3-7.6)	8.4 (7.6-9.5)	***0.0001***	7.8 (7-8.5)	9.2 (8.2-10.7)	***0.0001***	7.8 (6.8-8.9)	8.5 (7.6-9.6)	***0.027***
HEART RATE (BPM)	95 (88-103)	96 (90-102)	*0.378*	96 (89-103)	102 (94-110)	***0.0001***	96 (86-104)	100 (94-112)	***0.019***
STROKE VOLUME (ML)	73 (65-82)	86 (76-101)	***0.0001***	81 (72-92)	92 (80-107)	***0.0001***	80 (72-100)	83 (76-98)	*0.457*
CONTRACTILITY									
VELOCITY INDEX (1/1000/S)	80 (69-90)	55 (44-70)	***0.0001***	88 (74-100)	60 (45-70)	***0.0001***	72 (57-90)	50 (41-59)	***0.0001***
ACCELERATION INDEX (1/100/S^2)	170 (141-202)	110 (88-138)	***0.0001***	183 (150-219)	112 (82-148)	***0.0001***	144 (109-186)	90 (80-124)	***0.0001***
LEFT VENTRICULAR EJECTION TIME	230 (218-244)	234 (223-247)	*0.122*	236 (222-249)	228 (215-242)	***0.006***	244 (225-261)	234 (212-254)	***0.044***
VASCULAR									
TOTAL PERIPHERAL RESISTANCE (DYN.SEC/CM^5)	980 (883-1082)	847 (743-956)	***0.0001***	856 (760-955)	780 (626-847)	***0.0001***	928 (780-1067)	880 (761-1060)	*0.645*
TOTAL ARTERIAL COMPLIANCE (ML/MMHG)	1.9 (1.6-2.3)	2 (1.6-2.4)	*0.146*	2 (1.8-2.4)	2.2 (1.7-2.7)	*0.055*	2 (1.5-2.4)	1.9 (1.5-2.4)	*0.62*
RENAL VEINS									
LEFT VENOUS PULSE TRANSIT TIME (S)	0.30 (0.25-0.34)	0.33 (0.29-0.38)	***0.0001***	0.30 (0.26-0.35)	0.35 (0.30-0.40)	***0.0001***	0.38 (0.32-0.43)	0.43 (0.39-0.51)	***0.003***
RIGHT VENOUS PULSE TRANSIT TIME (S)	0.27 (0.21-0.32)	0.33 (0.26-0.38)	***0.0001***	0.31 (0.25-0.36)	0.35 (0.31-0.40)	***0.0001***	0.37 (0.33-0.43)	0.45 (0.39-0.48)	***0.005***
LEFT RENAL INTERLOBAR VEIN INDEX	0.44 (0.39-0.50)	0.42 (0.36-0.46)	***0.001***	0.43 (0.36-0.50)	0.38 (0.33-0.45)	***0.0001***	0.36 (0.30-0.41)	0.32 (0.29-0.38)	*0.109*
RIGHT RENAL INTERLOBAR VEIN INDEX	0.46 (0.41-0.52)	0.42 (0.37-0.50)	***0.002***	0.42 (0.36-0.49)	0.37 (0.32-0.43)	***0.0001***	0.32 (0.26-0.37)	0.28 (0.24-0.33)	*0.074*
HEPATIC VEINS									
LIVER VENOUS PULSE TRANSIT TIME (S)	0.16 (0.12-0.22)	0.22 (0.17-0.26)	***0.0001***	0.21 (0.15-0.30)	0.27 (0.21-0.38)	***0.0001***	0.36 (0.25-0.43)	0.40 (0.29-0.50)	***0.045***
HEPATIC VEIN INDEX	1.43 (0.89-1.56)	1.04 (0.43-1.51)	***0.0001***	0.83 (0.24-1.42)	0.42 (0.15-0.68)	***0.0001***	0.19 (0.13-0.42)	0.17 (0.13-0.36)	*0.622*
UTERINE ARTERIES									
LEFT ARTERIAL PULSE TRANSIT TIME (S)	0.26 (0.24-0.29)	0.28 (0.26-0.31)	***0.0001***	0.28 (0.25-0.31)	0.30 (0.27-0.32)	***0.001***	0.3 (0.27-0.36)	0.34 (0.30-0.38)	*0.06*
RIGHT ARTERIAL PULSE TRANSIT TIME (S)	0.27 (0.24-0.29)	0.28 (0.25-0.30)	***0.005***	0.29 (0.26-0.32)	0.31 (0.28-0.33)	***0.0001***	0.31 (0.28-0.35)	0.34 (0.30-0.38)	***0.048***
FLUID									
TOTAL BODY WATER (L)	33 (31-35)	37 (35-40)	***0.0001***	34 (32-36)	39 (36-41)	***0.0001***	36 (34-38)	40 (37-44)	***0.0001***
EXTRACELLULAR WATER (L)	14 (13-15)	16 (15-18)	***0.0001***	15 (13-16)	17 (16-18)	***0.0001***	16 (15-17)	18 (17-21)	***0.001***
INTRACELLULAR WATER (L)	19 (18-20)	21 (19-22)	***0.0001***	19 (18-20)	21 (20-23)	***0.0001***	20 (19-21)	22 (20-24)	***0.0001***
THORACIC FLUID CONTENT (1/KΩ)	25 (24-27)	23 (21-26)	***0.0001***	26 (24-28)	24 (22-27)	***0.0001***	26 (24-30)	24 (22-27)	***0.0001***

DISCUSSION

According to our data, obese pregnant women have significantly higher body water volumes, associated with higher blood pressures and alterations in heart, arterial and venous system function. The circulatory evolution during pregnancy between obese and non-obese patients was comparable in the first part of pregnancy, but differed in the second part with a CO decrease in third trimester in the obese patients. Our data comply with a state of high volume load in first and second trimester in obese women, but a volume overload in third trimester.

Our study is one of the first to assess all levels of the maternal circulatory function as one integrated system in a large sample of obese patients at each trimester of pregnancy. The use of a non-invasive technology with a standardized protocol and known inter- and intra-observer correlations is an advantage. Bio-impedance may be criticized as being less valid than maternal echocardiography or dye dilution plasma volume measurements, however our results are in line with these gold-standard methods [21]. We acknowledge that the number of pregnancies with longitudinal measurements in each trimester is low and no correction for multiple testing was performed, due to which some of the significant results can still relate to chance. Non-pregnant, obese patients were not included in the study, nor hypertensive, obese pregnant patients or those with small for gestational age neonates, as they are part of another analysis by our study group to be reported separately.

Obesity is a physiologic state of chronic volume load, induced by high intra-abdominal pressure and adipose accumulation within and around the kidneys and other organs[121,142]. It causes the activation of renin-angiotensin-aldosterone system (RAAS), where the circulating aldosterone increases the renal tubular reabsorption. Body water volume rises consequently, inducing a cascade of higher venous return, SV, CO and blood pressures. The persistent effect of higher blood volumes leads to left ventricular hypertrophy, with systolic and diastolic dysfunction[119,121,142]. Our data show higher baseline volumes (TBW, ECW, ICW, CO, SV) and blood pressures (SBP, DBP, MAP) in obese compared to the non-obese group (Table 2.2.3, Figure 2.2.1). Obese women suffer from an almost depleted splanchnic reserve volumes, due to a shift of stored splanchnic venous blood into the circulation[120]. The adipose tissue

surrounding the maternal blood vessels causes the release of inflammatory mediators changing the vasculatory structure and tone, with vessel diameter increase and permeability rise[120,126]. This is also compatible with our results at baseline: TPR is low, indicating vasodilatation, APTT/VPTT's are high and HVI/RIVI is low, indicating easily expandable blood vessels.

Pregnancy is also a physiological state of volume load which need an adapted cardiovascular system to preserve all hemodynamical functions. The physiological cascade is initiated by the fall of the peripheral resistance, increasing HR and CO. A blood pressure fall results, activating the RAAS system and initiating a rise in volumes to restore the blood pressure[10,41]. The persistent volume load triggers left ventricular hypertrophy remodelling with an increase in myocardial contractility: higher SV, CO and HR. Our results are in line with this. Even though pregnancy is a natural process, a percentage of women with a normal pregnancy outcome were reported at the edge of decompensation at term, suffering from myocardial dysfunction due to the chronic volume load and constant remodelling. As such, for some women normal pregnancy can become a state of volume overload[143].

Obesity and pregnancy are both burdened with high body fluid levels. Our data show that the average amount of fluid present in the obese maternal body in first trimester is at the same level or even higher than a non-obese maternal body in third trimester. The capacity to respond to all physiological pregnancy demands is therefore reduced in obese patients[133,144]. The cardiovascular adaptation until mid-gestation is similar in the obese and non-obese groups, except for the HR increase and the TPR decrease which is less pronounced in the obese group and is both associated with the observed higher blood pressures[131]. An obese patient in mid-gestation must deal with a high circulatory and high capacitance volume state. In second part of pregnancy, this condition merely becomes a state of volume overload, expressed by a decrease in CO which is not observed in normal weight women. Obese patients have a baseline low venous and arterial tone (Table 2.2.3) to accommodate the higher blood volumes and maintain blood pressure as normal as possible. This population is very susceptible for small changes in TPR, raising the blood pressures as consequence[145]. Due to the adipose tissue around the blood

vessels, an obese patient is reported to start pregnancy already with a chronic state of inflammation, related to a pre-existing endothelial dysfunction[126,130,146]. Shear stress is induced by the high circulating blood volumes, releasing endothelial mediators which stimulate the structural remodelling of the blood vessels[147]. The high amount of adipose tissue together with high volumes might lead to a disturbed vascular reaction and higher risk of complications. Those complications might predispose to or even trigger preeclampsia, which is suggested to occur in 2 types: 1) A placental type with poor foetal growth, high TPR and low CO [92] and 2) a maternal type with normal foetal growth, normal to high CO and low TPR [145]. We reported that obese women are more susceptible for the latter type [148], most likely due to their pregestational high flow state. An early identification and intensified cardiovascular follow-up in this population may help to tackle the adverse outcomes. Results concerning these two phenotypes of preeclampsia are however still conflicting [15,148-150].

In this study, we have demonstrated that cardiovascular function of obese pregnant women is characterized by higher maternal body volumes, higher blood pressures and associated altered changes in heart, arterial and venous function. The combination of pregnancy-induced volume changes and pregestational obesity-induced high volumes brings a pregnant woman in mid-gestation to a state of high volume load, which will gradually shift to a volume overload in third trimester. These data should be taken into account when interpreting cardiovascular measurements in obese women, with respect to gestational complications such as hypertension of foetal growth restriction. It is also an interesting physiological phenomenon for further research into medication for resolving hypertension by reducing the body volume (diuretics) or plasma reduction.

CHAPTER 2.3

Uterine Flow Promoting Phenomenon in Normotensive Pregnancies with Healthy Neonates Small for Gestational Age

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ABSTRACT

Objective

A normal pregnancy requires an appropriate adaptation of the maternal circulation, whereas pregnancies complicated with small for gestational age (SGA) neonates have diverse circulatory deficits. For this study, we hypothesize that the maternal hemodynamic function of all major components of the circulation differ between normotensive pregnancies with SGA and appropriate/large (non-SGA (NGA)) neonates.

Methods

An observational study was conducted in 3 trimestrial cohorts of normotensive pregnancies, categorized after birth according to neonatal birth weight percentile (BW%) as SGA (n=158; BW% $\leq$ 10) or NGA (n=1,038; BW% > 10). Standardized electrocardiogram-Doppler ultrasound, impedance cardiography, and bio-impedance were used to assess the maternal heart, arteries, veins and fluid. Linear Mixed Models were used to compare cardiovascular parameters in each trimester between SGA and NGA.

Results

In SGA, compared to NGA, total peripheral resistance (TPR) was higher and total arterial compliance, cardiac output (CO) and total body water (TBW) were lower throughout pregnancy. Third trimester TPR increased simultaneous with decreasing uterine artery resistance and this effect was more pronounced in SGA than NGA. In NGA but not SGA, a positive correlation was found between BW% and CO & TBW and a negative correlation between BW% and TPR.

Conclusion

SGA pregnancies are characterized by lower maternal body fluid volume and CO, while normal blood pressures are maintained via increased TPR. The latter combined with decreased uterine artery resistance is responsible for a uterus-flow-promoting phenomenon, which is more pronounced in SGA than NGA, and indicates that larger fractions of CO are shifted to the uterus.

INTRODUCTION

Pregnancy needs a coordinated process at each level of the circulation: the heart, the arteries, the microcirculation, the veins and the blood. A cascade of vasodilatation and lower blood pressures followed by volume restoring mechanisms ensure an adequate uteroplacental blood supply throughout pregnancy[10]. Many studies highlight an impaired cardiovascular adaptation of the maternal circulation in pregnancies complicated by intra-uterine growth restriction (IUGR) and/or birth of small for gestational age (SGA) neonates. In each trimester of these pregnancies, lower plasma volumes[151], cardiac output[108] and/or smaller left atrial diameter were reported[108,152] In advanced stages of pregnancy, this was associated with higher total peripheral resistance[153], lower heart rate[152], lower stroke volume[152], and higher blood pressures.[152]

None of these studies however evaluated all aspects of the circulation simultaneously, or have information in all trimesters. Therefore, we aim to investigate the maternal circulatory differences between normotensive pregnancies with SGA neonates and appropriate/large (non-SGA (NGA)) neonates by applying a combined assessment of the most important parts of the circulation (heart, central and peripheral arteries, central veins and body fluid) during first, second and third trimester. We hypothesize that the differences are type-specific.

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 singleton pregnancies presenting at the obstetric ultrasound scanning clinic at Ziekenhuis Oost-Limburg Genk between 1/1/2006-31/12/2016 were invited to participate in an observational study on maternal cardiovascular function, as part of the ongoing Hasselt University Study Project on Maternal Venous Hemodynamics. Three cohorts were considered: women included in the first trimester (< 15 weeks), second trimester (15+0 to 27+6 weeks) and third trimester (≥ 28 weeks). All women were invited for longitudinal measurements, of which 51% eventually did partly (2 trimesters)

and 3.5% completely (3 trimesters). After birth, the neonatal birth weight percentile (BW%) was used to categorize these data as SGA (BW% ≤ 10) or NGA (BW% > 10). Prenatal ultrasound and foetal Doppler data of the SGA neonates were retrieved retrospectively from the electronic records. Normotension was defined as sphygmomanometricly measured values < 140/90 mmHg in standing position. Multiplet pregnancies (n=34) or women with chronic cardiovascular disease (n=42) were excluded from this analysis, as well as women who developed gestational hypertension (n=136), preeclampsia (n=246) or HELLP (n=32). Results of measurements in these groups will be reported in a following paper. Demographic details were maternal age, pregestational BMI, gestational age at assessment and at delivery, parity, smoking, medication, neonatal birth weight and percentile.

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. All patients had all assessments in 1 session. A standardized protocol with known inter- and intra-observer correlations was used as reported in previous studies[12].

Impedance Cardiography (ICG)

The Non-Invasive Continuous Cardiac Output Monitor (NICCOMO, Medis Medizinische Messtechnik GmbH, Ilmenau, Germany) was used for automated blood pressure measurements on the right arm and with an appropriate cuff width at standard time points. ICG analysis was performed with four electrodes (two on the axillary line under the thorax and two in the neck) eliminating skin resistance. The examination was performed after stabilization of cardiovascular function in supine and standing position, as reported. Parameters were classified into five groups: blood pressures [systolic (SBP), diastolic (DBP), mean arterial pressure (MAP), pulse pressure (PP)], flow parameters [heart rate (HR), stroke volume (SV), cardiac output (CO)], contractility parameters [pre-ejection period (PEP), left ventricular ejection time (LVET), velocity index (VI), acceleration index (ACI), heather index (HI)], thoracic fluid parameters [thoracic fluid content (TFC)], vascular parameters [total arterial compliance (TAC), total

peripheral resistance (TPR)]. The latter was calculated using the formula (MAP x 80) / CO[138,139].

Electrocardiogram (ECG)-Doppler Ultrasound

An ECG was combined with Doppler ultrasonography of the maternal renal interlobar veins, hepatic veins and the arcuate uterine arteries 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-variability[101]. Parameters of arteries and veins were divided into 2 groups: pulse transit times and impedance indices.

The venous pulse transit time (VPTT) is the time interval between the P-top from the ECG-wave and the A-wave from the Doppler pulse wave (PA in ms). In the arteries (arterial pulse transit time, APTT), the time interval starts at the Q-wave on the ECG and ends at the start of the Doppler end-diastolic point D (QD in ms). The pulse transit times (APTT + VPTT) are adjusted for heart rate, which is variable due to advancing gestation, and thereby divided by RR (time interval between two consecutive R-waves of the ECG signal)[82].

At the venous side, the maximum and minimum flow velocity is measured from the renal and hepatic Doppler signal. An impedance index is calculated using the formula [(Maximum Velocity-Minimum Velocity)/Maximum velocity].[136,140] This renal interlobar vein index (RIVI) and hepatic vein index (HVI) are considered the venous equivalents of the arterial Resistive Index (RI) which is calculated by the formula (Peak systolic velocity – End diastolic velocity)/Peak systolic velocity. In the uterine arcuate arteries, RI and Pulsatility Index (PI, (Peak systolic velocity – minimal diastolic velocity)/Mean velocity) were measured as reported[12,141].

Bio-impedance

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[26]. 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) could be estimated by bio-impedance, as the total of intracellular water (ICW) and extracellular water (ECW), including interstitial, transcellular water, and plasma volume.

Uterine Flow Promoting Peripheral Resistance

From the analysis of our data, a new parameter was introduced combining parameters derived from ICG and ECG-Doppler assessments: TPR and APTT respectively. Both parameters were used for analysis in previous studies[12,22]. TPR is calculated as (MAP*80)/CO. Uterine arterial pulse transit time (APTT) is used as a measure for uterine arterial resistance. This parameter is derived from uterine arterial Doppler flow as time interval between ECG Q-wave and the start of the systolic Doppler wave. As such, APTT is directly related to uterine arterial compliance. The Uterine Flow Promoting Peripheral Resistance (UFPPR) is calculated as TPR/(1000*APTT) and describes the relationship between systemic and uterine vascular resistance.

STATISTICS

Normality was checked via Shapiro-Wilk. An independent t-test at 5% significance level was used to compare SGA and NGA for continuous demographic data. Chi-square test was used for categorical demographic variables. Data were presented as mean ± SD or n (%).

Linear Mixed Models for repeated measurements were used to examine differences between SGA and NGA and between trimesters. A random patient effect was used to correct for the correlation between trimestrial measurements of a pregnancy. Fixed effects of trimester and group (SGA or NGA), 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). The impact of demographical influences (BMI, smoking, nulliparity, and age) on the cardiovascular parameters was assessed by adding these patient characteristics in the linear mixed model. Corrections for multiple testing were not implemented.

Pearson Correlation Coefficient was calculated to assess the relation between BW% and CO, TPR & TBW.

RESULTS

A total of 1,196 normotensive pregnant women were included, of which 158 delivered SGA and 1,038 NGA neonates. For 541 pregnancies, a cardiovascular assessment was done only in one trimester, for 611 pregnancies cardiovascular data were collected in two trimesters and finally for 44 pregnancies cardiovascular data for all three trimesters were present. Numbers of pregnancies with a cardiovascular assessment in each trimester for SGA and NGA are presented in Figure 2.3.1.

Patient and outcome characteristics are enlisted in Table 2.3.1. To discover if the SGA neonates were pathological or constitutionally small, the prenatal umbilical artery PI was retrieved from the medical files. For 69/158 (44%) SGA infants a PI measurement was found, of which 60 (87%) were <95th percentile. The growth of SGA neonates without umbilical artery Doppler measurements (56%) was considered normal at routine third trimester ultrasound scan, and therefore no Doppler assessments were performed. As such, the majority of SGA neonates (94%) were not pathological but simply constitutionally small.

Detailed hemodynamic features are listed in Table 2.3.2. Figure 2.3.2A presents the difference of TBW, CO, MAP, and TPR in first, second and third trimester. Except for TPR and CO, all parameters showed a similar change throughout the pregnancy. In each trimester, CO, HR, and SV were lower and TPR higher in the SGA group compared to NGA (Table 2.3.2). DBP and MAP were not different in the first and second trimester, but were higher in the SGA group in third trimester (Figure 2.3.2A, Table 2.3.2). As compared to NGA, SGA showed for HR, CO, SV, TBW, TAC, right APTT, and all VPTT's lower values in first trimester, whereas TPR, HVI, left PI & RI were higher. CO increased from first to second trimester in both NGA and SGA, but in the third trimester a decreasing trend was observed in SGA, whereas there was an increasing trend in NGA (Figure 2.3.2A, Table 2.3.2). TPR decreased from first to second trimester in both NGA and SGA and increased again in third trimester (Figure 2.3.2A, Table 2.3.2). This TPR rise was more pronounced for SGA than NGA (Figure 2.3.2A). TBW

increased from first to third trimester, but all values of the SGA group were lower (Figure 2.3.2A). Venous and arterial pulse transit times rose with gestational age, whereas impedance parameters decreased (Figure 2.3.2B).

Figure 2.3.3 shows the UFPPR in each gestational trimester for SGA and NGA pregnancies. In NGA, UFPPR is highest in the first trimester and decreases in the second and third trimester. In each trimester, UFPPR is significantly higher in SGA than in NGA. Contrary to NGA, left UFPPR in SGA is higher in the third than in the second trimester.

As is shown in Table 2.3.3, there were weak, but significant correlations between BW% and CO, BW% and TPR, BW% and TBW, BW% and ECW in the NGA group, present at each trimester. In the SGA group, none of those correlations were significant.

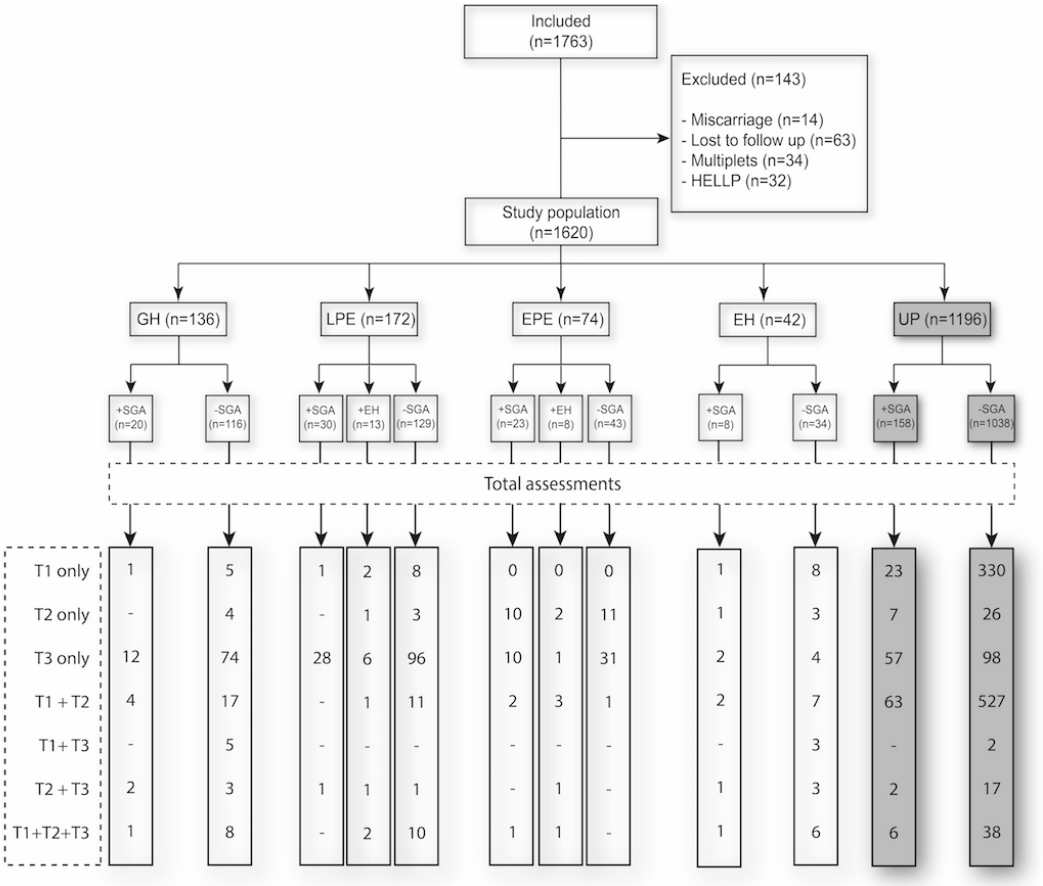

Figure 2.3.1: Flowchart from pregnancies included in the observational study as part of the Hasselt University Study Project on Maternal Venous Hemodynamics. The grey coloured parts are used for this study's analysis. 1196 normotensive pregnancies were divided after birth into Appropriate for Gestational Age (-SGA, represent NGA) and Small for Gestational Age (SGA), based on birth weight percentile. Assessments per patient were done in the first, second or third trimester (1T, 2T, 3T resp.) alone or in multiple trimesters. *GH: Gestational Hypertension; LPE: Late preeclampsia; EPE: Early preeclampsia; EH: Essential hypertension; UP: uncomplicated pregnancy.*

Table 2.3.1: Patient and outcome characteristics Appropriate for Gestational Age (NGA) and Small for Gestational Age (SGA). Data are presented as mean ± SD or n (%). Differences between SGA and NGA are presented as p-values. p<0.05 was considered significant.

	NGA (N=1,038)	SGA (N=158)	P-VALUE
CHARACTERISTICS AT INCLUSION			
MATERNAL AGE, YEARS	31±5	30±5	***0.018***
GESTATIONAL AGE AT CV ASSESSMENT, WEEKS+DAYS			
FIRST TRIMESTER	12w2d±0w5d	12w1d±0w4d	*0.558*
SECOND TRIMESTER	20w4d±1w3d	20w6d±1w5d	*0.235*
THIRD TRIMESTER	32w4d±3w3d	33w3d±3w1d	*0.089*
PRE-PREGNANCY BMI, KG/M²	24.8±5.3	23.5±5.25	***0.0001***
NULLIPARITY	663 (64%)	105 (66%)	*0.624*
CIGARETTE SMOKER	165 (16%)	59 (37%)	***0.0001***
MEDICATION			
ANTIHYPERTENSIVES	0	0	---
ANTICOAGULANTS	25 (2%)	2 (1%)	*0.410*
OUTCOME CHARACTERISTICS			
BIRTH WEIGHT, G	3,393±528	2,468±553	***0.0001***
BIRTH WEIGHT, PERCENTILE	56±26	5.8±4	***0.0001***
GESTATIONAL AGE AT DELIVERY, WEEKS	39±2	38±3	***0.0001***

Table 2.3.2: Hemodynamic differences in each trimester of Small for Gestational Age (SGA) and Non-SGA (NGA). Data are presented as least-square means ± SD

	FIRST TRIMESTER			SECOND TRIMESTER			THIRD TRIMESTER		
	SGA	NGA	*p-value*	SGA	NGA	*p-value*	SGA	NGA	*p-value*
ICG MEASUREMENTS									
PRESSURES									
DIASTOLIC BLOOD PRESSURE (MMHG)	75 ± 1.69	76 ± 0.58	*0.1188*	73 ± 1.85	74 ± 0.67	*0.5838*	82 ± 1.99	79 ± 1.15	*0.0810*
MEAN ARTERIAL PRESSURE (MMHG)	85 ± 1.79	86 ± 0.62	*0.3091*	83 ± 1.94	84 ± 0.7	*0.5775*	92 ± 2.1	89 ± 1.19	***0.0193***
FLOW									
CARDIAC OUTPUT (L/MIN)	6.8 ± 0.28	7.2 ± 0.1	***0.0177***	7.4 ± 0.3	8 ± 0.11	***0.0002***	7.3 ± 0.33	8.2 ± 0.18	***0.0001***
HEART RATE (BPM)	93 ± 2	96 ± 1	***0.0120***	94 ± 2	97 ± 1	***0.0120***	96 ± 2	99 ± 2	***0.0120***
STROKE VOLUME (ML)	72 ± 3	76 ± 1	***0.0066***	79 ± 3	83 ± 1	***0.0066***	79 ± 3	83 ± 2	***0.0066***
VASCULAR									
TOTAL PERIPHERAL RESISTANCE (DYN.SEC/CM^5)	1,047 ± 39	991 ± 13	***0.0070***	940 ± 41	869 ± 15	***0.0016***	1,063 ± 45	902 ± 25	***0.0001***
TOTAL ARTERIAL COMPLIANCE (ML/MMHG)	1.84 ± 0.09	1.96 ± 0.04	***0.0077***	1.99 ± 0.06	2.12 ± 0.04	***0.0077***	1.87 ± 0.1	1.99 ± 0.07	***0.0077***
DOPPLER-ECG MEASUREMENTS									
RENAL VEINS									
LEFT VENOUS PULSE TRANSIT TIME (S)	0.28 ± 0.01	0.3 ± 0.01	***0.0012***	0.3 ± 0.01	0.32 ± 0.01	***0.0012***	0.38 ± 0.01	0.40 ± 0.01	***0.0012***
RIGHT VENOUS PULSE TRANSIT TIME (S)	0.26 ± 0.01	0.28 ± 0.01	***0.0028***	0.3 ± 0.01	0.32 ± 0.01	***0.0028***	0.37 ± 0.01	0.4 ± 0.01	***0.0028***
RIGHT RENAL INTERLOBAR VEIN INDEX	0.45 ± 0.02	0.46 ± 0.01	*0.2453*	0.43 ± 0.02	0.41 ± 0.01	*0.0609*	0.36 ± 0.02	0.32 ± 0.01	***0.0060***
HEPATIC VEINS									
LIVER VENOUS PULSE TRANSIT TIME (S)	0.17 ± 0.02	0.19 ± 0.01	***0.0039***	0.23 ± 0.02	0.26 ± 0.01	***0.0039***	0.33 ± 0.02	0.36 ± 0.01	***0.0039***
HEPATIC VEIN INDEX	1.29 ± 0.08	1.19 ± 0.03	***0.0213***	0.88 ± 0.08	0.78 ± 0.04	***0.0213***	0.44 ± 0.09	0.34 ± 0.07	***0.0213***
UTERINE ARTERIES									
LEFT RESISTIVITY INDEX	0.67 ± 0.02	0.64 ± 0.01	***0.0083***	0.55 ± 0.02	0.52 ± 0.01	***0.0083***	0.53 ± 0.02	0.50 ± 0.02	***0.0083***
LEFT PULSATILITY INDEX	1.03 ± 0.04	0.98 ± 0.02	***0.0146***	0.78 ± 0.04	0.73 ± 0.02	***0.0146***	0.74 ± 0.05	0.69 ± 0.04	***0.0146***
RIGHT ARTERIAL PULSE TRANSIT TIME (S)	0.25 ± 0.01	0.27 ± 0.01	***0.0001***	0.28 ± 0.01	0.30 ± 0.01	***0.0001***	0.32 ± 0.01	0.34 ± 0.01	***0.0001***
BIO-IMPEDANCE MEASUREMENT									
TOTAL BODY WATER (L)	32.01 ± 0.84	33.94 ± 0.35	***0.0001***	33.08 ± 0.84	35.01 ± 0.35	***0.0001***	34.10 ± 0.9	36.04 ± 0.55	***0.0001***
EXTRACELLULAR WATER (L)	13.71 ± 0.46	14.66 ± 0.19	***0.0001***	14.42 ± 0.46	15.37 ± 0.19	***0.0001***	15.12 ± 0.48	16.08 ± 0.27	***0.0001***
UTERINE FLOW PROMOTING RESISTANCE									
LEFT UTERINE FLOW PROMOTING RESISTANCE (DYN.SEC/CM^2)	4.11 ± 0.2	3.77 ± 0.07	***0.0023***	3.44 ± 0.22	3.06 ± 0.08	***0.0015***	3.74 ± 0.24	2.95 ± 0.13	***0.0001***
RIGHT UTERINE FLOW PROMOTING RESISTANCE (DYN.SEC/CM^2)	4.25 ± 0.16	3.72 ± 0.07	***0.0001***	3.52 ± 0.16	2.99 ± 0.07	***0.0001***	3.41 ± 0.17	2.88 ± 0.11	***0.0001***

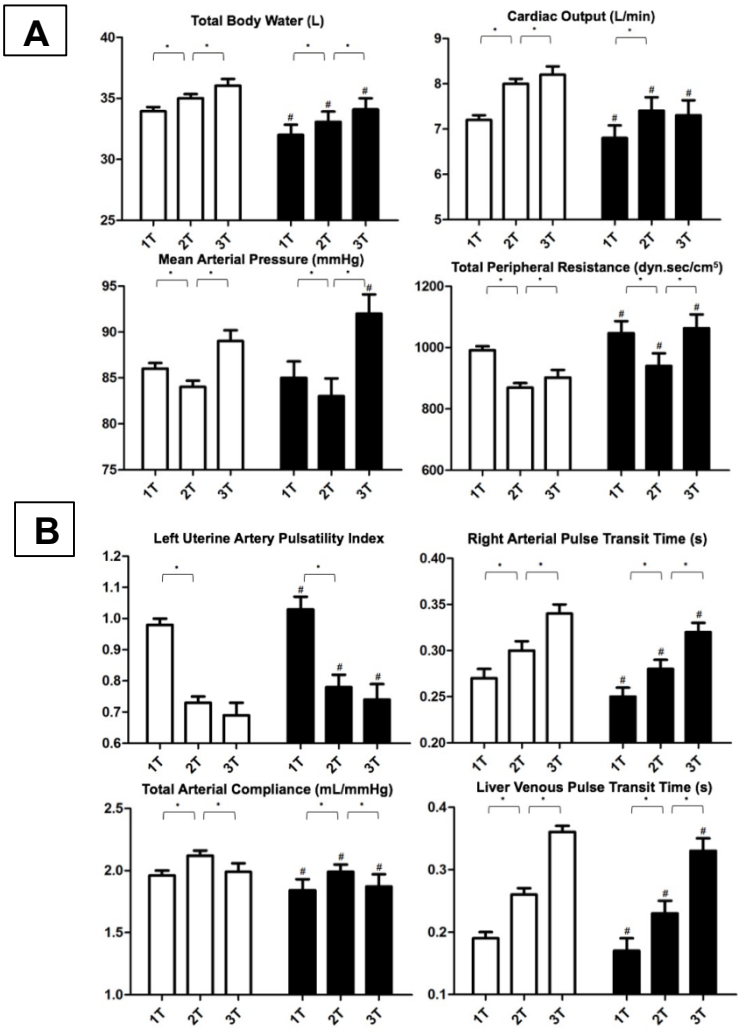

Figure 2.3.2: Average hemodynamic evolution of A: Total Body Water, Cardiac Output, Mean Arterial Pressure and Total Peripheral Resistance; B: left uterine Pulsatility Index, right Uterine Artery Pulse Transit Time, Total Arterial Compliance and hepatic Vein Pulse Transit Time between normotensive women, giving birth to neonates Appropriate for Gestational Age (NGA, white) and Small for Gestational Age (SGA, black). Data are presented as least-square means ± SD. $p<0.05$ was considered significant. *Significant difference between trimesters in NGA or SGA. #Significant difference from uncomplicated pregnancy in the same trimester.

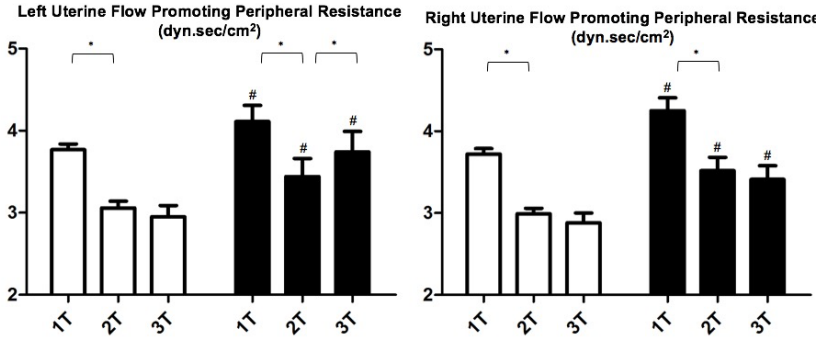

Figure 2.3.3: Uterine Flow Promoting Resistance in first, second and third trimester of normotensive women, giving birth to neonates Appropriate for Gestational Age (NGA, white) and Small for Gestational Age (SGA, black). Total Peripheral Resistance (TPR) in dyn.sec/cm5 = Mean Arterial Pressure x 80/Cardiac output. Left & right arterial pulse transit time (APTT) = ECG-P to Doppler-A time interval (ms)/duration of cardiac cycle (ECG R-R interval, ms). Uterine Flow Promoting Peripheral Resistance in dyn.sec/cm^2 = TPR/(APTTx1000). The higher UFPPR, the larger the fraction of maternal cardiac output to the uterine circulation. Data are presented as least-square means ± SD. p<0.05 was considered significant. *Significant difference between trimesters in NGA or SGA. #Significant difference from uncomplicated pregnancy in the same trimester.

Table 2.3.3: Pearson Correlation Coefficients (PCC) between birth weight percentile (BW%) and cardiac output (CO), total peripheral resistance (TPR), total body water (TBW) and extracellular water (ECW) for Appropriate for Gestational Age (NGA) vs. Small for Gestational Age (SGA). p<0.05 was considered significant.

		NGA			*SGA*		
TRIMESTER	**Correlation**	**PCC**	**R^2**	**p-value**	**PCC**	**R^2**	**p-value**
1	BW% and CO	0.223	0.05	**0.0001**	0.127	0.02	0.242
	BW% and TPR	-0.19	0.04	**0.0001**	-0.14	0.0001	0.197
	BW% and TBW	0.252	0.06	**0.0001**	0.098	0.01	0.447
2	BW% and CO	0.165	0.03	**0.0001**	0.068	0.005	0.585
	BW% and TPR	-0.163	0.03	**0.0001**	-0.054	0.003	0.665
	BW% and TBW	0.243	0.06	**0.0001**	0.000	0	0.998
3	BW% and CO	0.229	0.05	**0.004**	-0.131	0.02	0.308
	BW% and TPR	-0.109	0.01	0.177	0.186	0.03	0.145
	BW% and TBW	0.296	0.09	**0.002**	-0.115	0.01	0.53

DISCUSSION

In our analysis, normotensive SGA pregnancies are characterized by lower maternal body fluid volume and CO, while a clinically normal blood pressure is maintained via a higher TPR. The latter, in combination with a gradual decrease of uterine artery resistance, is responsible for shifting a larger proportion of CO to the uterus, a so-called "uterus-flow promoting" (UFP) phenomenon.

Our study is one of the first to assess the cardiovascular system as a functional circuit: volumes, heart, arterial and venous hemodynamics are evaluated in one simple session. A standardized protocol using non-invasive techniques with known inter- and intra-observer correlations is applied[101]. Bio-impedance may be criticized as being less valid than maternal echocardiography or dye dilution plasma volume measurements, however our results are in line with these so-called gold standard methods[21]. We acknowledge that the number of pregnancies with longitudinal measurements in each trimester is low and no correction for multiple testing was performed, due to which some of the significant results can still relate to chance.

Blood pressures in first trimester are within the normal reference range in SGA and NGA, but its components, CO & TPR, differ significantly between SGA and NGA[108,152,153]. As such, our study illustrates a false clinical perception of normal maternal hemodynamics via measurement of normal blood pressures in the SGA group. Plasma volume, a component of TBW, has repeatedly been reported to be lower in SGA pregnancies[151,153], and this condition is associated with lower preload, SV and CO[69,153-155]. Our results are in line with these reports. When approaching term, blood pressures rise gradually, driven by neurohormonal control mechanisms coordinating the balance between vascular tone and volume[156]. In SGA however, there is a lack of sufficient body fluid volume, which reflects a failure to further increase the CO (Figure 2.3.2A). It is still unclear whether this is due to a pregestational venous underfilling[157,158], or to an impaired gestational expansion process[153,159]. In our study, low VPTT's are present in SGA, which can be considered a reflection of higher venous activity trying to increase the venous return and preload to accommodate CO at the expense of the venous reserve capacity[151]. Reduced APTT and TAC, together

with a higher PI, RI and TPR in SGA[76,153], reflect an overall increased arterial resistance to maintain a normal blood pressure by rising the afterload. This results in higher blood pressures in SGA in third trimester, however still within the acceptable clinical reference ranges. Both in normal and hypertensive pregnancies, higher blood pressures have been linked with lower birth weights[160].

In both SGA and NGA, there is a functional UFP mechanism that supports the direction of a fraction of maternal CO towards the uterus and its contents. A good-working uterine artery is extremely important to preserve continuous, adequate oxygen and nutrients delivery to the foetus[161]. Guedes-Martins et al.[161] showed rising PI and RI during pregnancy in the internal iliac artery, but in contrast a decreasing PI and RI in the uterine artery. This means after implantation, functional remodelling occurs in the pelvic circulation, where the uterine artery transforms into a high capacitance and low resistance vessel. The internal iliac artery, the vessel preceding the uterine artery, remains a resistance vessel. Blood from the internal iliac artery will preferably go into the low resistance uterine artery instead of high resistance arteries of pelvic organs. This redistribution phenomenon favouring blood flow to the uterus has also reported by others[162]. In addition, it is shown that Angiotensin II increases the uterine resistance, but to a lesser extent than the simultaneous systemic resistance rises of TPR or MAP. The systemic and uterine reaction act probably through different mechanisms. The maintenance of uterine blood flow depends on uterine resistance, but also perfusion pressure, which suggest a local autoregulation mechanism[163,164]. The ratio TPR/APTT, labelled as Uterine Flow Promoting Peripheral Resistance, seems an appropriate descriptive parameter for the balance between the resistance in the systemic and uterine circulation. A high value for UFPPR represents a state where peripheral resistance increased more than uterine arterial resistance. As for any liquid, the blood flow always prefers the circuit with lowest resistance, and therefore UFPPR relates directly to the fraction of cardiac output shifted to the uterus. Our data support a physiologic condition where larger fractions of CO are shifted to the uterus in SGA pregnancies (Figure 2.3.4).

This UFP mechanism is stronger in SGA than in NGA pregnancies, probably because of the hemodynamic maladaptations (lower APTT, PI, VPTT and TAC + higher TPR), indicating stiffer vascular walls at arterial and venous sites. These signals seem an attempt to prioritize maternal blood volume distribution to the uterus, despite the lower CO-values in SGA. Larger fractions of CO are shifted to the uterus in SGA pregnancies[76,153].

The lack of correlation between SGA BW% and CO, which is in contrast with normotensive NGA pregnancies[97,106] (Table 2.3.3) and with those we formerly reported for preeclampsia[105], indicates that UFPPR might be insufficient, resulting in the birth of a healthy baby with birth weight low for gestational age. Similarly, the positive correlation between BW% and TBW was only found in NGA but not in SGA pregnancies[165,166]. Higher values of TPR were reported for advanced SGA pregnancies[96,97], together with an inverse correlation between TPR and BW%[96,152]. We found that - to a lesser extend – this was also true in first and second trimester for NGA, but not for SGA.

Our observations warrant for a normal blood pressure representing normal maternal hemodynamics, and illustrate that cardiovascular function should be visualized as a circuit. Our results open the discussion whether low maternal body fluid content is a maternal precondition or develops after abnormal placentation. Our study supports the exploration of therapeutic intravascular volume expansion as prevention for SGA births when detecting low maternal body fluid content.

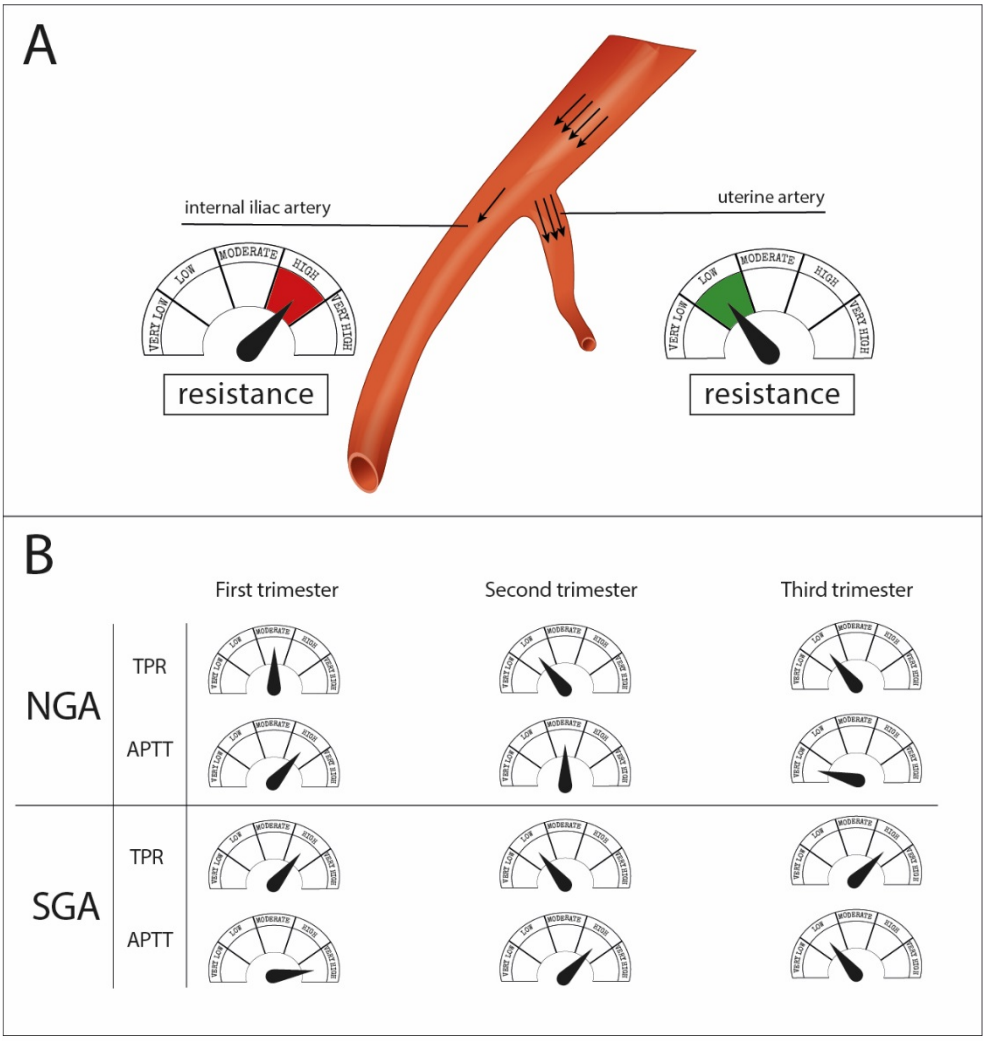

Figure 2.3.4: A: The peripheral resistance is higher than the uterine arterial resistance, which supports the redirection of blood towards the uterus. B: In a normal pregnancy, there is a decrease of both peripheral and uterine artery resistance from first to third trimester. This change is more pronounced in the uterine than in the peripheral circulation. This condition drives a gradually larger proportion of iliac arterial blood into the direction of the uterus. In SGA pregnancies, first trimester peripheral and uterine artery resistance are higher than in a normal pregnancy to accommodate for low body water volume. Uterine arterial resistance decreases from first to third trimester, whereas this is not true for peripheral resistance. As such, in the third trimester, a larger fraction of iliac arterial blood is shifted into the direction of the uterus than in uncomplicated pregnancy.

PART III

MATERNAL HEMODYNAMICS IN ABNORMAL PREGNANCIES

OBJECTIVE | To explore the physiology in pregnancies complicated with gestational hypertensive disorders (Chapter 3.1).

CHAPTER 3.1

Gestational Hypertensive Diseases are Clinical End-Stages of Volume Expansion upon Type-Specific Maternal Cardiovascular Dysfunction

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ABSTRACT

Objective

To define characteristics of maternal cardiac, arterial, venous and volume regulating functions in each trimester of uncomplicated pregnancies (UP) and those complicated with gestational hypertension (GH), early-onset (EPE) and late-onset preeclampsia (LPE).

Methods

Women with singleton pregnancy and without pre-existing cardiovascular, renal, endocrine, hematologic or auto-immune diseases were included during obstetric ultrasound scan appointment or after admission for gestational hypertensive disease (GHD). All women had non-invasive cardiovascular assessments with combined Doppler-ECG, associated with bio-impedance cardiography and total body water (TBW) estimation, according to a reported standard protocol. After birth, outcome was categorized according to ISSHP criteria as UP, GH, preeclampsia <34w (EPE) or ≥34w (LPE). A linear mixed model for repeated measurements including demographics was used in SAS for intergroup comparison.

Results

A total of 2,022 assessments were done, of which 1,660 (82%) in UP, 157 (7.8%) in GH, 161 (7.9%) in LPE and 44 (2.2%) in EPE. Throughout pregnancy, TBW increased in all women. All GHD differed from UP by first trimester cardiac dysfunction. This was associated with hepatic venous dysfunction evolving to combined hepatic and renal interlobar vein dysfunction in EPE and LPE, but not GH.

Conclusion

Our results are the first to show a simultaneous increase of total body water with gradual worsening of cardiovascular dysfunction in all women with GHD. The end-stage clinical presentations relate to type-specific maternal cardiovascular dysfunction in the first trimester.

INTRODUCTION

Pregnancy is a specific physiological condition in a woman's life, requiring major adaptations from the cardiovascular system, starting already very soon after conception[10]. 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[41]. Late stages of uncomplicated pregnancy are characterized by physiologic features of volume overload, but a large fraction of apparently normal pregnancies also show pathophysiologic maladaptive cardiovascular characteristics[143]. Today, it is unclear whether maternal hemodynamic dysfunction in pathologic pregnancies is to be considered a cause or a consequence of poor placentation[167].

For this study, we hypothesize that first trimester maternal hemodynamic functions of all major components of the circulation, including heart, central and peripheral arteries, central veins and body fluid content, are different between uncomplicated pregnancies and those complicated with types of gestational hypertensive diseases (GHD), and that these differences are type-specific.

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 normal singleton pregnancies presenting at the obstetric ultrasound scanning clinic at Ziekenhuis Oost-Limburg Genk, as well as women with suspected new-onset hypertension in ambulatory or hospital setting, were invited to participate in this observational cohort study between 2011-2016, as part of the ongoing Hasselt University Research Project of Maternal Venous Hemodynamics. All women were invited for longitudinal measurements and 48% eventually did so. At birth, data on gestational outcome was categorized according to the criteria revised by the International Society for Studies of Hypertension in Pregnancy (ISSHP)[168]. Gestational hypertension (GH) was defined as new-onset hypertension without proteinuria, other organ dysfunction or foetal growth restriction. Preeclampsia was defined as new-onset hypertension with proteinuria ≥300mg/24h, other organ dysfunction or foetal growth restriction, labelled as early-onset at clinical presentation <34 weeks (EPE) and late-onset at presentation ≥34 weeks (LPE). Patients who gave birth to baby's small for gestational age (birth weight ≤ 10th percentile), including the one's in combination with GHD, were excluded from this analysis as they are part of another report. Multiplet pregnancies or women with chronic cardiovascular, renal, endocrine, hematologic or auto-immune diseases are also excluded (Figure 3.1.1). Demographic details were maternal age (years), pregestational BMI, gestational age at assessment and at delivery, parity, smoking, medication, neonatal birth weight and percentile.

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 3.1.1). A standardised protocol was used as reported in previous studies[24,136,137].

Table 3.1.1: Overview of all parameters derived in one cardiovascular assessment session with the three techniques. ECG: electrocardiogram; ICG: impedance cardiography.

	ECG-DOPPLER	ICG	BIO-IMPEDANCE
HEART		Heart Rate (HR) Stroke Volume (SV) Cardiac Output (CO) Pre-ejection Period (PEP) Left Ventricular Ejection Time (LVET)	
ARTERIES	Arterial Pulse Transit Time (APTT) Pulsatility Index (PI) Resistivity Index (RI)	Velocity Index (VI) Acceleration Index (ACI) Heather Index (HI) Total Arterial Compliance (TAC) Total Peripheral Resistance (TPR) Systolic Blood Pressure (SBP) Diastolic Blood Pressure (DBP) Mean Arterial Pressure (MAP) Pulse Pressure (PP)	
VEINS	Hepatic Venous Pulse Transit Time (VPTT) Left and Right Renal VPTT Hepatic Vein Index (HVI) Renal Interlobal Vein Index (RIVI)		
FLUID		Thoracic Fluid Content (TFC)	Total Body Water (TBW) Extracellular Water (ECW) Intracellular Water (ICW)

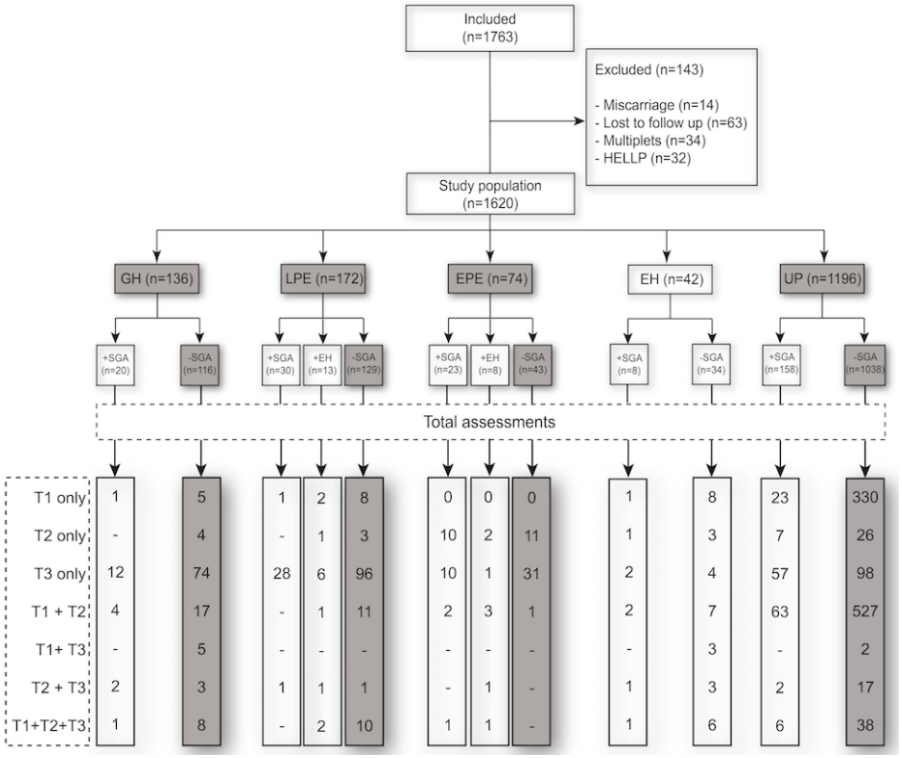

Figure 3.1.1: Flowchart from pregnancies included in the observational study as part of the Hasselt University Study Project on Maternal Venous Hemodynamics. The grey colored parts are used for this study's analysis. In 1,326 pregnant women were 2,022 assessments performed. After birth patients were divided 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.) alone or in multiple trimesters. *SGA: Small for gestational age, EH: Essential hypertension.*

Impedance Cardiography (ICG)

The Non-Invasive Continuous Cardiac Output Monitor (NICCOMO. Medis Medizinische Messtechnik GmbH. Ilmenau. Germany) was used for standardised automated sphygmomanometric blood pressure measurement on the right arm and with an appropriate cuff width. Impedance cardiography was performed using four electrodes (two on the axillary line under the thorax and two in the neck) eliminating skin resistance. The examination was performed after stabilisation of cardiovascular function in supine and standing position. Parameters were classified into five groups: blood pressures [systolic (SBP), diastolic (DBP), mean arterial pressure (MAP), pulse pressure (PP)], flow parameters [heart rate (HR), stroke volume (SV), cardiac output (CO)], contractility parameters [pre-ejection period (PEP), left ventricular ejection time (LVET), velocity index (VI), acceleration index (ACI), heather index (HI)], thoracic fluid parameters [thoracic fluid content (TFC)], vascular parameters [total arterial compliance (TAC), total peripheral resistance (TPR)]. The latter was calculated using the formula (MAP x 80) / CO[138,139].

ECG-Doppler Ultrasound

An electrocardiogram was combined with Doppler ultrasonography of the maternal renal interlobar veins, hepatic veins and the arcuate uterine arteries 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-variability[101]. Parameters of arteries and veins were divided into 2 groups: pulse transit times and impedance indices.

The heart rate corrected venous pulse transit time (VPTT) is the time interval between the P-top from the ECG-wave and the A-wave from the Doppler pulse wave (PA in ms). In the arteries (heart rate corrected arterial pulse transit time, APTT), the time interval starts at the Q-wave on the ECG and ends at the start of the Doppler end-diastolic point D (QD in ms). The pulse transit times are adjusted for heart rate, which is variable due to advancing gestation, and thereby divided by RR (time interval between two consecutive R-waves of the ECG signal)[82].

At the venous side, the maximum and minimum flow velocity is measured from the renal and hepatic Doppler signal. An impedance index is calculated using the formula [(Maximum Velocity-Minimum Velocity)/Maximum velocity][136,140]. This renal interlobar vein index (RIVI) and hepatic vein index (HVI) are considered the venous equivalents of the arterial Resistive Index (RI) which is calculated by the formula (Peak systolic velocity – End diastolic velocity)/Peak systolic velocity. In the uterine arcuate arteries, RI and Pulsatility Index (PI. (Peak systolic velocity – minimal diastolic velocity)/Mean velocity) were measured as reported[12,141].

Bio-impedance

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 [26]. 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) could be estimated by bio-impedance, as the total of intracellular water (ICW) and extracellular water (ECW), including interstitial, transcellular water and plasma volume.

Uterine Flow Promoting Peripheral Resistance

For each trimester and in both groups, the relation between vascular resistance in the systemic and uterine circulation was calculated as TPR/APTT in dyn.sec/cm². Because of the direct relation with the fraction of cardiac output redirected from the periphery to the uterine circulation, this parameter was labelled "Uterine Flow Promoting Peripheral Resistance" (UFPPR).

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 ± 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, due to multiple measurements in 48% of the patients. Fixed effects of trimester and outcome, 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). The impact of demographical influences (BMI, nulliparity and age) on the cardiovascular parameters was assessed by adding these patient characteristics in the linear mixed model. Corrections for multiple testing were not implemented.

RESULTS

A total of 2,022 assessments were done, of which 1,660 (82%) in women with UP, 157 (7.8%) in women with GH, 161 (7.9%) in women with LPE and 44 (2.2%) in women with EPE. Numbers of pregnancies assessed per group per trimester are enlisted in Tables 3.1.3-3.1.5. As explained, 48% of the women had multiple measurements during pregnancy. Patient demographics are shown in Table 3.1.2: GHD groups had more women with high BMI. Nulliparity and medication use were less in UP than in GHD, whereas the opposite was true for smoking. Birth weight percentile was lower in EPE only.

Table 3.1.3 shows the differences of first trimester cardiovascular characteristics between GHD groups and normal pregnancies. GH differs from UP by higher blood pressures, peripheral resistance, UFPPR, and lower CO. GH was the only GHD group with normal hepatic vein pulse transit time (Tables 3.1.3-3.1.5). LPE differs from UP by higher blood pressures, stroke volume but not cardiac output and peripheral resistance (Tables 3.1.3-3.1.5). EPE was the only group with first trimester increased Doppler measurements of uterine arterial resistance and venous impedance, with increased total body volume estimation. The data in Tables 3.1.4 and 3.1.5 shows for each GHD group a gradual worsening of cardiovascular functions, simultaneous with an increase of TBW.

Figure 3.1.2 shows for 1st, 2nd and 3rd trimester in all groups the least square averages +/- SD for MAP, CO, TPR, VI, PI, APTT, UFPPR, liver VPTT, HVI, right RIVI, TBW and ECW/ICW. As is illustrated, TBW increases in each group from 1st to 3rd trimester and in this, extracellular water increases more than intracellular water. This effect is most pronounced in EPE, followed by LPE and GH and least for UP. All evolutions in GHD groups show a gradual aggravation of overall maternal cardiovascular dysfunction from 1st to 3rd trimester, which is illustrated in Figure 3.1.3.

Table 3.1.2: Patient and outcome characteristics of women with an uncomplicated pregnancy (UP), gestational hypertension (GH), late (LPE) and early (EPE) preeclampsia. Data are presented as mean ± SD or n (%). *p<0.05 was considered significant from UP. *CV: Cardiovascular*

	UP *(N=1,038)*	GH *(N=116)*	LPE *(N=129)*	EPE *(N=43)*
CHARACTERISTICS AT INCLUSION				
MATERNAL AGE, YEARS	30±6	30±4	30±5	29±5
GESTATIONAL AGE AT CV ASSESSMENT, WEEKS				
FIRST TRIMESTER	12±0.8	12±0.9	11±0.9	12±1.2
SECOND TRIMESTER	21±1.5	20±1.8	22±2.1*	24±2.5*
THIRD TRIMESTER	33±3	37±3*	37±2*	32±0.9*
PRE-PREGNANCY BMI, KG/M²	24.7±5	26.6±6*	25.8±6*	26.8±5*
NULLIPARITY	764 (46%)	94 (60%)*	126 (75%)*	17 (59%)
CIGARETTE SMOKER	209 (17%)	9 (11%)*	5 (6.5%)*	1 (8%)*
MEDICATION *(ANTIHYPERTENSIVA)*	0 (0%)	31 (20%)*	30 (20%)*	1 (0.7%)
OUTCOME CHARACTERISTICS				
BIRTH WEIGHT, G	3,412±489	3,278±573*	3,077±573*	990±438*
BIRTH WEIGHT, PERCENTILE	56±26	52±27	51±28*	5.5±3.6*
GESTATIONAL AGE AT DELIVERY, WEEKS	39±2	39±2*	38±2*	30±3*

Table 3.1.3: Hemodynamic differences in first trimester of uncomplicated pregnancies compared with gestational hypertension (GH), late (LPE) and early (EPE) preeclampsia. Data are presented as least-square means ± SD. *ns=non-significant*

	UP (n=897)	***GH (n=35)***	***p-value***	***LPE (n=29)***	***p-value***	***EPE (n=1)***	***p-value***
DIASTOLIC BLOOD PRESSURE (MMHG)	76 (76-77)	85 (82-87)	***0.0001***	82 (80-84)	***0.0001***	80 (68-93)	*ns*
MEAN ARTERIAL PRESSURE (MMHG)	87 (86-87)	95 (92-97)	***0.0001***	93 (90-95)	***0.0001***	90 (77-103)	*ns*
CARDIAC OUTPUT (L/MIN)	6.9 (6.8-7)	6.7 (6.4-6.9)	***0.04***	7.1 (6.7-7.4)	*ns*	7.4 (5.7-9.2)	*ns*
STROKE VOLUME (ML)	74 (72-75)	70 (67-73)	***0.02***	79 (75-84)	***0.01***	67 (62-71)	***0.004***
HEART RATE (BPM)	96 (95-97)	96 (95-97)	*ns*	93 (90-95)	***0.01***	90 (86-94)	***0.009***
TOTAL PERIPHERAL RESISTANCE (DYN.SEC/CM^5)	1,023 (1007-1038)	1,134 (1082-1186)	***0.0001***	1,081 (1026-1136)	***0.04***	1,009 (752-1266)	*ns*
VELOCITY INDEX (1/1000/S)	78 (76-79)	77 (72-82)	*ns*	75 (70-80)	*ns*	102 (76-127)	*ns*
ACCELERATION INDEX (1/100/S^2)	164 (161-168)	166 (154-179)	*ns*	155 (142-169)	*ns*	178 (113-243)	*ns*
LEFT PULSATILITY INDEX	0.98 (0.95-1.00)	0.98 (0.95-1.00)	*ns*	0.97 (0.95-0.99)	*ns*	1.31 (1.22-1.40)	***0.0001***
LEFT RESISTIVITY INDEX	0.64 (0.63-0.65)	0.64 (0.63-0.65)	*ns*	0.61 (0.56-0.65)	*ns*	0.81 (0.77-0.86)	***0.0001***
LEFT ARTERIAL PULSE TRANSIT TIME (S)	0.26 (0.26-0.27)	0.26 (0.26-0.27)	*ns*	0.25 (0.24-0.26)	***0.002***	0.19 (0.17-0.20)	***0.0001***
LEFT UTERINE FLOW PROMOTING PERIPHERAL RESISTANCE (DYN.SEC/CM^2)	4.0 (3.9-4.1)	4.6 (4.4-4.8)	***0.0001***	4.3 (4.0-4.6)	***0.04***	7.0 (6.7-7.4)	***0.0001***
RIGHT PULSTILITY INDEX	0.91 (0.89-0.93)	0.91 (0.89-0.93)	*ns*	0.91 (0.89-0.94)	*ns*	invalid	*invalid*
RIGHT RESISTIVITY INDEX	0.61 (0.60-0.62)	0.61 (0.60-0.62)	*ns*	0.61 (0.60-0.62)	*ns*	invalid	*invalid*
RIGHT ARTERIAL PULSE TRANSIT TIME (S)	0.26 (0.26-0.27)	0.26 (0.26-0.27)	*ns*	0.26 (0.24-0.27)	*ns*	0.18 (0.17-0.20)	***0.0001***
RIGHT UTERINE FLOW PROMOTING PERIPHERAL RESISTANCE (DYN.SEC/CM^2)	3.9 (3.8-4.0)	4.5 (4.4-4.7)	***0.0001***	4.2 (3.9-4.5)	***0.05***	7.0 (6.7-7.3)	***0.0001***
HEPATIC VEIN INDEX	1.17 (1.13-1.21)	1.17 (1.13-1.21)	*ns*	1.25 (1.09-1.42)	*ns*	1.68 (1.51-1.85)	***0.0001***
LIVER VENOUS PULSE TRANSIT TIME (S)	0.19 (0.18-0.20)	0.19 (0.18-0.20)	*ns*	0.16 (0.14-0.18)	***0.002***	0.10 (0.07-0.14)	***0.0001***
RIGHT RENAL INTERLOBAR VEIN INDEX	0.46 (0.45-0.47)	0.46 (0.45-0.47)	*ns*	0.46 (0.43-0.49)	*ns*	0.54 (0.51-0.57)	***0.0001***
RIGHT VENOUS PULSE TRANSIT TIME (S)	0.28 (0.27-0.29)	0.28 (0.27-0.29)	*ns*	0.28 (0.27-0.29)	*ns*	0.23 (0.20-0.25)	***0.0002***
LEFT RENAL INTERLOBAR VEIN INDEX	0.44 (0.44-0.45)	0.44 (0.44-0.45)	*ns*	0.42 (0.39-0.45)	*ns*	0.50 (0.47-0.53)	***0.0008***
LEFT VENOUS PULSE TRANSIT TIME (S)	0.30 (0.29-0.31)	0.31 (0.30-0.33)	***0.04***	0.31 (0.29-0.34)	*ns*	0.43 (0.30-0.56)	***0.05***
TOTAL BODY WATER (L)	33.2 (32.8-33.5)	33.1 (31.9-34.2)	*ns*	33.5 (32.3-34.7)	*ns*	37.3 (35.5-39.2)	***0.0001***
EXTRACELLULAR WATER (L)	14.2 (14-14.4)	14.3 (13.7-14.9)	*ns*	14.5 (13.9-15.1)	*ns*	17.5 (16.5-18.5)	***0.0001***
INTRACELLULAR WATER (L)	18.9 (18.8-19.1)	18.9 (18.4-19.4)	*ns*	18.8 (18.3-19.3)	*ns*	19.8 (18.9-20.6)	***0.04***
ECW/ICW	0.75 (0.74-0.75)	0.75 (0.73-0.77)	*ns*	0.76 (0.75-0.78)	*ns*	0.86 (0.83-0.88)	***0.0001***

Table 3.1.4: Hemodynamic differences in second trimester of uncomplicated pregnancies compared with gestational hypertension (GH), late (LPE) and early (EPE) preeclampsia. Data are presented as least-square means ± SD. *ns=non-significant*

	UP (n=608)	***GH (n=32)***	***p-value***	***Late PE (n=25)***	***p-value***	***Early PE (n=12)***	***p-value***
DIASTOLIC BLOOD PRESSURE (MMHG)	74 (74-75)	84 (81-86)	***0.0001***	82 (79-85)	***0.0001***	98 (93-102)	***0.0001***
MEAN ARTERIAL PRESSURE (MMHG)	85 (84-85)	94 (91-96)	***0.0001***	93 (90-96)	***0.0001***	110 (106-115)	***0.0001***
CARDIAC OUTPUT (L/MIN)	7.7 (7.6-7.8)	7.5 (7.2-7.7)	***0.04***	7.3 (6.9-7.7)	*ns*	5.9 (5.2-6.5)	***0.0001***
STROKE VOLUME (ML)	81 (79-82)	77 (74-80)	***0.02***	77 (72-82)	*ns*	73 (69-78)	***0.004***
HEART RATE (BPM)	97 (96-98)	97 (96-98)	*ns*	94 (92-96)	***0.01***	92 (95-98)	***0.009***
TOTAL PERIPHERAL RESISTANCE (DYN.SEC/CM^5)	906 (889-922)	1,005 (948-1,061)	***0.0007***	1,040 (981-1,100)	***0.0001***	1,448 (1,347-1,548)	***0.0001***
VELOCITY INDEX (1/1000/S)	84 (82-85)	84 (78-89)	*ns*	73 (67-78)	***0.0001***	52 (43-61)	***0.0001***
ACCELERATION INDEX (1/100/S^2)	169 (165-173)	170 (157-184)	*ns*	147 (133-162)	***0.002***	102 (78-127)	***0.0001***
LEFT PULSATILITY INDEX	0.73 (0.70-0.75)	0.73 (0.70-0.75)	*ns*	0.72 (0.70-0.75)	*ns*	1.06 (0.97-1.15)	***0.0001***
LEFT RESISTIVITY INDEX	0.52 (0.51-0.53)	0.52 (0.51-0.53)	*ns*	0.51 (0.46-0.56)	*ns*	0.69 (0.65-0.73)	***0.0001***
LEFT ARTERIAL PULSE TRANSIT TIME (S)	0.28 (0.28-0.29)	0.28 (0.28-0.29)	*ns*	0.27 (0.26-0.28)	***0.002***	0.21 (0.19-0.22)	***0.0001***
LEFT UTERINE FLOW PROMOTING PERIPHERAL RESISTANCE (DYN.SEC/CM^2)	3.3 (3.2-3.4)	4.0 (3.8-4.2)	***0.0001***	3.9 (3.6-4.2)	***0.0006***	6.4 (6.0-6.7)	***0.0001***
RIGHT PULSTILITY INDEX	0.69 (0.66-0.71)	0.69 (0.66-0.71)	*ns*	0.69 (0.67-0.72)	*ns*	1.21 (1.06-1.36)	***0.0001***
RIGHT RESISTIVITY INDEX	0.50 (0.48-0.51)	0.50 (0.48-0.51)	*ns*	0.50 (0.49-0.51)	*ns*	0.75 (0.67-0.82)	***0.0001***
RIGHT ARTERIAL PULSE TRANSIT TIME (S)	0.29 (0.28-0.29)	0.29 (0.28-0.29)	*ns*	0.29 (0.27-0.31)	*ns*	0.20 (0.19-0.22)	***0.0001***
RIGHT UTERINE FLOW PROMOTING PERIPHERAL RESISTANCE (DYN.SEC/CM^2)	3.2 (3.1-3.3)	3.8 (3.7-4.0)	***0.0001***	3.7 (3.3-4.0)	***0.008***	6.3 (6.0-6.6)	***0.0001***
HEPATIC VEIN INDEX	0.78 (0.73-0.83)	0.78 (0.73-0.83)	*ns*	0.74 (0.55-0.92)	*ns*	1.29 (1.13-1.46)	***0.0001***
LIVER VENOUS PULSE TRANSIT TIME (S)	0.25 (0.24-0.26)	0.25 (0.24-0.26)	*ns*	0.21 (0.19-0.24)	***0.002***	0.16 (0.12-0.19)	***0.0001***
RIGHT RENAL INTERLOBAR VEIN INDEX	0.42 (0.41-0.43)	0.42 (0.41-0.43)	*ns*	0.38 (0.35-0.41)	***0.03***	0.50 (0.47-0.53)	***0.0001***
RIGHT VENOUS PULSE TRANSIT TIME (S)	0.31 (0.31-0.32)	0.31 (0.31-0.32)	*ns*	0.31 (0.30-0.32)	*ns*	0.26 (0.23-0.29)	***0.0002***
LEFT RENAL INTERLOBAR VEIN INDEX	0.43 (0.42-0.44)	0.43 (0.42-0.44)	*ns*	0.39 (0.36-0.43)	*ns*	0.48 (0.45-0.52)	***0.0008***
LEFT VENOUS PULSE TRANSIT TIME (S)	0.31 (0.30-0.32)	0.33 (0.31-0.34)	***0.04***	0.34 (0.31-0.37)	***0.03***	0.26 (0.21-0.30)	***0.012***
TOTAL BODY WATER (L)	34.2 (33.8-34.5)	34.1 (32.9-35.2)	*ns*	34.5 (33.3-35.7)	*ns*	38.3 (36.5-40.2)	***0.0001***
EXTRACELLULAR WATER (L)	14.9 (14.7-15.1)	14.9 (14.3-15.5)	*ns*	15.2 (14.6-15.8)	*ns*	18.1 (17.1-19.2)	***0.0001***
INTRACELLULAR WATER (L)	19.2 (19.1-19.1)	19.3 (18.8-19.7)	*ns*	19.1 (18.6-19.6)	*ns*	20.1 (19.2-20.9)	***0.04***
ECW/ICW	0.77 (0.76-0.77)	0.77 (0.75-0.79)	*ns*	0.79 (0.77-0.80)	*ns*	0.88 (0.85-0.90)	***0.0001***

Table 3.1.5: Hemodynamic differences in third trimester of uncomplicated pregnancies compared with gestational hypertension (GH), late (LPE) and early (EPE) preeclampsia. Data are presented as least-square means ± SD. *ns=non-significant*

	UP (n=155)	***GH (n=90)***	***p-value***	***Late PE (n=107)***	***p-value***	***Early PE (n=31)***	***p-value***
DIASTOLIC BLOOD PRESSURE (MMHG)	81 (80-82)	94 (93-96)	***0.0001***	97 (96-99)	***0.0001***	99 (96-102)	***0.0001***
MEAN ARTERIAL PRESSURE (MMHG)	91 (90-93)	106 (104-108)	***0.0001***	109 (108-111)	***0.0001***	111 (108-114)	***0.0001***
CARDIAC OUTPUT (L/MIN)	7.7 (7.5-7.8)	7.4 (7.2-7.6)	***0.04***	7.2 (7.0-7.5)	***0.0009***	6.9 (6.5-7.3)	***0.0007***
STROKE VOLUME (ML)	79 (77-81)	76 (73-79)	***0.02***	78 (75-80)	*ns*	73 (68-78)	***0.004***
HEART RATE (BPM)	98 (97-99)	98 (97-99)	*ns*	95 (92-97)	***0.01***	92 (89-96)	***0.009***
TOTAL PERIPHERAL RESISTANCE (DYN.SEC/CM^5)	982 (956-1009)	1,199 (1,162-1,236)	***0.0001***	1,253 (1,218-1,287)	***0.0001***	1,374 (1,309-1,439)	***0.0001***
VELOCITY INDEX (1/1000/S)	73 (71-76)	59 (56-62)	***0.0001***	54 (51-58)	***0.0001***	53 (47-59)	***0.0001***
ACCELERATION INDEX (1/100/S^2)	150 (143-157)	119 (110-128)	***0.0001***	113 (105-121)	***0.0001***	110 (94-125)	***0.0001***
LEFT PULSATILITY INDEX	0.69 (0.66-0.73)	0.69 (0.66-0.73)	*ns*	0.71 (0.68-0.75)	*ns*	1.02 (0.94-1.10)	***0.0001***
LEFT RESISTIVITY INDEX	0.50 (0.49-0.52)	0.50 (0.49-0.52)	*ns*	0.54 (0.51-0.56)	***0.02***	0.67 (0.63-0.71)	***0.0001***
LEFT ARTERIAL PULSE TRANSIT TIME (S)	0.31 (0.31-0.32)	0.31 (0.31-0.32)	*ns*	0.30 (0.29-0.31)	***0.002***	0.24 (0.23-0.25)	***0.0001***
LEFT UTERINE FLOW PROMOTING PERIPHERAL RESISTANCE (DYN.SEC/CM^2)	3.4 (3.2-3.5)	4.0 (3.8-4.2)	***0.0001***	4.6 (4.4-4.7)	***0.0001***	6.3 (6.0-6.7)	***0.0001***
RIGHT PULSTILITY INDEX	0.62 (0.58-0.65)	0.62 (0.58-0.65)	*ns*	0.65 (0.62-0.68)	*ns*	0.81 (0.71-0.90)	***0.0003***
RIGHT RESISTIVITY INDEX	0.46 (0.44-0.47)	0.46 (0.44-0.47)	*ns*	0.48 (0.46-0.50)	*ns*	0.57 (0.52-0.62)	***0.0001***
RIGHT ARTERIAL PULSE TRANSIT TIME (S)	0.33 (0.32-0.34)	0.33 (0.32-0.34)	*ns*	0.29 (0.28-0.30)	***0.0001***	0.25 (0.23-0.26)	***0.0001***
RIGHT UTERINE FLOW PROMOTING PERIPHERAL RESISTANCE (DYN.SEC/CM^2)	3.2 (3.1-3.4)	3.9 (3.7-4.0)	***0.0001***	4.5 (4.3-4.7)	***0.0001***	6.2 (5.9-6.5)	***0.0001***
HEPATIC VEIN INDEX	0.38 (0.31-0.45)	0.38 (0.31-0.45)	*ns*	0.60 (0.50-0.70)	***0.0002***	0.87 (0.71-1.03)	***0.0001***
LIVER VENOUS PULSE TRANSIT TIME (S)	0.35 (0.33-0.36)	0.35 (0.33-0.36)	*ns*	0.32 (0.30-0.34)	***0.002***	0.27 (0.23-0.30)	***0.0001***
RIGHT RENAL INTERLOBAR VEIN INDEX	0.32 (0.31-0.33)	0.32 (0.31-0.33)	*ns*	0.37 (0.35-0.38)	***0.0002***	0.40 (0.38-0.43)	***0.0001***
RIGHT VENOUS PULSE TRANSIT TIME (S)	0.39 (0.38-0.40)	0.39 (0.38-0.40)	*ns*	0.38 (0.37-0.39)	*ns*	0.33 (0.31-0.36)	***0.0002***
LEFT RENAL INTERLOBAR VEIN INDEX	0.36 (0.35-0.37)	0.36 (0.35-0.37)	*ns*	0.39 (0.37-0.41)	***0.008***	0.42 (0.39-0.45)	***0.0008***
LEFT VENOUS PULSE TRANSIT TIME (S)	0.39 (0.38-0.41)	0.41 (0.40-0.43)	***0.04***	0.38 (0.37-0.40)	*ns*	0.34 (0.31-0.36)	***0.0002***
TOTAL BODY WATER (L)	35.4 (34.8-35.9)	37.5 (36.5-38.5)	***0.0002***	41 (40-42)	***0.0001***	39.5 (37.7-41.4)	***0.0001***
EXTRACELLULAR WATER (L)	15.9 (15.6-16.2)	17 (16.5-17.6)	***0.0001***	19.7 (19.2-20.2)	***0.0001***	19.2 (18.2-20.2)	***0.0001***
INTRACELLULAR WATER (L)	19.7 (19.5-19.9)	20.3 (19.9-20.8)	***0.006***	21.5 (21-21.9)	***0.0001***	20.6 (19.7-21.4)	***0.04***
ECW/ICW	0.80 (0.79-0.81)	0.83 (0.82-0.85)	***0.0001***	0.91 (0.90-0.93)	***0.0001***	0.91 (0.88-0.94)	***0.0001***

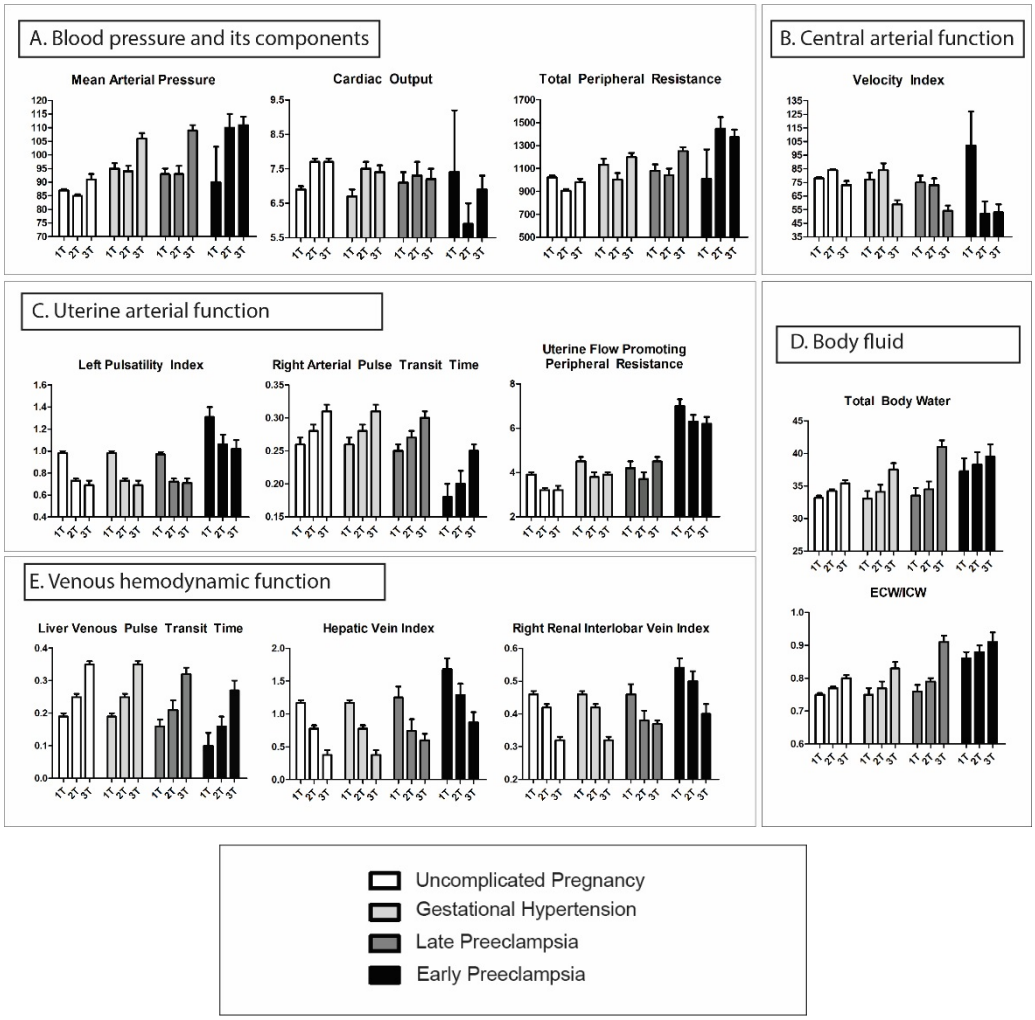

Figure 3.1.2: Average hemodynamic evolution of some cardiovascular parameters between women with uncomplicated pregnancies, gestational hypertension, late and early preeclampsia. Data are presented as least-square means ± SD. $p<0.05$ was considered significant.

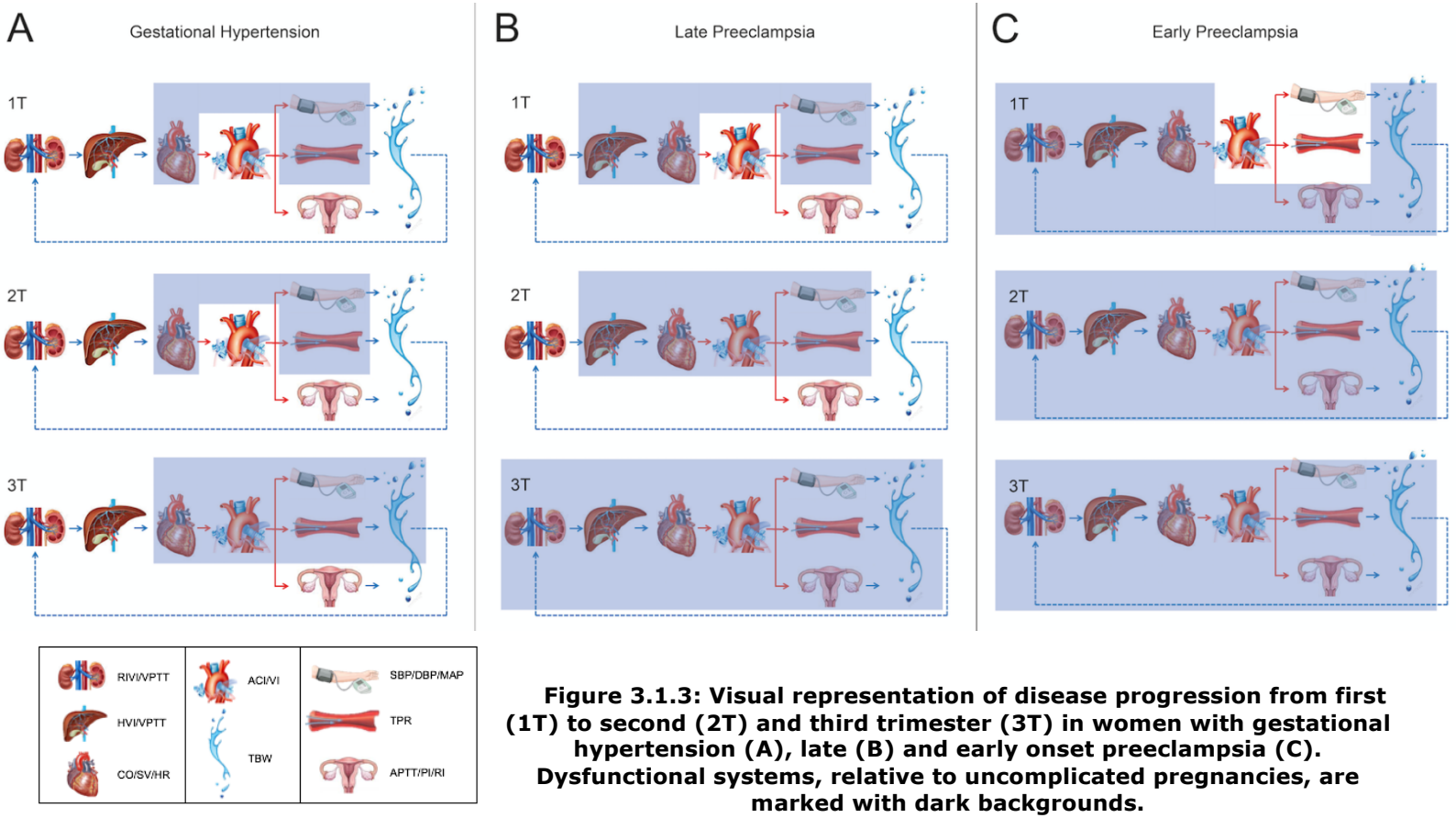

Figure 3.1.3: Visual representation of disease progression from first (1T) to second (2T) and third trimester (3T) in women with gestational hypertension (A), late (B) and early onset preeclampsia (C). Dysfunctional systems, relative to uncomplicated pregnancies, are marked with dark backgrounds.

DISCUSSION

The key findings of this study are (1) both in normal and hypertensive pregnancy with normal foetal growth, a woman's body is subject to a gradually increasing volume (over-)load, and (2) the clinical end-stage of gestational hypertensive diseases relates to the specific cardiovascular (dys-)function in the first trimester.

Our study is one of the first to assess all major components of the maternal circulation as one integrated functional circle: volumes, heart, arterial and venous hemodynamics. In this, a standardized protocol of non-invasive techniques with reported inter- and intra-observer correlations is used[24,82,101,136,137]. The bio-impedance technique may be criticized as being less valid than maternal echocardiography or dye dilution plasma volume measurements, however our results are in line with these so-called gold standard methods[21] and with other reports[28]. It should be appreciated that, similar to other reported methods[169], the bio-impedance methodology is very easy to perform with very low inter- and intra-observer variabilities, allowing a general application with a minimum of training or expertise. We acknowledge that the first trimester analysis of EPE with normal foetal growth is based on 1 patient only. Pregnancies complicated with (non-)hypertensive SGA are registered in our research program and are subject of another analysis (Figure 3.1.1). 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[170,171].

Our data in uncomplicated pregnancies are consistent with known features of gestational physiology[41,172]. It is generally accepted that an early postconceptional vasodilatation is responsible for a condition of intravascular under filling[173], which triggers volume expansion mechanisms[41,173]. The intravascular refill eventually 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[143]. To meet the increased workload for the heart to circulate large volumes of blood, cardiac functional and structural changes occur, supporting systolic function but hampering diastolic

properties[174]. This troubles venous return and predisposes to organ congestion[175]. In order to maintain optimal control of cardiac output, the venous compartment responds with autonomic nervous induced mobilization of stored blood volumes mainly from the splanchnic bed[176]. The data presented in this paper are consistent with this process, and account for both normal pregnancies as those with GHD. It is important however to appreciate that TBW volume exceeds that of plasma volume measurement, which is reported to be reduced in EPE. TBW is the sum of intra- and extravascular fluid which implies that volume expansion can exist with reduced plasma volume[151,177].

According to our data as presented in Figure 3.1.3, the deleterious cardiovascular effects caused by chronic volume overload are transmitted into retrograde direction from the arterial system, via the cardiac systolic and diastolic function to the venous compartment. When venous compensatory mechanisms fail, congestion induced organ failure may occur[178]. In non-pregnant individuals, the so-called cardio-hepatic and cardio-renal syndromes are typical 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 in pathologic pregnancy.

Today, it is becoming more and more evident that the type of gestational hypertensive disease 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[179]. Cardiovascular characteristics are reported to differ between gestational hypertension, early onset and late onset preeclampsia already before conception[180], during pregnancy[12] and in postpartum[181]. Our data presented in this paper clearly illustrate differences between GHD groups, some of which are present already in the first trimester. The process of volume expansion, as explained above, is superimposed on these subclinical abnormal conditions in early gestation and eventually leads to overt clinical disease, which is type-specific. This is illustrated schematically in Figure 3.1.3. Apart from the differences reported for

cardiac output and total peripheral resistance[15], cardiac function and morphology[15,182], central arterial[183] and uterine arterial function[184], we want to highlight in this paper the differences in venous hemodynamic function and uterine flow promoting peripheral resistance, as illustrated in Figure 3.1.2C and E. Hepatic vein pulse transit time is lower in EPE and LPE than in GH and UP, indicative for increased venous tone and reduced capacitance. In all types of GHD, UFPPR is higher than in uncomplicated pregnancy, indicating a redirection of larger fraction of CO from the periphery to the uterine circulation. This effect is most pronounced in early onset preeclampsia, and already present in the first trimester.

Gestational hypertensive diseases develop from volume expansion, superimposed upon first trimester maternal cardiac dysfunction, and present as preeclampsia only when venous hemodynamic dysfunction occurs. Increased total peripheral resistance in the maternal circulation serves as a uterus flow promoting phenomenon. To understand in full the pathophysiologic processes of GHD, a multiple functions evaluation of the maternal circulation is required, for both diagnosis and therapy.

PART VI

CLINICAL APPLICATION

OBJECTIVE | To explore the clinical relevance and the application of early gestational non-invasive maternal hemodynamics assessments.

CHAPTER 4.1

Optimization of simple sphygmomanometric blood pressure measurement in routine prenatal care

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Original paper

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ABSTRACT

Background: Despite reported early subclinical hypertension of women at risk, blood pressures at threshold 140/90 mmHg are used today to guide prenatal care. We aim to investigate the most appropriate gestation-specific threshold to measure early gestational blood pressures, allowing for a simple stratification between pregnant women at low/high risk for hypertension.

Methods: Singleton pregnancies were selected at Clinic Oost-Limburg, Genk, Belgium. A standard protocol was used to measure systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP) in supine and standing position, by mode of an oscillometric sphygmomanometer around 12 and 20 weeks of gestation. After delivery, outcome was categorized in normotensive or hypertensive pregnancies. In a subgroup, routine blood pressures retrieved from prenatal records were compared to standardized blood pressures. ROC analysis was used to define early gestational blood pressure thresholds with best discriminative performance for hypertension. All analyses were done in SPSS software ($\alpha \leq 0.05$).

Results: A total of 780 women were measured at 12 weeks, of which 433 pregnant women were re-evaluated around 20 weeks. At both occasions, blood pressures were significantly higher in hypertensive than in normotensive pregnancies ($p<0.0001$). Analysis showed for DBP in standing position at cut off 79 mmHg a sensitivity, specificity, positive predictive value and negative predictive value of 72%, 64%, 15,5% and 96% at 12 weeks and 86%, 69%, 20% and 98% at 20 weeks at cut off 77 mm Hg. At 20 weeks, Area Under the Curve (AUC) for DBP was 83% in standing position and 80% in supine position. For routine versus standardized blood pressure measurement, AUC was 66% versus 72% at 12 weeks and 69% versus 82% at 20 weeks respectively.

Conclusions: Simple blood pressure measurements with gestation-specific thresholds can easily be used worldwide towards improved planning of prenatal care as compared to current protocols.

INTRODUCTION

During normal pregnancy, the blood pressure decreases in the first 20 weeks and then gradually returns to preconceptional values when term approaches[185,186]. Around 6-8% of all expectant mothers will experience an aberrant blood pressure pattern leading to diverse hypertensive disorders, with maternal and neonatal mortality and morbidity such as cardiac arrest, renal failure, premature delivery, low birth weight, intra-uterine growth restrictions etc.[2,3]. Usually their blood pressure will remain stable during the first 20 weeks, where after an increase will initiate noticed in third trimester[187].

Today, a minimum of 140/90 mmHg measured at 2 occasions, > 6 hours apart, is generally used as threshold to diagnose hypertension in pregnancy[4]. Hypertension already noticed at < 20 weeks of gestation is labelled essential or chronic hypertension, and is considered a major risk factor for preeclampsia[188]. However, in most cases of gestational hypertension and preeclampsia, the hypertension is diagnosed at ≥ 20 weeks of gestation in women with "normal" blood pressure values earlier in pregnancy[4].

It is known that maternal cardiovascular (mal)adaptation during the first weeks of gestation plays a fundamental role in the regulation of blood pressure and the development of later hypertensive disorders[14,18]. Several studies[69,185,189] report already higher blood pressure values around 12 weeks of gestation in women who eventually develop preeclampsia, gestational or essential hypertension, compared to women who remain normotensive. Today, subclinical higher blood pressures (<140/90 mmHg) are not considered clinically relevant.

In this study, we evaluated whether early gestational diagnosis of subclinical hypertension would be helpful to identify the proportion of women destined to develop GHD, as early identification of those high risk cases could help decreasing the maternal and neonatal consequences[190].

METHODS

PATIENTS

Women with singleton pregnancies in first or second trimester, attending the obstetric ultrasound clinic (Ziekenhuis Oost-Limburg, Genk, Belgium) for their routine obstetrics scans, were invited to participate in a prospective, observational study. Approval of the Ethical Committee was obtained before study onset (MEC ZOL, reference: 13/090U). Blood pressures were measured as part of a reported standardized non-invasive cardiovascular assessment protocol using impedance cardiography (ICG), combined ECG/Doppler sonography and bio-impedance[24,136,137]. Oral informed consent was obtained before inclusion.

At birth, gestational outcome was defined and categorized in normotensive pregnancy (NP) or hypertensive pregnancies (HP), which included gestational hypertension (GH), preeclampsia (PE) and essential hypertension (EH). GH was diagnosed when a high blood pressure (≥140/90 mmHg) was observed after midpregnancy, without proteinuria, twice measured with 6h in between. The diagnosis of PE was determined when gestational hypertension was accompanied with de novo proteinuria (≥300 mg per 24 h). EH was defined as hypertension present before pregnancy or before 20 weeks of gestation [4]. Pregnancies diagnosed with isolated intra-uterine growth retardations (IUGR) and/or multiples were excluded from analysis as they are reported with different cardiovascular profiles[97,191]. Additionally, demographic details were recorded: maternal age (years), pregestational BMI, gestational age at assessment and at delivery, parity, cigarette usage, medication, neonatal birth weight and percentile.

PROTOCOL

The systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) of all patients were measured and registered around 12 weeks and/or 20 weeks of gestation.

The blood pressure measurements were performed as part of the Non-Invasive Continuous Cardiac Output Monitor assessment (NICCOMO, Medis Medizinische Messtechnik GmbH, Ilmenau, Germany) by use of an oscillometric sphygmomanometer at standardized time-points in a previously reported protocol [102]. Each patient performed the complete ICG examination first in

supine position and afterwards in standing position. Before the first blood pressure measurement, the patient was already comfortably in supine position for 5 minutes. 1,5 minutes after supine blood pressure measurement, the patient changed position to standing. The second blood pressure measurement was taken after a rest period of 2 minutes in standing position (Figure 4.1.1). Blood pressures were always taken on the right arm and with an appropriate cuff width.

STATISTICS

Normality was checked via Shapiro-Wilk for continuous variables. Even though there is a comparison of several parameters at two different time points (12 weeks and 20 weeks), each comparison is of the two-group type. To this end, the non-parametric Mann Whitney U was used at $\alpha<0.05$ to test the null hypothesis whether the distribution of the parameter of interest, at a given time point, is identical between the two groups. For categorical variables, Chi-square test was done. Data are presented as median and interquartile ranges (IQR) or n (%). ROC analysis was used to examine the different thresholds for each blood pressure in standing and supine position and sensitivity, specificity, positive and negative predictive value for prediction of hypertension were calculated. Youdens Index was used to identify the most appropriate threshold for every blood pressure measurement. All analyses were done in SPSS (SPSS Inc., Chicago, Illinois, USA).

SUB ANALYSIS

In a subgroup of the studied population, the standardized blood pressure values, measured as explained above, were compared to the blood pressures values at corresponding gestational age recorded in the prenatal files as part of the routine prenatal visits by the obstetrician or midwife. These latter blood pressures values were retrieved retrospectively from the patient's records.

Paired t-tests at nominal level $\alpha=0.05$ and Pearson Correlations Coefficients (PCC) were calculated between blood pressures measured in the standardized conditions versus the blood pressures measured at prenatal visit. All analyses were done in SPSS (SPSS Inc., Chicago, Illinois, USA).

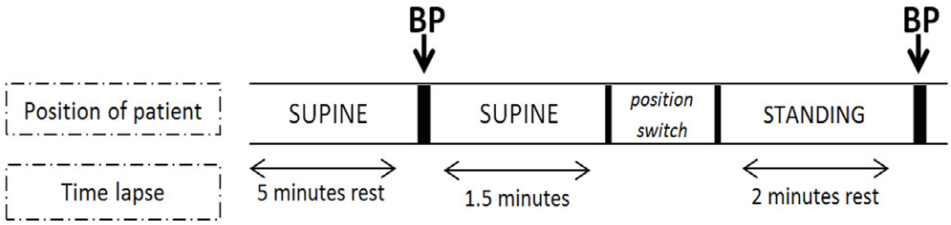

Figure 4.1.1: Graphical representation of the protocol

RESULTS

A total of 780 pregnant women had first trimester standardized blood pressure measurements; 433 of those women also had second trimester measurements. After birth, 716 patients were classified as normotensive and 64 as hypertensive patients at 12 weeks. At 20 weeks, 398 normotensive patients and 35 hypertensive patients were measured. A total of 90 pregnancies with isolated IUGR were excluded. The hypertensive group in first trimester included 24 women with GH (37.5%), 22 (34.5%) with PE and 18 (28%) with EH. A summary on maternal demographics is shown in Table 4.1.1. In the HP group, compared with NP, women were heavier, older and the nulliparity percentage is higher. The general use of medication is also significantly higher in the HP group, where 65% consists of blood pressure medication vs. 1.5% blood pressure medication in the NP group. Hypertensive patients delivered at an earlier gestational age and their neonates had a lower birth weight. Due to the slight differences between maternal age, pre-pregnancy BMI, and nulliparity between HP and NP (Table 4.1.1), the comparisons done were supplemented with linear regression analyses, comparing groups while correcting for potential confounders. The results are identical in the sense that all group comparisons remain highly significant.

The 12 and 20-week blood pressures (SBP, DBP and MAP) of NP and HP were compared and all values were significantly higher in HP at both gestational ages (Table 4.1.2). There were conducted several comparisons here and it is therefore prudent to apply a multiple comparisons correction. However, given the highly significant nature of the test statistics and the relatively modest number of tests, an adjusted alpha level still leaves the results highly

significant. Indeed, for the 12 tests reported in Table 4.1.2, the adjusted alpha level would be 0.00417; all p-values reported are well below this threshold.

Table 4.1.1: Patient and outcome characteristics of normotensive pregnancies (NP) and hypertensive pregnancies (HP). Data are presented as medians with interquartile ranges or n (%). Differences between NP and HP are presented as p-values. p<0.05 was considered significant.

	NP ***(N=716)***	**HP** ***(N=64)***	***P-VALUE***
CHARACTERISTICS AT INCLUSION			
MATERNAL AGE, YEARS	30 (27-33)	31 (28-35)	***0.029***
GESTATIONAL AGE AT INCLUSION, WEEKS	12w2d (11w5d-12w5d)	12w2d (11w4d-12w5d)	*0.557*
PRE-PREGNANCY BMI, KG/M²	23 (21-26)	24 (22-28)	***0.028***
NULLIPARITY	341 (47.6%)	40 (62.5%)	***0.023***
CIGARETTE SMOKER	67 (9.4%)	4 (6.3%)	*0.408*
CHRONIC HYPERTENSION	0	18 (28%)	--
GESTATIONAL HYPERTENSION	0	24 (37.5%)	--
PREECLAMPSIA	0	22 (34.5%)	--
MEDICATION	60 (8.4%)	20 (31.3%)	***0.0001***
OUTCOME CHARACTERISTICS			
BIRTH WEIGHT, G	3,425 (3,145-3,750)	3,205 (2,740-3,670)	***0.001***
BIRTH WEIGHT, PERCENTILE	57 (35-77)	52 (27-77)	*0.39*
GESTATIONAL AGE AT DELIVERY, WEEKS	39w5d (38w5d-40w4d)	38w5d (36w6d-39w6d)	***0.0001***

ROC analysis was used to evaluate the performance of SBP, DBP or MAP in supine and standing position to predict the hypertensive cases. The most appropriate thresholds for each blood pressure were identified via the Youdens Index (Table 4.1.3). Based on the AUC and Youdens Index, the DBP in standing position around 12 weeks and 20 weeks of gestation showed the best performance (Figure 4.1.2). This represents for 12 weeks at cut off 79 mmHg a 72% sensitivity, 64% specificity, 15,5% positive predictive value and 96% negative predictive value. Similarly at 20 weeks, a cut off of 77 mmHg showed an 86% sensitivity, 69% specificity, 20% positive predictive and 98% negative predictive value. Despite a significant difference between standing and supine blood pressure ($p<0.004$), the AUC's between standing and supine do not vary so much. At 20 weeks, AUC for DBP was 83% in standing position and 80% in supine position.

Table 4.1.2: Median + IQR for standardized SBP, DBP and MAP in supine and standing position at 12 weeks and 20 weeks. All comparisons were done using Mann Whitney-U test. Each comparison is significant with a p-value of <0.0001. ***IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure, NP, normotensive pregnancies; HP, hypertensive pregnancies.***

	12W		20W	
	NP	HP	NP	HP
SBP STANDING (MMHG)	115 (108-124)	124 (116-134)	113 (105-121)	122 (114-135)
DBP STANDING (MMHG)	75 (71-81)	82.5 (78-90)	73 (68-78)	82 (78-89)
MAP STANDING (MMHG)	85 (81-91)	92 (88-102)	83 (78-88)	92 (87- 99)
SBP SUPINE (MMHG)	113 (106-121)	123.5 (116-141)	110 (103-119)	122 (114-133)
DBP SUPINE (MMHG)	70 (66-75)	75 (71-85)	68 (64-73)	77 (71-84)
MAP SUPINE (MMHG)	80 (75-85)	86.5 (82-96)	78 (73-83)	86 (81-95)

Table 4.1.3: Detection performance of blood pressures. Sensitivity, specificity and FPR of each blood pressure, when using the most appropriate threshold indicated by ROC analysis and Youdens Index at 12 weeks and 20 weeks. *AUC, area under the curve; FPR, false-positive rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.*

	AUC (95% CI)	THRESHOLD	SENSITIVITY	SPECIFICITY	FPR
12 WEEKS					
SBP STANDING	0.696 (0.631-0.762)	122 mmHg	0.61	0.69	0.31
DBP STANDING	0.744 (0.68-0.808)	79 mmHg	0.72	0.64	0.36
MAP STANDING	0.744 (0.683-0.805)	87 mmHg	0.81	0.56	0.44
SBP SUPINE	0.726 (0.659-0.793)	116 mmHg	0.76	0.60	0.40
DBP SUPINE	0.739 (0.678-0.799)	71 mmHg	0.81	0.54	0.46
MAP SUPINE	0.744 (0.681-0.806)	83 mmHg	0.73	0.64	0.36
20 WEEKS					
SBP STANDING	0.712 (0.624-0.799)	111 mmHg	0.89	0.44	0.56
DBP STANDING	0.829 (0.765-0.893)	77 mmHg	0.86	0.69	0.31
MAP STANDING	0.805 (0.732-0.877)	86 mmHg	0.89	0.61	0.39
SBP SUPINE	0.731 (0.644-0.819)	118 mmHg	0.69	0.71	0.29
DBP SUPINE	0.798 (0.724-0.871)	71 mmHg	0.80	0.63	0.37
MAP SUPINE	0.810 (0.739-0.880)	81 mmHg	0.83	0.66	0.34

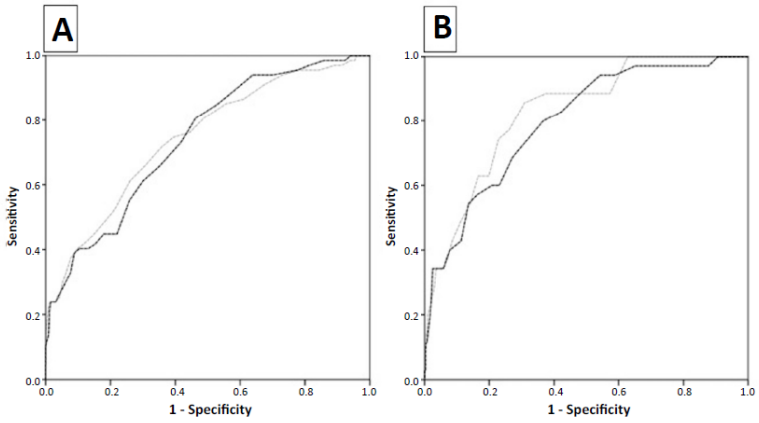

Figure 4.1.2: A: DBP ROC curves at 12 weeks, where grey indicates DBP standing (AUC: 0.744) and black indicates DBP supine (AUC: 0.739). B: DBP ROC curves at 20 weeks, where grey indicates DBP standing (AUC: 0.829) and black indicates DBP supine (AUC: 0.798). *DBP: Diastolic Blood Pressure; ROC: Receiver Operating Characteristic; AUC: Area Under the Curve.*

The sub analysis in 262 (33.6%) first trimester and 141 (32.6%) second trimester pregnancies showed a significant, but weak correlation between standardized DBP (stDBP) and routine DBP (rDBP) (12w: PCC = 0.425, $p<0.0001$; 20w: PCC = 0.429, $p<0.0001$). Paired t-test comparison revealed significant differences between stDBP and rDBP at 12 weeks (76 ± 7 mmHg vs. 71 ± 9 mmHg resp., $p<0.0001$) and 20 weeks (73 ± 7 mmHg vs. 69 ± 8 mmHg resp., $p<0.0001$) of gestation. AUC of routine versus standardized BP measurement was 66% versus 72% at 12 weeks and 69% versus 82% at 20 weeks respectively.

DISCUSSION

This study illustrates the potential of simple sphygmomanometric blood pressure measurements in early pregnancy for diagnosing subclinical hypertension. In our study, a standardized measurement of DBP in standing position showed the best performance with threshold 79 mmHg at 12 weeks and 77 mmHg at 20 weeks. These observations suggest that the general threshold of 140/90 mmHg should be adjusted in function of the gestational age, as the use of a lower threshold improves the early predictability of hypertension in pregnancy. Our findings are relevant to all prenatal care workers because (rudimentary) early gestational screening for hypertensive disease becomes universally available worldwide using a very simple and already generally applied technique of sphygmomanometric blood pressure measurement, without the need for other technologies or expensive devices.

The strength of this study is the rigid standardized protocol for measuring the blood pressures and the amount of inclusions. All women gave birth in the same hospital, where data on gestational, maternal and neonatal outcome were traceable in the hospital records. Our study population is however not yet large enough to adjust the general used threshold of 140/90 mmHg in clinic. The FPR presented in this paper can be lowered with implementation of other clinical or physical parameters to the screening process, but the lower thresholds can already serve as first discriminant tool seen the NPV is 96% at 12 weeks. With this accuracy, the focus lies not completely on detecting the hypertensive cases (as PPV is 15-20%), but more on eliminating the healthy cases with more certainty.

Subclinical higher blood pressures (<140/90 mmHg) in the first half of pregnancy are reported as a first sign of hypertension[185,192]. Our data are in line with this. Hypertensive disorders during pregnancy result from maternal cardiovascular maladaptation, initiated during the first weeks of gestation. Normally a physiological cascade is initiated by the fall of the peripheral vascular resistance, whereby heart rate and cardiac output increase. This vasodilatation lowers the blood pressures, because the cardiac output incline is not sufficient to prevent a blood pressure fall. Systolic as well as diastolic blood pressure keeps decreasing until 24 weeks. The peripheral vascular resistance is shown to be higher in future hypertensive patients and do not experience a blood pressure fall[10].

Based on our results, a DBP above 79 mmHg at 12 weeks or above 77 mmHg at 20 weeks identifies 2-3 times more patients at risk than the currently used threshold of 90 mmHg in the first and second trimester. We have at 12 weeks a 72% sensitivity and 64% specificity, but this improves when measuring at 20 weeks again: 86% sensitivity and 69% specificity. This suggests that the current obstetric practice may benefit from changing the currently used 'gold standard of blood pressure measurement' by using different and gestation specific cut off values, a suggestion which is has already be postulated by Hermida et al[193]. This may be useful to all clinics where technologies to screen for gestational hypertensive disease are not available and potentially to those women considered for initiating preventive medications such low-dose aspirin[85,86] or calcium[90]. Another opportunity could be the implementation of home blood pressure monitoring devices as follow up method, which - when used under standardized conditions- may offer valuable information without the need for increasing the number of prenatal visits or the risk of unnecessary medication intervention[194,195]. One study by Penny et al. on ambulatory automated blood pressure monitoring showed that a cut off of 135/85 mmHg had a better positive predictive value than 140/90 mmHg[196]. Also Gallery et al. identified lower 'at risk' blood pressure values at 17-20 weeks: the risks for hypertension were higher with blood pressure values above 110/75 mmHg sitting or 100/65 mmHg lying in left lateral position[185]. The latter group also observed that the fall in systolic and diastolic blood pressure from preconception to midgestation

was larger in the normotensive than the hypertensive group, which is completely in line with the physiology or mentioned above[185].

Our data also emphasizes the relevance of posture: standing blood pressure values were significantly higher than the supine values. The heart is required to pump more blood to the brain and needs therefore a higher pressure. As mentioned above in the study of Gallery, cut off values depend on how the patients are positioned and thus it is important to interpret the observations relative to position specific thresholds too[185]. Applied on our study, based on AUC's, we noticed a slightly better predictive outcome with standing blood pressures instead of supine blood pressures. There is however some inconsistency concerning the influence of position on the blood pressure: lower supine blood pressures are reported as compared to sitting[185,197,198], but also higher values have been observed[199] as well as no differences at all[200,201]. These conflicting results may relate to different populations or other methods of measurement.

This paper emphasizes the importance of a standard protocol, as the reliability of blood pressure measurements in routine care seems rather low[202]. Values obtained under standardized, calm conditions in a consequent position are more informative than those obtained as a routine clinical activity. Already in the 90s, some authors discussed that identification of high risk patients is better with an automated blood pressure protocol instead of a conventional measurement in the antenatal clinic. The clinical readings are influenced by inaccuracy due to observer bias, presence of the doctor (white coat hypertension), device bias etc.[196,203,204]. Benedetto et al. promotes a 24-hour blood pressure monitoring to estimate the risk. Aside the fact that Benedetto et al. also suggests lower blood pressure thresholds based on his results, it is easier to perform only a short protocol on each patient in clinic instead of a 24-hours protocol[192]. Since blood pressure values are the main indicator of hypertension, doctors and midwives should pay more attention to the measurement technique and to opting for the best performing protocol which is gestation-specific, position-specific, population-specific and possibly clinic-specific depending on the used method[185,205-207]. Reports mention that 45% of the obstetricians never use an appropriate cuff[208] or 66% report the blood pressure to the nearest 5 mmHg,

which automatically leads to over- or underestimation[209]. Routine antenatal visits are troubled with fast and non-standardized blood pressure measurement in patients who had to sit in the waiting room for minutes to hours or were rushed because of an appointment delay[206,207]. This scenario is to be prevented with a standardized protocol, where the measurement of taking the blood pressure is a real moment. Ciccone et al. showed improved clinical outcome of patients suffering from cardiovascular diseases, diabetes or heart failure due to the active clinical implementation of health care managers (specially trained nurses) as compared to a doctor visit alone[210]. Parallel to this study, midwives could be an added value in the disease management for gestational hypertensive disorders.

From the data presented in this paper, we conclude that a simple blood pressure measurement, if measured in a standardized way, can already be very valuable to classify the complete patient population into high vs. low risk at their first prenatal visit. This might be an important starting point for a universal screening tool, certainly for patients in their first pregnancy. Applying a threshold of 79 mmHg at 12 weeks or 76 mmHg at 20 weeks gives us at least a ≥ 96% negative predictive value, which is helpful to exclude hypertensive disorders early in pregnancy, leaving a "high" risk group requiring a somewhat closer observation or advanced screenings tests with multi-marker algorithms.

CHAPTER 4.2

Relevance of maternal hemodynamics assessment in phenotype-specific screening for gestational hypertensive diseases

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ABSTRACT

Objective

Gestational hypertensive diseases are associated with early maternal cardiovascular dysfunctions. Our aim was to investigate the relevance of maternal hemodynamics assessment in screening for different types of gestational hypertensive diseases.

Methods

Pregnant women were measured in first and second trimester via standardized electrocardiogram-Doppler ultrasonography, Impedance Cardiography and bio-impedance, acquiring function information on heart, arteries, veins and body fluid. Separate prediction algorithms were developed to predict early preeclampsia, late preeclampsia and gestational hypertension.

Results

A total of 969 pregnant women were screened, from which 8 developed Early-onset Preeclampsia, 29 Late-onset Preeclampsia, 35 Gestational Hypertension and 897 women with a normal outcome. A combined screening of maternal characteristics with cardiovascular parameters from first and second trimester offers high performance screenings models with Area Under the Curve of 99.9% for Early-onset Preeclampsia, 95.3% for Late-onset Preeclampsia and 94% for Gestational Hypertension.

Conclusion

In screening for gestational hypertensive diseases, a high performance and type-specific algorithm based on maternal characteristics and hemodynamics seems feasible, but requires validation in a large prospective study.

INTRODUCTION

Gestational hypertensive disorders (GHD), comprising gestational hypertension (GH), preeclampsia and complications of chronic hypertension, attribute to maternal and perinatal mortality and morbidity, and are linked to health problems in later life[211]. Its etiology is considered multifactorial, is still not completely understood and troubles prediction or anticipating deterioration. Aside chronic hypertension, onset of GHD's develop in the second half of pregnancy. The detection of subclinical signs in early pregnancy opens perspectives for prophylactic treatment or preventive measures towards reduction of the adverse maternal and neonatal outcome[5].

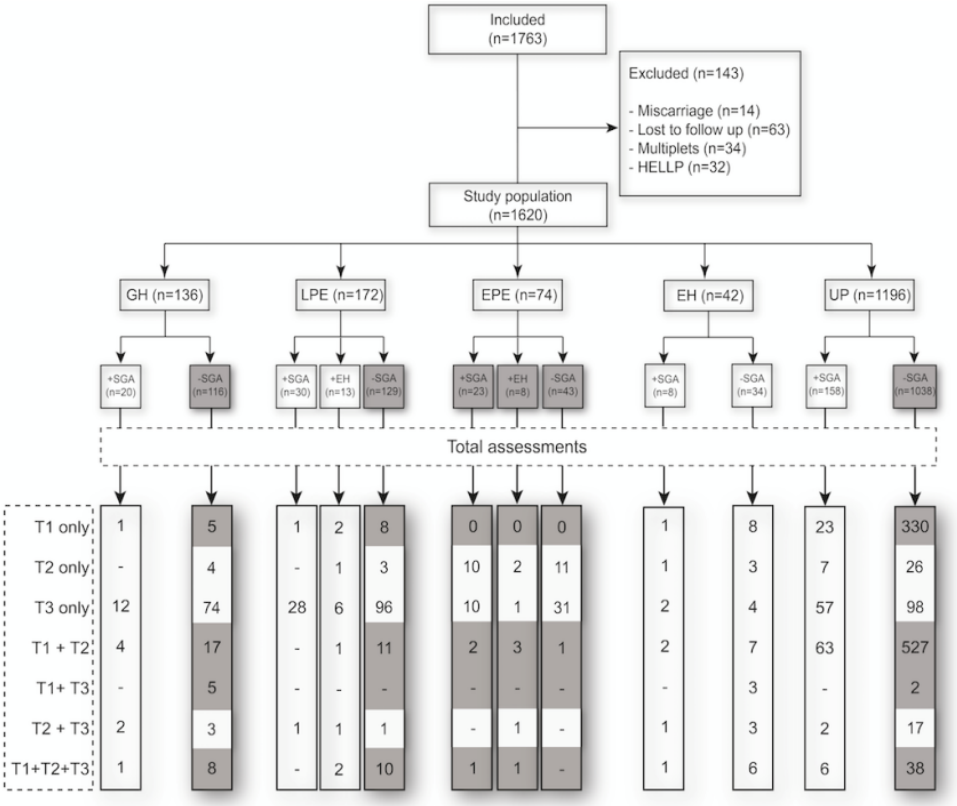
Current screening programs are based on a combination of maternal characteristics (age, ethnicity, body mass index, nulliparity, family or personal history) with biophysical (mean arterial pressure, pulsatility index) and biochemical markers (soluble Fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), pregnancy-associated plasma protein A (PAPP-A)), offering high detection rates of >90% for early-onset preeclampsia (EPE) at 10% false positive ratio. However, for late-onset preeclampsia (LPE) or gestational hypertension (GH), those models are troubled with a rather poor performance[212-214]. Other efforts were done seeking other biomarkers[215,216], metabolites[217], aorta intima media thickness[211], flow mediated dilatation of the brachial artery[218] or proteomics[219], but neither of them were highly promising.

We recently reported that hypertensive disorders in pregnancy are clinical end-stages of early maternal cardiovascular dysfunction, with abnormal measures in first trimester at the level of heart, arteries, veins and body fluid content. From the first trimester onward, we aimed to develop prediction algorithms for GH, EPE and LPE by non-invasive assessment of the maternal circulation.

METHODS

STUDY DESIGN

Approval of the Ethical Committee was obtained before study onset (MEC ZOL, reference: 13/090U) and informed consent before inclusion. Women with singleton pregnancies between 8^{+0} - 15^{+6} weeks of gestation presenting at the obstetric ultrasound scanning clinic at Ziekenhuis Oost-Limburg Genk were invited at random to participate in this observational study between 2011-2016 obtaining information on maternal hemodynamics, as part of the ongoing Hasselt University Research Project of Maternal Venous Hemodynamics. The cardiovascular assessment was repeated between 18^{+0} - 27^{+6} weeks of gestation in 64% of the patients, the other 36% were not reassessed due to practical reasons. Pregnancies complicated with essential hypertension (EH, with or without small for gestational age (SGA), n=28), superimposed late preeclampsia with or without SGA (n=5), HELLP with or without SGA (n=3) and isolated SGA (n=92) were excluded from the algorithm analysis, as well as multiplet pregnancies (n=2). GH and LPE with SGA were eliminated from analysis too, because of low numbers and heterogeneity (Appendix 4.2.1).



Appendix 4.2.1: Flowchart summarizing the total patients and assessments in each trimester, gathered from the observational study between 2011-2016 as part of the Hasselt University Research Project of Maternal Venous Hemodynamics. The grey zones are the patients included in this analysis. *T1: trimester 1; T2: trimester 2; T3: trimester 3; GH: Gestational Hypertension; LPE: Late preeclampsia; EPE: Early preeclampsia; SGA: Small for gestational age.*

DEFINITIONS OF GESTATIONAL HYPERTENSIVE DISORDERS

Diagnosis were made according to the ISSHP guidelines[5]. After birth, these data were categorized in normotensive pregnancy (NP), GH, EPE, LPE, EH and all classified according to birth weight percentile ≤ or > 10% as SGA or non-SGA respectively. GH was defined as a non-proteinuric hypertension, developed after 20 weeks of gestation. Preeclampsia was defined as new-onset hypertension with proteinuria ≥300mg/24h, labelled as early-onset at clinical presentation of <34 weeks and late-onset at presentation of ≥34 weeks of gestation. EH was

non-proteinuric hypertension with need for antihypertensive medication, developed <20 weeks. The three groups used for analyses are represented in Appendix 4.2.1.

MATERNAL CHARACTERISTICS

Maternal characteristics were obtained through history taking and retrospective review of the medical records for each patient. This included maternal age, pregestational weight, length, pregestational body mass index (BMI), allergy, parity, history on diabetes, intra-uterine death, intra-uterine growth restriction, thrombophilia or hypertension.

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 4.2.1). A standardised protocol was used as reported in previous studies[24,136,137].

Table 4.2.1: Overview of all parameters derived in one cardiovascular assessment session with the three techniques. ECG: electrocardiogram; ICG: impedance cardiography.

	ECG-DOPPLER	ICG	BIO-IMPEDANCE
HEART		Heart Rate (HR) Stroke Volume (SV) Cardiac Output (CO) Pre-ejection Period (PEP) Left Ventricular Ejection Time (LVET)	
ARTERIES	Left and Right Arcuate Arterial Pulse Transit Time (APTT) Left and Right Arcuate Artery Pulsatility Index (PI) Left and Right Arcuate Artery Resistivity Index (RI)	Velocity Index (VI) Acceleration Index (ACI) Total Peripheral Resistance (TPR) Diastolic Blood Pressure (DBP) Mean Arterial Pressure (MAP)	
VEINS	Hepatic Venous Pulse Transit Time (VPTT) Left and Right Renal VPTT Hepatic Vein Index (HVI) Left and Right Renal Interlobal Vein Index (RIVI)		
FLUID			Total Body Water (TBW) Extracellular Water (ECW) Intracellular Water (ICW)

Impedance Cardiography (ICG)

The Non-Invasive Continuous Cardiac Output Monitor (NICCOMO. Medis Medizinische Messtechnik GmbH. Ilmenau. Germany) was used for standardised automated sphygmomanometric blood pressure measurement on the right arm and with an appropriate cuff width. Impedance cardiography was performed using four electrodes (two on the axillary line under the thorax and two in the neck) eliminating skin resistance. The examination was performed after stabilisation of cardiovascular function in supine and standing position. Only parameters from standing position were used in the analysis. Parameters were classified as blood pressures [diastolic (DBP), mean arterial pressure (MAP)], flow parameters [heart rate (HR), stroke volume (SV), cardiac output (CO)], contractility parameters [pre-ejection period (PEP), left ventricular ejection time (LVET), velocity index (VI), acceleration index (ACI)], vascular parameters [total peripheral resistance (TPR)]. The latter was calculated using the formula (MAP x 80) / CO[138,139].

ECG-Doppler Ultrasound

An electrocardiogram was combined with Doppler ultrasonography of the maternal renal interlobar veins, hepatic veins and the arcuate uterine arteries 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-variability[101]. Parameters of arteries and veins were divided into 2 groups: pulse transit times and impedance indices.

The heart rate corrected venous pulse transit time (VPTT) is the time interval between the P-top from the ECG-wave and the A-wave from the Doppler pulse wave (PA in ms). In the arteries (heart rate corrected arterial pulse transit time, APTT), the time interval starts at the Q-wave on the ECG and ends at the start of the Doppler end-diastolic point D (QD in ms). The pulse transit times are adjusted for heart rate, which is variable due to advancing gestation, and thereby divided by RR (time interval between two consecutive R-waves of the ECG signal)[82].

At the venous side, the maximum and minimum flow velocity is measured from the renal and hepatic Doppler signal. An impedance index is calculated using the formula [(Maximum Velocity-Minimum Velocity)/Maximum velocity][136,140]. This renal interlobar vein index (RIVI) and hepatic vein index (HVI) are considered the venous equivalents of the arterial Resistive Index (RI) which is calculated by the formula (Peak systolic velocity – End diastolic velocity)/Peak systolic velocity. In the uterine arcuate arteries, RI and Pulsatility Index (PI, (Peak systolic velocity – minimal diastolic velocity)/Mean velocity) were measured as reported[12,141].

Bio-impedance

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 [26]. 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) could be estimated by bio-impedance, as the total of intracellular water (ICW) and extracellular water (ECW).

Uterine Flow Promoting Peripheral Resistance

We recently reported the qualitative assessment of systemic support of uterine perfusion. For each trimester and in both groups, the relation between vascular resistance in the systemic and uterine circulation was calculated as TPR/APTT in dyn.sec/cm². Because of the direct relation with the fraction of cardiac output redirected from the periphery to the uterine circulation, this parameter was labelled "Uterine Flow Promoting Peripheral Resistance" (UFPPR).

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 ± SD or n (%). This analysis was done in SPSS (SPSS Inc., Chicago, Illinois, USA).

To classify a pregnancy as NP or GHD, using demographic and maternal hemodynamics data the following methods for classification were considered and compared for their performance based on sensitivity and specificity: Linear Discriminant Analysis (LDA), Stepwise Discriminant Analysis, Partial Least Square Discriminant Analysis (PLS-DA), and k-Nearest Neighbors algorithm (k-NN). The number of neighbors in the k-NN algorithm was allowed to vary from 5 to 35 neighbors in steps of 5. The explanatory variables used in these classification algorithms were grouped into 4 sets of variables: "demographic", "impedance cardiography", "ultrasound" and "bio-impedance". All measured cardiovascular parameters were converted to multiples of the expected normal median (MoM) per trimester. To be able to evaluate the added value of (1) using multiple non-invasive techniques characterizing the cardiovascular profile and (2) the increased performance when using both week 12 and week 20 data, all classification algorithms were implemented using (A) demographic variables only; (B) demographic data and one set of cardiovascular data at week 12; (C) demographic data and three sets of cardiovascular data at week 12; (D) demographic data and one set of cardiovascular data both at weeks 12 and 20; and finally, (E) demographic data and three sets of cardiovascular data both at weeks 12 and 20. All pregnancies are used in the training set and cross-validation is used to quantify the performance. The number of observations in the training set decreases substantially when using multiple sets of cardiovascular data (based on ultrasound, impedance cardiography and bio-impedance variables) and data from both trimesters, due to missing data in one of the sets.

The classification algorithms were used to discriminate NP from GH, NP from EPE and NP versus LPE. Comparison of the different classification algorithms indicates that performance of the PLS-DA in general is best. Sensitivities, specificities, positive predictive values, negative predictive values, receiver operating curves (ROC) and likelihood ratios presented in this manuscript, are

obtained with the PLS-DA with cross validation. SAS (SAS 9.4, Institute Inc., Cary, NC USA) was used for this data analysis.

RESULTS

A total of 969 pregnant women were screened at their first ultrasound appointment. Eight were categorized as EPE, 29 LPE, 35 GH and 897 NP. Patient and outcome characteristics of the four outcome groups are shown in Table 4.2.2.

The best performance of each prediction algorithm is acquired by adding all the cardiovascular parameters of first and second trimester to the maternal characteristics. Concrete this means, a set of demographical variables (maternal age, allergy, parity, length, BMI, history of hypertension/thrombophilia/IUGR/intra-uterine death/diabetes) with the three sets of cardiovascular parameters (presented in Table 4.2.1), measured in first and second trimester (Figure 4.2.1). Positive likelihood ratios are between 7.27-7.40 and the negative between 0 and 0.18.

EARLY PREECLAMPSIA

The detection rate (DR) of EPE is 100% with false positive ratio (FPR) of 0%. Positive predictive value (PPV) is 67% and negative predictive value (NPV) is 100%. The area under the curve (AUC) is 99.8% (Figure 4.2.1A).

LATE PREECLAMPSIA

At 14% FPR, the detection rate is 100%. The PPV is 21% and NPV 100%. The AUC for LPE is 94% (Figure 4.2.1B).

GESTATIONAL HYPERTENSION

The GH algorithm is characterized by a detection rate of 84% at 12% FPR. This provides a PPV of 23% and NPV of 99%. The AUC is 95.3% (Figure 4.2.1C).

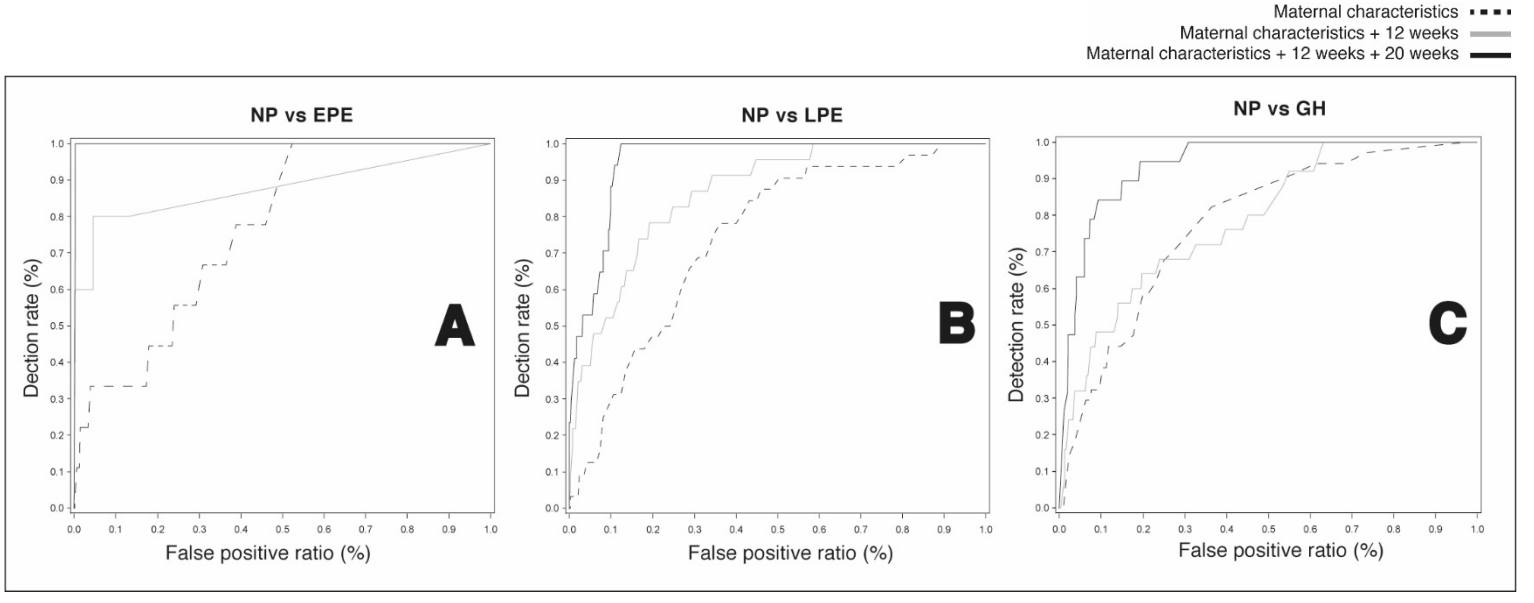


Figure 4.2.1: Receiving operating characteristics (ROC) curves of maternal characteristics, in stepwise combination with three sets of first and/or second trimester maternal hemodynamical parameters for the predication of early-onset preeclampsia (A), late-onset preeclampsia (B) and gestational hypertension (C). *NP (Normotensive pregnancy); EPE (early-onset preeclampsia); LPE (late-onset preeclampsia); GH (gestational hypertension)*

Table 4.2.2: Patient and outcome characteristics in the four outcome groups. Data are presented as median (IQR) or n (%). *p<0.05 was considered significant different from normotensive pregnancy (NP).

	NORMOTENSIVE PREGNANCY (NP) *(N=897)*	EARLY-ONSET PREECLAMPSIA (EPE) *(N=8)*	LATE-ONSET PREECLAMPSIA (LPE) *(N=29)*	GESTATIONAL HYPERTENSION (GH) *(N=35)*
CHARACTERISTICS AT INCLUSION				
MATERNAL AGE, YEARS	30 (27-33)	30 (25-36)	30 (27-34)	30 (27-33)
PREGESTATIONAL MATERNAL WEIGHT, KG	64 (58-74)	**76 (64-84)***	66 (62-82)	65 (59-79)
PREGESTATIONAL MATERNAL HEIGHT, CM	166 (161-170)	166 (163-170)	166 (165-170)	167 (162-170)
PREGESTATIONAL BMI, KG/M²	23.3 (21-26.8)	**27.3 (23.3-29.8)**	24.1 (22.4-30.2)	23.6 (22-27.9)
GESTATIONAL AGE AT ASSESSMENT, WEEKS+DAYS				
FIRST TRIMESTER	12w2d (11w5d-12w5d)	**13w (12w3d-13w2d)***	**11w5d (11w1d-12w5d)***	12w2d (11w6d-12w5d)
SECOND TRIMESTER	20w2d (19w6d-20w5d)	**21w (20w3d-26w3d)***	**20w5d (20w1d-21w4d)***	20w2d (19w5d-20w6d)
MEDICAL HISTORY				
DIABETES MELLITUS	116 (12.9%)	2 (25%)	6 (20.7%)	6 (17.1%)
THROMBOPHILIA	33 (3.7%)	1 (12.5%)	1 (3.4%)	2 (5.7%)
ALLERGY	177 (19.7%)	0 (0%)	4 (13.8%)	**13 (37.1%)***
OBSTETRIC HISTORY				
INTRA-UTERINE DEATH	15 (1.7%)	0 (0%)	1 (3.4%)	1 (2.9%)
INTRA-UTERINE GROWTH RESTRICTION	7 (0.8%)	0 (0%)	0 (0%)	1 (2.9%)
NULLIPARITY	472 (52.6%)	4 (50%)	**8 (27.6%)***	14 (40%)
HYPERTENSION				
FAMILY HISTORY	41 (4.6%)	1 (12.5%)	1 (3.4%)	2 (5.7%)
PREVIOUS PREGNANCY	55 (6.1%)	2 (25%)	4 (13.8%)	**10 (28.6%)***
OUTCOME CHARACTERISTICS				
BIRTH WEIGHT, G	3,425 (3,145-3,734)	**1,300 (572-1,712)***	**3,230 (2,690-3,656)***	3,405 (3,040-3,720)
BIRTH WEIGHT, PERCENTILE	57.5 (33-77.5)	**7.5 (3.8-48.8)**	63.8 (28.1-79.4)	52.5 (23.5-82.5)
GESTATIONAL AGE AT DELIVERY, WEEKS + DAYS	39w5d (38w5d-40w3d)	**31w5d (27w-32w5d)***	**37w5d (36w5d-39w6d)***	39w3d (38w5d-40w5d)

DISCUSSION

This study demonstrates that prediction algorithms based on hemodynamic parameters in combination with maternal characteristics have good performances for type-specific screening of GH, EPE and LPE in early pregnancy with AUC above 94% and detection rates above 84%.

Our study is the first to assess all major components of the maternal circulation as one integrated functional circle: volumes, heart, arterial and venous hemodynamics and use this as fundaments in a prediction tool. A standardized protocol of non-invasive techniques with reported inter- and intra-observer correlations is used[24,82,101,136,137]. The bio-impedance technique may be criticized as being less valid than maternal echocardiography or dye dilution plasma volume measurements, however our results are in line with these so-called gold standard methods[21] and with other reports[28]. It should be appreciated that, similar to other reported methods[169], the bio-impedance methodology is very easy to perform with very low inter- and intra-observer variabilities, allowing a general application with a minimum of training or expertise. We acknowledge that the EPE group was based on very few measurements and that SGA in GH and LPE were not considered in this analysis, which is an important limitation of our study. Our current analysis however illustrates the usefulness of maternal hemodynamics as algorithm fundament.

Current guidelines on screening and management of women at high risk for hypertension in pregnancy are based on maternal risk factors only, and performance is rather low with 35% detection rate for preeclampsia and 40% for early preeclampsia[220,221]. In practice, diagnosing GHD is based on elevated blood pressures and/or proteinuria during a routine clinical visit in late second or third trimester, and at that stage disease is already established and preventive therapy is not useful anymore. Therefore, various models were investigated to improve first trimester prediction. The current best approach combines maternal characteristics with first trimester uterine artery Doppler pulsatility index, MAP and a combination of biomarkers (PlGF, sFlt-1 or PAPP-A), reaching detection rates of >90% for EPE and between 35-76% for LPE by a 10% FPR[212-214]. This means EPE has a good detection rate, but performance on LPE is poor[212-214,220,222]. Prediction of GH scores even lower (18-21% at 5% FPR)[214,223].

Compared to those latter models, the prediction models in this study show better overall detection rates.

Multiple aberrant maternal cardiovascular signs are reported already in first trimester[10]. Type-specific cardiovascular characteristics are reported, allowing early discrimination between GH, EPE and LPE[12], even in first trimester[10]. Therefore, we tried a different approach based on cardiovascular measurements in first trimester, with a follow-up in second trimester. Following ACOG[13], the ideal screening test for hypertension in pregnancy would require high LR for a positive test as well as low LR for a negative result. Based on our results, our proposed models have general low LR's when using maternal characteristics alone. There is an improvement when adding first trimester cardiovascular parameters, and the best performance is obtained when both first and second trimester cardiovascular parameters are added. This might imply the importance of cardiovascular follow-up during pregnancy in order to counter adverse effects[13].

Our approach offers perspectives for a rationalized guidance of clinical management in screening, prevention and treatment of GHD. Screening for GHD should start with a standard first trimester cardiovascular assessment of all pregnant women attending to the clinic. Women at risk could be considered for preventive treatment such as low-dose aspirin depending on the grade of cardiovascular maladaptation and the predicted risk profile[224,225]. Adding a second trimester assessment could confirm more accurately the risk status and determine a personalized follow up monitoring, such as remote monitoring[226] and/or hemodynamic-based antihypertensive therapy[227]. The screenings algorithms used in this study demonstrate for the first time an appropriate and competing tool in predicting GHD based on maternal hemodynamics instead of biomarkers, but is still subject to further investigation on feasibility and improvement. Further research is necessary to validate the performance in a new population cohort, potentially extending the protocol with the biomarker approach.

GENERAL DISCUSSION

AND

SUMMARY

GENERAL DISCUSSION

The aim of this doctoral thesis was to non-invasively assess the function of all levels of the maternal circulation during early pregnancy and its relation to maternal and foetal outcome. First, major findings of the different chapters are summarized. Next, future perspectives are discussed.

CHAPTER 1 MATERNAL HEMODYNAMICS: GENERAL ASPECTS

The first part of this thesis focused on increasing our knowledge about the maternal physiology occurring in a normal pregnancy. Chapter 1 is the result of a comprehensive literature study, in which all relevant cardiovascular changes in the first trimester are summarized. It is already known that the majority of circulatory functions are adapted by the end of the first trimester. Implantation induces a physiological cascade, with cardiovascular changes found as early as 5 weeks of gestation: reduced peripheral vascular resistance, higher cardiac output, higher heart rate, higher stroke volume and higher plasma volume. The blood pressure decreases, due to an imbalance between the reduction of vascular resistance and the rise in cardiac output. As reaction, volume restoring mechanisms are activated, which leads to sodium and water reabsorption. Total body water, including plasma volume, increases, leading to a rise in venous return to restore the fallen blood pressure. A higher venous compliance is necessary to accommodate the higher venous compartment capacity. Due to the continuous increasing flow, morphological adaptations to the heart occur.

The literature study of Chapter 1 confirms that a normal pregnancy comes along with many circulatory changes. It is therefore important to investigate the circulation as completely as possible in a pregnancy, meaning (1) with the most applicable, easy and non-invasive techniques, (2) preferably in the first, second and third trimester and (3) make corrections for the demographical effects (obesity, smoking, age) as they might have an influence on the results. In our research group, a combination of non-invasive techniques was standardized and validated in the past. We use the ECG-Doppler ultrasonography to measure the function of the main arteries and veins, together with Impedance Cardiography for heart function and Bio-Impedance for volume function to assess the major elements of the maternal circulation.

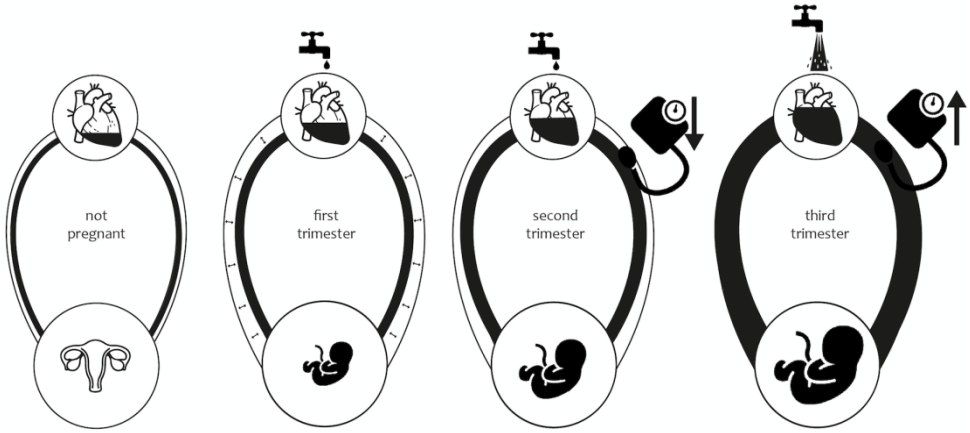


Figure 1: Simplified illustration of the physiological cascade after implantation *(cf. Chapter 1)*. Reduced peripheral resistance and increased cardiac output are the two main changes in the first trimester. There is a blood pressure decrease in second trimester, whereas the blood volume has to increase more as reaction. The third trimester has a normal blood pressure again, characterized by higher blood volumes.

CHAPTER 2 MATERNAL HEMODYNAMICS IN NORMAL PREGNANCIES

In Chapter 2.1, we used the combination of techniques as mentioned above in a pregnant healthy population and demonstrated a direct relation between the neonatal birth weight and the venous function of the liver. The liver is able to mobilize stored blood from the splanchnic bed, which is a necessary step in the physiological cascade of the volume restoring mechanisms that are activated early in pregnancy. This means that the venous system plays an important role, as well as its interaction with the heart. We observed a significant correlation between the hepatic parameters (Venous pulse transit time (VPTT), hepatic vein impedance index (HVI)) and the cardiac output, as such the liver functions as a cardiac output-regulating mechanism. It was shown before that a low cardiac

output is associated with growth-restricted babies, a correlation we also found in our population. In addition, there appears to be a relation between the hepatic hemodynamics and birth weight. It is possible that the hepatic venous system might have an impact on the foetal growth during pregnancy. This latter statement should however be investigated more carefully, but in the light of this thesis, it gives a first glimpse of the importance of a well-adapted venous function to counter the adverse neonatal effect of a growth restricted baby. This finding was also mentioned in the Referee Commentary of Duvekot in 2015[228].

In Chapter 2.2, we investigate the influence of one of the main risk factors for hypertensive diseases during pregnancy: a high maternal pregestational weight. When not pregnant, obesity is a state of cardiovascular dysfunction at multiple levels: systolic and diastolic dysfunction (higher cardiac output, stroke volume, heart rate etc.), ventricular hypertrophy (due to higher venous return), higher blood pressures and impaired vascular function. Unsurprisingly, obesity is also a tremendous risk factor for hypertensive disorders in pregnancy, because of the necessity of a well-functioning cardiovascular system during pregnancy. We observed 2 groups of women with normotensive, uncomplicated pregnancies in first, second and third trimester with a normal weight (BMI 20-25 kg/m^2) and obese weight (BMI $\geq$30 kg/m^2). After implantation, the same circulatory changes occurred between obese and non-obese women, but the changes in obese women were superimposed on the cardiovascular deficits they already had. Specifically, this means that the activated volume mechanisms will lead to a circulatory state of volume overload in obese pregnant women. The cardiovascular capacity to respond to further changes is already diminished at mid-gestation. This volume overload might trigger hypertensive diseases like preeclampsia. The women in our study maybe were at the edge of decompensation at the end of pregnancy, but it did not evolve to a pathological condition. This study highlights additionally the importance of demographical influences, such as BMI, when interpreting the results of a cardiovascular assessment. Also smoking, age, gestational age, etc., might be important to take into account.

In Chapter 2.3 we tried to understand the pathophysiologic evolution of a normotensive woman giving birth to a small for gestational age neonate.

Multiple maternal cardiovascular characteristics were already measured separately, such as low plasma volumes, cardiac output, heart rate, stroke volume and high blood pressures and peripheral resistance. In our combined assessment, we found that small for gestational age neonates are related to low maternal plasma volume throughout pregnancy. There is a lack of sufficient body fluid expansion as response to volume restoring mechanisms. Therefore, the venous system is more active, trying to increase the venous return and cardiac output. Also, the arterial system is more active, trying to maintain the blood pressure. During a pregnancy, the maternal circulation regulates the uterine perfusion, sending large fractions of the circulating blood to the uterus and foetus. This uterine flow promoting mechanism is activated more in pregnancies with small for gestational age neonates. This means a bigger fraction of the (low) cardiac output is shifted to the uterus but in the end, it is still insufficient to preserve a normal growth. In Chapter 2.1 we found a significant correlation between birth weight and cardiac output in healthy patients, this is not true in this study's population from first trimester onwards. This might imply that the uterine flow promoting mechanism is inadequate. This "Uterine Flow Promoting Peripheral Resistance" (UFPPR) is a new concept in current thinking of gestational physiology. It should be appreciated that UFPPR is the fraction of peripheral resistance, specifically contributing to promotion of uterine flow. The units of UFPPR are identical to the units of TPR. For the calculation of the uterine flow promoting fraction, uterine artery pulse transit time index is used: this is defined as the ratio of QD/RR. There is an inverse relation between APTT and uterine artery resistance and has no units. As UFPPR is a new concept in gestational physiology, it needs confirmation of more research in relation to CO and uterine blood flow.

In this article, the main finding was the presence of a low maternal plasma volume, which we couldn't measure exactly. Bio-impedance measures TBW, ICW and ECW. The latter contains plasma volume, and gives thus an indirect idea of its behaviour. Use of bio-impedance is therefore criticised widely and plasma dilution is still the preferred method. In contrast to bio-impedance is plasma dilution expensive, less patient friendly and needs expertise. In addition, bio-impedance is proven to be reliable in pregnant women by diverse studies of the last years[229,230] and has equivalent conclusions concerning the known (in)direct

behaviour of plasma volume during pregnancy. For this we would like to refer to (1) the case report of Smeets et al.[231] which proved a fluid accumulation from 7 weeks onwards with an immediate decrease after delivery. This information was gathered through an implantable cardioverter defibrillator (ICD, Protecta XT VR, Medtronic, Brussels, Belgium) and not by plasma dilution. (2) The article discussed in Chapter 3 states that each gestational hypertensive diagnose encounters fluid accumulation, measured with bio-impedance and detected from first trimester onwards. This physiological finding is analogue to exact plasma volume measurements. (3) In a preliminary analysis, outside the scope of this thesis, we compared the first trimester fluid balance between all the types of hypertensive diseases and found detailed differences concerning ECW and thus plasma volume behaviour. Therefore, we believe that bio-impedance is an important and promising measuring tool registering objective and trustworthy parameters and should not be underestimated anymore in current obstetric practise.

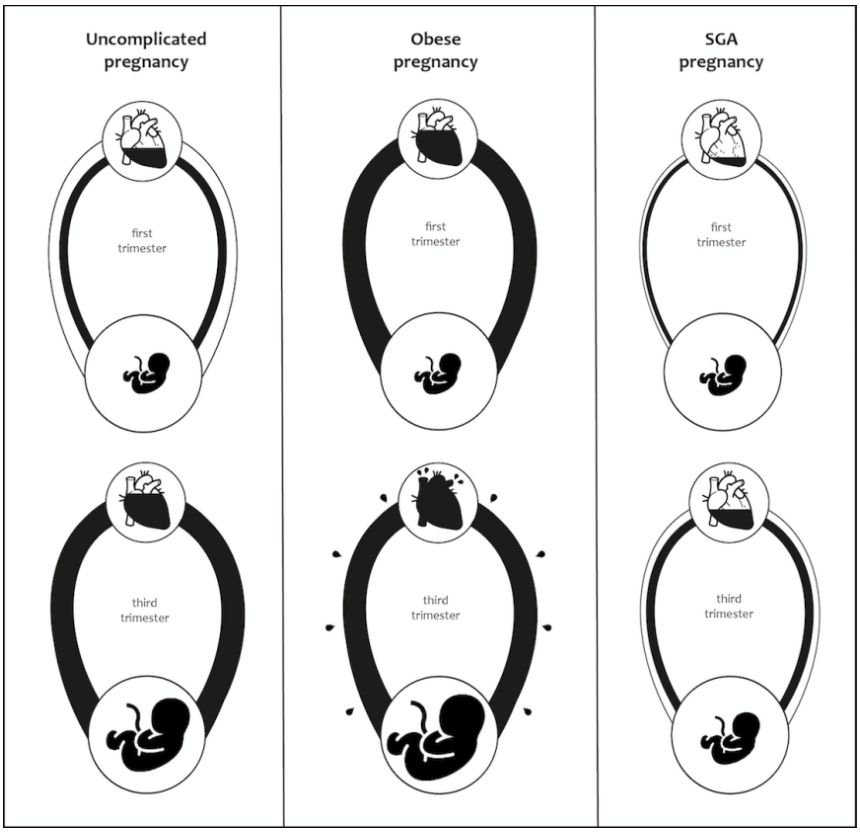


Figure 2: Illustration of the volume load differences between an uncomplicated pregnancy, an obese pregnancy and a pregnancy complicated with a small for gestational age (SGA) neonate (*cf. Chapter 2).* An obese pregnancy is characterized by a high volume load in first trimester and a volume overload in third trimester. This is in contrast to an SGA pregnancy with lower maternal volumes during the whole pregnancy.

CHAPTER 3 MATERNAL HEMODYNAMICS IN ABNORMAL PREGNANCY

Chapter 3 sheds light on the circulatory function of gestational hypertension, early preeclampsia and late preeclampsia. In the first trimester, many pathological signs are already assessable. Both hypertensive and uncomplicated pregnancies trigger the same body fluid expansion mechanisms, but changes in hypertensive pregnancies are superimposed on certain cardiovascular maladaptations present in the first weeks of gestation, and hamper the adaptive

capabilities. It became clear that the different types of hypertension are linked to specific, type-dependent cardiovascular characteristics in all trimesters. GH differs from UP by higher blood pressures, peripheral resistance, UFPPR, and lower CO. When this is combined with a first trimester venous dysfunction, late preeclampsia is pending. Characteristics of increased Doppler measurements of uterine arterial resistance and venous impedance, with increased total body water, low stroke volume and heart rate is suggestive for early preeclampsia. This means that the first trimester combination of cardiovascular characteristics can identify a specific type of hypertension and we can carefully state, that prediction is a possible application. Further along in pregnancy, there is a gradual worsening of the cardiovascular characteristics preceding the clinical disease.

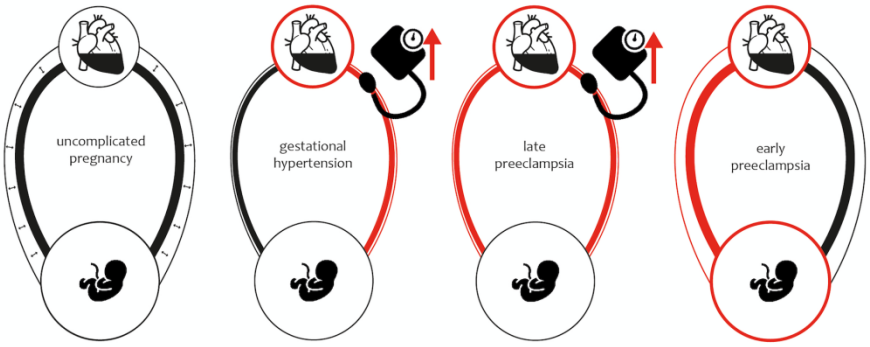


Figure 3: Illustration of the type-specific first trimester differences between gestational hypertension, late and early preeclampsia compared to an uncomplicated pregnancy *(Cf. Chapter 3).* Gestational hypertension is characterized by higher blood pressures, peripheral resistance and lower CO. Involvement of veins are a typical preeclamptic sign. Early preeclampsia has an additional sign of high uterine arterial resistance, high total body water, low stroke volume and low heart rate.

CHAPTER 4 CLINICAL APPLICATION

Investigating the maternal circulatory changes throughout pregnancy (Chapter 2-3), revealed sufficient information necessary for a potential clinical application. The first trimester of pregnancy is the most relevant period to assess the maternal cardiovascular system for the first time. Preventive measures such as increased or decreased physical activity, specific management of prenatal care and delivery or start of medication (i.e. Aspirin and Calcium) are still useful. Further it can determine the follow-up trajectory of pregnancies at risk.

In Chapter 4.1, we investigated the clinical value of a simple blood pressure measurement, which is applied widely in prenatal clinics, in stratifying patients into high or low risk for hypertension. In current practice, a threshold of 140/90 mmHg is used at all times to diagnose hypertension in pregnancy as well as for non-pregnant individuals. The normal physiological evolution states that blood pressures decrease in the first 20 weeks (due to the imbalance between changes in vascular resistance and cardiac output, Chapter 1), gradually returning to preconceptional values (due to an increased cardiac output) in the second phase of pregnancy. It is already known that hypertensive pregnancies do not have this physiological drop in blood pressures, which means, compared to normotensive pregnancies, they experience subclinically higher blood pressures but do not reach the threshold of 140/90 mmHg. This is probably a consequence of the specific cardiovascular characteristics present in the first part of pregnancy in the different hypertensive types (Chapter 3). In this study, we could show that applying thresholds of 79 and 77 mmHg diastolic blood pressure at 12 resp. 20 weeks, could improve the discrimination between normal and hypertensive evolution (Negative predictive value >96%). This is a rather rudimentary screening, but due to its simplicity and cheapness, it is easily applicable in hospitals where there are no opportunities for intensive screening programs, such as third world countries, and yet identify the possible at-risk group requiring a closer observation.

In Chapter 4.2, we provide a first attempt of early screenings algorithms based on maternal hemodynamical parameters (heart, arteries, veins and body fluid) and demographical factors. For these algorithms, it is necessary to execute the

trio combination of ECG-Doppler ultrasonography, Impedance Cardiography and Bio-Impedance, which require the correct devices and Doppler knowledge. This study demonstrates three algorithms to differentiate between uncomplicated from early preeclampsia, uncomplicated from late preeclampsia and uncomplicated from gestational hypertension. The best approach was adding information of maternal characteristics together with cardiovascular parameters of 12 weeks and 20 weeks. Area Under the Curve was 99,9% for early preeclampsia, 95,3% for late preeclampsia and 94% for gestational hypertension. Current screening programs are mainly based on biomarkers and score well on detecting early preeclampsia, but lack a good performance on detecting late preeclampsia or gestational hypertension. For this, we believe maternal hemodynamics might be used in a feasible screenings tool, but is still subject of further investigation. A new, large, multicentre prospective study should be performed to validate and refine this algorithm, and check its application in daily clinic. This is a topic of a new doctoral thesis project in preparation. Due to its statistical complexity, the individual contribution of each parameter in the current algorithm cannot be defined today. For now, it contains all cardiovascular parameters and an extended list of demographic factors. Future research is required to evaluate the contribution of each individual parameter. This step is to be initiated before the algorithm can be implemented in clinic.

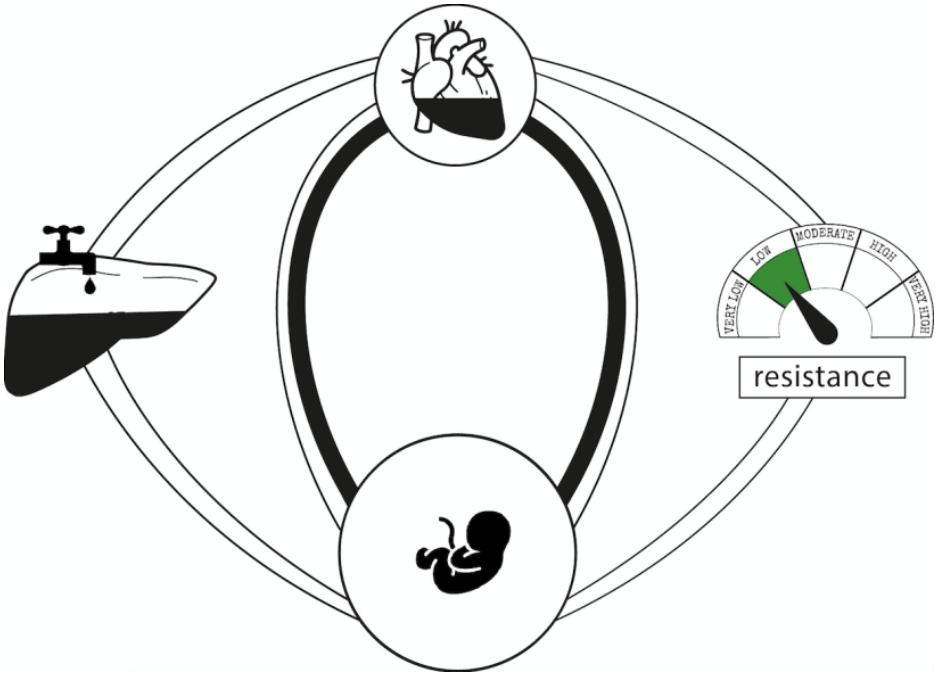


Figure 4: This figure summarizes all new cardiovascular concepts. Left, on the venous side: The liver as regulator of cardiac output and birth weight *(cf. Chapter 2.1)*. Right, on the arterial side: The role of the Uterine Flow Promoting phenomenon, sending larger fractions of cardiac output to the uterus *(cf. Chapter 2.3)*. Both concepts are part of the fundaments used in the screenings algorithm. *(cf. Chapter 4)*

FUTURE PERSPECTIVES

In Chapter 2 and 3 some fundamental findings were described about the pathophysiology of gestational hypertensive disorders and restricted growth, which gives a profound insight in the origin and evolution of the maternal hemodynamics during pregnancy. However, to understand why these gestational diseases arise, more research is necessary including more pathological cases. A big longitudinal, observational study would elucidate probably more accurate information. It would also be interesting to expand and "complete" our standardized protocol and add cardiovascular information about the microcirculation or plasma volume. The microcirculation could be non-invasively measured by diverse techniques, like capillaroscopy, near infrared spectroscopy or transcutaneous oxygen tension[232]. A correct measure of plasma volume is preferably done by indicator dilution technique[233]. Both components would provide us with an improved understanding of the precise pathophysiology.

The algorithm might be an important goal achieved during and after this thesis, it is important to further validate and test its feasibility and performance by continuously screening more patients, possibly in a new, prospective, (multicentre) study. Keeping track of predictions vs. outcome will be necessary to test the effective performance. Combining our algorithm with information on biomarkers, which are already proven to be useful as markers for early preeclampsia[234], or microcirculation, could be an interesting next step to increase its sensitivity and specificity. Once a reliable screening method is developed, a clear at-risk group could be defined early in pregnancy and implementation in daily practice should be managed. Those patients could benefit from a close follow-up method such as remote monitoring which registers daily blood pressures and is already proven to be a promising tool in prenatal care[226].

Another very useful application of knowing the type-specific aberrant maternal hemodynamical characteristics in each trimester is a personalized therapy, which intervenes with the underlying cardiovascular maladaptations. Currently, antihypertensive medications (beta blockers, combined alpha and beta blockers, calcium antagonists, adrenergic false transmitters, presynaptic alpha receptor

modulators, nitrates or diuretics) are focused on controlling the blood pressure. However, blood pressure is the result of cardiac output and peripheral resistance, parameters which are not measured conventionally and, as shown in this thesis multiple times, are often too high or too low and vary during the pregnancy. Each antihypertensive product has its own action mode, but they are used entangled. Understanding the underlying hemodynamics allows for a more personalized and rational treatment. For example, a cardiovascular profile with high volumes, high cardiac output and low venous and arterial tone will, in theory, benefit more from a diuretics therapy[227]. This item is still very controversial, but is therefore an ideal subject for research.

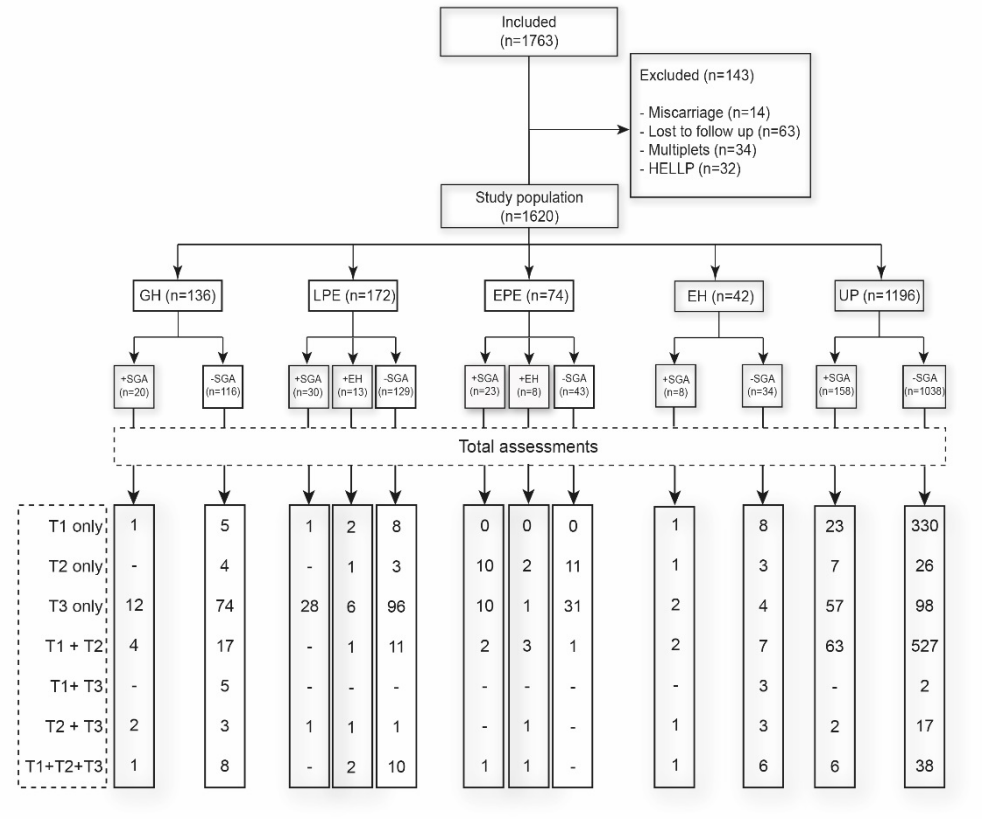


Figure 5: Flowchart of all included patients
GH: gestational hypertension; LPE: late preeclampsia; EPE: early preeclampsia; EH: essential hypertension; UP: uncomplicated pregnancy; SGA: small for gestational age

The dataset includes still 2 groups which are not yet analysed: (1) Subjects with chronic hypertension in combination with early and late preeclampsia and (2) Subjects with gestational hypertensive disorders in combination with small for gestational age neonates (Figure 5). In anticipation of a complete analysis, I would like to give a preview on the main findings:

(1) Chronic hypertension is a hypertensive disorder, initiated before pregnancy or before 20 weeks of gestation. During the pregnancy period, some patients develop to preeclampsia, some don't. The explanation for this might be found in the veins. As shown in Table 1 second trimester venous measurements in chronic hypertension without superimposed preeclampsia suggest enhanced venous hemodynamic function as compared to uncomplicated pregnancies. This is not true for chronic hypertension with superimposed early and late preeclampsia.

Table 1: Hemodynamic differences in second trimester of uncomplicated pregnancies compared with chronic hypertension and chronic hypertension superimposed with early and late preeclampsia. Data are presented as medians and interquartile ranges. *p<0.05 is considered significant.*

	UNCOMPLICATED PREGNANCY *(N=608)*	CHRONIC HYPERTENSION *(N=24)*	*P-VALUE*	CHRONIC HYPERTENSION WITH EARLY PREECLAMPSIA *(N=7)*	*P-VALUE*	CHRONIC HYPERTENSION WITH LATE PREECLAMPSIA *(N=5)*	*P-VALUE*
HEPATIC VENOUS PULSE TRANSIT TIME	0,21 (0,16-0,30)	0,28 (0,20-0,35)	*0,061*	0,15 (0,15-0,28)	0,444	0,29 (0,24-0,40)	0,092
LEFT RENAL VENOUS PULSE TRANSIT TIME	0,31 (0,27-0,36)	0,35 (0,32-0,38)	***0,007***	0,33 (0,30-0,49)	0,155	0,35 (0,30-0,49)	0,15
RIGHT RENAL VENOUS PULSE TRANSIT TIME	0,32 (0,26-0,37)	0,35 (0,30-0,41)	***0,046***	0,38 (0,30-0,48)	0,063	0,37 (0,34-0,47)	**0,047**
HEPATIC VEIN IMPEDANCE INDEX	0,67 (0,24-1,39)	0,37 (0,15-0,76)	***0,05***	0,85 (0,08-1,4)	0,941	0,21 (0,15-0,93)	0,236
LEFT RENAL INTERLOBAR VEIN IMPEDANCE INDEX	0,42 (0,36-0,49)	0,35 (0,30-0,39)	***0,0001***	0,44 (0,31-0,61)	0,938	0,37 (0,26-0,59)	0,957
RIGHT RENAL INTERLOBAR VEIN IMPEDANCE INDEX	0,41 (0,35-0,48)	0,35 (0,31-0,42)	***0,003***	0,38 (0,31-0,48)	0,493	0,33 (0,29-0,36)	**0,014**

(2) Gestational hypertensive disorders are the result of cardiovascular dysfunctions, just as small for gestational age. In Chapter 2.3 we discussed small for gestational age without considering hypertension. In Chapter 3 we explained the differences between the types of hypertensive disorders without considering growth restriction. From these chapters, we concluded that (a) poor foetal growth is associated with low maternal cardiac output and total body water volume, and (b) venous hemodynamic dysfunction is a feature of preeclampsia but not gestational hypertension. The preliminary current analysis is in line with these observations: gestational hypertension + small for gestational age presents with low cardiac output without venous dysfunction, whereas preeclampsia (early or late-onset) + small for gestational age presents with low cardiac output ànd venous dysfunction. In late preeclampsia, low cardiac output is also linked with a low total body volume.

Table 2: Hemodynamic differences in first trimester of uncomplicated pregnancies compared with gestational hypertension, early and late preeclampsia with small for gestational age neonates. Data are presented as least-square averages ± SD. *p<0.05 is considered significant; ns = non-significant*

	UNCOMPLICATED PREGNANCY *(N=897)*	GESTATIONAL HYPERTENSION *(N=6)*	*P-VALUE*	LATE PREECLAMPSIA *(N=1)*	*P-VALUE*	EARLY PREECLAMPSIA *(N=3)*	*P-VALUE*
CARDIAC OUTPUT	6,9 (6,8-7,0)	5,9 (5,4-6,4)	***0,0001***	5,6 (5,1-6,0)	***0,0001***	5,9 (5,4-6,4)	***0,0001***
TOTAL BODY WATER	33,11 (32,75-33,46)	33,11 (32,75-33,46)	*ns*	24,5 (18-31)	***0,009***	35,4 (33,3-37,6)	***0,04***
EXTRACELLULAR WATER	14,16 (13,97-14,36)	14,16 (13,97-14,36)	*ns*	9,6 (6,1-13,2)	***0,012***	15,6 (14,1-17)	*ns*
INTRACELLULAR WATER	18,9 (18,8-19,1)	18,9 (18,8-19,1)	*ns*	14,9 (11,9-17,9)	***0,008***	18,9 (18,8-19,1)	*ns*
HEPATIC VENOUS PULSE TRANSIT TIME	0,19 (0,18-0,20)	0,19 (0,18-0,20)	*ns*	0,12 (0,08-0,16)	***0,0003***	0,14 (0,1-0,18)	***0,02***
LEFT RENAL VENOUS PULSE TRANSIT TIME	0,30 (0,29-0,31)	0,27 (0,24-0,30)	***0,0458***	0,21 (0,06-0,36)	*ns*	0,30 (0,29-0,31)	*ns*
RIGHT RENAL VENOUS PULSE TRANSIT TIME	0,28 (0,27-0,29)	0,28 (0,27-0,29)	*ns*	0,27 (0,11-0,44)	*ns*	0,28 (0,27-0,29)	*ns*
HEPATIC VEIN IMPEDANCE INDEX	1,17 (1,13-1,22)	1,17 (1,13-1,22)	*ns*	1,52 (1,32-1,71)	***0,0006***	1,6 (1,4-1,8)	***0,0001***
LEFT RENAL INTERLOBAR VEIN IMPEDANCE INDEX	0,44 (0,43-0,45)	0,44 (0,43-0,45)	*ns*	0,48 (0,44-0,52)	***0,04***	0,37 (0,28-0,46)	*ns*
RIGHT RENAL INTERLOBAR VEIN IMPEDANCE INDEX	0,46 (0,45-0,47)	0,46 (0,45-0,47)	*ns*	0,53 (0,490,56)	***0,0001***	0,45 (0,37-0,53)	*ns*

SUMMARY

In 2015, approximately 65,000 deliveries occurred in Flanders, from which 4.6% were complicated by hypertension during pregnancy. This disease is linked to maternal and neonatal morbidity. It covers three types of hypertension: (1) gestational hypertension, (2) early/late preeclampsia and (3) chronic hypertension. Current research is focused on understanding the pathophysiology and developing prediction models.

It is already known that maternal cardiovascular maladaptations could lead to hypertension during pregnancy. Exploring the maternal cardiovascular functioning is possible through easy, safe and non-invasive techniques. In this thesis, we used a trio of standardized and validated techniques to assess the maternal circulation: an ECG-Doppler ultrasonography for arteries and veins, impedance cardiography for heart function and bio-impedance for body volume balance. These techniques were applied to 1,763 pregnant women in first, second or third trimester.

In this thesis, we added some novel insights to the current (patho)physiologic understanding of hypertensive disorders in pregnancy, but also to the development of small babies. A first trimester assessment already reveals sufficient information to distinguish between small for gestational age neonates, gestational hypertension, early and late preeclampsia. Small for gestational age neonates are related to low maternal body volumes with activated compensating venous and arterial systems. Gestational hypertension has cardiac dysfunction, higher peripheral resistance and already higher blood pressures in first trimester. An additional venous dysfunction is a typical preeclamptic characteristic. An additional uterine arterial dysfunction with high total body water is related to early preeclampsia. A gradual (trimestral) worsening of the cardiovascular characteristics manifests and identifies with more certainty the different types in second or third trimester. During pregnancy, the uterine circulation is directed by the maternal circulation, which sends large fractions of blood to the uterus. We showed that this mechanism is more activated in pathological pregnancies, than in uncomplicated pregnancies.

In addition, we translated these typical cardiovascular aberrations to a clinical prediction model. This gives the opportunity to screen the pregnant population for gestational hypertension, early and late preeclampsia in first and second trimester. A tailored therapeutic management, based on the type of hemodynamic aberrations, and intensified follow-up through remote monitoring of blood pressures becomes the next step in managing hypertension in pregnancy.

SAMENVATTING

In 2015 werden 65.000 zwangerschappen geregistreerd in Vlaanderen, waarvan circa 4,6% gecompliceerd waren met hypertensie tijdens de zwangerschap. Deze aandoening is geassocieerd met maternale (moederlijke) en neonatale morbiditeit. Hypertensie tijdens de zwangerschap omvat drie types: (1) gestationele hypertensie, (2) vroege en late zwangerschapsvergiftiging (preeclampsie) en (3) chronische hypertensie. Met het huidige onderzoek trachten we het achterliggende mechanisme en het ontstaan van deze aandoeningen te achterhalen. Bovendien is er nood aan een vroegtijdige screeningsprocedure om risicopatiënten in kaart te brengen.

Het is reeds gekend dat foutieve veranderingen in het hart en de bloedvaten tijdens de zwangerschapsperiode kunnen leiden tot hypertensie. Een meting van het hart en de bloedvaten tijdens de zwangerschap kunnen een idee geven over hoe goed of slecht ze functioneren. Dit is mogelijk aan de hand van een aantal eenvoudige, veilige en niet-invasieve technieken. In deze thesis maakten wij gebruik van 3 gestandaardiseerde en gevalideerde technieken: 1) ECG-Doppler echografie om de functie van de aders en slagaders te meten, 2) Impedantie Cardiografie om het functioneren van het hart te meten en 3) Bio-Impedantie om het totale lichaamsvocht en de vochtbalans te schatten. Deze technieken werden toegepast bij 1.763 zwangere vrouwen in hun eerste, tweede of derde zwangerschapstrimester.

Deze thesis heeft bijgedragen aan een heel aantal nieuwe inzichten over de (patho)fysiologie van hypertensieve zwangerschappen, maar ook het basisprobleem van kleine baby's werd achterhaald. Zo stellen we met behulp van een meting in het eerste trimester typische kenmerken vast waarmee we een cardiovasculair onderscheid kunnen maken tussen groei restrictie (kleine baby's), gestationele hypertensie, vroege en late zwangerschapsvergiftiging. Groeirestrictie is geassocieerd met een laag maternaal lichaamsvolume en compenserende aders en slagaders. Gestationale hypertensie kenmerkt zich door een hoge bloeddruk, een hoge weerstand van de bloedvaten en hartafwijkingen. Vertonen de aders bovendien afwijkingen, dan wijst dit richting zwangerschapsvergiftiging. Een bijkomende verstoring aan de

baarmoederslagaders samen met een hoge vochtbalans is karakteristiek voor het vroege, ernstige type van zwangerschapsvergiftiging. Naarmate de zwangerschap vordert, des te meer zullen de bloedvaten en het hart eronder lijden en zullen deze afwijkende signalen beter meetbaar worden. Tijdens de zwangerschap sturen het hart en de bloedvaten van de moeder een grote hoeveelheid bloed naar de baarmoeder, maar dit mechanisme is meer geactiveerd in pathologische zwangerschappen in vergelijking met normale zwangerschappen.

Deze afwijkende cardiovasculaire kenmerken zijn krachtig genoeg om reeds in het eerste en tweede trimester een onderscheid te maken tussen de verschillende types van hypertensie. Hierdoor is er een duidelijke medische basis om vroegtijdig in de zwangerschap te screenen. Op basis van deze afwijkingen in het hart en de bloedvaten is een gepersonaliseerde en aangepaste therapie mogelijk in de toekomst. Bovendien zijn patiënten met een verhoogd risico gebaat bij een intensievere follow-up tijdens de zwangerschap. Hier kan telemonitoring van de bloedruk(ken) een belangrijke rol spelen.

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SCIENTIFIC ACHIEVEMENTS

PEER-REVIEWED PAPERS

1. Gyselaers W, Staelens A, Mesens T, Tomsin K, Oben J, **Vonck S**, Verresen L, Molenberghs G.
Maternal venous Doppler characteristics are abnormal in preeclampsia but not in gestational hypertension.
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2. **Vonck S**, Staelens A, Mesens T, Tomsin K, Gyselaers W.
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3. Staelens A, **Vonck S**, Mesens T, Tomsin K, Molenberghs G, Gyselaers W.
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Clin Exp Pharmacol Physiol. 2015; 42(10):1036-44

4. **Vonck S**, Swinnen SP, Wenderoth N, Alaerts K.
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5. Staelens A, Bertrand P, **Vonck S**, Malbrain M, Gyselaers W.
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7. **Vonck S**, Oben J, Staelens AS, Lanssens D, Tomsin K, Gyselaers W.
B4. Normal and abnormal blood pressures in early pregnancy: are we using the right cut off values?
J Matern Fetal Neonatal Med. 2016;29(sup2):9.

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G5. 12-week cardiovascular profiles differ between patients with essential hypertension, gestational hypertension, late preeclampsia and intra-uterine growth retardation.
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Why non-invasive maternal hemodynamics assessment is clinically relevant in early pregnancy: a literature review.
BMC Pregnancy Childbirth. 2016;16(1):302.

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12. **Vonck S**, Oben J, Staelens AS, Lanssens D, Molenberghs G, Gyselaers W.
Optimization of simple sphygmomanometric blood pressure measurement in routine prenatal care.
Health Care Current Reviews. 2017;5(1):185.

13. Lanssens D, Vandenberk T, Smeets C, De Cannière H, Molenberghs G, Van Moerbeke A, van den Hoogen A, Robijns T, **Vonck S**, Staelens A, Storms V, Thijs I, Grieten L, Gyselaers W.
Remote monitoring of hypertension diseases in pregnancy: a pilot study.
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Maternal hemodynamics: a method to classify hypertensive disorders of pregnancy.
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OTHER PUBLICATIONS

15. Nulens K & Quintiens J, Staelens A, Dethier K, **Vonck S**, Gyselaers W.
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Tijdschrift voor geneeskunde. 2014; 70(20):1186-1195.

17. Bollen I & Broekx L, **Vonck S**, Staelens A, Lanssens D, Gyselaers W.
Maternale cardiovasculaire veranderingen in de vroege zwangerschap.
Tijdschrift voor geneeskunde. 2015; 71(22):1473-1482.

SUBMITTED

18. **Vonck S**, Staelens AS, Lanssens D, Tomsin K, Oben J, Bruckers L, Gyselaers W. *Uterine flow promoting peripheral resistance in normotensive pregnancies with healthy neonates small for gestational age.*

19. **Vonck S**, Staelens AS, Lanssens D, Tomsin K, Oben J, Bruckers L, Gyselaers W. *Obesity in pregnancy causes a volume overload in third trimester.*

20. Gyselaers W, **Vonck S**, Staelens AS, Lanssens D, Tomsin K, Oben J, Bruckers L. *First trimester maternal cardiovascular dysfunctions characterize gestational hypertensive diseases.*

21. **Vonck S**, Staelens AS, Lanssens D, Tomsin K, Oben J, Bruckers L, Gyselaers W. *Relevance of maternal hemodynamics assessment in phenotype-specific screening for gestational hypertensive diseases.*

BOOK CHAPTER

1. **S. Vonck** and W. Gyselaers
Dysfunction of the venous system before and during preeclampsia
Maternal Hemodynamics (In Press)

PRESENTATIONS

ORAL

1. **S. Vonck** and W. Gyselaers
'The maternal cardiovascular profile'
4th Euregional Meeting: Departments of Gynecology and Obstetrics of the Universities of Aachen, Genk and Maastricht.
Location: Uniklinik RWTH Aachen, Germany. Date: 14 March, 2014.

2. **S. Vonck**
'"The practice of" measuring plasma volume and body fluids'
1st International Congress on Maternal Hemodynamics.
Location: Hasselt, Belgium. Date: 16-18 October, 2014.

3. **S. Vonck**, J. Oben, A. Staelens, D. Lanssens, K. Tomsin, W. Gyselaers
'Screening for gestational hypertensive disease using biophysical cardiovascular parameters'
Maternal Hemodynamics Workshop
Location: Maastricht, The Netherlands. Date: 11-12 December, 2015.

4. **S. Vonck**, J. Oben, A. Staelens, D. Lanssens, K. Tomsin, W. Gyselaers
'12 week cardiovascular profiles differ between patients with essential hypertension, gestational hypertension, late preeclampsia and intra-uterine growth retardation'
2nd International Congress on Maternal Hemodynamics.
Location: Rome, Italy. Date: 12-14 May, 2016.

5. **S. Vonck**, J. Oben, A. Staelens, D. Lanssens, K. Tomsin, W. Gyselaers
'Normal and abnormal blood pressures in early pregnancy: are we using the right cut off values?'
2nd International Congress on Maternal Hemodynamics.
Location: Rome, Italy. Date: 12-14 May, 2016.

6. **S. Vonck**, A. Staelens, D. Lanssens, K. Tomsin, J. Oben, W. Gyselaers
'Physiology of an uncomplicated pregnancy'
Maternal Hemodynamics Workshop
Location: London, UK. Date: 24 November, 2017.

POSTER
7. **S. Vonck**, A. Staelens, T. Mesens and W. Gyselaers.
'Bioimpedance is usefull to measure intra- and extracellular water in normal and hypertensive pregnancies'
European Conference Perinatological Medicine
Location: Firenze, Italy. Date: 3-7 June, 2014.

8. **S. Vonck**, A. Staelens and W. Gyselaers.
'Relation between cardiovascular function and body fluids during pregnancy'
4th International fluid Academy Days.
Location: Antwerp, Belgium. Date: 27-29 November, 2014.

9. **S. Vonck**, A. Staelens, M. Malbrain and W. Gyselaers
'Longitudinal measurement of extracellular and intracellular water in normal pregnancy and preeclampsia'
8th International DIP symposium
Location: Berlin, Germany. Date: 15-18 April, 2015.
10. **S. Vonck**, A. Staelens, M. Malbrain and W. Gyselaers
'Bio-impedance measurement of extracellular water and plasma volume in normal pregnancies and preeclampsia'
8th International DIP symposium
Location: Berlin, Germany. Date: 15-18 April, 2015.

11. **S. Vonck**, A. Staelens, W. Gyselaers
'Fetal growth restrictions are characterized by maternal low body fluids'
Knowledge for Growth
Location: Gent, Belgie. Date: 26 May, 2016.

12. **S. Vonck**, J. Oben, AS Staelens, D. Lanssens, G. Molenberghs, W. Gyselaers
'Optimisation of simple sphygmomanometric blood pressure measurement in routine prenatal care'
Knowledge for Growth
Location: Gent, Belgie. Date: 18 May, 2017

DANKWOORD

En dan nu het meest gelezen stuk van heel deze thesis… ☺

In 2013 kwam ik, nog een beetje groen achter mijn oren, aan in Genk. Blij met de kans om klinisch onderzoek te mogen voeren in een onderwerp dat nog steeds heel veel vraagtekens bevat(te). Heel dit doctoraatsproject en traject is enkel succesvol geworden door de gedreven begeleiding van mijn promotor, Prof. Dr. Wilfried Gyselaers.

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"If you don't know
where you're going,
any road will take you
there."
- Lewis Carroll