Heymans Institute of Pharmacology, Unit of Clinical Pharmacology

Faculty of Medicine and Health Sciences

Ghent University

Pregnancy and Tocolysis: Effects on Haemodynamics and Arterial Stiffness

Isabelle Fabry

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De aanhouder wint…

Voor Louis,

Voor Lucas,

Voor Julie.

Promotor:

Prof. Dr. Lucas Van Bortel

Heymans Institute of Pharmacology,.Unit of Clinical Pharmacology, Ghent University, Belgium

Co-Promotor:

Prof. Dr. Jan Staessen

Studies Coordinating Centre, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium;

VitaK Research and Development, Maastricht University, Maastricht, The Netherlands

Doctoral Guidance Committee:

Prof. Dr. Marleen Temmerman

Department of Obstetrics and Gynaecology, Ghent University and Hospital, Belgium

Members of the Jury:

Prof. dr. ir. Patrick Segers

IBiTech - bioMMeda, Ghent University-iMinds Medical IT, Ghent, Belgium

Prof. dr. Ernst Rietzschel

Department of Internal Medicine, Ghent University and Hospital, Belgium

Prof. dr. Steven Weyers

Department of Obstetrics and Gynaecology, Ghent University and Hospital, Belgium

Prof. dr. Romain Lefebvre

Heymans Institute of Pharmacology, Ghent University, Belgium

Prof. dr. Guy Joos

Department of Respiratory Medicine, Ghent University and Hospital, Belgium

Dr. Floris Vanmolkot

Department of Internal Medicine, Maastricht University Medical Centre, The Netherlands

Prof. dr. Kennedy Cruickshanck

Professor of Cardiovascular Medicine and Diabetes, Division of Diabetes and Nutrition, King's College, London; Hon Consultant Physician, St Thomas' & Guy's Hospitals & Clinical Research Facilities, King's Health Partners, United Kingdom

Pregnancy and Tocolysis: Effects on Haemodynamics and Arterial Stiffness

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Zwangerschap en Tocolyse: Effecten op de Hemodynamica en de Vaatwandstijfheid

Content

Outline of the Thesis

The present thesis consists of four parts:

The first part is an introduction consisting of two chapters, starting with a review (Chapter 1) concerning the hypertensive disorders during pregnancy with focus on differential diagnosis and treatment options. In Chapter 2 the methods, used in the thesis, are described with also their physiologic background. In the second part, the maternal haemodynamic system is explored starting with the problem statements and aims of part II in Chapter 3. The arterial stiffness indices have never been followed in a longitudinal, descriptive setting during pregnancy. Arterial stiffness measurement have been shown to be of predictive value in the general population. Nothing is yet known how the indices of arterial stiffness will relate to each other during pregnancy and measured longitudinally. Since blood pressure monitoring is of paramount importance during pregnancy, we described the temporal blood pressure changes taken by self-monitoring at home versus office measurements (Chapter 4) and evaluated self-assessed blood pressure data with an attempt to make reference values during pregnancy (Chapter 5). The second part ends with the effect of pregnancy on arterial stiffness, where we assessed peripheral and central blood pressures, carotid and aortic stiffness and wave reflections during pregnancy (Chapter 6).

Part III focuses on the effects of tocolytical treatment on the maternal haemodynamic system, particularly ritodrine and atosiban. The problem statements and aims are mentioned in Chapter 7 which is followed by an overview of tocolytical treatment options in Chapter 8. Until now, only subjective reporting of side effects during ritodrine-use was noted. The (lack of cardiovascular) effects of the newer but criticized tocolyticum, atosiban, were only reported in sponsored trials. The purpose of this study was to unravel the pharmacodynamical effects and the differences of the effects between ritodrine and atosiban on the blood pressure and blood pressure amplification, the cardiac function, the large arteries and resistance vessels in a placebo-controlled study, mentioned in Chapter 9. The thesis ends in Part IV with the general discussion which focuses on the headings per chapter (Chapter 10) and the summary/samenvatting (Chapter 11).

List of Abbreviations

AAMI	Association for the Advancement of Medical Instrumentation
ACE	angiotensin converting enzyme
Ad	arterial cross-sectional diameter at end-diastole
ADH	anti-diuretic hormone
AIx	augmentation index
ANP	atrial natriuretic peptide
APA	antiphospholipid antibodies
APA-syndrome	asthma polyposis aspirin syndrome
ARB	angiotensin receptor blocker
BA	brachial artery
BHS	British Hypertension Society
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BSA	body surface area
CC	cross-sectional compliance
CCA	common carotid artery
CFA	common femoral artery
cfPWV	carotid-femoral pulse wave velocity
cGMP	cyclic guanosin monophosphate
CI	cardiac index
CO	cardiac output
COX	cyclooxygenase
CRP	C-reactive protein
CT	computer tomography
CV	cardiovascular
D	lumen diameter
DBP	diastolic blood pressure
DC	distensibility coefficient
DD	diameter at end-diastole
DS	diameter at end-systole
E	evening
E_{inc}	incremental elastic modulus
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EU	European Union
FDA	Food and Drug Administration
FF	form factor

FLEMENGHO	The Flemish Study on Environment, Genes and Health Outcomes
FVI	flow velocity index
HBP	home blood pressure(s)
HELLP	haemolysis, elevated liver enzymes, low platelets
HR	heart rate
HT	hypertension
HUS	haemolytic uremic syndrome
ICAM-1	intercellular adhesion molecule -1
ICH	International Conference on Harmonisation
IDHOCO	The International Database of HOme blood pressure in relation to Cardiovascular Outcome
IL-6	interleukine-6
IU	intra-uterine
IV	intravenous(ly)
LMWH	low molecular-weight heparin
M	morning
MAP	mean arterial pressure
MHz	Mega-hertz
MRI	magnetic resonance imaging
N	number
NICE	National Institute for Health and Care Excellence
NO	nitric oxide
NOs	nitric oxide synthetase
NS	not significant
OBP	office blood pressure(s)
P	percentile
PP	pulse pressure
PP	postpartum
PTP	pre-pregnancy time point
PWF	pressure wave form(s)
PWR	pulse wave reflections
PWV	pulse wave velocity
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RA	radial artery
RAAS	renin-angiotensin-aldosterone system
SAC	systemic arterial compliance
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of mean
SI	stroke index
SLE	systemic lupus erythematosus
SMCs	smooth muscle cells
SSN	supra-sternal notch
SV	stroke volume

SVR	systemic vascular resistance
TEE	trans-oesophageal echocardiography
TNF	tumour necrosis factor
TPR	total peripheral resistance
TPRI	total peripheral resistance index
TTP	thrombotic thrombocytopenic purpura
USA	United States of America
VCAM-1	vascular cell adhesion molecule-1
VS	Verenigde Staten
WCH	white coat hypertension
ρ	rho, density of blood

Part I: Introduction

Chapter 1 Diagnosis and Treatment of Hypertensive disorders during Pregnancy

Based on: Diagnosis and treatment of hypertensive disorders during pregnancy

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1.1 Introduction

During pregnancy, haemodynamic and metabolic adaptations ensure adequate perfusion and nutrient delivery to the foetus. Hypertensive disorders complicate 1 out of 10 pregnancies, entailing an increased risk for maternal and foetal morbidity and mortality. Identification of risk factors, an early diagnosis of elevated blood pressure and subsequent antihypertensive treatment are of paramount importance. Although descriptions of haemodynamic changes during the course of pregnancy are plentiful, evidence-based guidelines for the treatment of hypertensive disorders during pregnancy are sparse. In this review, we summarise the mechanisms of blood pressure control and plasma volume regulation in normotensive and hypertensive pregnant women. In addition, we reviewed current recommendations for the diagnosis and treatment of hypertension during pregnancy.

1.2 Haemodynamic and endocrine adaptations to pregnancy

1.2.1 Haemodynamic changes

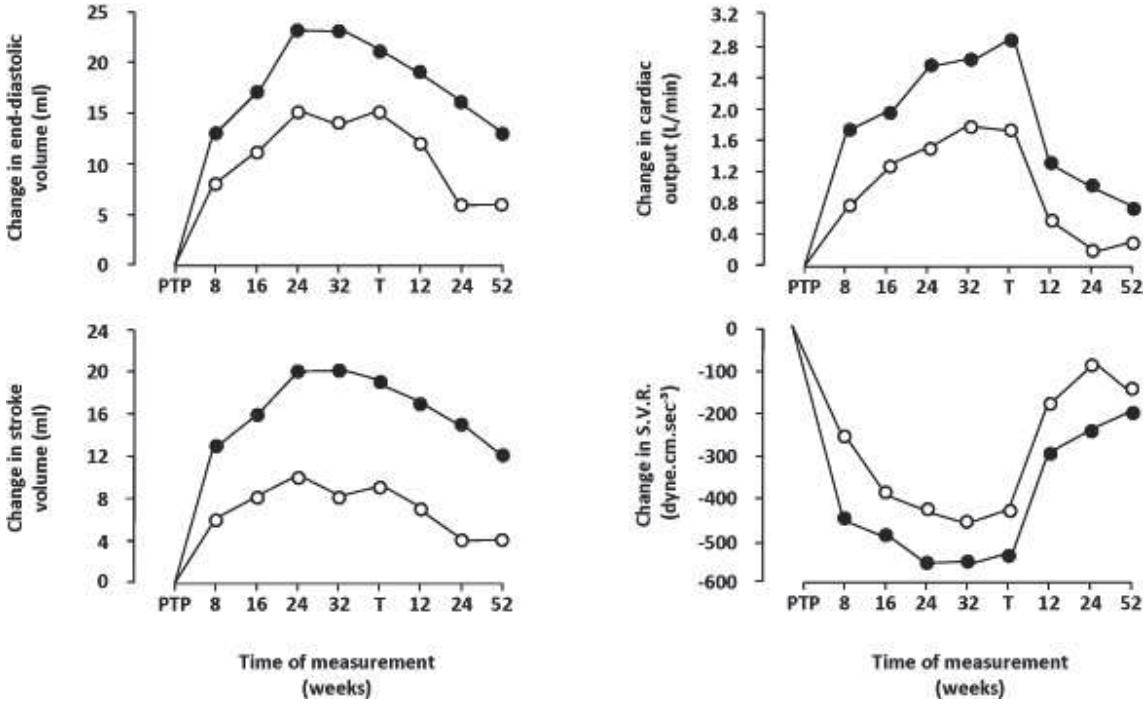
Profound cardiovascular adaptations start in the late luteal phase of the menstrual cycle (Table 1.1). These haemodynamic alterations peak in the second trimester of pregnancy and return to non-pregnant levels near term[1;2]. They disappear within the first days after delivery, although abnormalities in volume homeostasis may persist for up to a year, called the protracted effect of pregnancy on the volume status[3] (Figure 1.1).

Table 1.1: Summary of the important haemodynamic changes during pregnancy.[4]

Increased	Decreased
Uterine blood flow	Systemic vascular resistance
Plasma volume	Pulmonary vascular resistance
Red blood cell mass	Haematocrit
Cardiac diastolic dimension	Colloid osmotic pressure
Stroke volume	Plasma albumin concentration
Heart rate	Arterial carbon dioxide tension
Arterial oxygen consumption	Arterial hydrogen ion concentration
Venous capacitance	Arterial blood pressure

The changes in the maternal haemodynamics in early pregnancy involve hormones that induce vasodilatation of the arterial and venous vasculature.[5] These endocrine triggers already arise in the late luteal phase and cause a generalised fall in systemic vascular tone. Lower vascular resistance is one of the earliest maternal adjustments to pregnancy.[6] Decreased vascular responsiveness to angiotensin II and norepinephrine and increased endothelial production of prostacyclin and nitric oxide (NO) may play a role as exemplified by the increased urinary excretion of kallikreine, cyclic guanosine monophosphate (cGMP-second messenger of NO) and prostacyclins.[7;8] The subsequent rise in vascular capacitance creates a state of relative under filling and initiates the cardiovascular adaptation to pregnancy.[9-12]

Figure 1.1 Haemodynamic adaptations before, during and after pregnancy[13]



PTP: pre-pregnancy time point; T: term; S.V.R.: systemic vascular resistance; Course of cardiac end-diastolic volume, stroke volume, cardiac output and systemic vascular resistance before and throughout pregnancy until 52 weeks postpartum. Open circles: data from 15 nulliparous; blinded circles: data from 15 parous women.

Figure adapted with permission from.[13]

The sensors perceiving and controlling intravascular volume are reset during normal pregnancy, enabling the maternal circulation to accommodate a gradual expanding plasma volume (to 40% at term) without provoking a natriuretic response.[8] Meanwhile, red blood cell mass increases by 30%, which is less than the expansion of the plasma volume. This explains to the so-called pregnancy-anaemia. The plasma protein concentration and plasma osmolality likewise decrease during pregnancy.[4]

Afterload reduction activates baroreceptors. As a consequence heart rate, stroke volume and cardiac contractility increase and venous blood shifts towards the arterial compartment.[1;6;14] To meet the higher basal oxygen consumption in pregnant women (up to 50mL/min at term), cardiac output increases.[4]

Systolic and diastolic blood pressures drop slightly during normal pregnancy as does pulse pressure with the maximum change found in the second trimester. When measuring blood pressure in pregnant women one should always account of posture, because in the supine position the pregnant uterus compresses the inferior caval vein, thereby reducing venous return and cardiac output.[1;4]

1.2.2 Endocrine changes

The secretion of adrenal steroids (aldosterone and cortisol) is elevated during pregnancy (to three times the non-pregnant levels).[15] Volume retention and restoration of the preload is due to activation of the renin-angiotensin-aldosterone system (RAAS) and stimulation of the secretion of cortisol and antidiuretic hormone (ADH)[9;12;16;17]. A concomitant decrease of atrial stretch suppresses the release of atrial natriuretic peptide (ANP).[18]

The endocrine adaptations induce water and salt retention, so that at the end of pregnancy 6-8 l of extra water are distributed among the foetus, the amniotic fluid and all the intra-and extracellular tissues of the mother.[19]

In summary, the normal pregnancy is characterised by a generalised reduction of systemic vascular resistance and blood pressure and an increase in cardiac output and blood volume to ensure an adequate utero-placental circulation and increased blood flow to the breast and kidneys of the mother.[4]

1.3 Diagnosis of hypertensive disorders during pregnancy

1.3.1 Guidelines

Hypertension affects 10% of all pregnancies.[20;21] Therefore, blood pressure should be measured regularly in pregnant women. The guidelines of the American College of Obstetricians and Gynecologists identify two subgroups: mild (140-159/90-110 mmHg) and severe (>160/110 mmHg) hypertension.[21;22] The diagnosis of an elevated blood pressure and the differential diagnosis of hypertensive disorders during pregnancy are not easy. Hypertension in pregnancy is defined as two recordings of a blood pressure of at least 140/90 mmHg at two occasions, separated by an interval of at least 6 hours. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, women with a systolic blood pressure of 120-139 mmHg and/or a diastolic blood pressure of 80-89 mmHg should be considered as pre-hypertensive.[23] The European Society of Hypertension recommends a threshold of ≥140 mmHg systolic and/or ≥ 90 mmHg diastolic on repeated measurements.[24] Nevertheless, the threshold of 140/90 mmHg might be too high for young subjects, such as women of childbearing age. Thus, based on this threshold, the prevalence of hypertensive disorders during pregnancy might be underestimated.[20]

1.3.2 Risk factors

Women with severe hypertension prior to pregnancy, hypertension in the first trimester despite use of antihypertensive medications, or both and those with adverse outcomes in a previous pregnancy are at very high risk of superimposed pre-eclampsia (50%-75%), foetal growth retardation (25%-40%), and abruptio placentae (10%-20%). Chronic hypertension tends to be more prevalent in Black women, women with obesity or diabetes and older (>35 years) women.[21;25;26] Smoking enhances the risk and severity of adverse pregnancy outcomes, such as gestational hypertension. However recent epidemiologic data suggest that the risk of pre-eclampsia is decreased by 30% among young smokers without pre-gestational hypertension.[27]

1.3.3 Possible diagnoses

This section describes the most common hypertensive disorders during pregnancy.[28] Abnormal placentation is thought to be the cornerstone in the process of aberrant maternal-foetal interaction and placental hypoperfusion. Neurohormonal feedback induces or exacerbates maternal hypertension in an attempt to maintain placental perfusion and foetal growth.[20]

1.3.3.1 Chronic hypertension

Chronic hypertension, present before pregnancy or before 20 weeks of gestation, complicates approximately 3% of all pregnancies. Essential hypertension is the most common cause.[21] When blood pressure decreases during mid-pregnancy, the blood pressure tends to become "normal". At the end of pregnancy, when blood pressure returns to pre-gravid levels, women with pre-existing chronic hypertension might be diagnosed as hypertensive for the first time. When blood pressure fails to normalise after delivery (longer than 12 weeks postpartum), the diagnosis of chronic hypertension can only be made retrospectively.[20]

Therefore, women should be evaluated prior to conception to define their blood pressure status, and, if hypertensive, to assess the severity, possibly remediable causes, and the presence of target organ damage. As a general rule, women have a lower blood pressure than men, but with the increasing prevalence of obesity and the metabolic syndrome a growing proportion of women present with hypertension at younger age.[23] Up to 30% of women with chronic hypertension develop pre-eclampsia.

1.3.3.2 Gestational hypertension

Gestational hypertension is hypertension occurring for the first time during the second half of pregnancy in the absence of proteinuria. It occurs in 6% of all pregnancies. Women with gestational hypertension progress to pre-eclampsia in 15% to 45% of cases.[20;21;23;29]

These patients should be monitored very closely to determine whether pre-eclampsia or other causes of gestational hypertension exist. Early delivery and foetal monitoring are sometimes needed because gestational hypertension, when severe, may lead to higher rates of premature delivery and growth retardation than mild pre-eclampsia. When blood pressure remains elevated after delivery, the diagnosis of chronic hypertension should be kept in mind. It is very important to differentiate pre-eclampsia, a pregnancy-specific syndrome from pre-existing chronic hypertension or gestational hypertension.

1.3.3.3 Pre-eclampsia / Eclampsia

In addition to an elevated blood pressure, the diagnosis of pre-eclampsia no longer requires the appearance of proteinuria in the third trimester of pregnancy in women without proteinuria before pregnancy.[30;31] Evidence shows organ problems with the kidneys and liver can occur without signs of proteinuria, and that the amount of protein in the urine does not predict how severely the disease will progress. Prior to 2013, most healthcare providers traditionally adhered to a rigid diagnosis of preeclampsia based on blood pressure and protein in the urine (proteinuria).

Pre-eclampsia occurs in 3-5% of pregnancies.[20;21] The convulsive form of pre-eclampsia, eclampsia, affects 0.1% of all pregnancies.[20;21] Pre-eclampsia and eclampsia are responsible for 12% of the global maternal deaths.[30] The syndrome is more common in nulliparous women, in multiple gestation, in women with a history of gravid or non-gravid hypertension or renal disease or in women with a positive family history of pre-eclampsia in a first degree relative.[23]

Preeclampsia is now to be diagnosed by persistent high blood pressure that develops during pregnancy or during the postpartum period that is associated with a lot of protein in the urine or the new development of decreased blood platelets, trouble with the kidney or liver, fluid in the lungs, or signs of brain trouble such as seizures and/or visual disturbances.

The haemodynamic changes and adaptations during pregnancy might unmask underlying endothelial dysfunction, leading to clinical syndromes as pre-eclampsia and eclampsia that resolve with termination of pregnancy. The disease is characterised by systemic vasoconstriction and reduced plasma volume, leading to systemic ischemia, which is the substrate for hypertension and multi-organ dysfunction. Pre-eclamptic patients might be at higher risk of developing cardiovascular diseases later in life.[32;33] They have approximately a 2-to 3-fold higher risk in developing early cardiac, cerebrovascular, and peripheral arterial disease, and cardiovascular mortality.[34-38] Similarities exist between the metabolic abnormalities that are associated with increased risk for cardiovascular diseases and pre-eclampsia. These include insulin resistance, obesity and lipid abnormalities. In pre-eclampsia, as in atherosclerosis, oxidative stress resulting from free radicals contributes to endothelial dysfunction. Evidence for this feature includes increased lipid peroxidation, diminished activity of antioxidant enzymes and an increased capacity of the placenta to generate reactive oxygen species.[39;40]

An inflammatory response is one of the adaptations that occur during normal pregnancy. It probably reflects an immune reaction of the maternal body to foetal antigens. This inflammatory response may be exaggerated in pre-eclampsia as exemplified by the higher neutrophil activation compared with normal pregnancies (reflected by higher levels of neutrophil elastase, VCAM-1 (vascular cell adhesion molecule-1), ICAM-1 (inter-cellular adhesion molecule-1), TNF (tumour necrosis factor) and IL-6 (interleukine-6)). A high CRP(C-reactive protein)-level in pre-eclampsia illustrates the continuum between hypertensive disorders during pregnancy and cardiovascular diseases later in life.[41-43]

1.3.3.4 HELLP-syndrome

Haemolysis (H) combined with a micro-angiopathic blood smear, increased liver enzymes (EL), and low platelets (LP) in pregnancy was first described in 1982 and affects six in 1000 pregnancies.[44] 5–10%

of women with pre-eclampsia develop HELLP.[45] Risk factors to develop HELLP-syndrome include advanced maternal age, multiparity and white ethnic origin.[46] The neonatal mortality rate can be very high (6-70%) due to premature delivery or maternal complications.

Very often, the patient gets a non-obstetric diagnosis, which leads to an inadequate treatment. HELLP patients often report right upper quadrant pain, nausea and vomiting. Hypertension and proteinuria are present in 85% of the cases. HELLP starts usually in the second or third trimester, but can also develop in the near postpartum without any sign or symptom of pre-eclampsia. The patients need aggressive therapy to prevent maternal and neonatal mortality. Delivery of the baby is the definitive treatment of severe HELLP syndrome.

1.3.4 Differential diagnoses

Pregnant women developing severe symptoms suggestive of pre-eclampsia before 30 weeks should be tested for autoimmune disorders or acquired thrombophilia's.

1.3.4.1 Acute fatty liver of pregnancy

Acute fatty liver of pregnancy affects approximately 1 of 10 000 pregnancies and presents in late pregnancy (27 – 40 weeks). It is caused by a recessive inherited defect in foetal long chain 3-hydroxyacyl-coenzyme A hydrogenase. This mutation causes mitochondrial dysfunction with accumulation of fatty acid metabolites. The mother presents with progressive fatigue, malaise, anorexia, nausea, vomiting and mid-epigastric or right upper quadrant pain and jaundice. Hepatic dysfunction leads to mental changes, hypertension, proteinuria, severe hyperglycaemia and coagulopathy. The fatty infiltration of the liver may be diagnosed by ultrasound, CT or MRI imaging of the abdomen. However, the diagnostic standard is liver biopsy, but this is rarely done in practice due to procedural risk. Bilirubin levels are typically higher (5-10 mg/dL) than seen in pre-eclampsia (2-3 mg/dL). Recent data indicate maternal perinatal mortality rates of approximately 10%.[21] The only treatment is immediate delivery.[47]

1.3.4.2 Thrombotic microangiopathies

Thrombotic thrombocytopenic purpura (TTP) and haemolytic uremic syndrome (HUS) are extremely rare during pregnancy and the postpartum period (<1 case in 100 000 pregnancies) but have a very dire outcome. Maternal survival improved from 40% to 90-100%. However, the maternal morbidities continue to be high. The foetal and neonatal mortality can be as high as 40%. The classic pentad of TTP and HUS (thrombocytopenia, microangiopathic haemolytic anaemia, neurologic abnormalities, fever and renal dysfunction) has significant clinical overlap with eclampsia. Symptoms of eclampsia before 20 weeks of

gestation might herald TTP/HUS[21;48] and one should always differentiate between both entities because of their different treatment options. Late in pregnancy, it is difficult to differentiate the common preeclampsia/HELLP syndromes from TTP-HUS. Both diagnoses should be considered later in the pregnancy and during puerperium.[49;50] It should also be noted that TTP-HUS and preeclampsia/HELLP syndrome may coexist in about 17% of cases.[51]

A high index of suspicion is essential for the timely diagnosis and treatment of TTP-HUS. Delivery of the baby is the definitive treatment of severe preeclampsia/HELLP syndrome. If a patient recovers after delivery, TTP-HUS is unlikely.[52] Generally, plasma exchange or infusion of fresh frozen plasma should be considered when a woman presents with TTP-HUS symptoms during puerperium.[49] It should be assertively considered if symptoms and signs persist after delivery. Moreover, if severe thrombocytopenia, haemolytic anaemia, renal failure and mental status changes are present, TTP-HUS should be diagnosed and treated with plasma exchange or fresh frozen plasma, regardless of the time of the pregnancy.[53]

1.3.4.3 Systemic Lupus Erythematosus (SLE)

SLE is an auto-immune disorder occurring frequently in women in their childbearing years with diverse clinical findings, which can be mild or severe and may include multiple organ systems (kidneys, lungs, liver and brain).[21;54] It may develop for the first time during pregnancy or in the postpartum period. For women with systemic lupus erythematosus (SLE), particularly those with pre-existing renal disease or with active lupus, the risk of developing preeclampsia is up to 14% higher than it is among healthy individuals.[55] In patients with lupus nephritis, the clinical and laboratory findings are similar to those of severe pre-eclampsia (hypertension, proteinuria and microscopic haematuria). Most patients in the acute phase have skin and joint lesions. APAs (lupus anticoagulant and/or anti-cardiolipin antibodies) are present in 30-40% of women with SLE. These patients are at increased risk for thrombotic events with tissue ischemia secondary to an event. The clinical picture then becomes very similar to that of the HELLP syndrome, eclampsia, TTP and HUS. Maternal morbidity and mortality are high in those with renal and central nervous system involvement and in those with anti-phospholipid (APA) syndrome. Maternal mortality is almost 50% in patients who develop catastrophic APA syndrome due to acute thrombotic microangiopathy. Because of placental infarctions or haemorrhage, foetal and neonatal morbidity and mortality is very high (foetal death in 4-19% and preterm delivery in 38-54% of the cases).[56]

Recent evidence recommends low-dose aspirin administration (50-150mg/day) for all pregnant women with SLE, with therapy being initiated prior to 16 weeks of gestation and continuing throughout

pregnancy.[57] Women with SLE and APA syndrome should continue aspirin treatment as a preeclampsia prophylaxis and add heparin or LMWH.[58]

1.4 Treatment of hypertensive disorders during pregnancy

1.4.1 Guidelines and goals

The treatment of severe hypertension (SBP>160 mmHg, DBP > 110mmHg) has the primary goal to reduce the risk of severe maternal morbidity (cerebral haemorrhage, liver rupture, renal insufficiency and abruptio placentae) and foetal morbidity (preterm birth). There is little evidence to support aggressive medical interventions for levels of blood pressures below 160 mmHg systolic or 110 mmHg diastolic. In such patients, the decision to treat hypertension must be individualised.[22]

According to a recent Cochrane review[59], recommended antihypertensive medications are all better than placebo. They are useful and effective in preventing haemodynamic complications and progression to severe hypertension. There are, unfortunately, insufficient data to firmly recommend at which level of blood pressure antihypertensive drug treatment should be started. Whether or not the appearance of proteinuria justifies lower thresholds to initiate antihypertensive treatment also remains to be elucidated.

The safety of the mother must come first and one should consider early delivery of the foetus. Immediate goals of therapy in severe hypertension during pregnancy are a 25% reduction of mean arterial pressure (MAP) within 2 hours of the clinical presentation and a goal below 160/110 mmHg in the next hours. Abrupt reductions of MAP by more than 25% might lead to end-organ hypo-perfusion or foetal injury due to placental infarction.[29]

The current management of pre-eclampsia includes close monitoring of maternal and foetal signs and symptoms, rest at home or in the hospital, antihypertensive drugs to control hypertension, and timely delivery (according to gestational age, disease severity, and results of maternal-foetal monitoring). Several groups of antihypertensive medications are frequently used.

Clinicians should make an educated choice based on already known effects on maternal and foetal morbidity of the particular drug (Table 1.2 & Table 1.3).

Table 1.2 Food and Drug Administration (FDA) categorisation of drug risks to the foetus.[60]

FDA categorisation
Category A
Controlled studies in women fail to demonstrate a risk to the foetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of foetal harm appears remote.
Category B
Either animal-reproduction studies have not demonstrated a foetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
Category C
Either studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the foetus.
Category D
There is positive evidence of human foetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Category X
Studies in animals or human beings have demonstrated foetal abnormalities, or there is evidence of foetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

1.4.2 First choice antihypertensive drugs

1.4.2.1 Methyldopa

Alpha-methyldopa does not reduce the utero-placental blood flow and hence no effect on the foetal growth. This drug has been used extensively in obstetrics for years and has been considered useful as a maintenance therapy to gradually lower the blood pressure. It is one of the Food and Drug Administration class B medication for hypertension.[21;61] Known side effects are mostly minor like postural hypotension, dizziness and liver function disorders.

1.4.2.2 Calcium channel blockers

Calcium channel blockers are safe molecules (Table 1.3). No adverse neonatal events have been registered until today.[62] The more commonly used drug is nifedipine. It exists in fast and slow release preparations. The preference goes to the slow release form in order to prevent sudden onset of maternal hypotension and reflex tachycardia with foetal distress consequently. Because of the increased renal and hepatic clearance related to pregnancy, starting doses and administration frequency often require adjustments.[61]

1.4.3 Second-line antihypertensive drugs

1.4.3.1 Beta-blockers

The use of this group may lead to intra-uterine growth retardation. However the evidence is based on a small placebo-controlled trial with atenolol.[63] Labetalol (α-and β-receptor antagonist) is more safe and can be used both orally and intravenously. It gives a gradual decrease of the blood pressure without hypo-perfusion of the utero-placental vasculature. High intravenous dosages shortly before delivery may cause therapy-resistant neonatal hypotension and bradycardia. Although labetalol has a long history of safety, some studies have associated it with foetal growth retardation.

1.4.3.2 Hydralazine

Hydralazine is a potent vasodilator and can be given intravenously or intramuscularly in hypertensive emergencies. The blood pressure lowering effect cannot always be controlled which sometimes lead to maternal hypotension and foetal distress.[21;29]

1.4.4 Absolutely contra-indicated antihypertensive drugs

1.4.4.1 ACE-inhibitors and ARBs

ACE-inhibitors and ARBs are generally considered unsafe for the foetus and contraindicated for the whole course of pregnancy.[61] These classes should also not be prescribed to women intending to become pregnant. They introduce foetal renal insufficiency with oligohydramnios and secondary effects like pulmonal hypoplasia, intrauterine growth retardation, dysmorphia and even foetal death.[64]

1.5 Conclusion - Discussion

Hypertensive disorders occur in 10% of pregnancies, and entail an increased risk for foetal and maternal morbidity and mortality throughout pregnancy and the post-partum period. Current guidelines support pharmacologic interventions in patients with SBP >160 mmHg and/or DBP >110 mmHg. Risk assessment, early diagnosis and adequate treatment of elevated blood pressure during pregnancy reduces morbidity and mortality in both mothers and infants.

Table 1.3 Summary of antihypertensive drugs.[21;29;61-65] ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; HT: hypertension; IU: intra-uterine; CV: cardiovascular; I.V.: intravenously

Drugs		Indication	Foetal Risk	Breast Feeding
Beta-blockers				
Acebutolol	B	HT, ventricular arrhythmias	Crosses placenta. No reports of IU growth retardation, β-blockade near term	Secreted into milk, not recommended
Atenolol	D	HT	Crosses placenta. Toxic at high doses. IU growth retardation β-blockade near term	Secreted into milk, not recommended
Betaxol	C	HT, glaucoma	Teratogenic in animals, β-blockade near term	Secreted into milk, no data available
Bisoprolol	C	HT	Foetotoxic in animals, β-blockade near term	Secreted into milk in animals, no data available
Carvedilol	C	HT, angina	Foetotoxic in animals, no well controlled human data	Secreted into milk, not recommended
Labetalol	C	HT, sympathicolysis	Crosses placenta, IU growth retardation, induction of foetal lung maturation near term	Secreted into milk, safe under observation
Metoprolol	C	HT, sympathicolysis	Crosses placenta. Foetotoxic in animals. IU growth retardation, neonatal β-blockade	Compatible, safe with neonatal observation
Nebivolol	C	HT	Not recommended	Secreted into milk, not recommended
Pindolol	B	HT	Crosses placenta, no anomalies. IU growth retardation, neonatal β-blockade	Compatible, safe with neonatal observation
Propranolol	C	HT, hyperthyroidism, tachycardia	Embryotoxic in animals, not recommended in humans	Compatible, safe with neonatal observation
Calcium Channel Blockers				
Verapamil	C	HT, antiarrhythmic	Embryotoxic in animals, maternal hypotension with foetal hypoxia when given I.V.	Nursing should be discontinued
Dihydropyridines				
Amlodipine	C	HT	Prolongs labour in animals, no human data	No data available
Felodipine	C	HT	Teratogenic in animals, no adequate human data	Unknown excretion
Nifedipine	C	HT, vasospastic angina	Teratogenic in animals, CV defects in 1st trimester, growth retardation	Compatible, safe under observation
Diltiazem	C	HT, angina	Teratogenic in animals, CV defects in 1st trimester	Compatible, safe under observation
ACE inhibitors				
	D*	HT	Teratogenic in animals and humans from 2nd trimester no human data from 1st trimester	No significant excretion into milk, compatible
ARB				
	D*	HT	Teratogenic in animals and humans from 2nd trimester no human data from 1st trimester	Not recommended during breastfeeding
Alpha-blockers				
Prazosine	?	HT, Raynaud syndrome	Not recommended	Not recommended during breastfeeding
Central antihypertensives				
Clonidine	C	HT	Limited human data with CV defects	Not recommended during breastfeeding
Guanfacine	B	HT	Limited human data; no adverse effects in animals	No data available
Methyldopa	B	HT	Limited human data; no adverse effects in animals	No significant excretion into milk, compatible
Moxonidine	?	HT	Not recommended	Not recommended during breastfeeding
Diuretics				
Thiazides		HT, oedema	Not recommended: potassium depletion in foetus	Supresses lactation, not recommended
loopdiuretics				
Bumetanide	C	HT	Not teratogenic in animals, CV defects in 1st trimester in humans	Supresses lactation, not recommended
Furosemide	C	HT, congestive heart failure	Crosses placenta. Hypospadias in 1st trimester in humans	No data available
Vasodilators				
Hydralazine	C	HT	Crosses placenta, maternal and foetal lupus-like syndrome	Excreted into milk, safe in breastfeeding

Chapter 2 Description of the Methods

2.1 Description of the Methods

2.1.1 Standardised measurement conditions.

Haemodynamic measurements were done in the supine position and under standardised conditions (derived from the Task Force III, clinical applications for arterial stiffness)[66]:

Table 2.1.Recommendations on general user procedures for clinical studies: standardise the subject condition.

I.	Subjects will be at rest for at least 10 min in a quiet room at room temperature
II.	Prolong resting period or cancel measurements in conditions where subjects' basal conditions are substantially altered, like when outside temperature is high or immediately after strenuous exercise.
III.	Subjects have to refrain from smoking, eating, and drinking beverages containing caffeine for at least 3 h before assessments. Unless measurements are performed early in the morning, advise a light meal 3 to 4 h before assessments.
IV.	Subjects should refrain from drinking alcohol 10 h before measurements.
V.	Subjects may neither speak nor sleep during assessments.
VI.	Investigators should mention in which position measurements have been done (supine, sitting). The supine position is preferred.
VII.	For repeated measures, subject measurements should be performed at the same time of the day and in the same position.
VIII.	Be aware of possible white coat arterial stiffness, and if suspected, perform repeated measurements within one visit or in additional visits to detect it.
IX.	Be aware of possible disturbance of data due to cardiac arrhythmia.

2.1.2 Blood pressure

2.1.2.1 Standardised brachial blood pressure and heart rate

Semi-recumbent brachial systolic (SBP) and diastolic (DBP) blood pressure and heart rate are recorded at the upper arm with a validated semi-automated oscillometric device (OMRON 705IT, OMRON Healthcare, Hoofddorp, The Netherlands). Blood pressure and heart rate are recorded in triplicate at all visits and this after several minutes of rest in the left-sided lateral position to overcome external uteral compression of the arterial vessels. At screening, the blood pressure will be measured at both arms to detect differences due to peripheral vascular disease. The higher value will be taken as the reference. The mean of all coupled recordings will be used for data analysis. Brachial pulse pressure is calculated as SBP-DBP.

2.1.2.2 Office brachial blood pressure

This measurement was done at the outpatients clinic for obstetrics of Ghent University Hospital as usual care procedure in each pregnancy trimester. The blood pressure was taken auscultatory or oscillometrically using ERKA® monitors (D-83646 Bad Tölz, Germany) or DINAMAP Pro Care 300 (DPC 300N-DN, GE Healthcare, Chalfont St Giles, UK) devices, respectively. The measurements were taken in the sitting or semi-recumbent position without strict standardisation of a preceding period of rest.

2.1.2.3 Home blood pressure measurement

Home blood pressures were measured within one week. Women were instructed to obtain two measurements at an interval of 1 minute in the morning and two in the evening for 7 consecutive days, each time after having rested for 5 minutes in the sitting position.[67] For analysis, the first 2 days were excluded and the measurements of the remaining 5 days were averaged. Home blood pressures were measured using validated devices, either the OMRON *705IT* (HEM-759-E; Omron Healthcare Europe, Hoofddorp, The Netherlands) or the OMRON *M6* Comfort (HEM-7221-E) which implements the same algorithm and is equivalent.[68] Women with an arm circumference of less than 32 cm used a standard cuff with an inflatable bladder of 22 × 12 cm, those with a greater arm circumference used a cuff with a 35 × 15 cm bladder. Throughout the study each woman measured blood pressure with the same device and the same cuff size.

2.1.3 Arterial Stiffness Indices

2.1.3.1 Definition

Arteries provide the circuit for the heart for the blood distribution. Besides their conduit function, they also act as a buffer to cushion large pulsations generated by the heart and transform these into a steady blood flow. This is particularly relevant for the large elastic arteries, such as the aorta and the carotid arteries.[69] Through repetitive cycles, aggravated by oxidative stress[70], arteries may show signs of 'material fatigue', characterised by a loss of elasticity.[71] This leads to several unfavourable implications for the human body. When arteries are stiffened, the afterload is elevated with an increased work for the heart.[72] In addition, the loss of buffering function results in transmission of large pulsations into the microcirculation, which may induce remodelling of the arterioles[73] or cause damage to the capillaries of end-organs like e.g. the brain, kidneys, eyes or the placenta in case of pregnancy.[74]

Arterial stiffness is at the same time a consequence of damage on the vasculature, but also a cause of further harm, constituting an intermediate end-point.[75] The importance of assessing arterial stiffness for risk classification cannot be overestimated. There is no single measure of a persons' arterial stiffness. The arterial

tree is composed of heterogeneous arteries, varying in histologic and/or elastic properties,[76] the 'arterial stiffness' will differ depending on the specific location.[76] When interpreting stiffness measurements, the context (i.e. the location) is therefore of critical importance. For example, stiffness measured at the carotid artery is often referred to as 'elastic artery stiffness' while the same measurement done at the femoral artery is considered 'muscular artery stiffness'. They should not be used interchangeably since they can act differently on the same intervention (e.g. pharmacologic intervention) or adaptation (e.g. pregnancy).

Another distinction that deserves more attention is the one between 'compliance' and 'distensibility' as measures of arterial stiffness. Both terms are used quite randomly in literature. Although compliance is related to arterial stiffness, it is actually a measure of the buffering capacity of the artery, which is also dependent on the vessel calibre. Therefore, arterial distensibility, which is less dependent on the arterial dimensions, can be considered as a better marker for (the inverse) of arterial stiffness.

We distinguish between local, regional and global stiffness measures.

Local stiffness is defined as the arterial stiffness of a particular cross-sectional site. It can be determined on almost all superficial large and medium-sized arteries (e.g. on the brachial, carotid and femoral artery) using ultrasound. Because of limited resolution, ultrasound is not well suited to measure local stiffness of deeper lying arteries (e.g. the aorta).[77] By reducing the distance between transducer and artery (e.g. using trans-oesophageal echocardiography, TEE)[78] or by using non-ultrasound-based methods (e.g. magnetic resonance imaging, MRI) it is possible to measure local stiffness of the aorta.[79] These techniques are actually not widely applied and local stiffness is most frequently examined using ultrasound on the carotid artery (to measure elastic arterial stiffness) and femoral artery (to measure muscular artery stiffness). Elastic arteries are probably the most interesting to consider, since they are abundant in elastic molecules, which are prone to degeneration due to ageing and oxidative stress.[80] Knowing the stiffness of the femoral (muscular) artery may as well provide complementary information. Muscular artery stiffness may reflect the status of smooth muscle cells, regulating the vascular tone.[81] In addition, it has been postulated that when elastic arteries lose their elasticity, their buffering function is transferred to muscular (e.g. femoral) arteries, which limit the loss of compliance through an increase in diameter.[82;83]

Measuring local stiffness of an artery requires knowing the relative change in volume, for a given change in pressure. This yields a complete description of the pressure-volume relationship.

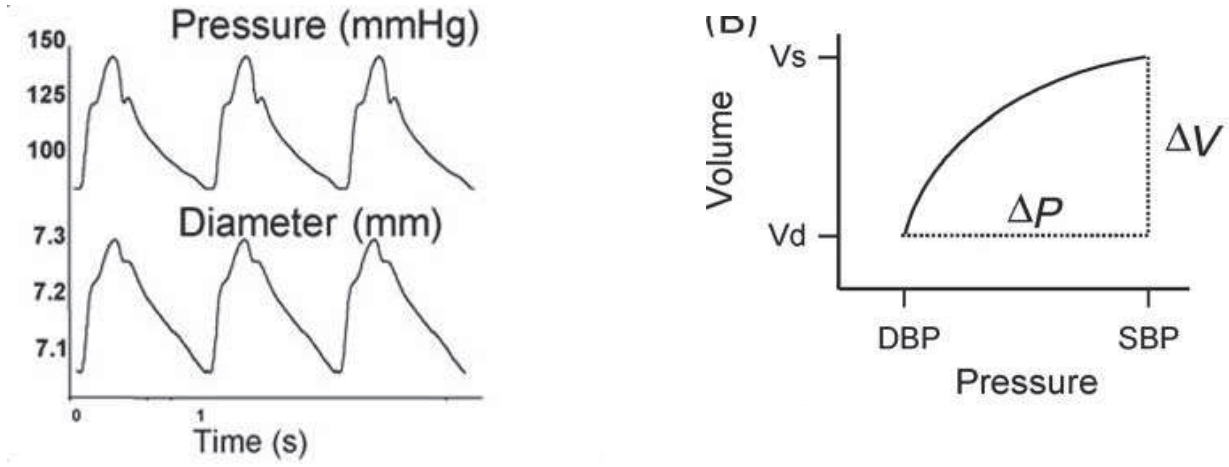


Figure 2.1 Overview of pressure and distension waveforms aligned in time (left), resulting in an approximation of the pressure-volume relationship between diastole en systole (right).[84]

Because of the phenomenon of pulse pressure amplification, brachial pulse pressure (PP) should not be used for calculation of local stiffness at another arterial site. The pulse pressure at a given location is the amplitude of the blood pressure waves. This wave has a forward and backward component, the latter arising from the wave reflections. The closer to the reflection sites (i.e. the closer to the periphery), the earlier the forward and backward waves interact, boosting the amplitude of the of the blood pressure wave. Hence, PP will physiologically increase going from central (e.g. carotid artery to peripheral to brachial arteries).

At the most superficial arteries, it is, however, impossible to measure the local PP using conventional methods. Instead applanation tonometry is employed, which also capture the arterial pressure wave shape at a particular arterial (e.g. femoral or carotid) site. This only yields a curve without reliable absolute levels of arterial pressure. To overcome this, a calibration scheme is employed.

Calibration is based on the validated assumption that DBP and MAP remain constant throughout the large arteries, while SBP and PP (the difference between SBP and DBP) change.[85]

SBP at an arterial site (SBP_X) is $SBP_X=DBP+PP_X$.

Using our calibration method, PP at an arterial site (PP_X) can be calculated from PP at the brachial artery (PP_{BA}) as

$PP_X=PP_{BA}$ x FF_{BA}/FF_X[86]

FF_{BA} and FF_X are the form factors (FF) at the brachial artery and the target artery, respectively, and are measures of how peaked the waveforms are at the respective sites defined as:[87]

$FF_X=(MAP-DBP)/PP_X$

Since applanation tonometry is not applicable in all individuals (e.g. not in obese persons), arterial distension waves can also be used as an alternative to calculate local PP. The approach is similar, with the only exception that the FF's are then derived from distension instead of pressure curves.[88]

Volume and volume change are approximated by cross-sectional area and cross-sectional area change respectively, assuming that longitudinal movement of the vessel wall is negligible.[89] These can be determined using ultrasound. In particular, algorithms based on echo-tracking have been developed, which allow to accurately (resolution = 1.7μm)[90] follow displacement of arterial wall time. This yields measures of diastolic diameter, systolic diameter and distension, which is the difference between these two. When diameter, distension and PP are known, functional wall properties can be calculated. As noted above, it is important to distinguish between cross-sectional compliance (CC), which is an indicator of the buffering capacity, and the distensibility coefficient (DC) as a measure of elasticity.

$$CC = \frac{\Delta A}{\Delta P} = \frac{\Pi(D_s^2 - D_d^2)}{4\Delta P}$$

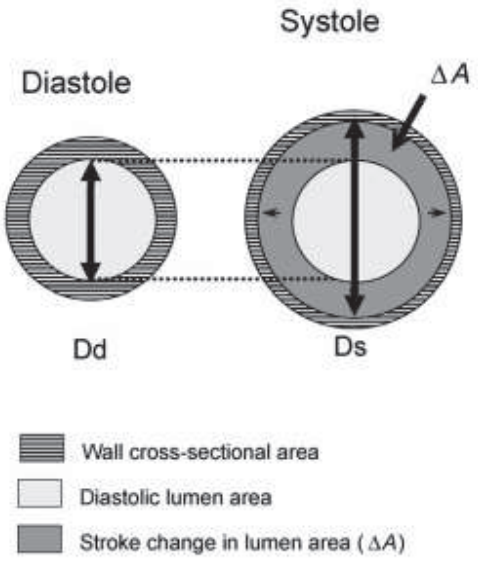
$$DC = \frac{\Delta A \big/ A_d}{\Delta P} = \frac{(D_s^2 - D_d^2)}{D_d^2 \Delta P}$$

Where ΔA is the systolic-diastolic change in arterial cross-section at a given location; ΔP is the local pulse pressure (PP) at a given location; D_s is the arterial diameter at systole; D_d is the arterial diameter at end-diastole; A_d is the arterial cross-section at end-diastole.

We can deduce that CC relates to DC as *CC=DC x A.* In other words, compliance is the product of elasticity and total cross-sectional area.[83]

Figure 2.2 Schematic representation of the stroke change (ΔA) in lumen cross-sectional area.[84]

D_s is the arterial diameter at systole; D_d is the arterial diameter at end-diastole; ΔA is the change in arterial cross-section.



Regional stiffness corresponds with the stiffness of a large or medium-sized segment, often containing multiple arterial beds. It always refers to a measure of (the inverse) of distensibility. The stiffness of an arterial region can be quantified using the concept of pulse wave velocity (PWV), which is based on the assumption that waves are transmitted faster through a segment with stiff vessel walls than through a segment with distensible walls. From the Moens-Korteweg[91] and Bramwell-Hill[92] equations, it follows that PWV is inversely proportional to the elasticity of the vessel wall.

$$PWV = \sqrt{\frac{h \times E_{inc}}{\rho \times D}}$$

In which h= wall thickness; E_{inc}= the incremental elastic modulus, ρ= blood density and D= lumen diameter.

$$PWV = \sqrt{\frac{1}{\rho \times DC}}$$

In which ρ= blood density and DC= cross-sectional distensibility coefficient.

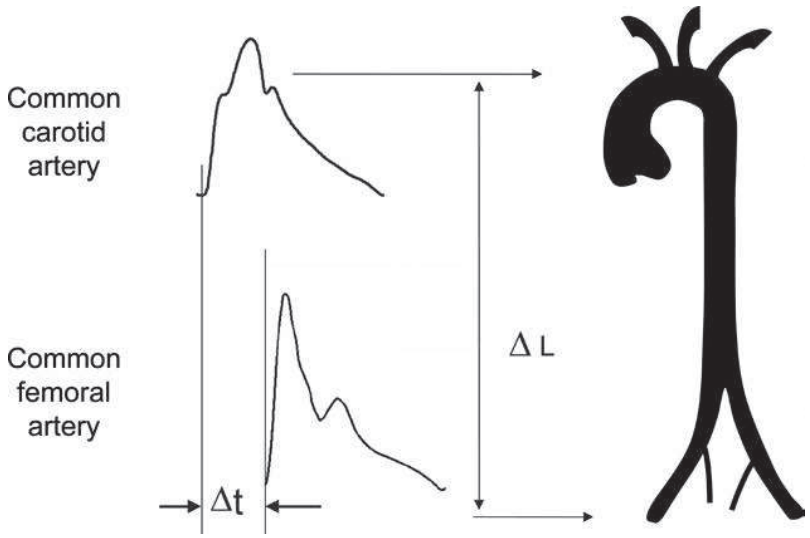
PWV can be measured between any two arterial sites (Figure 2.3), but the vast majority of the studies focus on carotid-femoral (cf-PWV). This is because 1) carotid and femoral arteries are easily accessible and 2) between the carotid and femoral artery lies the aorta, which is of major interest. The aorta and its primary branches are what the heart sees and is thus most affected by.[93] In addition, the aorta is made up of (mainly) elastic tissue

(with exception of the abdominal aortic and iliac part), which is more sensitive to the effect of ageing and cardiovascular risk factors compared to muscular wall material.[94] Therefore, the gold standard method for assessing regional stiffness is carotid-femoral PWV.

To measure cf-PWV, travelled distance (ΔL) is divided by transit time (Δt), or

$$PWV = \frac{\Delta L}{\Delta t}$$

Figure 2.3 Overview of the measurement locations along the arterial tree, accompanied by the sample pressure waveforms (left) obtained at either site.[84] ΔL represents the travelled distance, Δt the transit time.



Transit time can be measured non-invasively by detection of pressure, flow or distension waves at each respective site.[95] This can be done simultaneously or sequentially, by gating both signals to the R-top of an electrocardiogram. Travelled distance is harder to estimate non-invasively. The arterial travelled paths cannot be seen from the outside and have to be approximated by superficial measurements. In addition, a correction factor needs to be incorporated, since waves are travelling at the same time in opposite directions.[96] This is dealt with by measuring the direct distance between femoral and carotid measurement sites, and multiplying this number with 0.8, which is known as the '80% rule'.[97] Recently, different proposed distances have been compared with the real travelled distance measured by magnetic resonance imaging (MRI). This study[98] showed that the direct carotid-femoral distance largely overestimates the real travelled distance by 25.4%, whereas the subtracted distances using the distances to common femoral artery and common carotid artery from suprasternal and sternal notch substantially underestimate the real travelled distance by 10.3 and 29.2%, respectively. Of all currently used distances the 80% of the direct carotid-femoral distance (common carotid artery-common femoral artery x

0.8) appeared the most accurate, only slightly overestimating the real traveled distance by 0.4%. It is also easy to use, and is less influenced by large bellies and large breasts. The new standard cut-off value for cf-PWV is 10 m/s instead of 12 m/s which was the standard when using the 100% direct common carotid artery common femoral artery distance measurement.[97]

Global stiffness refers to the stiffness of the entire arterial tree. However, the term 'stiffness' is actually a misnomer here, since this always corresponds with a measure of the total arterial compliance. Therefore, the term 'systemic arterial compliance' (SAC) would be more appropriate. SAC can be approximated by looking at the pressure change (PP) for a given stroke volume (SV), or

$$SAC = \frac{SV}{PP}$$

However, this is merely an approximation, since it assumes the entire stroke volume is stored in the large elastic arteries, neglecting peripheral outflow. To more accurately determine SAC, three-or four element Windkessel models should be employed.[99;100] This strategy is used by a commercially available device, which combines information of blood flow, pressure and pressure decay to obtain SAC.[101;102] A more detailed description of SAC is beyond the scope of this thesis.

2.1.3.2 Local arterial stiffness and buffering capacity

Local arterial stiffness was calculated at the common carotid artery (CCA) and the common femoral artery (CFA) from diastolic diameter (D_d), arterial distension during the cardiac cycle (ΔD) and local PP. Local D_d and ΔD were estimated from arterial diameter distension waveforms recorded with a wall-tracking vascular echo-scanner (Wall Track System, Esaote, Genoa, Italy) [103] equipped with a 7.5-10 MHz linear-array. Wall motion was tracked at the interface between media and adventitia at both (near and far) walls, at 1-2 cm proximal to the bifurcation of the CCA or the CFA. The median of three recordings, each lasting for 5-6 seconds, was used for data analysis. In our hands, reproducibility of diameter and distension expressed as coefficient of variation was 4% and 6% for the CCA and 3% and 7% for the CFA. Arterial cross-sectional compliance (CC), a measure of buffering capacity, and distensibility coefficient (DC), a measure of elasticity, were calculated as described above.

2.1.3.3 Local pulse pressure

Carotid and femoral PP were obtained by recording local pressure waveforms (PWFs) non-invasively and calibrated them using brachial artery DBP and MAP. PWFs were obtained using applanation tonometry (Sphygmocor®, AtCor Medical, Syndey, Australia). Pulse pressure amplification was calculated by dividing peripheral over central (carotid) PP.

2.1.3.4 Regional Stiffness

Regional stiffness was quantified by the carotid-to-femoral pulse wave velocity (CF-PWV). Cf-PWV was calculated using the 80%-rule, i.e. 0.8 x direct carotid-femoral distance-transit time.[97] To calculate the transit time, pressure waveforms were obtained non-invasively at the common carotid artery (CCA) and the common femoral artery (CFA) using applanation tonometry (Sphygmocor®, AtCor Medical, Syndey, Australia). The transit time was then the time delay between the feet of the two waveforms, which were identified using the intersecting tangents algorithm.[104] The travelled distance was estimated by taking the surface distance between the recording sites in the supine position using a tape measure, or anthropometer (Figure 2.4) if a straight line could not be obtained.

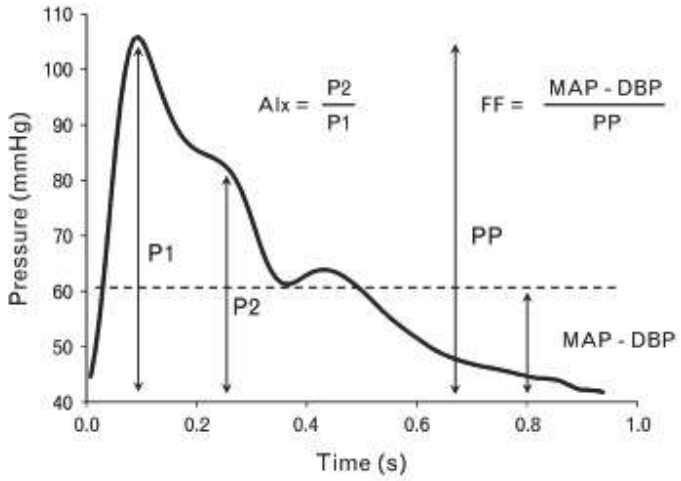
Figure 2.4 Picture of a sliding calliper or anthropometer.

2.1.4 Wave reflections

Pressure waves have a forward and backward component, the latter arising from wave reflections.

Augmentation index (AIx) has been proposed as a surrogate measure for wave reflection. Central augmentation index (AIx) was calculated from the carotid PWFs as the ratio of the amplitude of the pressure wave above its systolic shoulder, or P2/P1. Carotid AIx is a surrogate for aortic AIx[105]. Although AIx is being widely used, it is rather a poor measure of the magnitude of wave reflections.

Figure 2.5 Arterial pressure wave, indicating the first (P1) and the second (P2) inflection points used to calculate the augmentation index (AIx).[106]



2.1.5 Micro-circulation

2.1.5.1 Cardiac output

Cardiac output (CO) was measured using echocardiography (AU5, Esaote, Genoa, Italy). Measurements were performed in the left lateral position. Aortic diameter (D) was measured at least three times using pulsed ultrasound at 2.5 MHz from a standard two-dimensional long-axis parasternal view at the site of the aortic annulus; the median of these readings was used in the subsequent calculations. Aortic blood velocity profiles (at least 5 beats) were measured across the aortic valve with continuous ultrasound using an apical window. Stroke volume (SV) was calculated from aortic cross-sectional area (CSA_{ao}) multiplied by the flow velocity integral (FVI).

$CSA_{ao}$was calculated as $\pi D^2/4$

$SV = FVI \times CSA_{ao}$

$CO = SV \times HR$

HR (heart rate), as determined from the duration of the cardiac cycle on the FVI.[107] In our hands, reproducibility of aortic diameter (D) and the FVI expressed as coefficient of variation was 4% and 6% respectively.

To relate the heart function to body size, CO and SV were divided by the body surface area (BSA) which was calculated by the Dubois & Dubois formula[108] to get the cardiac index (CI) and the stroke index (SI).

2.1.5.2 Total peripheral resistance

Total peripheral resistance (TPR) determines the relationship between mean arterial pressure (MAP) and the cardiac output (CO), as shown in:

$$TPR = \frac{MAP}{CO}$$

As such, it represents the state of the microcirculation (TPR is mainly regulated by the arterioles). By normalizing for the body surface area (BSA), the total peripheral index is obtained (TPRI).

2.2 Reproducibility of measurements

Prior to all studies, intra-observer reproducibility tests have been performed for cardiac output, AIx, cf-PWV, femoral and carotid diameter and femoral and carotid distension. These tests consisted of two sessions of triplicate measurements, separated in time (>1h) on 10 subjects, yielding intra-and intersession coefficients of variation. The results of these tests are tabulated in Table 2.2.

Table 2.2.Results of reproducibility tests.

	Intra-session CV	Inter-session CV
Cardiac output		
Aortic diameter	4.33%	4.02%
FVI	5.57%	6.40%
cf-PWV	4.30%	2.40%
Carotid Artery		
AIx (tonometry)	4.00%	4.00%
diameter	4.15%	3.90%
distension	6.50%	5.25%
Femoral Artery		
diameter	3.00%	3.15%
distension	6.80%	7.20%
Brachial Artery		
AIx (tonometry)	5.46%	6.50%

CV: coefficient of variation. Cf-PWV: carotid-femoral pulse wave velocity.

Part II: Haemodynamic adaptations during pregnancy

Chapter 3 Problem statement and aims of part II

Worldwide, hypertensive disorders complicate 10% of all pregnancies. They cause one in 50 stillbirths, 10% of all preterm births, and one third of severe maternal morbidity.[109;110] In view of these statistics, an early diagnosis and treatment of pregnancy-related hypertensive disorders is of paramount importance.

Blood pressure course during pregnancy has been an important scope of many articles,[1;111-113] and descriptions of haemodynamic changes during the course of pregnancy are plentiful. Evidence-based guidelines for the treatment of hypertensive disorders during pregnancy have recently been reviewed by the NICE and the ESC Clinical Guidelines.[114;115] Notwithstanding the discussion whether current blood pressure thresholds are appropriate in pregnancy, blood pressure measurement may be an easy way to reveal haemodynamic changes and underlying problems of the cardiovascular system during pregnancy.[116;117]

The majority of existing studies are cross-sectional and longitudinal studies with recruitment from early pregnancy on, are lacking. The aim of Chapter 4 is to describe the blood pressure course during pregnancy in a longitudinal way and to analyse the agreement of blood pressures taken in two different settings: at home (self-measured, Home blood pressure, HBP) and at the outpatients obstetric clinic (Office blood pressure, OBP).

Current guidelines[67] for home blood pressure monitoring endorse home or self-measurement of blood pressure as an adjunct to conventional sphygmomanometry at the office, because self-measurement has several major advantages. Guidelines define hypertension on self-measurement as a blood pressure of 135 mmHg systolic or 85 mmHg diastolic or more. The validity of these cut-off points in pregnancy can be questioned since they have not been tested in this condition and ignore the effects of pregnancy on blood pressure. To our knowledge very few studies[118-121] proposed thresholds for blood pressure during pregnancy and none included limits for the self-measured blood pressure. To address this issue, Chapter 5 investigates healthy women having a normal pregnancy and includes a quantitative literature review.

Pregnancy is associated with significant changes in maternal cardiovascular physiology, including an increased cardiac output[122]and decreased total vascular resistance.[123] The latter is the result from the development of the low-resistance utero-placental vascular system.[124] Peripheral vasodilation[125] leads to the 'mid-trimester blood pressure dip'.[126] Parameters of arterial wave reflection have been shown to drop as well during pregnancy.[127-135] However, these indices are often composite measures, not only dependent on the magnitude of wave reflection, but also on the wave speed (i.e. arterial stiffness) and other confounders (e.g. heart rate, height).[136] Observations are therefore not always consistent.[137;138] Sub-optimal study design could be responsible for these heterogeneous results. Some studies were cross-sectional,[127;131;135] others longitudinal but lacking a control group.[128-130;132;133;138;139] One longitudinal study incorporated a control group,[134] but did not track

control subjects longitudinally as well, which means seasonal effects or familiarisation with technique may have confounded the results. Nevertheless, better characterising arterial stiffness variables and their interactions with pregnancy may be clinically important, as arterial stiffness and wave reflections can be increased in pathophysiological conditions such as preeclampsia,[134] even in the preclinical stage.[140]

Therefore, the aim of Chapter 6 is to investigate longitudinal changes in arterial stiffness and wave reflection throughout normal pregnancy in healthy women and in healthy non-pregnant control subjects.

Chapter 4 Self-measured blood pressure monitoring is an asset during pregnancy; a longitudinal study in white European women.

(Added value of home blood pressure during pregnancy).

Submitted to Journal of Hypertension.

Isabelle Fabry, Jelle Bossuyt, Kristien Roelens, Lucas Van Bortel.

Abstract

Objective: The goal of this study was to determine the added value of home blood pressure (HBP) to routine daily practice office blood pressure (OBP) during pregnancy.

Study design: Healthy pregnant women (n=100) underwent OBP and HBP monitoring at 12, 20 and 35 weeks of pregnancy. Pregnant women were instructed to perform HBP according to ESH-task force for HBP guidelines. OBP was taken as is usually done in the routine clinical setting.

Results: Systolic OBP was at least 5 mmHg higher than systolic HBP in a majority of pregnant women, ranging from 74% at 12 weeks to 60% at 35 weeks of pregnancy. For diastolic OBP this was 40% and 32%, respectively. Based on OBP, 9, 15 and 3% of pregnant women were classified as hypertensive at 12, 20 and 35 weeks, respectively, while HBP classified 0, 0 and only 3% of women as hypertensive at 12, 20 and 35 weeks, respectively. One pregnant woman had masked hypertension at weeks 12 and 20, which disappeared at week 35.

Conclusion: The present study shows that office blood pressure taken in the routine clinical setting misclassified a substantial part of pregnant women as hypertensive. This was more pronounced in early and mid than in late pregnancy. This study shows that also in pregnancy home blood pressure may be of added value in the follow up of pregnant women particularly when office blood pressure arises above threshold levels.

4.1 Introduction

Hypertensive disorders complicate 1 out of 10 pregnancies, entailing an increased risk for maternal and foetal morbidity and mortality.[141] Identification of risk factors, an early diagnosis of elevated blood pressure and subsequent close monitoring may be of paramount importance. Although blood pressure course during pregnancy has been an important scope of many articles,[1;111-113] and descriptions of haemodynamic changes during the course of pregnancy are plentiful, evidence-based guidelines for the treatment of hypertensive disorders during pregnancy have been recently been reviewed by the NICE and the ESC Clinical Guidelines [114;115] While the European Society of Hypertension recommends a threshold of ≥140 mmHg systolic (SBP) and/or ≥ 90 mmHg diastolic (DBP) on repeated measurements at the office and a threshold of ≥135 mmHg systolic and/or ≥ 85 mmHg diastolic for home blood pressure measurement[114], recent data show lower normal values during pregnancy, which may challenge the current thresholds.[116;120] Notwithstanding the discussion whether current blood pressure thresholds are appropriate in pregnancy, blood pressure measurement may be an easy way to reveal haemodynamic changes and underlying problems of the cardiovascular system during pregnancy.[116;117]

The majority of published studies in pregnancy are cross-sectional or encompasses random inclusion. Longitudinal studies with recruitment from early pregnancy on, are lacking in white European women. The aim of this longitudinal study was to describe the blood pressure course during pregnancy in a white, normotensive population and to analyse the agreement of blood pressure taken in two different settings: at home (self-measured, home blood pressure, HBP) and at the outpatients obstetric clinic (office blood pressure, OBP).

4.2 Methods

4.2.1 Subjects

We recruited women during the first trimester of pregnancy at Ghent University Hospital. Pregnant women from 20 to 40 years old were eligible for study entrance. The exclusion criteria encompassed a history of giving birth before 18 years of age, pregnancy of more than 12 weeks at presentation, previous or current cardiovascular disease, diabetes mellitus or endocrine disorders, a body mass index of 30 kg/m^2 or higher, substance abuse, and insufficient language skills to understand the informed consent form or the care givers.

Among 371 women consecutively screened, 167 complied with all entry criteria and were invited to participate. Of those invited, 100 gave written informed consent. The participation rate was therefore 59.9%. Fifty women could not participate due to time restrictions in their private life, 7 women had a gestational age older than 12 weeks and 10 women were excluded by several reasons (3 women weren't able to understand the

investigator due to language problems, two women were diagnosed with diabetes, three had moderate nicotine abusus and 2 other women didn't show up at the screening). All women were presented a medical self-administered questionnaire inquiring their medical and obstetrical history, past and current use of medications, self-scored physical and mental health, lifestyle and socio-economic status.

4.2.2 Design

This study was a longitudinal, follow-up study during pregnancy. Subjects pregnant up to 12 weeks were screened and measurements were performed at 12 (±1), 20 (±1) and 35 (±1) weeks of gestation when they had an appointment at the maternal health clinic. The study was approved by the Ethics Committee of Ghent University with reference number B67020084197 and conducted according to ICH Good Clinical Practice and the Declaration of Helsinki (last amended in 2008 in Seoul). All participants gave written informed consent.

4.2.3 Measurements

4.2.3.1 Home blood pressure measurement (HBP)

Home blood pressures were measured within one week after the obstetrical visit of the 12th, 20th and 35th week of gestation. Women were instructed to obtain two measurements at an interval of 1 minute in the morning and two in the evening for 7 consecutive days, each time after having rested for 5 minutes in the sitting position.[67] For analysis, the first 2 days were excluded and the measurements of the remaining 5 days were averaged. Home blood pressures were measured using validated devices, either the OMRON *705IT* (HEM-759-E; Omron Healthcare Europe, Hoofddorp, The Netherlands) or the OMRON *M6* Comfort (HEM-7221-E) which implements the same algorithm and is equivalent.[68] Women with an arm circumference of less than 32 cm used a standard cuff with an inflatable bladder of 22 × 12 cm, those with a greater arm circumference used a cuff with a 35 × 15 cm bladder. Throughout the study each woman measured blood pressure with the same device and the same cuff size at the same arm (right arm). At the screening, blood pressure was measured at both arms to detect a difference of ≥ 10 mmHg. There was no detected blood pressure difference.

4.2.3.2 Office brachial blood pressure (OBP)

This measurement was done at the outpatients clinic for obstetrics of Ghent University Hospital as usual care procedure in each pregnancy trimester. The blood pressure was taken auscultatory or oscillometrically using ERKA® monitors (D-83646 Bad Tölz, Germany) or DINAMAP Pro Care 300 (DPC 300N-DN, GE Healthcare, Chalfont St Giles, UK) devices, respectively. The measurements were taken in the sitting or semi-recumbent

position without strict standardisation of a preceding period of rest, the used arm, the right cuff-size or number of readings.

4.2.4 Data-analysis

IBM® SPSS® software version 19 (SPSS Inc., Chicago, IL) was used for database management and statistical analysis. We evaluated departure from normality by the Kolmogorov-Smirnov statistic.[142] As this test revealed no statistically significant deviation from normality, we compared blood pressure levels across the 3 time periods and between OBP and HBP by analysis of variance for repeated measures and paired Student's t-tests as appropriate. For multiple comparisons, we adjusted *P*-values by Bonferroni's method. In all analyses, significance was a *P*-value of <0.05.

Misclassification as hypertensive is defined as having 'white coat hypertension' (OBP of ≥ 140/90 mmHg and a HBP of < 135/85 mmHg).

4.3 Results

4.3.1 Subjects

The study population consisted of 100 white European women. Table 4.1 lists their characteristics at enrolment in the first trimester of pregnancy. All women were normal at clinical examination and scored their mental and physical health as "normal" (17.0% and 20.0%, respectively), "good" (44.0% and 48.0%) to "very good" (39.0% and 32.0%). Nearly all (99.0%) had a stable relationship with partner where 47.0% already had children. All participants had a desired pregnancy.

The majority of women (80.0%) had a college or university degree (Table 4.1). In general, they had a healthy life style. Regular consumption of vegetables or fruits (≥3 portions per day) and of fish (≥1 portion per week) was reported by 38 (38.0%) and 30 (30.0%) women, respectively, whereas only 8 (8.0%) ate fast food once per week or more frequently. Of 81 women (81.0%), who engaged in recreational sports before conception, 38 (38.0%) continued during pregnancy. Smoking and drinking habits were moderate and encompasses no more than 3 cigarettes a day and no more than one alcohol consumption a week. No woman reported substance abuse.

One participant took cortisone inhalation as maintenance therapy for mild asthma. All other women were in good health. All women were normotensive at study entrance.

Table 4.1 Characteristics of women at enrolment and neonates outcomes

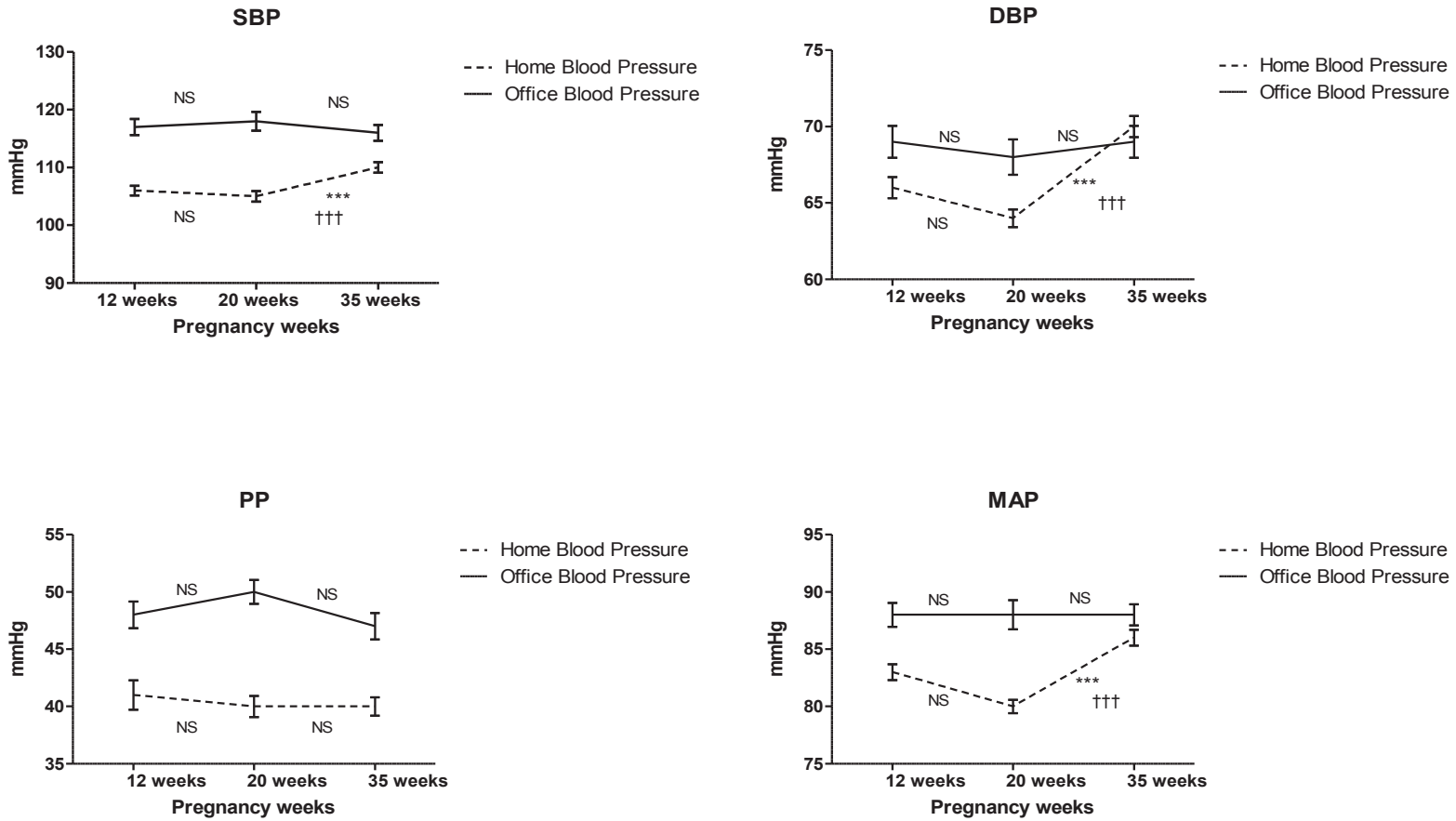
Characteristic	Statistic	Characteristic	Statistic
Women (n=100)	Mean ± SD	Neonates (n=100)	Mean ± SD
Age (yrs)	29.4 ± 3.9	Birth weight (g)	3397 ± 448
Weight (kg)	66.2 ± 9.6	Length (cm)	50.7 ± 2.1
Height (m)	1.68 ± 0.04		
Body mass index (kg/m2)	23.5 ± 3.4		
Number (%)		Number (%)	
Nulliparous	38 (38.0)	Girls	46 (46.0)
Higher education	80 (80.0)	Boys	54 (54.0)
Jobless	4 (4.0)	Breast fed	77 (77.0)
Living with partner	99 (99.0)	Bottle fed	30 (30.0)
Current smoking	3 (3.0)	Breast and bottle fed	7 (7.0)
Alcohol use	3 (3.0)		
Sports before pregnancy	81 (81.0)		

BP: blood pressure; HR: heart rate; Body mass index is weight in kilogram divided by height in meters squared. Higher education refers to having college or university degree. Alcohol use is drinking no more than one consumption per week. Smoking is no more than 3 cigarettes a day. Sports indicates membership of a sports club. Feeding characteristics were asked for at 6±1 weeks postpartum.

4.3.2 Blood pressures

Complete longitudinal office and home blood pressure data of all 3 trimesters of pregnancy were available in 74 women. Figure 4.1 represents the evolution of the SBP, DBP and PP at the office and at home. In the first trimester the blood pressures were 118±13 / 69±8 and 105±8 / 66±6 mmHg for OBP and HBP, respectively. At 20 weeks of pregnancy, OBP was 118±15 / 68±10 mmHg and HBP 104±9 / 65±6 mmHg. These blood pressure values did not differ statistically from the values at 12 weeks. Office blood pressure also did not differ between the second and the third pregnancy trimester (117±13 / 70±10 mmHg). In contrast, HBP increased ($P<0.001$) from the second to the third trimester (110±9 / 70±7 mmHg).

Figure 4.1. Time course of home blood pressures (HBP) and office blood pressures during pregnancy.



Values are means and based on 74 subjects with complete OBP and HBP measurements. Significance of the difference with the previous period: NS= not significant, *** $P<0.001$. Significance of the difference with the first trimester of pregnancy: NS= not significant, ††† $P<0.001$. The error bars denote the standard error of the mean

Table 4.2. Blood pressure classification per pregnancy trimester.

	OBP mmHg	HBP mmHg	Week 12	Week 20	Week 35
Subjects			N=87	N=91	N=86
True Hypertension	≥140/90	≥135/85	0%	0%	3%
White Coat Hypertension	≥140/90	<135/85	9%	15%	3%
Masked Hypertension	<140/90	≥135/85	1%	1%	0%
Normotension	<140/90	<135/85	90%	84%	94%
OBP-HBP ≥ 5mmHg					
Systolic			74%	71%	60%
Diastolic			40%	43%	32%

N is the study population per pregnancy trimester where the women have both data on office blood pressure and on home blood pressure. 'OBP-HBP> 5mmHg' means that office blood pressures are at least 5 mmHg higher than home blood pressures. The results are not different when using only longitudinal, complete data of 74 women

Table 4.2 summarises the percentages per pregnancy trimester for the blood pressure classification. White coat hypertension occurred mainly in the first two trimesters whereas true hypertension occurred in the last trimester (3%), and 1 pregnant woman (1%) showed masked hypertension.

In 69% of office blood pressures SBP was ≥5mmHg higher than home SBP, while this was true for 39% of DBP.

4.4 Discussion

To the best of our knowledge this is the first study to compare longitudinally self-measured blood pressures at home (HBP) with routine office blood pressures (OBP) during pregnancy. The study shows that routine daily practice OBP measurements overestimated blood pressure in a large majority of blood pressure readings during pregnancy (69% for SBP and 39% for DBP), misclassifying up to 15% of pregnant women as hypertensive according to current ESH guidelines.[114] Limited standardisation mainly due to time constraints can largely account for these findings. Indeed, OBP was taken by a nurse or midwife but without focus on standardisation, particularly in terms of 5 minutes of rest, quiet room, relaxed position, the consistent use of the same (validated) apparatus and Korotkoff sound. In addition, the blood pressure readings were mostly followed by a foetal echography, which very likely put stress on women. Home blood pressure monitoring may be an asset to overcome this misclassification. Self-monitoring of the blood pressure at home is being increasingly used in many countries and well accepted in hypertensive patients from the general population[67] and may be used as an asset to monitor the blood pressure during pregnancy. It has been claimed to be particularly useful in women with a high risk of developing cardiovascular complications during pregnancy, including obesity or diabetes mellitus, age above 35 years, black ethnicity, adverse outcomes in a prior pregnancy and severe hypertension prior to pregnancy.[21;25;26;141]

Despite the relatively small study population, the course of the home blood pressure data throughout pregnancy are consistent with other – cross sectional and longitudinal - data in the literature: only minor changes in SBP occur over time while DBP reaches a nadir in midpregnancy.[1;143] In accordance with previous data, the present office blood pressure data did not change significantly during pregnancy.[144] They were consistently higher than those taken by self-measurement except for the DBP in the last trimester. The latter can be due to the more frequent visits to the outpatients clinic, a more relaxed approach at the end of pregnancy and a prolonged rest due to the simultaneous cardio-tocographic registration. It is not clear whether the natural course of the blood pressure from mid-pregnancy to near term, or the so-called nest-syndrome in the last pregnancy trimester making the mothers more physically active at home, may also have influenced the difference between office and home blood pressure readings.

The strength of the present study lies in the longitudinal design with complete data throughout pregnancy in 74 women, the adherence to the ESH guidelines for home blood pressure measurement,[67] and the real routine daily practice setting for office measurements. The study population was highly selected and consisted of apparently healthy women without cardiovascular diseases. The two oscillometric devices (OMRON® 705IT and OMRON® M6) in the present study implemented the same algorithm[68] and were both validated for self-measurement according to AAMI (Association for the Advancement of Medical Instrumentation) and BHS (British Hypertension Society) guidelines.[145-148] These devices, however, have not been specifically validated in pregnant women. This may be a limitation of the study but until now, only 3 algorithms for home blood pressure devices have been tested for use in pregnancy and passed validation criteria.[149-151] The devices used at the outpatients clinic (ERKA® monitors or DINAMAP Pro Care 300) are also not validated in pregnant women. To date, only one algorithm has been validated for clinical use in pregnancy.[152] The smaller size of the subpopulation with complete blood pressure data compared with the whole study population lies both in the study design as in the turnover of the blood pressure monitors. The turnover of the devices was at some time points not as fast as it should be. Some women could not start with their monitoring week within the exact time window. The consequence was exclusion of those data in the longitudinal analysis.

There is a need for better standardisation.[114] Special precautions have to be taken for the posture of the mother and the choice of the Korotkoff tone to measure the DBP.[1] The ESC 2011-guidelines on the Management of Cardiovascular diseases in Pregnancy advise the sitting or the left lateral recumbent position to counterbalance the progressive influence of the growing uterus on the cardiovascular system.[115] Apart from these special precautions, it can be imagined that strict implementation of a standardised office blood pressure measurement may be difficult in a crowded, obstetric outpatients clinic. Therefore, the standard procedure of the obstetric outpatients clinic of the University Hospital Ghent advises to repeat blood pressure measurements in a quiet room with an automated blood pressure device and the patient in semi-recumbent position in pregnant women with elevated blood pressure. In addition, other external factors like an imminent foetal echography might also increase office blood pressure. When these external factors cannot always be avoided we suggest a faster attempt to start home blood pressure monitoring when the office blood pressure readings rise above 140/90 mmHg.

4.5 Conclusions

The present study shows that office blood pressures taken in the routine clinical setting misclassified a substantial part of pregnant women as hypertensive. This was more pronounced in early than in late pregnancy. This study clearly suggests that also in pregnancy self-assessment of blood pressure monitoring may be an asset in blood pressure follow up and can avoid misclassification of pregnant women as hypertensive. The present

study advocates a more stringent standardisation of routine daily practice blood pressure measurements. However this may be difficult in the setting of an obstetric outpatients clinic. As an alternative, a faster attempt to start home blood pressure monitoring should be made when office readings are above 140/90 mmHg.

Chapter 5 Reference values and upper normal limits for the Self-Measured Blood Pressure During Pregnancy and in Postpartum

In preparation

Isabelle Fabry, Lucas Van Bortel, Lutgarde Thijs, Marleen Temmerman, Jan Staessen.

Abstract

Objective: This study aimed to determine normal values for home (HBP) blood pressure in each pregnancy trimester and in the postpartum.

Study design: Healthy women with uncomplicated pregnancies (n= 82) underwent standardised HBP monitoring at 12, 20 and 35 weeks of pregnancy; and 53 women were followed up to 6 weeks postpartum. For HBP monitoring mothers followed ESC/ESH guidelines. As upper limits of normal HBP, we calculated the 95th percentile and the mean+2SD. We combined our results with previously published HBP in a meta-analysis.

Results: Systolic HBP (in mm Hg) averaged (±SD) 105.2±8.0 at 12 weeks, did not change at 20 weeks (104.5± 8.9; P=0.306), increased to 109.2±8.4 (P<0.001) at 35 weeks, and fell to 104.3±8.3 (P=0.001) in the postpartum. From 12 to 20 weeks, diastolic HBP (in mm Hg) decreased from 66.6±6.3 to 64.9±6.1 (P=0.001) and next increased to 70.3±7.0 (P< 0.001) at 35 weeks with no further change in the postpartum (68.7±7.6; p=0.12). Home heart rate (in beats per minute) tended to increase from 78±11 to 80±8 and to 82±8 at 12, 20 and 35 weeks (P≤0.058) and dropped to 72±8 (P<0.001) in the postpartum. The present study suggests that the upper normal limits for HBP should be as low as 120/80 mmHg at 12 weeks, 120/75 mmHg at 20 weeks, 125/85 at 35 weeks and 120/80 in the postpartum.

Conclusion: Proposed upper normal limits are all 5 to 15 mmHg lower than the current thresholds (135/85 mmHg) of the ESH-guidelines for HBP monitoring.

5.1 Introduction

Increased metabolic needs, hormones regulating the sodium balance and vascular tone, and compression of venous return by the pregnant uterus drive the haemodynamic adaptations of the maternal circulation in pregnancy. During normal pregnancy, both systolic and diastolic blood pressure decrease slightly between 13 and 18 weeks of gestation, but after 25 weeks start to rise again.[116;153] Worldwide, hypertensive disorders complicate 10% of all pregnancies. They cause one in 50 stillbirths, 10% of all preterm births, and one third of severe maternal morbidity.[109;110] In view of these statistics, an early diagnosis and timely treatment of pregnancy-related hypertensive disorders may be of paramount importance.

Current hypertension guidelines[67] endorse self-measurement of blood pressure as an adjunct to conventional office blood pressure measurement (OBP), because self-measurement has several major advantages: (1) it provides multiple blood pressure readings over several days, weeks or months; (2) it is carried out in the usual environment of each individual, away from the medical setting and the physician's office, conditions known to raise blood pressure in many subjects (white-coat effect); and (3) home or self-measured blood pressure (HBP) is more closely related to hypertension-induced target organ damage and predicts the risk of cardiovascular events better than conventional sphygmomanometry in the office.[154] Guidelines define hypertension on self-measurement as a blood pressure of 135 mmHg systolic or 85 mmHg diastolic or more.[67] These cut-off points ignore the effects of pregnancy on blood pressure. To our knowledge, few studies[118-121] proposed thresholds for blood pressure during pregnancy and none included limits for the self-measured blood pressure. To address this issue, we investigated healthy women having a normal pregnancy and we did a quantitative literature review.

5.2 Methods

5.2.1 Subjects

The Ethics Committee of the Medical Faculty of the University of Ghent approved the study. We recruited women during the first trimester of pregnancy at Ghent University Hospital. Eligible women were healthy and from 20 to 40 years old. The exclusion criteria encompassed a history of giving birth before 18 years of age, pregnancy of more than 12 weeks at presentation, previous or current cardiovascular disease, diabetes mellitus or endocrine disorders, a body mass index of 30 kg/m2 or higher, substance abuse, and insufficient language skills to understand the informed consent form or the care givers.

Among 371 women consecutively screened, 167 complied with all entry criteria and were invited to participate. Of those invited, 100 gave written informed consent. The participation rate was therefore 59.9%. We excluded 18 women from analysis, because the self-recorded blood pressure was unavailable for one or more of

the required time points (n=14) or because of withdrawal of consent (n=4), leaving 82 for analysis. Incomplete data (n=25) and loss-to-follow-up reduced the number of analysable women in the postpartum to 53.

Women also completed a self-administered questionnaire inquiring into their medical and obstetrical history, past and current use of medications, self-scored physical and mental health, lifestyle and socio-economic status.

5.2.2 Blood Pressure Measurement

5.2.2.1 Home Blood Pressure Measurement

Participating women measured their home blood pressure within one week after the obstetrical visits at the 12th, 20th and 35th week of gestation and at 6 weeks postpartum. Women were instructed to obtain two measurements at an interval of 1 minute in the morning and evening for seven consecutive days, each time after having rested for 5 minutes in the sitting position.[67] For analysis, the first two days were excluded and the measurements of the remaining five days were averaged. Home blood pressures were measured using validated devices, either the OMRON 705IT (HEM-759-E) or the OMRON M6 Comfort (HEM-7221-E), which implemented the same algorithm and were equivalent.[155] Women with an arm circumference of less than 32 cm used a standard cuff with an inflatable bladder of 22 × 12 cm was; those with a greater arm circumference used a cuff with a 35 × 15 cm bladder. Throughout the study women measured blood pressure with the same device and the same cuff size.

5.2.2.2 Office Brachial Blood Pressure

This measurement was done at the outpatients clinic for obstetrics of Ghent University Hospital as usual care procedure in each pregnancy trimester. The blood pressure was taken auscultatory or oscillometrically using ERKA® monitors (D-83646 Bad Tölz, Germany) or DINAMAP Pro Care 300 (DPC 300N-DN, GE Healthcare, Chalfont St Giles, UK) devices, respectively. The measurements were taken in the sitting or semi-recumbent position without strict standardisation of a preceding period of rest. Heart rate was not noted in the patient-record.

5.2.3 Review of the Literature

We searched for relevant publications in Medline published before 31 December 2013, using the search terms: “home” AND “blood pressure” AND “pregnancy”. The computer search was supplemented by manual searches via the references of published articles. Studies qualifying for review had to include healthy pregnant women, who had recorded their self-measured blood pressure at home during each trimester of pregnancy.

Articles were assessed for methodological quality against the QUADAS criteria (Quality Assessment of Diagnostic Accuracy Studies).[156] Two reviewers (I.F. and J.A.S.) extracted the summary statistics from each article. Information retrieved from the studies included year of publication, number of participants, age distribution, the device used for self-measurement, the number of self-recorded blood pressures obtained by each woman, and the timing and number of self-measurements selected for analysis. Authors were contacted for missing data and for summary statistics that could not be calculated from the published results.

5.2.4 Statistical Analysis

IBM® SPSS® software version 18 (SPSS Inc., Chicago, IL) was used for database management and statistical analysis. In the analysis of our own data, we evaluated departure from normality by the Kolmogorov-Smirnov statistic and skewness by the computation of the coefficient of skewness.[142] We compared blood pressure levels in the morning vs. evening and across the four time periods within subjects by analysis of variance for repeated measures and paired Student t-tests as appropriate. For multiple comparisons, we adjusted P-values by Bonferroni's method.

In a fixed effect meta-analysis, we computed pooled means and standard deviations, while weighing for study size. For comparison of mean values of blood pressure between studies, we applied Student t-test for unpaired observations. Significance was a P-value of 0.05 or less.

For the determination of the upper normal limits at each pregnancy trimester for the self-measured blood pressure at home, we used the 95th percentile method as the non-parametric method and the mean plus 2SD-method as the parametric alternative. The mean value of both results was taken and rounded off to the nearest 5 or 10 mmHg.

5.3 Results

5.3.1 Characteristics of Women

The study population consisted of 100 Caucasian women. Table 5.1 lists their characteristics at enrolment in the first trimester of pregnancy. All women had a normal physical examination and scored their mental and physical health as "normal" (17.0% and 20.0%, respectively), "good" (44.0% and 48.0%) to "very good" (39.0% and 32.0%). Nearly all (99.0%) had a stable relationship with a partner and 47.0% already had children. All participants had a desired pregnancy.

The majority of women (80.0%) had a college or university degree (Table 5.1). In general, they had a healthy life style. Regular consumption of vegetables or fruits (≥3 portions per day) and of fish (≥1 portion per week)

was reported by 38 (38.0%) and 30 (30.0%) women, respectively, whereas only 8 (8.0%) ate fast food once per week or more frequently. Of 81 women (81.0%), who engaged in recreational sports before conception, 38 (38.0%) continued sporting during pregnancy. Smoking and drinking habits were moderate and no woman reported substance abuse. One participant took cortisone inhalation as maintenance therapy for mild asthma. All other women were in good health and were normotensive at enrolment.

Table 5.1 Characteristics of women at enrolment and neonates outcomes.

Characteristic	Statistic	Characteristic	Statistic
Women (n=100)	Mean ± SD	Neonates (n=100)	Mean ± SD
Age (yrs)	29.4 ± 3.9	Birth weight (g)	3397 ± 448
Weight (kg)	66.2 ± 9.6	Length (cm)	50.7 ± 2.1
Height (m)	1.68 ± 0.04		
Body mass index (kg/m2)	23.5 ± 3.4		
Number (%)		Number (%)	
Nulliparous	38 (38.0)	Girls	46 (46.0)
Higher education	80 (80.0)	Boys	54 (54.0)
Jobless	4 (4.0)	Breast fed	77 (77.0)
Living with partner	99 (99.0)	Bottle fed	30 (30.0)
Current smoking	3 (3.0)	Breast and bottle fed	7 (7.0)
Alcohol use	3 (3.0)		
Sports before pregnancy	81 (81.0)		

BP: blood pressure; HR: heart rate; Body mass index is weight in kilogram divided by height in meters squared. Higher education refers to having college or university degree. Alcohol use is drinking no more than one consumption per week. Sports indicates membership of a sports club. Feeding characteristics were asked for at 6±1 weeks postpartum.

5.3.2 Blood Pressure and Pulse Rate

Table 5.2 summarises the parametric statistics describing the distributions of systolic and diastolic blood pressure and pulse rate as self-measured by the patients during the three trimesters of pregnancy and the postpartum. Table 5.3 provides the corresponding non-parametric statistics. No differences in blood pressure data were noted between nulli-vs multiparae.

Table 5.2 Parametric statistics of the distributions of the self-measured blood pressures and pulse rate at home in 82 women during and 53 women after pregnancy.

Statistic	First	Second	Third	Post
Systolic pressure (mmHg)				
Mean	105.2	104.5	109.2	104.3
SD	8.0	8.9	8.4	8.3
Skewness	0.300	0.543	0.449	0.164
Kurtosis	–0.340	0.966	0.642	0.032
P-value	0.371	0.603	0.966	0.459
Diastolic pressure (mmHg)				
Mean	66.6	64.9	70.3	68.7
SD	6.3	6.1	7.0	7.6
Skewness	0.124	0.445	1.005	–1.132
Kurtosis	0.237	0.818	2.942	5.571
P-value	0.934	0.456	0.338	0.422
Pulse rate (beats/min)				
Mean	78	80	82	72
SD	11	8	8	8
Skewness	3.980	0.359	0.431	0.290
Kurtosis	27.086	0.672	1.409	-0.097
P-value	0.020	0.968	0.623	0.865

First, second, third and post refer to the trimesters of pregnancy and the postpartum, respectively.

P-values to test normality of the distribution were derived by the Kolmogorov-Smirnov statistic.

Table 5.3 Non-parametric statistics of the distributions of the self-measured blood pressures and pulse rate at home in 82 women during and 53 women after pregnancy.

Statistic	First	Second	Third	Post
Systolic pressure (mmHg)				
P_5	91.0	92.0	95.7	89.5
P_{10}	96.2	94.7	98.6	92.0
P_{50}	103.7	103.2	109.2	104.6
P_{90}	117.6	115.3	120.3	116.3
P_{95}	120.1	117.0	121.4	121.5
Diastolic pressure (mmHg)				
P_5	57.5	56.6	59.5	59.8
P_{10}	59.2	58.2	61.2	61.0
P_{50}	66.0	64.5	70.3	67.4
P_{90}	74.5	73.6	78.3	77.6
P_{95}	78.8	76.9	83.0	79.8
Pulse Rate (beats/min)				
P_5	66	69	70	59
P_{10}	68	72	72	61
P_{50}	77	80	82	72
P_{90}	86	89	92	83
P_{95}	92	96	94	86

First, second, third and post refer to the trimesters of pregnancy and the postpartum, respectively. P_5, P_{10}, P_{50} (median), P_{90} and P_{95} refer to the 5th, 10th, 50th, 90th and 95th percentiles of the distributions.

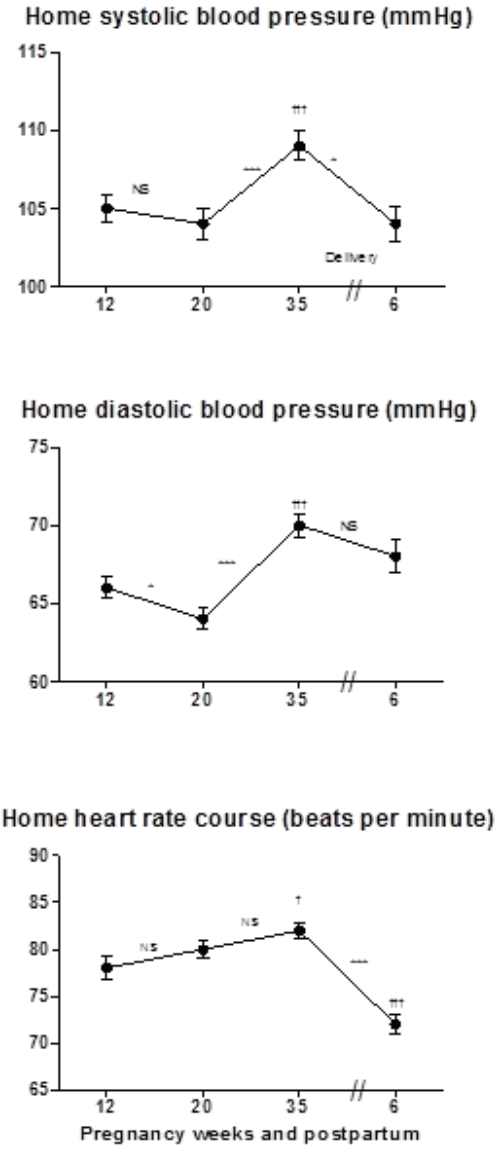
5.3.2.1 Time Course of Blood Pressure and Pulse Rate

All changes over time in the haemodynamic measurements were significant in the repeated measures ANOVA (P<0.001; Figure 5.1). In 82 women, systolic blood pressure at home did not change from the first to the second trimester (105.2 [95% CI: 103.5 - 106.9] vs. 104.5 [95% CI: 102.6 -106.4] mmHg; P=0.36), next increased to 109.2 [95% CI: 107.4 – 111.0] mmHg (P<0.001) from the second to the third trimester of pregnancy. In 53 women with available data, systolic blood pressure decreased from the third trimester to the postpartum (108.6 vs. 104.3 [95% CI: 102.1 – 106.5] mmHg; P<0.001; Figure 5.1).

In 82 women, diastolic blood pressure decreased from the first to the second trimester (66.6 [95% CI: 66.2 – 68.0] vs. 64.9 [95% CI: 63.6 – 66.2] mmHg; P=0.001), subsequently increased to 70.3 [95% CI: 68. 8 – 71.8] mmHg (P<0.001) from the second to the third trimester of pregnancy. In 53 women, diastolic blood pressure remained unchanged from the last trimester to the postpartum (69.6 vs. 68.7 [95% CI: 66.7 – 70.8] mmHg; P=0.001; P=0.12; Figure 5.1).

Pulse rate did not change significantly during pregnancy: 78 [95% CI: 76 – 80] beats per minute to 80 [95% CI: 78 – 82] beats per minute, (P=0.058), but in 53 women decreased from the last trimester to the postpartum (82 [95% CI: 80 – 84] vs. 71.6 [95% CI: 70 – 74] beats per minute; P=0.001; Figure 5.1).

Figure 5.1 Time course of home blood pressure and heart rate during pregnancy (n=82) and in the postpartum in 53women.



Values are means ± SEM. Significance of the difference with the previous period: ns=not significant, * $P<0.05$, and *** $P<0.001$. Significance of the difference with the first trimester of pregnancy: † $P<0.05$, and ††† $P<0.001$.

5.3.2.2 Diurnal Differences in the Measurements at Home

Morning and evening levels of the home blood pressure differed for systolic pressure (106.1 vs. 108.4 mmHg; P=0.008), but not for diastolic pressure (66.8 vs. 67.2 mmHg; P=0.75). The diurnal difference in systolic blood pressure was 1.4 mmHg (P=0.008), 2.3 mmHg (P<0.001) and 3.9 mmHg (P<0.001) in the first, second and third trimester. In the postpartum period, the diurnal systolic difference weakened to 1.0 mmHg (P= 0.17). The corresponding diastolic differences were 0.4 mmHg (P=0.76), 0.4 mmHg (P=0.72), 0.4 mmHg (P=0.75), and 0.2 mmHg (P=0.89), respectively. The time course of the morning systolic and diastolic blood pressure values did not materially differ from those reported in Figure 5.1.

Heart rate was similar in the morning and evening in the first trimester of pregnancy (79.3 vs. 78.8 beats per minute; P=0.67), but in the second trimester (80.9 vs. 79.4 beats per minute; P=0.023) and the third trimester (83.6 vs. 81.7 beats per minute; P=0.016), and in the postpartum (74.2 vs. 70.5 beats per minute; P<0.001) heart rate was lower in the evening than in the morning. The diurnal differences averaged 1.5 beats per minute (P=0.023), 1.9 beats per minute (P=0.016) and 3.7 beats per minute (P<0.001) in the second and third trimester of pregnancy and in the postpartum, respectively.

5.3.2.3 Differences between Conventional Office Blood Pressure and Self-Measured Blood Pressure

There were no significant changes over time in the course of the conventional data (P=0.829). In 82 women the systolic blood pressure at the office did not change from the first to the second trimester (117.1 vs. 117.5 mmHg; P=0.83), next stabilized at 117.3 mmHg (P=0.79) from the second to the third trimester of pregnancy. In 53 women with available data, systolic blood pressure decreased not significantly from the third trimester to the postpartum (117.3 vs. 111.5 mmHg; P=0.45).

In 82 women, diastolic blood pressure did not change from the first to the second trimester (68.9 vs. 68.1 mmHg; P=0.49), subsequently increased to 70.3 mmHg (P=0.15) from the second to the third trimester of pregnancy. In 53 women, diastolic blood pressure decreased not significantly from the last trimester to the postpartum (70.3 vs. 66.1 mmHg; P=0.41).

The differences between the conventional systolic and self-measured systolic blood pressure were significant at every time point (P≤0.001). For the diastolic pressures, the conventional and self-measured data only differed significantly in the first and second trimester. At 35 weeks of gestation the data were simile (70.3 vs. 70.3 mmHg; P=0.96) with a same trend in the postpartum period (66.1 vs. 65.4 mmHg; P=0.48).

5.3.2.4 Reference values and Proposal for Upper Normal Limits

We used two methods to determine upper normal limits for the self-measured blood pressure at home. For the non-parametric method, we used the 95th percentile method; for the parametric method, we determined the mean plus 2 SD's. Table 5.4 lists the so obtained thresholds.

Table 5.4 Thresholds for home blood pressure and pulse rate based on parametric and non-parametric statistics in 53 healthy women by type of measurement.

Statistic	First	Second	Third	Post
mean+2SD				
Systolic, mmHg	121	122	125	120
Diastolic, mmHg	79	77	84	84
Pulse rate, bpm	100	96	98	88
95th percentiles				
Systolic, mmHg	120	117	121	122
Diastolic, mmHg	79	77	83	80
Pulse rate, bpm	92	96	94	86
Proposed (rounded) thresholds				
Systolic, mmHg	**120**	**120**	**125**	**120**
Diastolic, mmHg	**80**	**75**	**85**	**80**
Pulse rate, bpm	**95**	**95**	**95**	**85**

First, second, third and post refer to the trimesters of pregnancy and the postpartum, respectively; bpm: beats/min.

5.4 Meta-Analysis

Figure 5.2 Flow chart illustrating the selection of studies for review

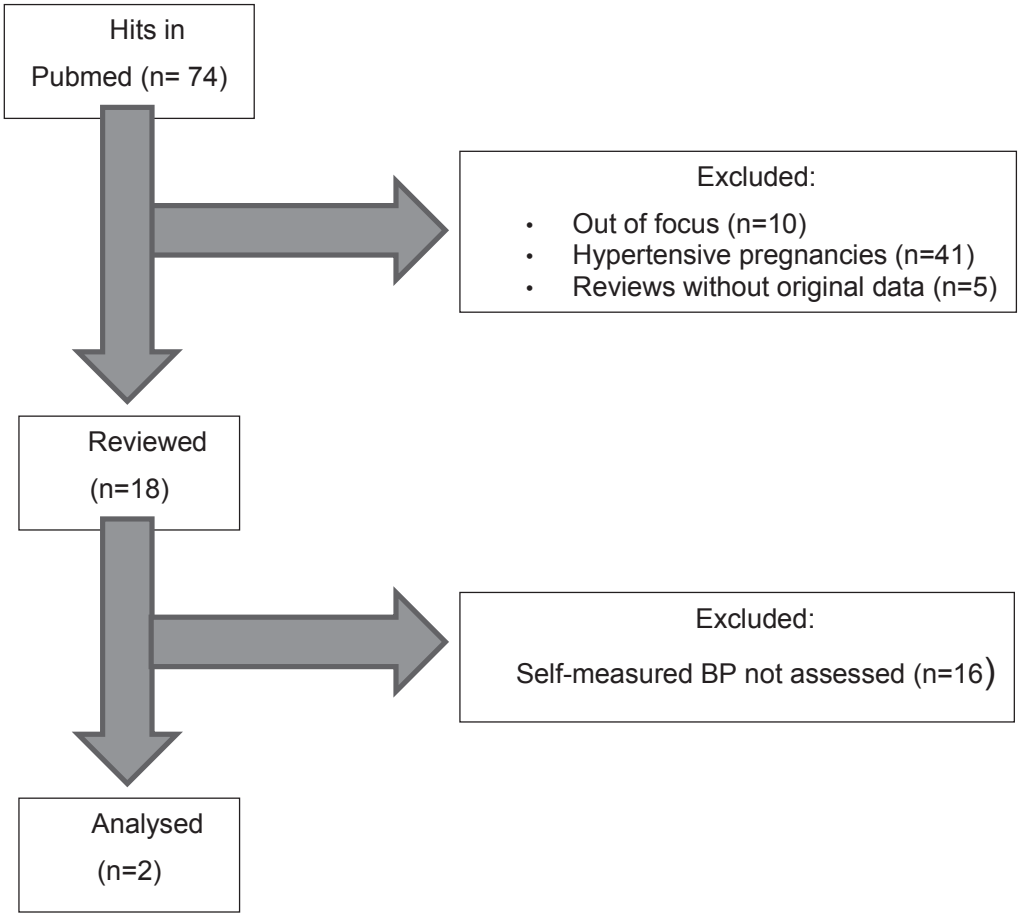


Figure 5.2 lists the studies selected to be included in the meta-analysis. Of the studies available for analysis, only two[120;143] assessed the self-measured blood pressure (Table 5.5). Denolle et al.[120] implemented a scheme of self-measurement at home, which was similar to that in our current study. Metoki et al.[143] instructed women to take their self-measured blood pressure each day in the morning after enrolment in the study, irrespective of the date of conception. There are no data for the postpartum period. The summary statistics available for analysis originated from Japanese[143] and French[120] women. There was no indication that the same subjects were included in more than one report. Figure 5.3 displays mean values ± SD for the reviewed and our current manuscript.

At 12 weeks, there were no significant differences between our estimates of average systolic blood pressure and the corresponding values reported by Denolle et al. (102.0 ± 8.0 mmHg) or Metoki et al. (103.2 ± 12.0 mmHg). However, at 12 weeks, our estimate of average diastolic blood pressure was 5 to 6 mmHg higher than the estimates in the two other studies (66.6 ± 6.3 vs. 61.8 ± 8.8[143] and 60.0 ± 7.0[120] mmHg; $P<0.001$). At 20 weeks,

systolic blood pressure was significantly higher in our study compared to the data of Denolle et al. and Metoki et al (104.5 ± 8.9 mmHg vs.101.0[120] ± 8.0 vs. 101.8 ± 7.9[143]; P<0.001). Our estimate of average diastolic blood pressure at 20 weeks was 4 to 5 mmHg higher compared with the two other studies (64.9 ± 6.1mmHg vs. 59.8 ± 5.8[143] and 57.0 ± 8.0[120] mmHg; P≤ 0.0033). In the last trimester, at 35 weeks, the estimates of average home systolic and diastolic blood pressures were higher in our own compared with the data of Denolle et al. but simile with the data of Metoki et al. (109.2 ± 8.4/70.3 ± 7.0 vs. 110.1± 9.7/66.6 ± 7.7mmHg[143] vs. 105.0 ± 8.0/62.0 ± 9.0mmHg[120]; P≥0.001).

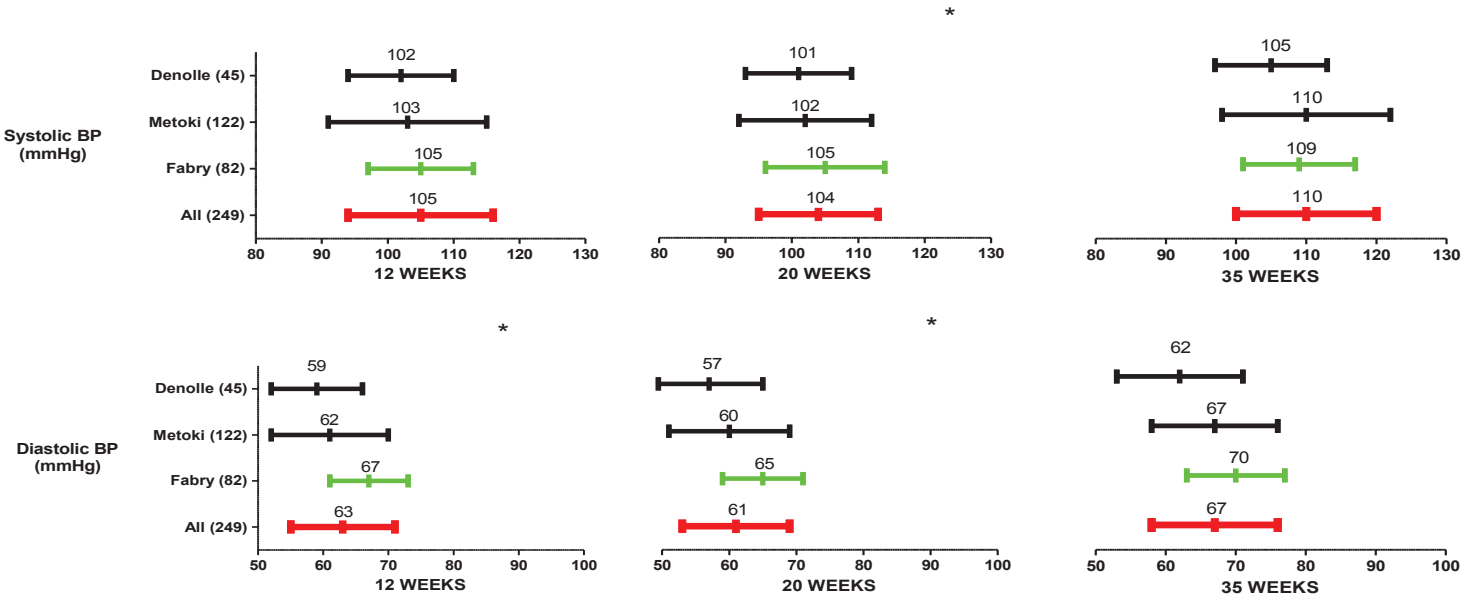
The course of the systolic and diastolic blood pressures from 12 to 20 weeks did not differ between our own and the two other studies (systolic/diastolic changes, -0.7/-1.7 vs. -1.4/-1.8[143] vs. -1.0/-2.0[120] mmHg; P=0.306 for systolic changes and P≤0.001 for diastolic changes). From 20 to 35 weeks, the systolic and diastolic home blood pressures increased by +4.7/+5.4 mmHg (P≤0.001) in our current study and by +8.3/+6.8 mmHg (P≤0.001) in Metoki's study, whereas systolic and diastolic blood pressures changed in the same order over this time period in the study by Denolle et al. +4.0/5.0 mmHg (P≤0.001).

Table 5.5 Characteristics of studies

Studies	Subjects		Self-measurements			
	N	Age, y	Device	Trimester	Days	Timing
Denolle, 2005	45	30±7	Hestia Pharma D2	1,2,3	7 (6)	M+E (3)
Metoki, 2008	122	31±5	Omron HEM 747/780 IC	1,2,3	>100 (all)	M (1)
Fabry, Present	82*	29±4	Omron M6 / 705 IT	1,2,3,PP	7 (5)	M+E (2)

Studies are identified by first author and year of publication. All studies included only healthy women (number of subjects and mean age ± SD are given), * indicates that the data of 82 women during pregnancy and 53 in the postpartum. Days refers to the number of recording days. PP indicates postpartum. The number of days included in the analyses are given between parenthesis; first or first two days were excluded to account for familiarising. M/E indicates morning/evening with number of consecutive measurements given between parenthesis.

Figure 5.3 Outcome of the meta-analysis with data of Denolle et al.[120] and Metoki et al.[143]



The data are grouped per time period (12, 20 or 35 weeks). Horizontal lines represent the mean (number of women) ± the standard deviation. The number between parentheses is the sample size of the study. The columns in black are the data of Denolle et al. and Metoki et al. The column in green represents the data of the current study. The column in red represents the pooled mean and the pooled standard deviation. * means a statistical significant difference among the study data of that time point. See text for the detailed information.

5.5 Discussion

To our knowledge, this is the first study proposing reference values and upper limits of normal for home blood pressure monitoring during pregnancy and the postpartum.

In this study, all women were normotensive throughout their whole pregnancy and postpartum. This allowed us to study the natural course of blood pressure during pregnancy. Currently published thresholds for the self-measured blood pressure during pregnancy[20-22] have been derived from normal reference populations without accounting for the profound haemodynamic changes that occur during pregnancy.[1;6;141] In two population studies (the FLEMENGHO-study[157] and the IDHOCO-database[158]), the home blood pressure data measured by observers in non-pregnant women of childbearing age (20-40 years, n= 436 and 1447 respectively) were at least 8 to 13 mmHg higher for the systolic and 4 to 7 mmHg higher for the diastolic values compared to the data of self-measured systolic and diastolic blood pressure during pregnancy in our current study. In addition, compared to the threshold of 135/85 mmHg for home blood pressure monitoring in the ESH guidelines,[159] our proposed upper normal limits for SBP and DBP are 5 to 15 mmHg lower depending on the pregnancy trimester. Therefore, based on the current guidelines, the prevalence of hypertensive disorders during pregnancy might be underestimated. Our lower thresholds may represent a warning at a lower threshold and therefore at an earlier stage for possible cardiovascular complications during pregnancy, such as gestational hypertension or preeclampsia.[160]

Until now, there is limited evidence to support aggressive medical intervention during pregnancy for levels of blood pressure below 160 mmHg systolic or 110 mmHg diastolic.[21;161] In such patients, the decision to treat the high blood pressure must be individualised.[22] Taking into account risk factors may help. These include obesity, diabetes mellitus, age above 35 years, Black ethnicity, adverse outcomes in a prior pregnancy and severe hypertension prior to pregnancy.[21;25;26;141]

The Avon Longitudinal Study of Parents and Children[162] used repeated measurements [median (interquartile range) 10 (9–11) per woman] for 10327 women. Multilevel models were used to derive longitudinal reference ranges for systolic and diastolic blood pressure from 12 to 40 weeks gestation for women with normal pregnancies without essential hypertension or preeclampsia who delivered an appropriate-size-for-gestational age infant at term. In normal pregnancies, mean systolic and diastolic blood pressures in nulliparous women were 112.1 mmHg (95% confidence interval, 88.6–135.5 mmHg) at 12 weeks and 65.4 mmHg (48.9–81.9 mmHg). At 37 weeks, the corresponding levels were 116.0 mmHg (92.3–139.7 mmHg) and 70.0 mmHg (52.2–87.9 mmHg), respectively. Reference ranges for multiparous women were 1–2 mmHg lower throughout pregnancy. This is in contrast with our results where no differences in the blood pressure data, the self-measured as the conventional ones, were noted between nulli-and multiparous women. Our mean systolic blood pressures

were all 6 to 7 mmHg lower compared with the data of The Avon Longitudinal Study of Parents and Children but with a same course during pregnancy. The conventional blood pressure data are consistently higher than the self-measured ones, except for the diastolic blood pressures in the last trimester and the postpartum period. The latter may be due to the more frequent visits to the outpatients clinic at the end of pregnancy, a more relaxed approach and a prolonged rest period during the simultaneous cardio-tocographic registration.

Using lower blood pressure values may lead to maternal and foetal monitoring in an earlier stage before signs of placental dysfunction arise. The cost/benefit of such strategies should be further investigated. One should keep in mind that in the first trimester, when pregnant women consult the physician for the first time, blood pressure might already be lower than before conception because haemodynamic adaptations already occur in the late luteal phase and the early pregnancy.[6;128;129] A decrease in systolic and diastolic blood pressure of 4 and 6 mmHg, respectively, has been reported from before conception to early pregnancy.[128] As a consequence, undiagnosed hypertensive women may become normotensive due to the physiological blood pressure fall. A blood pressure rise later in pregnancy, may be interpreted as gestational hypertension instead of pre-existing hypertension.[161]

The present study must be interpreted within the context of its potential limitations and strong points. First, the study is not outcome-based and has a relatively small sample size of highly selective women. Although the number of 82, we proposed upper limits of normal derived from the present study which are supported by pooled data from the present and two other studies of the self-measured home blood pressure during pregnancy.[120;143] Differences between those studies may at least in part be explained by the use of different devices and measurement protocols. Second, the number of women lost to follow-up during the postpartum. Third, the use of blood pressure monitoring devices which have not been specifically validated in pregnant women. The two oscillometric devices (OMRON® 705IT and OMRON® M6) in the present study implemented the same algorithm. They were validated according to AAMI (Association for the Advancement of Medical Instrumentation) and BHS (British Hypertension Society) guidelines. But until now, only 3 algorithms for home blood pressure devices have been tested for use in pregnancy and passed validation criteria.[149-151]

The strength of the present study lies in its longitudinal design. We obtained data of 82 women throughout pregnancy and in 53 of them also from the postpartum. We adhered to the ESH guidelines for home blood pressure measurement[67] and collected simultaneous blood pressure readings at the outpatients clinic. Moreover, we recruited a healthy reference group without cardiovascular disease.

5.6 Conclusion

This study proposes upper thresholds for the self-measured blood pressure at home during pregnancy and the postpartum based on longitudinal data obtained in 82 healthy women with normal pregnancy. The proposed upper limits of normal are during pregnancy 5 to 15 mmHg lower than the thresholds proposed by the ESH. They might increase awareness of the potential cardiovascular complications of pregnancy. The pregnant population should be treated as a niche population.

The results, however, must be interpreted in their context since this study was not meant to be outcome-based. Further investigation, based on large, epidemiologically based trials with both maternal and foetal outcome data, is needed to elucidate whether these upper limits of normal might contribute to a better prevention of cardiovascular complications in the mother and the neonate.

Chapter 6 Changes in arterial stiffness during pregnancy are age-dependent; a longitudinal controlled study.

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Isabelle Fabry, Jelle Bossuyt, Lucas Van Bortel.

Abstract

Objective: Pregnancy is associated with significant changes in maternal cardiovascular physiology, including a decrease in blood pressure and arterial wave reflections. Whether arterial stiffness is also reduced is subject of debate. Therefore, our aim was to investigate indices of arterial stiffness and wave reflections at each trimester of pregnancy in a prospective longitudinal controlled study.

Design and methods: Measurements were performed at 12, 20 and 35 weeks of gestation in pregnant women and at similar time intervals in non-pregnant control subjects, and included peripheral and central blood pressures (BP), augmentation index (AIx) and arterial stiffness measures (carotid and aortic pulse wave velocity (PWV)). Carotid artery pressures were taken as central BP.

Results: 94 healthy women with a normal pregnancy and 26 healthy non-pregnant control subjects were included. Diastolic BP (DBP), mean arterial pressure (MAP), and aortic stiffness (PWV) showed a U-shaped pattern ($p<0.04$), characterised by a drop (MAP: -2.2 mmHg, $p=0.020$; PWV: -0.5 m/s, $p=0.005$) or no change from 12 to 20 weeks of gestation, followed by a rise (DBP: +5.5 mmHg, $p<0.001$; MAP: +3.2 mmHg, $p<0.012$) or no change between 12 and 35 weeks of gestation. AIx decreased ($p=0.026$) while heart rate increased from 12 to 35 weeks of gestation. Pregnant women over the age of 30 had a higher increase ($p<0.05$) in aortic and carotid stiffness from week 20 to 35 weeks of gestation.

Conclusions: In contrast to the younger pregnant women, aortic stiffness increased from week 20 to week 35 in pregnant women above the age of 30 years. Whether this increase in aortic stiffness from mid to late pregnancy may contribute to the higher pregnancy risk in this older age group has to be further investigated. This study confirmed that pregnancy is associated with a U-shape pattern in blood pressure and a drop in AIx during pregnancy.

6.1 Introduction

Pregnancy is associated with significant changes in maternal cardiovascular physiology, including an increased cardiac output [122] and decreased total vascular resistance.[123] The latter is the result of the development of the low-resistance utero-placental vascular system,[124] and peripheral vasodilation,[125] leading to the 'mid-trimester blood pressure dip'.[126] Parameters of arterial wave reflection have been shown to drop as well during pregnancy.[127-135] However, these indices are composite measures, not only dependent on the magnitude and site of wave reflection, but also on the wave speed (i.e. arterial stiffness) and other confounders (e.g. heart rate, height).[136] Whereas some studies observed a concomitant decrease in aortic (carotid-femoral) stiffness,[137;138] others did not.[127-129] One study showed a decrease in aortic stiffness but an increase in carotid stiffness during pregnancy.[138] However, sub-optimal study design could also be responsible for these heterogeneous results. Some studies were cross-sectional,[127;131;135] others longitudinal but lacking a control group.[128-130;132;133;138;139] Only one longitudinal study incorporated a control group,[134] but did not track control subjects longitudinally as well, which means seasonal effects or familiarisation with technique may have confounded the results. Consequently, better characterising changes in arterial stiffness variables during normal pregnancy may be clinically important, since arterial stiffness and wave reflections can be increased in pathophysiological conditions such as preeclampsia,[134] even in the preclinical stage.[140]

Therefore, the aim of the present study was to investigate changes in arterial stiffness and wave reflection throughout normal pregnancy in healthy women, compared to healthy non-pregnant control subjects followed longitudinally as well.

6.2 Methods

A longitudinal controlled study was carried out at the Heymans Institute of Pharmacology of the Ghent University, Belgium. The study was approved by the Ethics Committee of Ghent University with reference number B67020084197 and conducted according to ICH Good Clinical Practice guidelines and in compliance with the Declaration of Helsinki. All participants gave written informed consent.

6.2.1 Subjects

Pregnant women exhibiting a normal singleton pregnancy up to 12 weeks were recruited from the university hospital gynaecology department. Exclusion criteria were cardiovascular disease, diabetes or obesity (BMI > 30), smoking more than 10 cigarettes/day or drinking more than 3 units of alcohol/day, chronic medication use, particularly antihypertensive, vasoactive drugs or glucose-lowering drugs, first pregnancy before the age of 18, and not being able to obtain reliable haemodynamic or arterial stiffness data at screening.

Non-pregnant control subjects were recruited from the local community and matched with pregnant subjects for age, sex, body mass index (BMI) and blood pressures at inclusion. Control subjects had to meet the same in- and exclusion criteria, excluding the pregnant state. In addition, control subjects should be in the non-pregnant state for at least one year, and not breast-feeding for at least six months.

All subjects underwent three study visits (corresponding with 12, 20 and 35 weeks of gestation in pregnant women), during which haemodynamic measurements were performed.

6.2.2 Haemodynamic and arterial stiffness measurements

Haemodynamic measurements were done in supine position and under standardised conditions.[66] Supine brachial systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) were recorded with a validated semi-automated oscillometric device (OMRON M6, OMRON Healthcare, Hoofddorp, The Netherlands). Mean arterial pressure (MAP) was calculated from the area under the curve (AUC) of scaled brachial artery pressure waveforms (PWFs) obtained by applanation tonometry (Sphygmocor®, AtCor Medical, Sydney, Australia). Local blood pressure (BP) was obtained by recording local PWFs with applanation tonometry, calibrated using brachial artery DBP and MAP.[88] Carotid BP was taken as central BP. Pulse pressure (PP) amplification was calculated as brachial/carotid PP.

Aortic stiffness was measured along the carotid-femoral path, using applanation tonometry (Sphygmocor®, AtCor Medical, Sydney, Australia). Travel distance was measured at baseline using tape measure, and considered the same on subsequent visits. Carotid-to-femoral PWV was calculated using the 80%-rule (i.e. taking 80% of the direct carotid-femoral distance).[97]

Local arterial stiffness was calculated at the common carotid artery (CCA) from diastolic diameter (D_d), arterial distension during the cardiac cycle (ΔD) and local PP. Local D_d and ΔD were estimated from arterial diameter distension waveforms recorded with a wall-tracking vascular echo-scanner (Wall Track System, Esaote, Genoa, Italy) [103] equipped with a 7.5-10 MHz linear-array. See Chapter 2 for the detailed description.

Wave reflections were assessed by the augmentation index (AIx), which was calculated from the carotid PWFs as P2/P1, in which P2 indicates the amplitude of the late systolic peak and P1 indicates the amplitude of the early systolic peak.[163]

6.2.3 Statistical Analysis

The effect of pregnancy on each parameter was assessed using a mixed model, in which pregnancy, visit and the interaction term (visit x pregnancy) were added. A linear regression model was used to assess whether maternal age influences the effect of pregnancy and gestational age on the measured parameters, with the

following factors added to the model: age, age*pregnancy and age*pregnancy*visit. Arterial stiffness measures were corrected for MAP, and wave reflection measures for HR. P-values of $p<0.05$ were considered statistically significant. Data are reported as mean ± SD unless mentioned otherwise.

6.3 Results

6.3.1 Characteristics of Women

94 healthy pregnant women and 26 healthy controls were included in the study. Subject characteristics are shown in Table 6.1. All pregnant women exhibited a normal pregnancy, unaffected by pre-eclampsia or other complications. Pregnant women and controls did not differ in age, height and weight at inclusion.

Table 6.1 Subject characteristics

	Pregnant	Control	p-value
N	94	26	
Age (yrs, range)	29.2 (21-40)	28.4 (21-40)	0.428
Height (cm)	169.2 ± 5.7	170.0 ± 5.5	0.527
Weight (kg)			
12weeks	65.7 ± 9.8	64.2 ± 10.3	0.493
20weeks	69.5 ± 9.8	63.9 ± 10.1	0.011
35weeks	77.4 ± 10.7	63.9 ± 10.8	<0.001
Parity, n (%)			0.075
Nulliparous	38 (40)	16 (62)	
Multiparous	56 (60)	10 (38)	

6.3.2 Haemodynamic and arterial measurements

For each parameter, Table 6.2 compares the change from baseline (i.e. week 12) between pregnant women and controls at weeks 20 and 35, and contains a p-value of the interaction term 'visit x pregnancy' (denoting whether the course of the parameter is different between pregnant women and controls). The course of arterial stiffness and the peripheral haemodynamic parameters is visualised in Figure 6.1.

The overall change from baseline in peripheral and central blood pressures did not reach statistical significance during pregnancy. But because changes at 20 and 35 weeks of gestation were often in opposite

direction, the course of peripheral blood pressures showed a U-shape pattern and differed between pregnant women and controls ($p<0.02$). Although all peripheral blood pressure parameters on average tended to decrease at 20 weeks of gestation, only MAP reached statistical significance ($p=0.020$). At 35 weeks of gestation MAP and DBP increased ($p=0.015$ and $p<0.001$, respectively) versus baseline, while SBP on average only tended to increase. Because of the larger increase in DBP compared to SBP peripheral PP further decreased ($p=0.043$) at 35 weeks of gestation. Although on average the course of central SBP and central PP appeared to be similar to brachial SBP and PP, they did not reach statistical significance, which may at least in part be due to their variability being larger than at the brachial artery. Heart rate (HR) increased linearly ($p<0.001$) from the first to the second and third trimester of pregnancy.

MAP-adjusted aortic pulse wave velocity including its course changed ($p=0.035$) during pregnancy, making a nadir at week 20 ($p=0.005$), but this decrease was not statistically significant anymore at week 35. Although MAP-adjusted carotid PWV did not differ in course from controls during pregnancy, it tended to rise from 20 to 35 weeks of gestation ($p=0.06$). The diameter of the carotid artery and its course differed from controls during pregnancy ($P<0.01$), being not different from baseline at 20 weeks but rising from 20 to 35 weeks of gestation ($p<0.001$), which was maintained after adjustment for MAP ($p<0.001$). Carotid cross-sectional compliance and its course did not differ from controls during pregnancy ($p=0.452$).

HR adjusted augmentation index (AIx) displayed a significant drop at week 20 ($p=0.039$), which was maintained at week 35 ($p=0.020$).

Table 6.2. Changes in peripheral and central haemodynamics and arterial stiffness during pregnancy.

	Absolute value at baseline		Change in pregnancy from week 12 compared to control subjects		Fixed effect of "pregnancy"	Interaction term visit x pregnancy
	12weeks		20weeks	35weeks		
Brachial SBP (mmHg)						
Pregnant	104.8 ± 8.4	change	-2.0 (-4.7; 0.7)	+1.7 (-1.8; 5.2)		
Control	103.5 ± 7.6	p-value	0.152	0.343	0.418	0.017
Brachial DBP (mmHg)						
Pregnant	63.0 ± 6.9	change	-1.6 (-3.6; 0.4)	+5.5 (2.4; 7.5)		
Control	64.7 ± 6.2	p-value	0.124	<0.001	0.675	<0.001
Brachial PP (mmHg)						
Pregnant	41.8 ± 7.8	change	-0.4 (-3.4; 2.6)	-3.6 (-6.4; -0.1)		
Control	38.9 ± 7.1	p-value	0.799	0.043	0.139	0.018
MAP (mmHg)						
Pregnant	79.7 ± 6.6	change	-2.2 (-4.1; -0.4)	+3.2 (0.7; 5.7)		
Control	79.7 ± 5.9	p-value	0.020	0.015	0.782	<0.001
HR (/min)						
Pregnant	70.3 ± 8.5	change	+6.4 (2.8; 10.0)	+12.1 (7.9; 16.3)		
Control	66.7 ± 8.5	p-value	0.001	<0.001	<0.001	<0.001
Central SBP (mmHg)						
Pregnant	106.5 ± 12.3	change	-4.0 (-10.7; 2.6)	-0.5 (-6.7; 5.8)		
Control	103.4 ± 10.7	p-value	0.227	0.882	0.343	0.259
Central PP (mmHg)						
Pregnant	42.0 ± 11.0	change	-1.0 (-6.5; 5.8)	-4.1 (-9.3;1.1)		
Control	39.0 ± 10.9	p-value	0.653	0.173	0.359	0.181
PP amplification						
Pregnant	1.00 ± 0.07	change	+0.02 (-0.03; 0.07)	+0.01 (-0.03; 0.05)		
Control	1.01 ± 0.07	p-value	0.386	0.579	0.901	0.630
AIx (%)						
Pregnant	86.0 ± 24.5	change	-6.5 (-13.2.;-0.5)	-4.8 (-14.9;-1.8)		
Control	90.4 ± 21.7	p-value	0.039	0.020	0.026	0.289
Aortic PWV (m/s)						
Pregnant	6.8 ± 0.9	change	-0.5 (-0.8; -0.1)	-0.2 (-0.6; 0.2)		
Control	6.9 ± 0.8	p-value	0.005	0.285	0.035	0.035
Carotid PWV (m/s)						
Pregnant	5.0 ± 0.9	change	-0.1 (-0.6; 0.4)	+0.5 (-0.0;1.0)		
Control	5.2 ± 0.9	p-value	0.763	0.075	0.652	0.162

Absolute values are mean ± standard deviation. Changes are shown as mean and 95% confidence intervals. SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, PP = pulse pressure, HR = heart rate. PWV = pulse wave velocity adjusted for mean arterial pressure, AIx = Augmentation index corrected for heart rate.

6.3.3 The modifying effect of age

Several parameters changed with age regardless of pregnancy (PP decreased; Aortic PWV, carotid PWV and AIx increased; Table 6.3, first column). Age did not have a statistically significant effect on parameters during pregnancy (Table 6.3, second column) but SBP (p=0.074), DBP (p=0.101) and MAP (p=0.092) tended to rise more with ageing in pregnant women compared with controls, while the rise in carotid PWV tended to be less with ageing in pregnant women (p=0.068). Age alters the course of aortic PWV during pregnancy (Table 6.3, third column, p=0.039). Therefore, the sample of pregnant women was stratified into 3 age tertiles (T1, aged 21-26 y; T2, aged 27-30 y; T3, aged 31-42 y), and levels of aortic PWV were plotted per tertile (Figure 6.2 A). This graph shows a significant impact of age on the course of aortic PWV, leading to differences between age tertiles at 20 weeks of gestation (T1 vs T3 p=0.05) and at 35 weeks of gestation (T1 vs T3 p=0.003; T2 vs T3 p=0.043). A similar graph was constructed for carotid PWV (Figure 6.2 B), also showing an age-dependency at week 20 (T1 vs T3, p=0.01) and week 35 (T1 vs T3 p=0.009; and T2 vs T3, p=0.005)

The evolution of aortic PWV did not differ (p=0.377) between multiparous and nulliparous pregnant women (Figure 6.3A). The same holds for carotid PWV (p=0.632, Figure 6.3B).

Table 6.3 The impact of maternal age on haemodynamics and arterial stiffness during pregnancy.

	Age	Age*pregnancy	Age*visit*pregnancy
SBP (mmHg)	p=0.390	p=0.074	p=0.141
DBP (mmHg)	p=0.173	p=0.101	p=0.952
MAP (mmHg)	p=0.530	p=0.092	p=0.148
Brachial PP (mmHg)	p=0.008	p=0.678	p=0.448
Central PP (mmHg)	p=0.016	p=0.782	p=0.812
Central SBP (mmHg)	p=0.194	p=0.629	p=0.450
PP amplification	p=0.710	p=0.152	p=0.436
HR (/min)	p=0.734	p=0.180	p=0.258
Aortic PWV (m/s)	p=0.005	p=0.164	p=0.039
Carotid PWV (m/s)	p<0.001	p=0.068	p=0.229
Augmentation index (%)	p<0.001	p=0.571	p=0.445

P-values for each factor (Age, Age*pregnancy, Age*visit*pregnancy) were obtained from 12 different mixed models, each with the measured parameter as independent variable and including also pregnancy, visit and pregnancy*visit as fixed factors. The p-values in the first column indicate whether age has a fixed effect on each parameter, regardless of pregnancy. P-values in the second column whether the overall effect of maternal age is different in pregnant women vs controls. P-values in the third column indicate whether maternal age alters the course between pregnant women and controls. SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure, PP = pulse pressure, PWV = pulse wave velocity, HR = heart rate. Augmentation index was corrected for HR. Aortic and carotid PWV were corrected for MAP. Significant p-values ($p<0.05$) appear bold.

6.4 Discussion

To the best of our knowledge this is the first controlled study in which vascular parameters were measured longitudinally in pregnant women and at similar time intervals in non-pregnant controls. The present study shows that pregnancy-related changes in maternal haemodynamics are not confined to alterations in blood pressure and wave reflections, but also involve arterial stiffness changes. In particular, aortic (carotid-femoral) stiffness, independent of MAP, decreased from 12 to 20 weeks of gestation in all age ranges. Only in the age groups up to 30 years this decrease was also maintained at 35 weeks of gestation. Whether the rise in aortic stiffness from 20 to 35 weeks of gestation in pregnant women above 30 years contributes to the higher pregnancy risks in this older age group needs further investigation. Apart from suboptimal study design, this age-dependent course of aortic stiffness during pregnancy may also contribute to the differences in effects of pregnancy on arterial stiffness, reported in literature.[6-8,16,17] In addition, like Mersich et al.[17], the present study observed a different effect of pregnancy on arterial stiffness between the common carotid artery and aorta. This may be a third factor contributing to the inconclusive literature on the effect of pregnancy on arterial stiffness.

The course of aortic and carotid stiffness during pregnancy did not differ between nulliparous and multiparous women. This is in line with the findings of Mahendru et al.[128] and suggests that arterial stiffness may not contribute to the higher risk for maternal haemodynamic maladaptations and vascular complications observed in nulli-versus multiparae.[164]

The changes in arterial stiffness during pregnancy can be caused by both functional and structural changes in the vessel wall. The changes in arterial stiffness, occurring over a relatively short time window (8 weeks), make structural changes less likely, but cannot exclude vascular remodelling. Functional changes due to a NO-dependent decrease in tone of the vascular smooth muscle cells are very likely, since the higher cardiac output and consequently blood flow during pregnancy increases shear stress mediated NO-release in the vascular wall.[7;165] In addition, maternal hormones like estrogen[166], relaxin[167], and prostacyclin[8] could also contribute to the drop in cfPWV. The effect of vascular hormones may differ between arteries and may explain the different course in arterial stiffness observed in the present study between aorta and common carotid artery during pregnancy. This regional difference in arterial stiffness during pregnancy is in line with the findings of Visontai et al..[139] These authors hypothesised that vascular smooth muscle cells (SMCs) of the carotid artery may contain more vasoconstricting angiotensin II receptors and less vasorelaxing oestrogen receptors compared to the aortic SMCs. Therefore, increasing levels of both hormones could induce vasoconstriction of the carotid artery, while at the same time relaxing the aorta. In addition, the aorta contains relatively more vascular SMCs (particularly

the abdominal-femoral part) compared to the carotid artery, resulting in a larger effect of these hormones on the vessel wall.

Although a poor surrogate for pulse wave reflections, augmentation index (AIx) is largely used. The course of AIx in the present study is in line with earlier published reports.[127;129;130;132;134] AIx depends mainly on the heart rate, the distance of major wave reflections from the heart and the pulse wave velocity.[168] The latter 2 parameters are predominantly depending on the vascular tone and arterial stiffness, respectively. The fact that several studies [127-129] revealed a decrease in AIx without a consistent drop in arterial stiffness suggests that not changes in arterial stiffness but rather peripheral vasodilation is the main contributor to the reduction in AIx during pregnancy.

In this comprehensive controlled study, brachial and central (carotid) blood pressures were measured. The course of brachial systolic and diastolic blood pressure differed between pregnant women and controls, with a trend to decrease at 20 weeks of gestation and showing a rise mainly in DBP at week 35. These results are in line with older data.[1;169] As a consequence brachial pulse pressure decreased at 35 weeks. In contrast, like the present study, Elvan-Taspinar et al.[170] found that central systolic blood pressure and pulse pressure were not affected by pregnancy or pregnancy-induced complications (gestational hypertension, preeclampsia). This could at least in part be explained by the larger variability in these parameters. In contrast to central blood pressures obtained by commercial devices like Sphygmocor[128;132], the present study shows central SBP and PP not different from brachial pressure and central to brachial pulse pressure amplification was not different from 1. Our data are in line with data from the large (n=1873) Asklepios population study [171] which also showed a small central (carotid) –to-brachial pressure amplification depending on age being larger or even smaller than 1. This could in part be due to the use of the carotid artery pressure as central blood pressure, which SBP was shown to be on average 1.8 mmHg higher than the ascending aorta.[88] The validity of different methods to measure central blood pressure non-invasively has been extensively debated [172-175], including the calibration of the radial pressure wave with brachial blood pressures. A recent study confirmed that brachial-to-radial pressure amplification may be important [176], leading to a substantial underestimation of central blood pressure using the procedure advocated by the Sphygmocor device.

6.5 Strengths and limitations

The strength of this study is its longitudinal design, including measurements of the control group at each time point. This guarantees that the observed differences between time points are caused by the pregnancy and not being of seasonal or environmental nature.[177] The main limitation is the lack of pre-pregnancy baseline values. Indeed, studies reported cardiovascular adaptations already starting in the late luteal phase of the menstrual cycle.[1;6;129] These adaptations could have been missed when using first trimester values as baseline. A recent

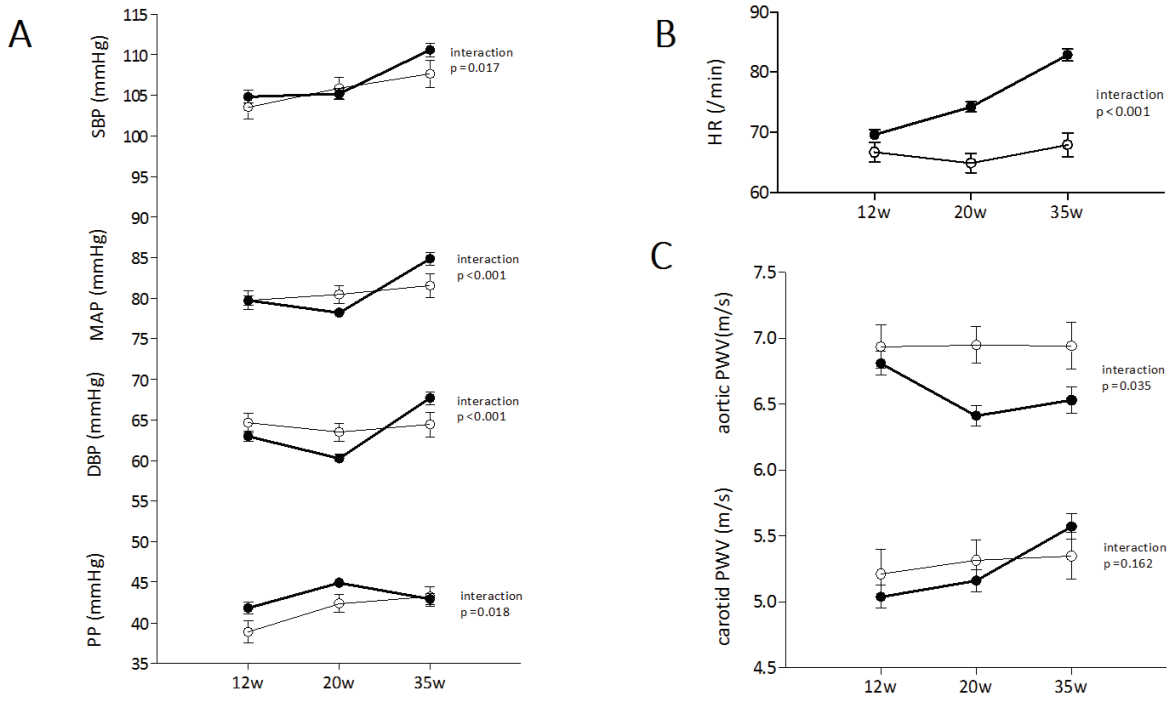
report [128] stresses the importance of pre-pregnancy and early pregnancy values since the majority of the central and brachial blood pressure drop (4-6 mmHg) and change in AIx (from 18 to 12%) was occurring in very early pregnancy. However, in contrast to the present study, that study was not controlled. As a consequence, a familiarizing or period/seasonal effects from the first visit at preconception to the next visit in early pregnancy cannot be excluded.

6.6 Conclusion

In contrast to the younger pregnant women, aortic and carotid stiffness increased from week 20 to week 35 in pregnant women above the age of 30 years. Whether this increase in arterial stiffness from mid to late pregnancy may contribute to the higher pregnancy risk in this older age group has to be further investigated. Arterial stiffness did not differ between nulli- and multiparous pregnant women, suggesting that arterial stiffness is not contributing to the higher risk for haemodynamic maladaptation and vascular complications observed in nulli- versus multiparae.

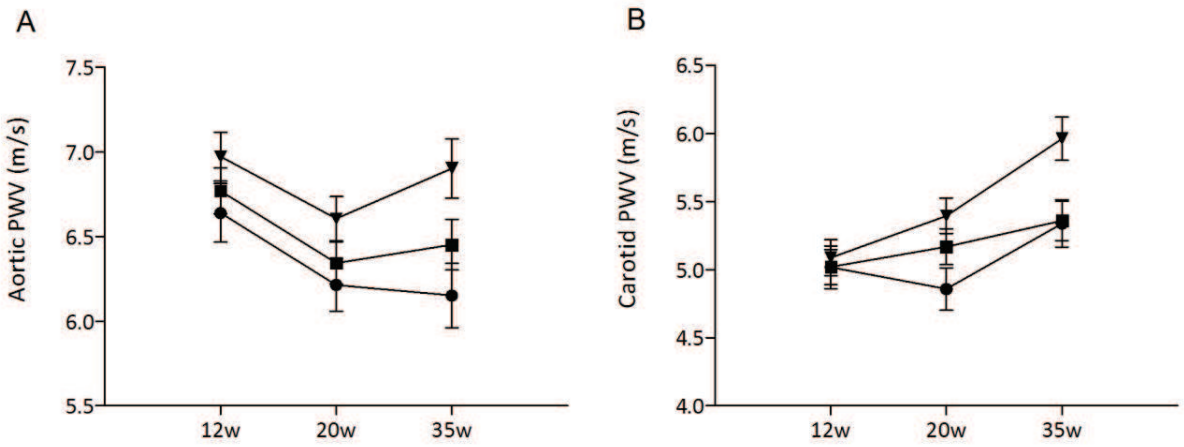
This study confirmed that pregnancy is associated with a U-shape pattern in blood pressure and a drop in AIx during pregnancy.

Figure 6.1 The influence of gestation on haemodynamics



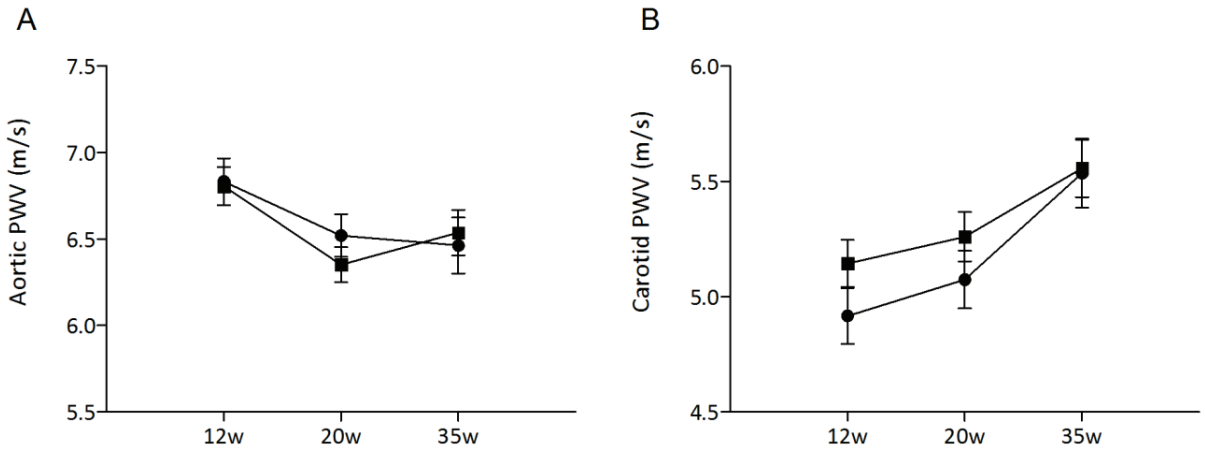
The influence of gestation on haemodynamics: Pregnant women (—●—) vs. non-pregnant controls (—⊖—). The p-value for the interaction term denotes whether the evolution over time is different between pregnant women and controls. Error bars denote the SEM. Figure A: Brachial blood pressures: SBP=systolic, DBP=diastolic , MAP=mean arterial pressure, PP= pulse pressure; Figure B: heart rate (HR); Figure C: arterial stiffness: PWV=pulse wave velocity. Aortic and carotid PWV were corrected for MAP.

Figure 6.2 The impact of maternal age on aortic (A) and carotid (B) stiffness in pregnant women



The youngest pregnant women (T1, aged 21-26y, ●) vs. middle tertile (T2, aged 27-30y, ■) vs. the oldest pregnant women (T3, aged 31-42y, ▼). PWV= pulse wave velocity. Aortic and carotid PWV were corrected for MAP. Error bars denote the SEM.

Figure 6.3 The impact of parity on aortic (A) and carotid (B) stiffness in pregnant women



The impact of parity on aortic stiffness in pregnant women. Nulliparous (●) vs. multiparous (■) pregnant women. PWV=pulse wave velocity. Aortic and carotid PWV were corrected for MAP. Error bars denote the SEM.

Part III: Pharmacodynamic effects of tocolytic drugs on the female cardiovascular system.

Chapter 7 Problem statement and aims of part III

Tocolytic therapy is administered when an acute episode of idiopathic preterm labour needs to be abolished. The goals of treatment of preterm labour are: Postponing delivery by at least 48 hours to achieve maximum effects of corticosteroids therapy to protect the preterm child; providing time to transport the mother to a tertiary maternal and foetal health centre; to ensure time to recover from underlying, self-limited conditions that can cause labour (e.g. infections) which are unlikely to cause recurrent preterm contractions.[178]

There are no evidence based guidelines to start tocolysis.[179] The semantic discussion about 'spontaneous abortion' versus 'preterm birth in an early pregnancy state' feeds the debate about the minimum gestational age to abolish premature contractions. There is greater consensus about the maximum gestational age which lies at 34 weeks of gestation.

Beta-2 adrenoceptor agonistic drugs like ritodrine have for many years been the reference tocolytic drugs in most countries.[180;181] Their efficacy in prolonging pregnancy compared to placebo is proven although no benefit in neonatal morbidity or mortality has been demonstrated.[182] Beta-mimetics are not highly selective and have many contraindications. Side-effects are frequently due to beta-1 and -2 adrenoceptor agonistic cardiovascular effects.[182]

Atosiban, a newer tocolytic drug, is a competitive antagonist of oxytocin at uterine oxytocin receptors and has less cardiovascular side effects.[183] A better tolerability is observed, but there is no advantage in improving foetal and maternal outcome in comparison with beta-mimetics. The benefit of safety with atosiban has to be balanced against its cost.[184;185] A study of Ferriols et al.[186] revealed that the cost-effectiveness obtained with a protocol including ritodrine as first-choice drug was three times less than when atosiban was used. Although large studies using atosiban have been performed in both pregnant and non-pregnant groups,[182;185;187-189] there is a mainly subjective reporting of adverse reactions during infusion with a focus on peripheral blood pressure data. In Chapter 8, a literature review of the most frequently reported tocolytical drugs is given with a recommendation on the use, based on the latest evidence.

Central blood pressure and pulse wave reflections may provide additional information regarding cardiovascular risk beyond peripheral blood pressure.[190-192] The central haemodynamic effects of tocolytic drugs have never been studied before in a single study.[193] The aim of Chapter 9 is to evaluate the acute effects of therapeutic doses of ritodrine and atosiban on central and peripheral blood pressure, central-to-peripheral blood pressure amplification, pulse wave reflections, cardiac function, the micro-circulation (total peripheral resistance) and the macro-circulation (large artery stiffness) in healthy young non-pregnant women.

Chapter 8 Tocolysis – Review of the literature.

8.1 Introduction

Preterm births account for approximately 70% of neonatal deaths and 36% of infant deaths as well as 25–50% of cases of long-term neurologic impairment in children in the USA.[194] Tocolytic therapy is acquired when an acute episode of idiopathic preterm labour needs to be abolished. It will not remove the underlying disorder that initiated the process of parturition nor reverse the parturitional changes in the uterus.

The goals of treatment of preterm labour are: [178]

1. Postpone delivery by at least 48 hours to achieve maximum effects of corticosteroids. Pre-delivery administration of corticosteroids can reduce the risk of neonatal mortality, acute respiratory distress syndrome, intra-ventricular haemorrhage and necrotising entero-colitis of the new-born;
2. Providing time to transport the mother to a tertiary maternal and foetal health centre in the case of preterm delivery;
3. To ensure time to recover from underlying, self-limited conditions that can cause labour (e.g. infections) which are unlikely to cause recurrent preterm contractions.

There are no evidence based guidelines for when to start treatment of preterm labour.[179] The lowest gestational age remains controversial.[195] Fifteen weeks has been arbitrarily selected, others use twenty weeks due to different definitions of "early pregnancy loss". The semantic discussion about 'spontaneous abortion' and 'preterm birth in an early pregnancy state' feeds the debate about the minimum gestational age to abolish premature contractions.

There is greater consensus about the maximum gestational age to start treatment of preterm labour. Thirty-four weeks of gestation defines the threshold at which foetal perinatal morbidity and mortality cannot overcome the associated maternal and foetal risks of tocolysis.[196-198]

Tocolysis is contra-indicated when the maternal and foetal risks of prolonging the pregnancy or the associated risks of tocolytica are greater than those associated with premature delivery. Contraindications include: [194]

Intra-uterine foetal demise

Lethal foetal anomaly

Non-reassuring foetal state

Severe foetal growth restriction

Severe preeclampsia or eclampsia

Maternal haemorrhage with haemodynamic instability

Chorioamnionitis (maternal fever and leucocytosis, tachycardia, fundal tenderness)

Preterm premature rupture of membranes without maternal infection

Maternal contraindications to tocolysis (agent specific)

Inhibition of premature delivery is not effective or successful in the presence of intra-amniotic infection or a cervical dilation greater than three centimeters.[179;194;199]

The selection of the tocolyticum, is based upon efficacy and safety and established in terms of significant clinical endpoints rather than surrogate endpoints. The drug has to be safe for the mother, foetus and neonate. Two meta-analyses [200;201] concluded that all of the commonly used tocolytical agents were more effective than placebo/no therapy for delaying delivery for 48 hours to seven days. No statistically significant differences were found for the other outcomes, including the neonatal outcomes of respiratory distress and neonatal survival.

8.2 Selection of tocolytical agents

8.2.1 Beta-adrenergic receptor agonists.

Ritodrine, Terbutaline, Salbutamol and Hexoprenaline.

Mode of action: Beta-adrenergic agonists cause myometrial relaxation by binding with β-2 adrenergic receptors. There is a risk of tachyfylaxis which is caused by desensitisation of the target cells.[202;203]

Efficacy: The efficacy has been evaluated in many trials, mainly with ritodrine as agent. A Cochrane review published in 2004 noted a decrease of women giving birth within 48 hours and possibly within seven days.[204]

Maternal side effects: The side effects are significant due to activation of β-1 and β-2 agonistic effects leading to increases in maternal heart rate and stroke volume, peripheral vasodilation and diastolic hypotension. Clinical manifestations are palpitations, tremor, dyspnoea and chest discomfort.[205]

Pulmonary oedema is very rare (0.3%) and is caused by concomitant factors like fluid overload and increased vascular permeability.[206]

Important metabolic effects are hyperglycaemia and hypokalaemia.

Foetal side effects: Beta-adrenergic agonists cross the placenta and cause analogous effects as in the mother. The foetus develops hyper-insulinaemia due to maternal hyperglycaemia. The foetal acid-base balance is seldom affected.[207]

There is a controversial relation of neonatal intraventricular haemorrhage with the administration of beta-adrenergic agonists. Some studies suggest an increased risk,[208;209] others concluded there is no effect on the risk.[210;211]

Prolonged administration of beta-adrenergic agonists in critical periods of foetal development may induce a permanent shift in the balance of sympathetic-to-parasympathetic tone leading to certain disease processes (autism spectrum disorders, psychiatric disorders, poor cognitive, motor function and school performance).[212] Other authors could not support this theory.[213]

Contra-indications: Tocolysis with beta-adrenergic agonists is relatively contraindicated in women with cardiac diseases and hyperthyroidism due to the chronotropic effects. Diabetic women should be monitored carefully. Women with a risk for massive haemorrhage should be watched with caution since the resultant cardiovascular effects may interfere with the maternal defence mechanisms against haemorrhage.[204]

8.2.2 Magnesium sulphate.

Mode of action: The precise mechanism of action is still unknown, despite over forty years of investigation. Probably, magnesium competes with calcium at the level of the membrane and inhibits intracellular processes. The net result is interference with myometrial contractility.[214;215]

Efficacy: Predelivery administration of magnesium sulphate is neuro-protective for the neonate.[216] But according to Mercer et al.[217] there is no clinically important tocolytical effect for magnesium sulphate. This information is based on a systematic review based on randomised, placebo-controlled trials.

Maternal side effects: there are fewer minor side effects in comparison with beta-adrenergic agonists. The risk of major adverse events is comparable. Diaphoresis and flushing are the most common side effects and are related to the maternal serum concentration of magnesium.[218]

Foetal side effects: A non-significant decrease in basal foetal heart rate and heart rate variability has been noted.[219] When given more than seven consecutive days, there might be an effect on the bone metabolism of the

foetus.[220] For this reason the ACOG (American College of Obstetricians and Gynecologists) advise to limit the use for up to 48 hours in women between 24 and 34 weeks of gestation.[216]

Contraindications: Magnesium sulphate is contra-indicated in women with myasthenia gravis and with cardiac conduction defects due to the anti-dromotropic effects of magnesium sulphate. One should be aware of renal function impairment and the dosing regimen of magnesium sulphate.[221;222]

8.2.3 Calcium channel blockers

Nifedipine

Mode of action: Calcium channel blockers decrease the intracellular free calcium content which results in myometrial relaxation.

Efficacy: unfortunately there are no placebo-controlled trials, but only comparative trials with ritodrine, magnesium sulphate or atosiban. The few meta-analyses did not find any significant difference in the rate of delivery in 48 hours to seven days. The only benefit is the significant reduction in maternal and foetal side effects.[223;224]

Maternal side effects: Since calcium channel blockers are peripheral vasodilators, they cause flushing, headache, hypotension and palpitations. The decrease in total peripheral resistance leads to reflex tachycardia and increase in stroke volume to maintain the blood pressure. The side effect profile is better than those of beta-adrenergic agonists.[225;226]

Foetal side effects: The decrease in total peripheral resistance raised concerns for a compromised uterine blood flow and foetal oxygen desaturation.[225] However, animal and human utero-placental blood flow studies using Doppler ultrasound did not substantiate these concerns.[227-229] There are no data regarding foetal side effects using oral doses commonly used for labour inhibition.

Contraindications: Calcium channel blockers are contra-indicated in women with ventricular dysfunction or congestive heart failure.[178] The concomitant use of calcium channel blockers and magnesium sulphate may lead to respiratory depression due to suppression of muscular contractility[230] and cardiac arrest due to negative inotropic effects.[231]

8.2.4 Cyclooxygenase (prostaglandin synthetase)inhibitors

Indomethacine

Mode of action: Cyclooxygenase, (COX) or prostaglandin synthetase, is the enzyme responsible for conversion of arachidonic acid to prostaglandins. Prostaglandins (E and F-type)[232] increase the intracellular calcium content, leading to enhanced myometrial contractions. Cyclooxygenase exists in two isoforms, COX-1 and COX-2. Different tissues express varying levels of COX-1 and COX-2. Although both enzymes act basically in the same fashion, selective inhibition can make a difference in terms of side-effects. COX-1 is considered a constitutive enzyme, being found in most mammalian cells. COX-2, on the other hand, is undetectable in most normal tissues. It is an inducible enzyme, becoming abundant in activated macrophages and other cells at sites of inflammation. It increases in the decidua and the myometrium at term but also in cases of premature labour.[233;234] Cyclooxygenase inhibitors decrease prostaglandin production.

Efficacy: indomethacin, a nonspecific COX-inhibitor, is the most commonly used tocolyticum in its class. A Cochrane review[235] based on two placebo-controlled trials showed a trend in the reduction of delivery rates within 48 hours to seven days after treatment initiation. There were no differences in neonatal outcomes, and in the premature closing of the ductus arteriosus. Indomethacin was also the most cost-effective tocolyticum in comparison with magnesium sulphate, nifedipine and terbutaline.[236]

Maternal side effects: Four percent of the patients receiving indomethacin may suffer from nausea, pyrosis and emesis. Platelet dysfunction may occur but alterations of the maternal cardiovascular system are minimal. [237]

Foetal side effects: The primary concerns for the foetus are premature constriction of the ductus arteriosus and oligohydramnios.[237] Since the first depends upon both gestational age and duration of exposure, indomethacin is not recommended after 32 weeks of gestation. It is recommended to use it for 48 hours or less and at the lowest possible dose to allow time for corticosteroid treatment but minimize neonatal complications.[238] Foetal echocardiography is recommended during the therapy. For the foetal side effects, there is no difference between selective and non-selective COX-inhibitors.[239]

Contra-indications: Maternal platelet dysfunction or bleeding disorders, hepatic dysfunction, dyspepsia, renal dysfunction and Asthma Polyposis Aspirin (APA)-syndrome.[237;240]

8.2.5 Oxytocin receptor antagonists

Mode of action: Atosiban is a selective oxytocin-vasopressin receptor antagonist and is commonly used in Europe but is not available in the United States. Oxytocin stimulates the release of calcium from the sarcoplasmatic reticulum from the myometric cells, causing contraction. Oxytocin antagonists compete with

oxytocin for binding to the oxytocin receptors.[241-243] Since there is an up-regulation of the oxytocin-receptors during the course of pregnancy, atosiban should be more effective in late pregnancy.

Efficacy: Atosiban is as effective as beta-adrenergic receptor agonists in preventing premature labour within 48 hours to seven days. The neonatal morbidity and mortality was similar compared with placebo. The use of atosiban was associated with significantly less maternal side effects compared with beta-adrenergic receptor agonists.[244]

Maternal side effects: The main side effects are local hypersensitivity reactions at the injection site. Adverse maternal side effects have not been reported yet.[245] Atosiban may compete with ADH in the kidney due to suboptimal receptor specificity, but there is no report of any clinical sequelae. There are significantly less side effects compared to any other drug class, used for inhibition of premature labour.[246]

Foetal side effects: Atosiban crosses the placenta with circulating levels being 88% lower than in the mother. There are no proven cardiovascular or other major complications.[247;248] There is, however, one report with a trend towards higher rate of foetal death in mothers on atosiban.[245] The link with atosiban is not completely clear, since the foetal deaths were more attributable to infection and extreme prematurity (<26 weeks of gestation). Another concern is the blockage of foetal vasopressin receptors, which could lead to changes in renal development, amniotic fluid volume and consequently lung development.[248]

Contra-indications: The United States Food and Drug Administration[60] did not approve atosiban as a tocolyticum, because of concerns for the foetus with a gestational age below 28 weeks of gestation. It is available, however, in Europe but the costs are very high.[249] The acquisition costs of atosiban for one administration cycle amounts 431 Euros versus 7,6 Euros for ritodrine.[250]

8.2.6 Nitric Oxide Donors

Mode of action: Nitric Oxide (NO) is produced in a variety of cells and is essential for the maintenance of normal smooth muscle tone. It is synthesised during the oxidation of L-arginine to L-citrulline which then diffuses. The reaction is catalysed by the enzyme nitric oxide synthase (NOs). The widespread distribution of NO to nearby cells leads to intracellular mechanisms causing smooth muscle cells relaxation.[251]

Efficacy: Because the use of transdermal nitro-glycerine is still in the pipe-line, there is not enough evidence to support its use for tocolysis.[252] There was a trend towards a reduction in delivery rates prior to 28 weeks of gestation, when compared to placebo.[253] Compared to beta-adrenergic agonists, there was a diverse outcome. Whereas the nitro-glycerine was as effective in delaying delivery for 48 hours in one study,[254] the outcome was the reverse in another study.[255]

Maternal side effects: Due to vasodilation, it causes maternal hypotension and headache. The uterine and placental blood flow might be compromised but neonatal side-effects have not yet been reported.[252]

Contra-indications: No use in women with known hypotension and with compromised pre-load cardiac dysfunctions.

8.2.7 Antibiotics

Infection of the genital tractus contributes in the pathogenesis of premature labour but there is no obvious role for antibiotic therapy in the prevention of prematurity.[194] A Cochrane review[256] evaluated the consistent use of prophylactic antibiotics concomitant with tocolysis in pregnancies up to 36 weeks. Compared to non-use of antibiotics, there was no prolongation of the pregnancy and no significant reduction in delivery rates within 48 hours after initiating the therapy. However, there was a significant reduction in maternal infection. A subgroup-analysis revealed that the use of antibiotics, specifically against anaerobes, induced a significant reduction in delivery rates within 7 days after initiating treatment and also less admissions to neonatology care services. However, there are no convincing arguments for a systematic screening of pregnant women for a subclinical intra-uterine infections. Another meta-analysis,[257] restricted to pregnancies up to 34 weeks, also concluded there was no prolongation of pregnancy with the use of antibiotics for spontaneous preterm labour.

8.3 Recommendations

Administration of tocolytical drugs should be restricted to women who will have advantages of delaying delivery. The purpose of tocolytic drug administration is to postpone threatening preterm delivery for at least 48 hours. This time window allows the maximal effect of antenatal corticosteroids and maternal transportation to a centre with specialised neonatal care facilities and to prolong pregnancy when there are underlying, self-limited causes of recurrent premature contractions.

The selection of the appropriate tocolyticum depends on efficacy and safety with the establishment of significant clinical endpoints rather than surrogate ones; safety should be evaluated for the mother, the foetus and the neonate.[194]

We suggest the following strategies, according to the gestational age:[194;246;258;259]

For women with a gestation between 24 to 32 weeks who are candidates for tocolysis, one can start with nifedipine. There is, however, an increased risk of respiratory depression and cardiac arrest when magnesium sulphate is used concomitantly with calcium channel blockers.[230;231]

Some reports suggest indomethacin as first-line therapy for labour inhibition[235;260] in cases when magnesium sulphate is administered for foetal neuroprotection.[216] After 32 weeks this drug should be avoided because of an increased risk for premature narrowing or closure of the ductus arteriosus when the indomethacin is continued for 72 hours. Recent reports are diverse with recommendations for indomethacin as tocolyticum[260] versus critical reports for the use in tocolysis.[261] In Belgium tocolysis is not a therapeutic indication anymore for indomethacin due to the side effect profile and is not recommended for tocolysis.

For women with a gestation of 32 to 34 weeks, the first-line agent is also nifedipine.[201] Although atosiban results in fewer maternal adverse effects and without a difference in perinatal mortality, it is much more expensive and doubts remain about possible foetal side effects.[249] Data on longer-term outcomes are limited. Beta-adrenergic agents are as effective but with more maternal and foetal side effects.[259]

In the absence of clinical signs of genital tract infection, broad spectrum antibiotics should not be administered.[262;263]

Table 8.1 Summary of tocolytical agents[60;65;202;208;214;215;217;219;222;225;227;228;234-236;241;246;249;253-256;256;264]

Drugs	FDA-classification	Mode of Action	Efficacy	Maternal side effects	Foetal side effects	Contra-indications
β-adrenergic receptor blockers	B					
ritodrine		binding with β-2 adrenergic receptors --> myometrial relaxation	postpone delivery in 48 hours to 7 days	palpitations, tremor, dyspnoea, chest discomfort. Pulmonary oedema. Hyperglycaemia	analogous effects. Hyperinsulinaemia	cardiac diseases, diabetes. Risk of massive haemorrhage
Magnesium Sulphate	A					
		Inhibition of intracellular processes (interaction Calcium) --> interference with myometrial contractility	no clinically important tocolytical effect	Diaphoresis, flushing	↓ heart rate and HR-variability	Myasthenia Gravis, cardiac conduction defect, ↓ renal function.
Calcium channel blockers	C					
nifedipine, amlodipine		↓ intracellular free calcium --> myometrial relaxation	no significant effect on delivery	peripheral vasodilation, reflex tachycardia with ↑ SV	No ↓uterine blood flow	ventricular dysfunction, congestive heart failure. Concomitant use of Mg-sulphate
Cyclo-oxygenase inhibitors	C					
diclofenac, meloxicam, celecoxib		↓ prostaglandin synthesis --> decreasing myometrial contractions	reduction on delivery rates in 48 hours to 7 days	nausea, pyrosis and emesis. Platelet dysfunction	constriction of ductus arteriosus. Oligohydramnios	Platelet dysfunction / bleeding disorders. Hepatic and renal dysfunction. Dyspepsia. APA-syndrome
Oxytocin receptor antagonists	NA					
atosiban, barusiban		↓ intracellular free calcium --> decreasing myometrial contractions	cfr β-adrenergic receptor blockers: postpone delivery in 48 hours to 7 days	local hypersensitivity on injection site. No clinically effect of ADH-competition in kidney.	blockage of ADH-receptors --> ↓ renal development, ↓ amniotic fluid volume --> ↓pulmonary development	No. Not FDA-approved.
Nitric Oxide Donors	C					
nitroglycerine		smooth muscle relaxation	not enough evidence	/	↓ heart rate and HR-variability	/
Antibiotics	B to D					
amoxicilline, ciprofloxacine, tetracycline		reduction of maternal infection --> no evidence for preventive therapy	no significant prolongation of pregnancy	/	/	/

Legend: FDA (Food and Drug Administration); HR (heart rate); SV (stroke volume); Mg (magnesium); APA (Asthma Polyposis Aspirin); ADH (antidiuretic hormone).

Chapter 9 The Haemodynamic effects of Tocolytic Medication.

Based on

Different effects of tocolytic medication on blood pressure and blood pressure amplification-

Isabelle Fabry, Peter De Paepe, Jan Kips, Sebastian Vermeersch and Lucas Van Bortel (2011)

European Journal of Clinical Pharmacology. 67 (1). p11-17

The influence of tocolytic drugs on cardiac function, large arteries, and resistance vessels.

Isabelle Fabry, Peter De Paepe, Jan Kips and Lucas Van Bortel (2011)

European Journal Of Clinical Pharmacology. 67(6). p.573-580

Abstract

Background: The importance of tocolysis has been discussed extensively. Beta-2 adrenoceptor agonistic drugs like ritodrine have been the reference tocolytic drugs in most countries. Cardiovascular side-effects are frequent. Atosiban, a newer tocolytic drug, is a competitive antagonist of oxytocin and has less cardiovascular side effects. Although large studies exists, there is mainly a subjective reporting of adverse reactions with a focus on blood pressure data.

Objectives: Evaluation of the acute effects of therapeutic doses of ritodrine and atosiban in comparison with placebo on central and peripheral blood pressures, central-to-peripheral blood pressure amplification, the augmentation index (AIx), cardiac function, large artery properties and resistance vessels in healthy non-pregnant female volunteers.

Methods: A double-blind, randomised, crossover trial was carried out in twenty healthy non-pregnant female volunteers. Haemodynamic measurements were done under standardised conditions.

Results: At steady state, central and peripheral pressures did not differ from placebo in the atosiban group. During ritodrine -infusion, central SBP increased with 11% versus placebo ($p = 0.012$) and peripheral SBP with 10% ($p = 0.004$). In contrast with atosiban and placebo, blood pressure amplification was absent in the ritodrine group. While the AIx did not change in the atosiban group, with ritodrine, the AIx tended to decrease. Ritodrine caused the cardiac function to increase with 79% compared to placebo due to a rise in heart rate (91%). TPRI decreased with 48%. Ritodrine increased the distensibility of the common carotid artery with 62% and the compliance with 83%, independent from blood pressure. Compliance of the common femoral artery increased independently of pressure with 33% and the distensibility with 59%. Aortic pulse wave velocity was not influenced by either medication.

Conclusions: The present study shows the significant and potential beneficial vascular effects of ritodrine on the cardiovascular system. Atosiban has no significant or clinically relevant cardiovascular effects and may be an appropriate alternative as tocolyticum particularly in cardiovascularly complicated pregnancies.

9.1 Introduction

The importance of tocolysis has been discussed extensively.[246;249] Beta-2 adrenoceptor agonistic drugs like ritodrine have been the reference tocolytic drugs in most countries.[180;181] Their efficacy in prolonging pregnancy compared to placebo is proven although no benefit in neonatal morbidity or mortality has been demonstrated.[182] Beta-mimetics are not highly selective and have many contraindications. Side-effects are frequent due to beta-1 and -2 adrenoceptor agonistic cardiovascular effects. Even serious complications such as pulmonary oedema and maternal death, though rare, have been reported.[182;265]

Atosiban, a newer tocolytic drug, is a competitive antagonist of oxytocin at uterine oxytocin receptors and has less cardiovascular side effects.[183] The 13th revision (08 July 2009) of the European Public Assessment Report (EPAR) on Tractocile® (atosiban) of the EMA (European Medicines Agency) states that atosiban has the same effect as beta-mimetics on surrogate endpoints related to tocolysis. A better tolerability was observed, but there was no advantage in improving foetal and maternal outcome in comparison with beta-mimetics. This benefit of safety with atosiban has to be balanced against its cost.[184;185] A study of Ferriols et al.[186] revealed that the cost-effectiveness obtained with a protocol including ritodrine as first-choice drug was three times less than when atosiban was used. In pregnant women with high risk of developing acute pulmonary oedema, or cardiovascular disease (e.g. preeclampsia, cardiomyopathies and cardiovascular syndromes), atosiban may be an appropriate alternative.

Although large studies using atosiban have been performed in both pregnant and non-pregnant groups[182;185;187-189], there is mainly a subjective reporting of adverse reactions during infusion with a focus on peripheral blood pressure data.

Central blood pressure and pulse wave reflections may provide additional information regarding cardiovascular risk beyond peripheral blood pressure.[190-192] The central haemodynamic effects of tocolytic drugs have never been studied before. In this study, the acute effects of therapeutic doses of ritodrine and atosiban were evaluated on central and peripheral blood pressure, central-to-peripheral blood pressure amplification and pulse wave reflections in healthy non-pregnant female volunteers.

We evaluated also the acute effects of therapeutic doses of ritodrine and atosiban on the cardiac function, micro-circulation (total peripheral resistance) and macro-circulation (large artery stiffness) in healthy non-pregnant female volunteers since the haemodynamic effects on the heart and on the micro-and macro-circulation have not been studied before in a single study.[193]

9.2 Methods

9.2.1 Subjects

Twenty healthy non-pregnant female volunteers, either non-smokers or smokers (≤10 cigarettes per day) with adequate non intra-uterine contraception were recruited from the local population. All participants gave written informed consent upon screening, which was organised within two weeks before the planned first drug administration. They were apparently healthy (no cardiovascular diseases – including arrhythmias, obstructive lung diseases, chronic kidney diseases or diabetes mellitus). Breastfeeding women or women with a severe addiction were excluded.

Subjects were asked not to eat, smoke and drink caffeine-containing beverages for at least 3 hours before and during the measurements. They also had to refrain from drinking alcohol for at least 10 hours before measurements.[266]

9.2.2 Design

A double-blind, randomised, placebo-controlled trial was carried out at the Drug Research Unit Ghent of the Ghent University Hospital, Belgium. The study was approved by the Ethics Committee of Ghent University and conducted according to ICH Good Clinical Practice and in compliance with the Declaration of Helsinki (last amended in 2008 in Seoul).

Twenty female volunteers were given atosiban (Tractocile®, Ferring, Sweden) and placebo (Glucose 5%) intravenously in a double-blind way. Eight of them were randomly chosen to also get ritodrine (PrePar®, Eumedica, Belgium) in a single-blind way. Between visits there was a wash-out period between two to seven days.

Randomization was done by guided ballot assuring [1] that all 6 possible sequences of atosiban, ritrodrine and placebo were allocated to the first 8 subject numbers at least once and not more than twice and [2] that in 10 subjects atosiban was administered before placebo and vice versa.

The effects of drugs were compared after 95 minutes of infusion when kinetic steady state was reached for atosiban and ritodrine, being 15 minutes after starting the highest dose (400µg/min) of ritodrine (see Table 9.1, Table 9.2 and Table 9.3.). Haemodynamic measurements were done by one investigator with the subjects in supine position and under standardised conditions (derived from the Task Force III, clinical applications for arterial stiffness[266]) in a temperature controlled room (22 ± 1 °C).

9.2.3 Medication

Medication and placebo were infused for 120 minutes at the left arm. Both atosiban and ritodrine were given with glucose 5% as vehiculum. Atosiban was given at a constant dose of 300µg/min at a constant infusion rate of 0.4ml/min. Ritodrine was given in a dose escalation scheme derived from the in-hospital setting, starting with a dose of 100µg/min gradually upgraded to a dose of 400µg/min. The infusion rate varied with each dosing step (from 0.23 to 0.53ml/min). Glucose 5% was given as placebo at a constant infusion rate of 0.4ml/min. Dosing was based on previous studies using atosiban or ritodrine[181;267-270] and on the manufacturers prescriptions. Each period, a total volume of 48ml was infused. Stopping criteria for dosing were: a heart rate increase above 75% of the age-based maximal heart rate or blood pressure changes from baseline of more than 30 mmHg for systolic (SBP) and 15 mmHg for diastolic blood pressure (DBP) or a SBP above 180 mmHg or less than 90 mmHg and DBP more than 110 mmHg. When the subject suffered intolerable side effects, the infusion was also ended.

Measurements were done at steady state of the distribution $T_{1/2}$ of ritodrine.

Table 9.1. Procedures: Ritodrine administration until 120 minutes.

Procedures	Time relative to drug administration
IV-administration of ritodrine"	START at time = 0; STOP at 125 minutes maximally
Vital signs #	15, 45 & 95 minutes postdose
Pulse Wave Analysis ##	95 minutes postdose
Wall Track Measurement ### and Cardiac Output	Start at 105 minutes postdose

"The subjects must be fasting for at least 3 hours before starting the infusion; STOP the infusion after 120 minutes (125 minutes at maximum);
Vital signs includes blood pressure, heart rate and ECG-monitoring for safety reasons;
PWA is RA (radial artery) and CCA (common carotid artery)-measurement (AIx-measurement); at 95 minutes also cf-PWV-measurement;
Measurement at the common carotid and common femoral artery.

Table 9.2 Procedures: Atosiban and Placebo administration until 120 minutes.

Procedures	Time relative to drug administration
IV-administration ofatosiban or placebo"	START at time = 0; STOP at 125 minutes maximally
Vital signs #	15, 35, 55, 75 & 95 minutes postdose
Pulse Wave Analysis ##	95 minutes postdose
Wall Track Measurement ### and Cardiac Output	Start at 105 minutes postdose

"The subjects must be fasting for at least 3 hours before starting the infusion; STOP the infusion after 120 minutes (125 minutes at maximum);
Vital signs includes blood pressure, heart rate and ECG-monitoring for safety reasons;
PWA is RA (radial artery) and CCA (common carotid artery)-measurement (AIx-measurement); at 95 minutes also cf-PWV-measurement;
Measurement at the common carotid and common femoral artery.

Table 9.3.Measurements from end of steady state measurements (120 maximally 125 minutes postdose = Time 0 Post End-infusion) till 2 (for Atosiban and placebo) or 6 hours Post End-Infusion (for Ritodrine).

Procedures	Time relative to end of infusion$
Vital signs #	0, 10, 20, 30, 40, 50, 60, 80, 90, 100, 110 & 120 minutes post end-infusion
Pulse Wave Analysis # & ##	0, 10, 20, 30, 40, 50, 60, 80, 90, 100, 110 & 120 minutes post end-infusion

$ Since time = 0 is subject-dependent , notation of clock time is recommended;
# Vital signs includes blood pressure, heart rate and ECG-monitoring; The 8 subjects receiving ritodrine will be monitored with BP and HR till 6 hours post-end-infusion (additional measurements at 150, 180, 240, 300 & 360 minutes post-end-infusion);
PWA is RA & CCA-measurement (AIx-measurement).

9.2.4 Measurements

9.2.4.1 Sphygmomanometry

Semi-recumbent brachial SBP and DBP and heart rate (HR) were recorded at the right upper arm opposite to the arm with the intravenous infusion line with a validated semi-automated oscillometric device (OMRON 705IT, OMRON Healthcare, Hoofddorp, The Netherlands).[271] Mean arterial pressure (MAP) was calculated by adding 40% of the pulse pressure (PP) to the measured DBP.[272]

9.2.4.2 Applanation tonometry

Radial (RA) and carotid (CCA) pressure waveforms (PWFs) were recorded non-invasively with a Sphygmocor® applanation tonometry system (AtCor Medical, Sydney, Australia).[273] To obtain local blood pressure at the CCA and RA, calibration of the recorded PWFs is required. Calibration is based on the validated assumption that DBP and MAP remain constant throughout the large arteries, while SBP and PP (the difference between SBP and DBP) change.[85] SBP at an arterial site (SBP_X) is $SBP_X=DBP+PP_X$. Using our calibration method, PP at an arterial site (PP_X) can be calculated from PP at the brachial artery (PP_{BA}) as

$PP_X=PP_{BA} \times FF_{BA}/FF_X$[86]

FF_{BA} and FF_X are the form factors (FF) at the brachial artery and the target artery, respectively, and are defined as:[87]

$FF_X=(MAP-DBP)/PP_X$

Brachial FF was calculated as $FF_{BA}=FF_{RA}+0.625(FF_{CCA}–FF_{RA})$. This formula estimates FF_{BA} from carotid (FF_{CCA}) and radial FF (FF_{RA}) assuming the ratio $(FF_{BA}-FF_{RA})/(FF_{CCA}-FF_{RA})$ to be fixed. This ratio was calculated in an age matched population (265 subjects (aged 19-40 years) from the Asklepios database[274] and from unpublished data).

9.2.4.3 Augmentation index

Carotid augmentation index (AIx) was calculated from the carotid pressure waveform as the ratio of the amplitude of the pressure wave above its systolic shoulder to the total pulse pressure.[275] Carotid AIx is a surrogate for aortic AIx and is considered to be an index of pressure wave reflection (PWR).[276] Since the AIx has an inverse, linear relationship with the HR, the AIx was corrected for HR.[277]

9.2.4.4 Cardiac Output

Cardiac output (CO) was measured using echocardiography (AU5, Esaote, Genoa, Italy). Measurements were performed in the left lateral position. Aortic diameter (D) was measured at least three times using pulsed ultrasound at 2.5 MHz from a standard two-dimensional long-axis parasternal view at the site of the aortic annulus; the median of these readings was used in the subsequent calculations. Aortic blood velocity profiles (at least 5 beats) were measured across the aortic valve with continuous ultrasound using an apical window. Stroke volume (SV) was calculated from aortic cross-sectional area (CSA_{ao}) multiplied by the flow velocity integral (FVI). See Chapter 2 for detailed description for CI and SI.

9.2.4.5 Microcirculation

The effects on the microcirculation were estimated using total peripheral resistance index (TPRI) which was calculated as MAP divided by the CI.

9.2.4.6 Macro-circulation

Large artery wall properties were assessed for the aorta using carotid-femoral pulse wave velocity (PWV), and local distensibility and compliance were measured at the right common carotid artery (CCA) and right common femoral artery (CFA).

PWV was measured using a Sphygmocor® (AtCor Medical, Sydney, Australia) system. [278;279] Surface distance between the two recording sites was measured in supine position using an anthropometer and the supra-sternal notch (SSN) as reference point: the distance CCA-to-SSN was subtracted from the distance SSN-to-CFA.

Arterial cross-sectional compliance (CC), a measure of buffering capacity and distensibility coefficient (DC), a measure of elasticity, were calculated as described in Chapter 2.

Arterial diameter distension waveforms were assessed with a wall-tracking vascular echoscanner (Wall Track System, Esaote, Genoa, Italy)[103] equipped with a 7.5-10 MHz linear-array as described earlier.

Femoral and carotid pressure waveforms (PWFs) were recorded non-invasively with a Sphygmocor® (AtCor Medical, Sydney, Australia).[273] To obtain local blood pressure at the CCA and CFA, calibration of the recorded PWFs was required. Calibration is based on the validated assumption that DBP and MAP remain constant throughout the large arteries, while SBP and PP (the difference between SBP and DBP) change.[85]

Additionally, isobaric wall properties (expressed as DC_{ISO} and CC_{ISO}) were calculated for each subject. The diameter and pressure waveforms were time-aligned using the peak as reference point. The resulting diameter-time recordings at CCA and CFA were analysed off-line using Matlab®. In each subject, CC and DC were

calculated over the blood pressure interval common in each treatment period (the highest DBP and the lowest SBP). In this way, the direct drug-induced changes in distensibility and compliance could be differentiated from the changes resulting from a change in blood pressure.

9.2.5 Data analysis

The median of 3 measurements was used for data-analysis. Statistics were done using IBM® SPSS® version 18 (SPSS Inc., Chicago, United States). Demographic differences between study groups were analysed using the non-parametric Mann-Whitney U test.

A non-parametric Friedman test was run on data of the 8 subjects who also received ritodrine to compare for repeated observations on the same subject. If statistically significant, this was followed by a Wilcoxon signed rank test for 2-point comparison.

Effects in the whole group were analysed by the non-parametric Kruskal-Wallis test. If statistically different ($p< 0.1$), a Mann-Whitney U test was run for 2-point comparison.

9.3 Results

9.3.1 Demographic data

At study entry, the subgroup of 8 subjects also receiving ritodrine did not differ statistically from the whole group (n=20; Table 9.4). All subjects received the total amount of the planned dose, which was 300µg/min for atosiban and 400µg/min as the highest dose for ritodrine.

Most of the adverse drug events were seen during ritodrine exposure, no adverse events happened during placebo or atosiban infusion (Table 9.5).

Table 9.4.Subjects' characteristics at study entry

Parameters	Characteristics		
	Double-blinded study part (n=20)	Single-blinded study part (n=8)	p-value*
Age (years)	25±7	25±11	0.862
BMI ($kg.m^{-2}$)	21±3	22±4	0.980
Height (m)	1.69±0.07	1.68±0.06	0.901
Smoking n (%)	4 (20)	1 (12.5)	0.784
SBP (mmHg)	101±7	101±9	0.826
DBP (mmHg)	65±5	67±6	0.748
HR (bpm)	58±8	58±9	0.901

Twenty non-pregnant, healthy female volunteers received atosiban and placebo in a double-blinded way whereas eight of them also received ritodrine in a single-blinded way; BMI (Body Mass Index); data of SBP (systolic BP), DBP (diastolic BP) and HR (heart rate) are median of tree measurements, bpm (beats per minute); *p-value is based on non-parametric Mann-Whitney U-test. All data are shown as mean ± standard deviation, except for smoking history.

Table 9.5.Adverse events during drug exposure.

Adverse event	Ritodrine (n=8)	Atosiban (n=20)	Placebo (n=20)
None	2	20	20
Tremor	3	0	0
Palpitations	6	0	0
Flushing	2	0	0

9.3.2 Central and peripheral blood pressure, and augmentation index

Data of blood pressure and augmentation index are shown in Table 9.6.. With ritodrine, central SBP (at the CCA) increased with 13% versus placebo (p = 0.012) and peripheral SBP (at the BA) increased with 12% (p = 0.004). But SBP at the radial artery did not differ statistically from placebo. Compared to placebo, the DBP and MAP in the ritodrine group decreased with 19% (p = 0.008) and 8% (p = 0.044), respectively. With atosiban, central and peripheral pressures did not differ from placebo.

With atosiban and placebo the systolic pressure rises from the central CCA towards the peripheral RA. Although not statistically significant (p = 0.180) from placebo and atosiban, with ritodrine there was a substantial loss of this systolic pressure amplification.

With ritodrine, the non-corrected AIx decreased (497%; p= 0.005) and the AIx corrected for heart rate (AIx@HR75) tended to decrease (289%; p= 0.225), while AIx did not change with atosiban.

Table 9.6.Effects on the central and peripheral blood pressures and augmentation indices

Parameter	Ritodrine (n=8)	Atosiban (n=20)	Placebo (n=20)	p-value[$]
SBP_{CCA} (mmHg)	115±12[*#]	102±8	102±7	0.012
SBP_{BA} (mmHg)	116±12[*#]	105±8	104±6	0.004
SBP_{RA} (mmHg)	117±14	110±10	110±6	0.180
BP amplification	2.47±8.85	8.07±5.73	8.33±4.07	0.180
DBP_{BA} (mmHg)	55±11[*#]	69±6	68±5	0.008
MAP (mmHg)	78±10[*#]	87 ±9	85±5	0.044
HR (bpm)	111±20[*#]	59±10	58 ±10	0.002
AIx	-19.43±6.75[*#]	4.89±5.04	4.89±5.80	0.005
AIx@HR75	-8.67±12.30	5.58±16.78	4.58±13.33	0.225

SBP (systolic BP), BP-amplification (blood pressure difference from CCA to RA in mmHg), DBP (diastolic BP), MAP (mean arterial pressure); HR (heart rate), bpm (beats per minute), AIx (augmentation index, not corrected for heart rate), AIx@HR75 (augmentation index at heart rate 75). [$] Friedman-test on 8 subjects receiving all treatments; [*] p<0.005 vs. atosiban, [#] p<0.005 vs. placebo. All data are shown as mean ± standard deviation.

9.3.3 Cardiac function, resistance vessels and large arteries

Table 9.7. Cardiovascular effects of ritodrine and atosiban in healthy non-pregnant women.

Parameters	Ritodrine (n=8)	Atosiban (n=20)	Placebo (n=20)	p-value[$]
CI ($l.min^{-1}.m^{-2}$)	3.15±0.92[*#]	1.85±0.58	1.76±0.47	0.001
SI ($mL.m^{-2}$)	28±6	31±6	30±7	0.802
HR (bpm)	111±20[*#]	59±10	58 ±10	< 0.001
TPRI ($kPa.l^{-1}.min^{-1}.m^{-2}$)	1.63±0.58[*#]	3.03±1.01	3.12±0.84	< 0.001
CCA diameter (mm)	6.52±0.93	6.25±0.63	6.23±0.66	0.400
DC_{CCA} ($10^{-3}kPa^{-1}$)	76.67±25.40[*#]	53.01±20.46	47.26±13.46	0.006
DC_{CCA_ISO} ($10^{-3}kPa^{-1}$)	72.49±25.17[*#]	52.39±20.55	44.98±12.40	0.007
CC_{CCA} ($mm^2.kPa^{-1}$)	2.55±0.90[*#]	1.58±0.49	1.39±0.35	0.003
CC_{CCA_ISO} ($mm^2.kPa^{-1}$)	2.45±0.91[*#]	1.56±0.48	1.34±0.34	0.003
CFA diameter (mm)	7.77±1.13	8.18±1.07	8.27±0.81	0.615
DC_{CFA} ($10^{-3}kPa^{-1}$)	32.47±16.16[*#]	19.40±9.19	20.43±9.30	0.057
DC_{CFA_ISO} ($10^{-3}kPa^{-1}$)	30.69±15.09	19.17±9.22	19.83±9.12	0.112
CC_{CFA} ($mm^2.kPa^{-1}$)	1.45±0.53[*#]	0.94±0.37	1.09±0.56	0.057
CC_{CFA_ISO} ($mm^2.kPa^{-1}$)	1.36±0.50[*#]	0.93±0.37	1.06±0.55	0.075
PWV ($m.s^{-1}$)	6.08±0.84	5.82±0.78	5.96±0.95	0.730

CI (cardiac index), SI (stroke index), HR (heart rate), TPRI (total peripheral resistance index), CCA (common carotid artery), CFA (common femoral artery), DC_{CCA} (distensibility coefficient of the CCA); DC_{CCA_ISO} (isobaric DC of the CCA); CC_{CCA} (compliance coefficient of the CCA); CC_{CCA_ISO} (isobaric CC of the CCA); DC_{CFA}(distensibility coefficient of the CFA); DC_{CFA_ISO} (isobaric DC of the CFA); CC_{CFA} (compliance coefficient of the CFA); CC_{CFA_ISO} (isobaric CC of the CFA), PWV (pulse wave velocity); [$]Kruskal-Wallis test on all subjects, comparing three groups :[*] significant versus atosiban; [#] significant versus placebo. All data are shown as mean ± standard deviation.

CI with ritodrine increased significantly versus placebo (79%). This was due to an increase in heart rate (91%) while stroke index did not change. Administration of atosiban did not change cardiac index, stroke index or heart rate versus placebo, neither did it change blood pressure and total peripheral resistance index. In contrast ritodrine increased systolic blood pressure and heart rate, decreased diastolic blood pressure while mean arterial pressure did not change statistically. Ritodrine also decreased total peripheral resistance with 48% (Table 9.7).

The diameters of the CCA and the CFA were not influenced by either treatment. Ritodrine had significantly increased DC and CC of the CCA (62% and 83%, resp.) and of the more muscular CFA (59% and 33%, resp.). Since changes in blood pressure can passively change arterial wall properties, direct tocolytic drug effects were

assessed at isobaric conditions. Except for DC_{ISO} of the CFA, which tended to increase (55%), all isobaric parameters remained significantly increased with ritodrine (DC_{ISO} and CC_{ISO} of the CCA 61% and 83%, respectively, and CC_{ISO} of the CFA 28%). Atosiban had no significant effects on the arterial wall properties of the CCA and CFA. The PWV was not influenced by ritodrine or atosiban but was positively correlated by MAP during ritodrine-infusion. Re-analysis with the adjusted parameter, did not influence the outcome.

9.4 Discussion

To the best of our knowledge this is the first placebo-controlled, randomised study investigating the effects of ritodrine and atosiban on the central blood pressure, pressure wave reflection and central-to-peripheral pressure amplification.[280-283] The results from this study show that ritodrine has important and significant effects on the cardiovascular system, whereas atosiban shows no significant effects on the parameters which we investigated.

9.4.1 Sphygmomanometer blood pressure

Similar effects have previously been reported. In studies with pregnant women, ritodrine caused a decrease in DBP (a drop of 4 and 7 mmHg from beginning to the end of the treatment[181;184;280]). In studies with other beta-receptor agonists, DBP and MAP were reduced because of peripheral vasodilatation.[284-286] For atosiban, no significant fall in DBP occurred, which is consistent with earlier work.[181;281;287;288]

9.4.2 Tonometry data

In a general population the best estimate of the brachial form factor is 0.4.[289] However this form factor can depend on different factors like age.[290] We also observed that medication can change substantially the form factor at different arterial sites (RA: 33.4 during placebo – 28.0 during ritodrine; CCA: 43.4 during placebo – 28.7 during ritodrine). Therefore in the present study the FF_{BA} of each measurement was estimated using a procedure that expresses the FF_{BA} as a (fixed) ratio of FF_{CCA} and FF_{RA}, circumventing the lack of brachial tonometry recordings.

The SBP_{CCA} during ritodrine was higher and AIx was lower in comparison with those during atosiban and placebo. No other data on the effect of these tocolytic drugs on central SBP or AIx are available in the literature.

AIx has been proposed as an index of early wave reflections at the central arteries. Heart rate is a well-known determinant of AIx. But also after adjustment to a heart rate of 75 beats per minute (bpm) AIx tended to be lower during ritodrine than during atosiban or placebo, suggesting that ritodrine reduces wave reflections. As pulse wave reflections occur at changes in impedance (like at arterial branches), the vasodilation with ritodrine may

account for the decrease in arterial impedance and reduction in wave reflections. Studies[284;286;291] investigating effects of salbutamol (another beta-receptor agonist) on arterial stiffness, revealed similar significant effects on AIx due to endothelial nitric oxide synthase (NOS)-dependent vascular relaxation.

In the present study, systolic pressure measured by applanation tonometry at the CCA was used as a non-invasive surrogate for cSBP.[86] The central blood pressure (cBP) may have a higher predictive value for cardiovascular events compared to traditional sphygmomanometer measurements since it is an important determinant of the left ventricular workload and coronary blood flow.[191] In contrast to peripheral blood pressure, early pulse wave reflections (PWR) can boost the cSBP reflected by a positive AIx. Early PWR is being recognised as an important factor that contributes to the increase in central blood pressure.[292] As AIx was negative with ritodrine, early wave reflections cannot contribute to the increase in cSBP during ritodrine, which is due to the beta-agonistic positive inotropic effect witnessed by the increase in heart rate.

During ritodrine, there was also a rise in SBP at both the levels of the BA and the RA. This is not in accordance with other studies reporting a decrease in sphygmomanometrically taken SBP.[181;184;280] This difference can be explained by the fact that the subjects in those studies were pregnant. Pregnant women in premature labour have an already higher baseline SBP in comparison with the non-pregnant group. It may not be excluded that in those studies with pregnant women, the anxiety for premature birth and the hospital setting artificially boosted SBP at the start of treatment. Finally, an altered effect of ritodrine in pregnant women cannot be fully excluded.[293;294] The effect of atosiban on the SBP, at the levels of the CCA, BA or RA in our study were not significantly different from placebo which is in accordance with other studies.[181;283]

9.4.3 Blood pressure amplification

Mean and diastolic blood pressure hardly change in the large artery tree.[85;86] In contrast, when early wave reflections are absent like in young subjects, a clear amplification of the systolic blood pressure from the heart to the periphery is present. This explains why blood pressure measured at the brachial artery may overestimate the pressure seen by the heart.[295] This pressure amplification is due to a gradual decrease in arterial compliance (C) from central to peripheral arteries[296] and can be influenced by pulse wave reflections.[297] For ritodrine, in contrast with atosiban and placebo, pressure amplification between the CCA and the upper limb is nearly absent (with a difference of only 2 mmHg between the CCA and the RA). This loss of pressure amplification with ritodrine can be explained by an increased arterial compliance, due to $beta_2$ mediated vasodilatation.[298]

9.4.4 Cardiac function and resistance vessels

Like other studies cardiac index increased with ritodrine[206;299] and remained unchanged with atosiban.[300] In the present study the increased cardiac output with ritodrine was predominantly due to a $beta_1$ mediated increase

in heart rate, while stroke index (SI) remained unchanged. The latter is not in accordance with other data where an increased stroke volume was found.[206;299] These studies refer to data in pregnant women which had already a decreased stroke volume due to the pregnant uterus.[301] The effect of ritodrine on stroke volume and stroke index was the net result of different effects: 1) The direct beta-receptor mediated increased cardiac contractility 2) and the decrease in afterload by the decrease in TPRI would increase SI, while 3) venous dilatation[299] had the opposite effect on SI by a decrease in cardiac filling and cardiac contractility. The decrease in TPRI (almost 50%) with ritodrine is in line with other data[206;299] and is due to $beta_2$ mediated vasodilation with ritodrine. The "flushing" in some subjects with ritodrine was reflecting this vasodilatation.

9.4.5 Large artery properties

Ritodrine had effects on both the arterial wall properties of the CCA as the CFA. These effects were also present under isobaric conditions, indicating a direct (acute) effect of ritodrine on the arterial walls of the CCA and CFA. This effect is at least in part due to smooth muscle relaxation in the arterial wall and is in line with the in vitro observation on the umbilical artery by Dennedy et al..[302] The large effect on the less muscular CCA is somewhat surprising and is correlated with the strong vasodilation, although an ancillary acute mechanism cannot fully be excluded. In contrast, stiffness of the more elastic aorta, measured by pulse wave velocity, did not change with ritodrine. However, a small direct effect hidden by the indirect effects of changes in blood pressure and heart rate could not be expelled.[303] We tested this hypothesis by correlating PWV with its two main confounders MAP and HR. Only the MAP was positively correlated with PWV but did not change the outcome after correction for it (from 6.08 m/sec to 6.07 m/sec).

9.4.6 Study limitations and clinical implications

The present study was carried out in non-pregnant women. It is not clear whether the present results in non-pregnant women can be fully extrapolated to pregnant women. Physiologic changes during pregnancy like an increase in cardiac output, a decrease in peripheral resistance[301;304] and modulation of oxytocin receptors during pregnancy[305;306] may alter the magnitude of the pharmacodynamic effects. On the other hand, pain and stress during premature labour may also confound the effects of tocolytic drugs. To elucidate these issues, this study would ideally be performed in late pregnant women without signs of premature labour. But this may be difficult because of ethical issues.

Some data-analyses were hampered by the small study population on ritodrine. However, the observed cardiovascular effects observed with ritodrine were large so that the main outcomes are not likely to be influenced by this small sample size.

Ritodrine has important but contradictory effects on the cardiovascular system like the heart rate and CI which are almost doubled in comparison with placebo. Also very divergent effects of ritodrine have been published like the effects on SBP starting from systolic hypotension and ending with an increased SBP like in the present study.[206;284;286]

The fall in DBP, MAP and AIx and the higher arterial elasticity and buffering capacity with the lower peripheral resistance due to the relaxation of the vascular smooth muscle cells, may appear an advantage in cases where the peripheral resistance is raised, like in gestational hypertension or pre-eclampsia. These effects are largely due to a $beta_2$-adrenergic mediated increase in endothelial nitric oxide release[307], which may alleviate the peripheral vasoconstriction due to endothelial dysfunction in cases of gestational hypertension or other vascular complications during pregnancy. However, a potential beneficial effect of ritrodrine may not be overestimated as this drug is only given for a short period of time and as the improved beta-adrenergic mediated endothelial NO release may not be present in subjects with an impaired NO pathway.[307] The latter might be the case in pregnancy since stimulated nitric oxide release was reduced in normal pregnancy and preeclampsia, while vascular smooth muscle sensitivity to nitric oxide was not altered.[308] Moreover, in hypertensive pregnancies, the circulating components of the RAAS (Renin-Angiotensin-Aldosterone system) are decreased and since beta-agonists increase the outflow of the RAAS[206;294;309], this could aggravate endothelial dysfunction and due to lowering the diastolic blood pressure, ritodrine may compromise the flow towards the placenta,[310;311] enhance the renal sodium absorption resulting in vascular overfilling with increased risk of pulmonary oedema and acute heart failure.[206;312] So, the potential beneficial vascular effects of ritodrine appear to be counterbalanced by its cardiac effects, which impels caution for the use of ritodrine in cardiovascular complicated pregnancies. In the UK, the Royal College of Obstetricians and Gynaecologists' guidelines on beta-mimetics recommend close monitoring of maternal pulse and blood pressure every 15 minutes during the infusion in every patient receiving a β-agonist as tocolyticum.[184]

Atosiban, on the other hand, was shown to have no significant cardiovascular effects which is in agreement with previous findings. Our data add substantial information by using more complex cardiovascular measurements. However, the high cost of atosiban and the similar tocolytic effectiveness compared to ritodrine [313;314], makes it not a cost-effective alternative for widespread use.

In conclusion, the present study shows potentially beneficial vascular effects of ritodrine. These effects appear to be counterbalanced by the cardiac effects. There are no clinically relevant effects of atosiban on the cardiovascular system. Since the tocolytic effectiveness is the same, atosiban may be a good alternative for ritodrine in pregnant women with cardiovascular complications.

Part IV: General discussion - Clinical Perspectives - Strengths and Limitations – Summary/Samenvatting

Chapter 10 General discussion – Strengths and Limitations – Scientific and Clinical Perspectives.

10.1 General discussion.

During pregnancy, haemodynamic and metabolic adaptations ensure adequate perfusion and nutrient delivery to the foetus. Worldwide, hypertensive disorders complicate 10% of all pregnancies. They cause one in 50 stillbirths, 10% of all preterm births, and one third of severe maternal morbidity.[109;110] In view of these statistics, an early diagnosis and treatment of pregnancy-related hypertensive disorders is of paramount importance. Therefore, identification of risk factors, as described in the first chapter, is necessary: a history of hypertensive disorder during a previous pregnancy and chronic hypertension - which is more prevalent among women of African descent - are the most important ones on top of the "classic" risk factors such as obesity, diabetes mellitus and smoking. Guidelines and goals are all still being debated, e.g. at what level of hypertension one should start with treatment. It is still not known whether lowering moderate chronic hypertension (150-160 mmHg systolic over 95-110 mmHg diastolic blood pressure) confers either maternal or fetal risk or benefit during pregnancy (see Table 10.1).[31]

Since time flies by, in Chapter 1 we originally used an older version for the definition of pre-eclampsia. According to the new ACOG guidelines[31], the diagnosis of preeclampsia no longer requires the detection of high levels of protein in the urine (proteinuria). Evidence shows organ problems with the kidneys and livers can occur without signs of protein, and that the amount of protein in the urine does not predict how severely the disease will progress. Prior to this time, most healthcare providers traditionally adhered to a rigid diagnosis of preeclampsia based on blood pressure and protein in the urine(proteinuria).

Preeclampsia is now to be diagnosed by persistent high blood pressure that develops during pregnancy or during the postpartum period that is associated with a lot of protein in the urine or the new development of decreased blood platelets, trouble with the kidney or liver, fluid in the lungs, or signs of brain trouble such as seizures and/or visual disturbances.

Table 10.1 Adverse outcomes in severe hypertensive disorders of pregnancy.[315]

Adverse outcomes in severe hypertensive disorders of pregnancy.
Abruptio placentae
Disseminated intravascular coagulopathy
Eclampsia
Acute renal failure
Liver haemorrhage or failure
Intracerebral haemorrhage
Hypertensive encephalopathy
Pulmonary oedema
Death
Long-term maternal complications
Atherosclerosis
Cardiovascular disease
End-stage renal disease
Stroke
Retinopathy
Foetal–neonatal complications
Severe intrauterine growth retardation
Oligohydramnios
Preterm delivery
Hypoxia–acidosis
Neurologic injury
Death
Long-term neonatal complications
Cerebral palsy
Foetal programming
Cardiovascular disease
Hypertension

Since it is generally accepted that safety of the mother comes first, premature ending of the pregnancy can be considered. Medical treatment outweighs placebo, whereby alpha-methyldopa (FDA class B medication), labetalol (class C medication) and calcium channel blockers (nifedipine, class C medication) are the first line drugs (see Chapter 1 for summary table (Table 1.3).[315]

In Chapter 3 we summarise the problem statements and aims of the first part of the thesis with a focus on the course of blood pressure during pregnancy, the method of blood pressure measurement and the effects of pregnancy on arterial stiffness (indices) beyond the course of blood pressure.

Risk assessment of a hypertensive disorder is part of good clinical practice.[315] Different blood pressure measurement methods have been proposed e.g. office, home and 24 hour ambulatory blood pressure measurements. There are a number of criticisms of conventional blood pressure measurement in diagnosing and managing the hypertensive pregnant patient.[316] Although for environmental reasons, the mercury column sphygmomanometer is not recommended anymore for estimation of the blood pressure at the office[114], it is still being used in some departments for blood pressure measurement. Both equipment and observer error have been implicated in providing inaccurate blood pressure measurements. Improper cuff size, for example, is a common reason for discrepancies noted with conventional blood pressure assessment. A standard cuff and bladder size should be used on patients with a midbiceps arm circumference < 32 cm, while a large cuff is more appropriate for those patients with an arm circumference ≥ 32 cm.

It has been demonstrated that the most frequent error in measuring blood pressure in the outpatient clinic is"miscuffing," with undercuffing large arms accounting for 84% of the "miscuffings".[317] The "ideal" cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2:1). A recent study comparing intra-arterial and auscultatory blood pressure concluded that the error is minimized with a cuff width of 46% of the arm circumference.[318] The recommended cuff sizes are:

- For arm circumference of 22 to 26 cm, the cuff should be "small adult" size: 12 x 22 cm
- For arm circumference of 27 to 34 cm, the cuff should be "adult" size: 16 x 30 cm
- For arm circumference of 35 to 44 cm, the cuff should be "large adult" size: 16 x 36 cm
- For arm circumference of 45 to 52 cm, the cuff should be "adult thigh" size: 16 x 42 cm

Mismatching of bladder and arm:

- Bladder too narrow or too short (Under-cuffing): Overestimation of BP—'cuff hypertension'

  Range of error: 3.2/2.4 to 12/8 mmHg, as much as 30mmHg in obesity

- Bladder too wide or too long (Over-cuffing): Underestimation of BP

  Range of error: 10 to 30mmHg

Under-cuffing more common than over-cuffing.[319]

Observer error and bias are additional problems that occur with conventional blood pressure assessment. Error may occur as a result of fatigue, poor memory, decreased visual or auditory acuity, and poor interpretation of Korotkoff sounds. In summary, there are three sources of error in the indirect measurement of blood pressure: (1) observer bias, (2) faulty equipment, and (3) failure to standardise the techniques of measurement.[320] Observer

bias often results from the tendency to 'normalise' slightly elevated blood pressure readings[321] as well as the practice of rounding off measurements to the nearest 5 or 10 mmHg.[322] Since the introduction of automated devices, readings are observatory independent and this tendency is banned.[114] In Chapter 4, we focused mainly on the differences between office blood pressure monitoring and self-assessed blood pressure readings in pregnant women. We analysed longitudinal data of 100 women with both self-assessed and office blood pressure readings. All women received a home blood pressure monitor using the same algorithm to avoid bias. The study population was rather small but highly selected. On the other hand, our results were in accordance to previous data of cross-sectional and longitudinal studies in pregnant women but with a lack of standardisation. The main conclusion of this chapter is the risk of misclassification of pregnant women as hypertensive based on office blood pressure readings. The main culprit is limited standardisation like in many, also non-obstetric, outpatient clinics.[321] The difference between the office and the self-assessed blood pressure readings – measured in a standardised way- was at least 5 mmHg in 69% of the systolic blood pressure readings. The risk of misclassification may lead to misinterpretations and erroneous medical decisions with potential harmful influence on the health of the mother and the unborn.

Home blood pressure monitoring, on the other hand, has major advantages above regular blood pressure monitoring at the office: it provides multiple readings in a pre-determined time frame and there is low risk of a white coat effect. More importantly, home blood pressure is closer related to hypertension-induced target organ damage and is a better risk predictor of cardiovascular events than conventional blood pressure measurement at the office.[67] More clinical evidence is needed to guide the management of hypertension during pregnancy. Clinical trials should specifically determine blood pressure thresholds and targets.[31] In Chapter 5 we tried to determine the upper normal thresholds of home blood pressure data in normal pregnancies. In a longitudinal study, consisting of 82 women with healthy pregnancies, we collected home blood pressure data, measured during one week, in each pregnancy trimester. The study population was highly selected with a more than moderate level of education and a great esteem on both physical and mental health. To date only small studies were published reporting self-monitored blood pressure data with random inclusion of women without standardised measurements.[116;120;143] Despite the lack of standardisation, the results were in accordance with our study, obtained in a standardised way but in a relatively small study sample. The proposed upper normal limits per pregnancy trimester were all lower than those proposed by the European Society of Hypertension.[67] We demonstrated that blood pressure monitoring at home is an easy way to follow blood pressures during pregnancy. It may be used when office blood pressure is elevated, when risk for cardiovascular complications during pregnancy is increased and might contribute in the prevention of cardiovascular complications in mother and neonate.

Chapter 6 focuses on the influence of pregnancy on the maternal cardiovascular physiology. The aim of this study was to investigate the changes in arterial stiffness and wave reflections in normal pregnancy to test their utility in pathophysiological conditions. Most of the numerous previous studies dealing with this subject dealt with cross-sectional data,[127;131;135] with a limited number of measurements, or did not include a control group.[128-130;132;133;138;139] Our study design included 94 pregnant and 26 non-pregnant women which had their measurements at similar time intervals and during the same time frame to overcome seasonal influences. The results were consistent with previous studies on peripheral and central haemodynamics: it confirmed diastolic blood pressure and wave reflections decline by the second trimester of pregnancy. In addition, a pressure-independent reduction in aortic (carotid-femoral), but not carotid artery stiffness, was observed, mainly in the age group beyond 30 years. This may suggest the different effects of hormonal changes on the elastic carotid and the more muscular (distal) aorta and pelvic arteries but also age-dependency. Further investigations are necessary in order to confirm our findings.

Arterial stiffness and wave reflections are increased in pathophysiological conditions such as preeclampsia,[134] even in the preclinical stage,[140] and can discriminate between normal and hypertensive pregnancies.[323] It could be interesting to screen pregnant women from this early stage on. Over the last few years, data have been accumulating about the increased risk of later-life cardiovascular disease in women with a history of pre-eclamptic pregnancy. This increase ranges from a doubling of risk in all cases to an eight- to nine-fold increase in women with preeclampsia who gave birth before 34±1 weeks.[31] This has been recognised by the American Heart Association, which now recommends including a pregnancy history in the evaluation of cardiovascular risk in women.[324;325] Preeclampsia does not cause cardiovascular disease, but both entities rather share common risk factors.[31] In the last 10 years, a better understanding of the pathophysiology of preeclampsia has been established. It is now considered rather a multi-systemic disease affecting all organ systems, beyond high blood pressure and renal dysfunction. The placenta is probably the root cause of preeclampsia. Placental dysfunction leads to maternal disease through putative primary mediators, including oxidative and endoplasmic reticulum stress and inflammation, and secondary mediators that include modifiers of endothelial function and angiogenesis. Endothelial dysfunction tends to precede the development of the clinical syndrome,[140;326] and therefore has the potential to be used as an early predictor of this condition. However, measurement of endothelial function is difficult, time consuming and not very reproducible. This study clearly shows that arterial stiffness can also be used as an early screening method.

The third part of this thesis start in Chapter 7 with the problem statement and aims and deals with tocolytic therapy and its potential effects on the female haemodynamic system and the cardiovascular function. Tocolytic therapy is an important intervention in obstetrics to delay preterm delivery. Although tocolytics have not been shown to improve neonatal outcomes, they can delay preterm delivery long enough to allow for administration

of antenatal corticosteroids or for maternal transport to a tertiary care facility.[327] In premature neonates, antenatal corticosteroids reduce morbidity and mortality.[328] Tocolytic therapy may therefore have an important role in improving outcomes from preterm delivery. In Chapter 8, a review of the literature shows the ambiguity in choosing the first-line tocolytic treatment. To date, many different drugs are being used as tocolytic therapy, but a standard first-line drug has not emerged;[262] options are plentiful and should be individualised. In a recent meta-analysis, prostaglandin inhibitors and calcium channel blockers had the highest probability of delaying delivery and improving neonatal outcomes.[262]

The aim of our study was to determine the effects of two controversial tocolytic drugs on the haemodynamics and the cardiovascular function of non-pregnant, female volunteers. The design of our study was a placebo-controlled, double-blind, randomised, crossover trial in 20 volunteers. Ritodrine, the gold standard since many years, is a $beta_2$-adrenoceptor agonist, highly effective in postponing delivery but with known maternal and foetal cardiovascular side effects. Atosiban is an oxytocin-receptor blocker, highly selective with no known maternal cardiovascular side effects but with suspected foetal side effects. Therefore, atosiban is not yet approved by the FDA. Although atosiban is a more expensive option, it is widely used in Europe. A majority of the pharmaco-kinetic and -dynamic studies was sponsored by the manufacturer of atosiban. None was placebo-controlled. The strengths of the study presented in Chapter 9 is the independent setting, with one investigator performing all measurements, including sphygmomanometry, applanation tonometry, wall track measurements and echocardiography. Ritodrine had major effects on the blood pressure and the blood pressure amplification due to direct and indirect $beta_2$-mediated effects. The effect of atosiban on these parameters was not different from placebo. We also focused on the effects of both tocolytics on cardiac function and the macro- and micro-circulation. We demonstrated the many divergent effects of ritodrine on the cardiovascular system, with a more than doubled heart rate in our study population in comparison with placebo or atosiban. The total peripheral resistance decreased with more than 50%. Those effects are important in a pregnancy setting, where the cardiovascular system is already being challenged. Our study was able to demonstrate the lack of haemodynamic effects of atosiban, whereas ritodrine has both direct and indirect effects on the whole cardiovascular system. The potentially beneficial vascular effects of ritodrine appear to be counterbalanced by its cardiac effects, which calls for caution for the use of ritodrine in cardiovascularly complicated pregnancies. Whether atosiban will become the new gold standard is still unclear. The use of atosiban should be evaluated individually.

10.2 Strengths and limitations

This thesis contributed to elucidate haemodynamic changes during pregnancy. We studied the effects in a longitudinal prospective design with non-pregnant subjects as control. The measurements were done by one, trained investigator in a fixed time period. This avoids inter-observer variability and is expected to increase

consistency of the results. The observed differences between time points were less influenced by seasonal or environmental effects.[143] On the other hand, our study population consisted of a dense and selective group with highly educated women with a great concern about their health. They were healthy, sportive and had a desired pregnancy when in the pregnant study-group. It could influence the study results, mainly those of the self-assessed blood pressure readings but our data were in line with other results. Those literature data were mainly extracted from cross-sectional studies[127;131;135] or longitudinal designs without control measurements. [128-130;132;133;138;139] The main limitations were the relatively small study sample with inclusion of both nulliparous and multiparous women, the lack of pre-pregnancy baseline values and the short recruitment period. If this study could be re-performed, the pre-pregnancy values must be included and the recruitment period should be as long as at least 350 women are included. With that number, one can also investigate the effects of the feeding-method (breast-versus bottle-feeding) on the haemodynamic system of the mother.

In the second part of this thesis, we worked with non-pregnant women of childbearing age to determine the cardiovascular effects of tocolytic medications. Due to the small study group of 20 women with 8 of them getting ritodrine, the statistical analysis was difficult. If possible, this study should be re-performed in a 20-20-20 design. On the other hand, the effects of ritodrine were that significant, it should not make any difference on the outcome of the study. However, it remains unclear whether the results could be extrapolated to a pregnant population. The goal, however, was to describe the direct and indirect effects of ritodine and atosiban on the female cardiovascular function without the challenge of pregnancy. It cannot be excluded that pharmacodynamic effects may be different in a pregnant body, as changes may occur not only on the cardiovascular[141] but also on the hepatic[329] and renal level.[330] Ideally, this study needs to be repeated in a late pregnant population without signs of premature labour but this achievement will remain impossible, due to ethical issues.

10.3 Clinical and scientific perspectives

This scientific work revealed several clinical perspectives. It is predicted that there will be an increasing rise in the incidence of hypertensive disorders in pregnancy, mainly due to increasing rates of obesity, diabetes mellitus as well as the advancing age of pregnant women.[31] In addition, haemodynamic adaptations to pregnancy and their underlying mechanisms require further investigation. There is an urgent need to repeat haemodynamic investigations in larger, longitudinal, epidemiological study designs to relate them to hormonal, biochemical and genetic changes. Educated and trained investigators, who use standardised methods for data collection, are an absolute necessity. The ultimate goal is to develop a clinical tool which can predict the risk of developing cardiovascular complications during pregnancy. Ideally, it can be used from the late luteal phase on, when there is a wish of conception, or in early pregnancy. The tool has to be easy, non-invasive, not time-consuming and with a high grade of implementation in the clinical setting. As mentioned in Chapter 6, arterial stiffness can be

measured from the early pregnancy on. Since cf-PWV has already been implemented in the follow-up of cardiovascular compromised persons at tertiary care centres, why not use it in a pregnant population? It is easy, non-invasive, relatively not time consuming and with a relatively good implementation in the clinical setting. It is already mentioned[97] as the golden standard for the assessment of arterial stiffness in the general population. However, to translate the cut-off level of 10m/s from the general population to the pregnant population needs further investigation. And what to do with the follow-up? When should you link an increase of the cf-PWV to a closer monitoring?

Another important issue is the difficulty to implement standardisation of blood pressure measurements in clinical practice. In Chapter 4, we expressed our concerns about the different results on blood pressure readings when done at the office versus at home. White coat hypertension (WCH) is a challenging diagnosis as it may lead to misclassification and possibly harmful treatment. For example, an increasing rate of caesarean sections has been reported in a population with WCH.[331;332] Maybe it is better to manage pregnant women as a niche population with their own reference values with upper limits above which closer follow up might be warranted. Using percentiles might even in an earlier stage provide signs for closer follow up. This has to be further investigated in a large, epidemiological data-set preferably including maternal and foetal outcome data. To date, there are several trials on blood pressures during pregnancy but all with divergent standards, research goals and designs. To build such a data set, the recruitment needs to be very strict and measurements well standardised, including the type of blood pressure monitoring (office readings versus self-assessed versus 24h blood pressure monitoring).

Ideally, every woman should be screened 'holistic' when she is planning to get pregnant. Since hypertension is the most common medical disorder of pregnancy and occurs in 10% to 12% of all pregnancies. The detection of elevated blood pressure during pregnancy is one of the major aspects of optimal prenatal care; thus, accurate measurement of blood pressure is essential.[333] Therefore, the blood pressure should be measured at every appointment under standardised conditions. When blood pressure values are more than 140 mmHg for systole and/or 90 mmHg for diastole, the measurement should be repeated, and if needed, in a relaxed space in semi-recumbent or the left lateral position. If the blood pressure remains high, the pregnant woman should collect home blood pressures during one week in standardised conditions:[67]

Conditions of measurement:

- At least 5-min rest, 30 min without smoking, meal, caffeine intake or physical exercise.
- Seated position in a quiet room, back supported, arm supported (for example, resting on the table).
- Subject immobile, legs uncrossed, not talking and relaxed.
- Correct cuff bladder placement at heart level.
- Results immediately reported in a specific logbook or stored in device memory.

Monitoring schedule:

- Seven-day home measurements (minimum 3 days).
- At initial assessment, when assessing treatment effects, and in the long-term follow-up before each clinic/office visit.
- Morning (before drug intake if treated) and evening (before eating) readings per day.
- Two measurements per occasion (1–2 min apart).
- Long-term follow-up: less frequent measurements (for example, once or twice per week) could be regularly performed aimed at reinforcing compliance, although isolated readings should never be used for diagnostic purposes.
- Overuse of the method and self-modification of treatment should be avoided.

Interpretation of the results:

- Average BP from several monitoring days should be considered.
- BP values measured on the first monitoring day should be discarded.
- Mean home systolic BP ≥ 135mmHg and/or diastolic BP ≥ 85mmHg should be considered as elevated.
- Systolic and diastolic home BP < 135 and < 85mmHg, respectively, should be considered normal in most subjects.

If the blood pressures at home are more than 135mmHg for the systole and 85 mmHg for diastole, closer follow-up has to start with regular Doppler ultrasound of the uterine arteries[334] and cf-PWV-measurements but with the consideration there are still no normal values for the pregnant population.[335]

To define what a high blood pressure is during pregnancy, Chapter 5 is more a wake-up call. There is an urgent need to define also normal values for OBP and HBP during pregnancy. To define at what level an intervention is needed to 'normalise' the blood pressure, one should collect different data on top of the blood pressure, like e.g. cf-PWV-data and Doppler ultrasound of the uterine arteries, to create cut-off values for the future. I propose that the triad of blood pressures (OBP with or without HBP), cf-PWV and Doppler ultrasound of the uterine arteries may lead us in the need and titration of a pharmacologic intervention. Since the blood pressure lowering effect may have diverse clinical effects on both the maternal and foetal haemodynamical system.

Finally, we could demonstrate that atosiban has, in comparison with placebo, no detectable or clinical effects on the cardiovascular system of women. Based on our data, atosiban may be safely used in pregnant women. However, to date, atosiban is a second-line agent due to major criticisms based on the facts 1) there are still concerns for the use before 28 weeks of gestation because of possible foetal harm (therefore no FDA-approval[60]), 2) it can only be used intravenously – in hospital setting - and 3) it has a strong negative cost-effectiveness balance: the cost of an atosiban-protocol is three times more than this of the ritodrine-protocol.[249] On the other hand, beta-mimetics help to delay birth but multiple adverse effects must be considered as shown in Chapter 9. A recent Cochrane review[336] concludes there are too few data (small trials and of insufficient quality) to support the use of any beta-mimetic for tocolysis. But when costs are that important, like e.g. in developing countries, the use of ritodine may be considered but only with close monitoring of the patient, in particular the cardiovascular system.

To date, like already mentioned in Chapter 8, the proposed first-line drugs for tocolysis are gestational age-dependent. When women are in their 24th to 32th gestational week and present with premature labour, one should start with a calcium channel blocker (nifedipine). There is, however, an increased risk of serious maternal side effects when nifedipine is administered simultaneously with magnesium sulphate (respiratory depression due to suppression of muscular contractility[230] and cardiac arrest due to negative inotropic effects[231]). In those cases, indomethacin (prostaglandin-inhibitor) may be used concomitantly with magnesium sulphate for foetal neuroprotection. There is plenty of criticism[260;261] for the use of indomethacin as tocolyticum due to the negative balance for the cost-effectiveness with short-and long term effects on the maternal and neonatal morbidity. In Belgium, indomethacin is not recommended and used anymore as tocolyticum. From 32 weeks of gestation till the maximum age (34 weeks), nifedipine is the first choice drug for tocolysis. From that stage on, magnesium-sulphate for neuroprotection is not recommended anymore. In cases of intolerance or contraindications for nifedipine, beta-mimetics and atosiban are suggested as second-line agent.

Chapter 11 Summary – Samenvatting

11.1 Summary

Profound cardiovascular adaptations occur during pregnancy to ensure adequate perfusion and nutrient delivery for the foetus. Hypertensive disorders complicate 10% of all pregnancies (Chapter 1). Identification of risk factors is necessary. Risk assessment for hypertensive disorders is part of good clinical practice.

The first part ends with Chapter 2 with a description of the used methods in this thesis and their theoretical background.

In Chapter 3 the problem statements and aims of the second part of the thesis are discussed with the focus on the course, the monitoring of blood pressures and the vascular physiology during pregnancy.

In Chapter 4 we compared home blood pressure data with office readings, taken at each pregnancy trimester. We analysed longitudinal data of 74 women who had self-assessed and office blood pressure readings. The main finding is the big difference between the two blood pressure reading methods, mainly in the second pregnancy trimester. The main culprit of the difference is a lack of standardisation in the outpatients clinic with higher blood pressure readings. The result is a tendency to misclassify the pregnant woman as hypertensive with medical decision-making based on these clinical data.

In Chapter 5 we collected in a longitudinal design home blood pressure data of 82 women from each pregnancy trimester in an attempt to determine upper normal thresholds for the blood pressure during normal pregnancy. The thresholds were 5 to 15 mmHg lower than those proposed by current guidelines intended for the normal, non-pregnant population.

Chapter 6 focusses on the vascular physiology during normal pregnancy using non-invasive methods assessing the changes in arterial stiffness and wave reflections throughout pregnancy. Characterising the arterial stiffness variables during normal pregnancy may be clinically important to understand the pathophysiological findings in hypertensive pregnancies. The main strength of this study is the longitudinal design following healthy women throughout their pregnancy with in the same time window also non-pregnant women as the matched control group. The study showed that arterial stiffness increased more from week 20 to 35 of gestation in pregnant women over the age of 30 years. Whether this finding may contribute to the higher pregnancy risk of older women has to be further investigated. In addition, the course of arterial stiffness did not differ between nulli- and multiparae, suggesting that arterial stiffness is not involved in the higher risk for complications of nulliparous pregnant women.

Chapter 7 includes the problem statements and aims of the third part of the thesis with the focus on tocolytic therapy. Preterm labour is the most frequently reported cause of perinatal morbidity and mortality in the Western

world . Tocolysis is the therapy to abolish preterm labour in an attempt to postpone delivery. It mostly concerns a pharmacologic intervention.

Chapter 8 consists of a review with a summary of the most frequently used tocolytic therapies worldwide with recommendations for the clinical use. Ritodrine is a beta$_2$-adrenoceptor agonist, highly effective in postponing delivery but with known maternal and foetal cardiovascular side effects. Atosiban is an oxytocin-receptor blocker, highly selective, with the same tocolytical effectiveness as ritodrine but without known maternal cardiovascular side effects. There are, however, suspected foetal side effects due to one report showing a trend towards higher rate of foetal death in mothers on atosiban. Another concern is the blockage of foetal vasopressin receptors, which could lead to changes in renal development, amniotic fluid volume and consequently lung development. Both medications are criticised due to their side-effect profile with still no FDA-approval for atosiban because of concerns for the foetus with a gestational age below 28 weeks of gestation. In addition, the cost-effectiveness obtained with the protocol including ritodrine as first-choice drug is three times less than when atosiban is used. There is a lack of independent (not sponsored), comparative studies with only subjective reporting of side effects in non-pregnant, healthy female volunteers.

We developed a randomised, double blinded, placebo controlled trial to compare the haemodynamic effects of both tocolytics.

In Chapter 9, we reveal the arterial stiffness parameters, the large artery properties, the microvasculature and the cardiac function when dosing ritodrine and atosiban. The main findings are that atosiban has no detectable or clinical effects on the cardiovascular system whereas ritodrine has both direct and indirect effects on it. Despite the favourable preservation of the cardiovascular function by atosiban, it still is not considered as first line tocolytic drug since there are indications of possible harm for the foetus, and it is very expensive.

11.2 Samenvatting

Tijdens de zwangerschap ontstaan er belangrijke cardiovasculaire aanpassingen die de doorbloeding van de placenta garanderen. De zwangerschap wordt in 10% van de gevallen gecompliceerd door hypertensie (Hoofdstuk 1). Identificatie van de risicofactoren is daarom erg belangrijk en de inschatting van het risicoprofiel is onderdeel van ‘good clinical practice’.

Het eerste deel van de thesis eindigt in Hoofdstuk 2 met een beschrijving van de gebruikte meetmethoden in deze thesis en hun theoretische achtergrond.

Hoofdstuk 3 omvat de probleem-en doelstellingen van het tweede deel van de thesis waarbij de focus ligt op de evolutie en de monitoring van de bloeddrukken en de vasculaire fysiologie tijdens de zwangerschap.

In Hoofdstuk 4 vergelijken we thuisbloeddrukmetingen met poliklinische bloeddrukmetingen in een groep van 74 zwangeren. We vonden een verschil met voornamelijk in het tweede zwangerschapstrimester een hoger gemeten bloeddruk in de polikliniek in vergelijking met de thuisbloeddrukwaarde. Een gebrek aan standaardisatie in de polikliniek ligt voor een belangrijk deel aan de basis van deze bevinding. Een zwangere kan dan al vlug worden bestempeld als hypertensief met repercussie op de medische opvolging.

In Hoofdstuk 5 gaan we verder in op het onderwerp en collecteerden we thuisbloeddrukmetingen bij 82 zwangere vrouwen gedurende één week op een vooraf bepaald tijdstip per zwangerschapstrimester. Het longitudinaal opgesteld design en de gestandaardiseerde metingen (cfr ESH-richtlijnen) zijn een meerwaarde van deze studie. Er werd een poging gewaagd om een referentiekader te ontwerpen voor de bloeddrukken tijdens de zwangerschap omdat er nog steeds gewerkt wordt met normaalwaarden/ 'upper normal limits' vanuit de algehele populatie met transitie naar een niche-groep als de zwangeren. De 'upper normal limits' liggen, afhankelijk van het zwangerschapstrimester, 5 tot 15 mmHg lager dan die van de algehele populatie (cfr ESH-guidelines).

In Hoofdstuk 6 bestuderen we de vasculaire fysiologie tijdens de normale zwangerschap met niet-invasieve meetmethoden om de veranderingen in arteriële stijfheid en polsgolfreflecties in beeld te brengen. Het beschrijven van de arteriële stijfheidsparameters tijdens de normale zwangerschap kan belangrijke klinische informatie opleveren om de pathofysiologische bevindingen van hypertensieve zwangerschappen te begrijpen. Het sterkste punt van deze studie is het longitudinale design waarbij vrouwen werden gevolgd tijdens hun zwangerschap. In hetzelfde tijdskader werd er ook een gematchte, niet-zwangere controlegroep opgevolgd. De studie toonde aan dat arteriële stijfheid meer toeneemt van de 20^{ste} naar de 35^{ste} zwangerschapsweek bij zwangeren boven de leeftijd van 30 jaar. Verder onderzoek is nodig waar deze bevinding past binnen het hoger zwangerschapsrisicoprofiel van oudere vrouwen. We konden eveneens aantonen dat de evolutie van de arteriële stijfheid tijdens de zwangerschap niet verschilt tussen nulli-en multiparae wat suggereert dat arteriële stijfheid geen rol speelt in het verhoogde risico op complicaties tijdens een eerste zwangerschap.

Hoofdstuk 7 houdt de probleem-en doelstellingen in van het derde deel van de thesis met de focus op tocolyse. In de Westerse wereld is vroegtijdig bevallen de meest gerapporteerde oorzaak van perinatale morbiditeit en mortaliteit. Tocolyse is de klinische interventie die idiopathische, vroegtijdige contracties tijdens de zwangerschap probeert onder controle te krijgen om zo een dreigende vroeggeboorte te vermijden. Het betreft meestal een farmacologisch ingrijpen.

In Hoofdstuk 8 wordt een overzicht gegeven van de meest courant gebruikte tocolytica. Aanbevelingen voor het gebruik in de kliniek worden op het einde van dit hoofdstuk gedaan. Eén van de meest beschreven middelen is ritodrine, een $beta_2$-adrenoceptor agonist, met een hoge effectiviteit om de vroeggeboorte uit te stellen maar met een welomschreven bijwerkingenprofiel ter hoogte van het hart-en bloedvatensysteem. Een ander, meer

bekritiseerd farmacon, is atosiban. Dit is een oxytocine-receptor antagonist met een evenwaardige tocolytische effectiviteit als ritodrine. In de literatuur worden weinig bijwerkingen bij de moeder beschreven. Nochtans wordt atosiban niet gebruikt in de VS omdat er nog geen FDA-goedkeuring is wegens bezorgdheid voor de foetus onder de leeftijd van 28 weken zwangerschap. Er zouden, gebaseerd op één rapport, letale bijwerkingen zijn bij de foetus doordat er meer foetale sterfte was bij moeders die onder atosiban stonden. Een andere bezorgdheid betreft de niet-selectieve binding op de foetale vasopressine–ADH-receptoren wat kan leiden tot veranderingen in de renale ontwikkeling en de hoeveelheid vruchtwater met als gevolg een negatief effect op de longontwikkeling. Daarenboven is een tocolyse-protocol, gebaseerd op atosiban, drie keer duurder dan een op ritodrine gebaseerd protocol. Er zijn in de literatuur weinig onafhankelijke, vergelijkende studies met atosiban terug te vinden met telkens een subjectieve rapportering van de bijwerkingen bij de gezonde, niet-zwangere proefpersonen.

We stelden daarom een gerandomiseerde, dubbelblinde, placebo-gecontroleerde studie op om de cardiovasculaire effecten van ritodrine en atosiban te vergelijken.

In Hoofdstuk 9 worden de effecten van de perifere en de centrale bloeddrukken beschreven met tevens het effect op de bloeddruk-amplificatie, de effecten op de grote bloedvaten (macro-vasculatuur), de totale perifere weerstand (micro-vasculatuur), de polsgolfreflecties en de cardiale functie. Atosiban heeft, in vergelijking met placebo, geen detecteerbare of klinische effecten op het hart- en bloedvatensysteem. Ritodrine daarentegen, heeft naast de gekende effecten op de hartslag, tevens significante effecten op de bloeddruk, de bloeddrukamplificatie, de polsgolfreflecties en de totale perifere weerstand. Op basis van deze studieresultaten lijkt atosiban een veilige optie voor de moeder. Desondanks wordt atosiban nog steeds niet beschouwd als een eerste-keuze tocolyticum wegens de mogelijke schade voor de foetus en de zeer hoge kostprijs.

Reference List

Reference List

(1) Duvekot JJ, Peeters LL. Maternal cardiovascular hemodynamic adaptation to pregnancy. *Obstet Gynecol Surv* 1994;49:S1-14.

(2) Voss A, Malberg H, Schumann A et al. Baroreflex sensitivity, heart rate, and blood pressure variability in normal pregnancy. *Am J Hypertens* 2000;13:1218-1225.

(3) Finn WL, Tunny TJ, Klemm SA, Jones IS, De VK, Gordon RD. Sodium and volume dysregulation after apparently normal pregnancy is suggested by abnormal levels of atrial natriuretic peptide, renin and aldosterone. *Clin Exp Pharmacol Physiol* 1991;18:269-273.

(4) Thornburg KL, Jacobson SL, Giraud GD, Morton MJ. Hemodynamic changes in pregnancy. *Semin Perinatol* 2000;24:11-14.

(5) Schrier RW, Briner VA. Peripheral arterial vasodilation hypothesis of sodium and water retention in pregnancy : implications for pathogenesis of preeclampsia-eclampsia. *Obstet Gynecol* 1991;77:632-639.

(6) Duvekot JJ, Cheriex EC, Pieters FA, Menheere PP, Peeters LH. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. *Am J Obstet Gynecol* 1993;169:1382-1392.

(7) Weiner CP, Thompson LP. Nitric oxide and pregnancy. *Semin Perinatol* 1997;21:367-380.

(8) Baylis C. Glomerular filtration and volume regulation in gravid animal models. *Baillieres Clin Obstet Gynaecol* 1994;8:235-264.

(9) Khraibi AA. Renal interstitial hydrostatic pressure and sodium excretion in hypertension and pregnancy. *J Hypertens Suppl* 2002;20:S21-S27.

(10) Khraibi AA, Yu T, Tang D. Role of nitric oxide in the natriuretic and diuretic responses in pregnant rats. *Am J Physiol Renal Physiol* 2003;285:F938-F944.

(11) Carbillon L, Uzan M, Uzan S. Pregnancy, vascular tone, and maternal hemodynamics : a crucial adaptation. *Obstet Gynecol Surv* 2000;55:574-581.

(12) Chapman AB, Abraham WT, Zamudio S et al. Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. *Kidney Int* 1998;54:2056-2063.

(13) Clapp JF, III, Capeless E. Cardiovascular function before, during, and after the first and subsequent pregnancies. *Am J Cardiol* 1997;80:1469-1473.

(14) Blake MJ, Martin A, Manktelow BN et al. Changes in baroreceptor sensitivity for heart rate during normotensive pregnancy and the puerperium. *Clin Sci (Lond)* 2000;98:259-268.

(15) Jensen E, Wood C, Keller-Wood M. The normal increase in adrenal secretion during pregnancy contributes to maternal volume expansion and fetal homeostasis. *J Soc Gynecol Investig* 2002;9:362-371.

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

(17) van der Post JA, van Buul BJ, Hart AA et al. Vasopressin and oxytocin levels during normal pregnancy : effects of chronic dietary sodium restriction. *J Endocrinol* 1997;152:345-354.

(18) Eguchi K, Oguni N, Sawai T, Yonezawa M. Comparison of plasma concentrations of arginine vasopressin (AVP) and atrial natriuretic peptide (ANP) in normal and preeclamptic pregnancies. *J Perinat Med* 1996;24:437-443.

(19) Ganzevoort W, Rep A, Bonsel GJ, de Vries JI, Wolf H. Plasma volume and blood pressure regulation in hypertensive pregnancy. *J Hypertens* 2004;22:1235-1242.

(20) Garovic VD, Hayman SR. Hypertension in pregnancy : an emerging risk factor for cardiovascular disease. *Nat Clin Pract Nephrol* 2007;3:613-622.

(21) Yoder SR, Thornburg LL, Bisognano JD. Hypertension in pregnancy and women of childbearing age. *Am J Med* 2009;122:890-895.

(22) Podymow T, August P. Update on the use of antihypertensive drugs in pregnancy. *Hypertension* 2008;51:960-969.

(23) Chobanian AV, Bakris GL, Black HR et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure : the JNC 7 report. *J Am Med Ass* 2003;289:2560-2572.

(24) Mancia G, De BG, Dominiczak A et al. 2007 ESH-ESC practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. *J Hypertens* 2007;25:1751-1762.

(25) Artal R, Lockwood CJ, Brown HL. Weight gain recommendations in pregnancy and the obesity epidemic. *Obstet Gynecol* 2010;115:152-155.

(26) Sibai BM, Gordon T, Thom E et al. Risk factors for preeclampsia in healthy nulliparous women : a prospective multicenter study. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *Am J Obstet Gynecol* 1995;172:642-648.

(27) Engel SM, Janevic TM, Stein CR, Savitz DA. Maternal smoking, preeclampsia, and infant health outcomes in New York City, 1995-2003. *Am J Epidemiol* 2009;169:33-40.

(28) Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 2000;183:S1-S22.

(29) Sibai BM. Caring for women with hypertension in pregnancy. *J Am Med Ass* 2007;298:1566-1568.

(30) Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death : a systematic review. *Lancet* 2006;367:1066-1074.

(31) Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol* 2013;122:1122-1131.

(32) Arnadottir GA, Geirsson RT, Arngrimsson R, Jonsdottir LS, Olafsson O. Cardiovascular death in women who had hypertension in pregnancy : a case-control study. *BJOG* 2005;112:286-292.

(33) Jonsdottir LS, Arngrimsson R, Geirsson RT, Sigvaldason H, Sigfusson N. Death rates from ischemic heart disease in women with a history of hypertension in pregnancy. *Acta Obstet Gynecol Scand* 1995;74:772-776.

(34) McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia : a systematic review and meta-analyses. *Am Heart J* 2008;156:918-930.

(35) Leeman M. Arterial hypertension in pregnancy. *Rev Med Brux* 2008;29:340-345.

(36) Buemi M, Bolignano D, Barilla A et al. Preeclampsia and cardiovascular risk : general characteristics, counseling and follow-up. *J Nephrol* 2008;21:663-672.

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

(38) Smith GN, Walker MC, Liu A et al. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. *Am J Obstet Gynecol* 2009;200:58.

(39) Poranen AK, Ekblad U, Uotila P, Ahotupa M. Lipid peroxidation and antioxidants in normal and pre-eclamptic pregnancies. *Placenta* 1996;17:401-405.

(40) Many A, Hubel CA, Fisher SJ, Roberts JM, Zhou Y. Invasive cytotrophoblasts manifest evidence of oxidative stress in preeclampsia. *Am J Pathol* 2000;156:321-331.

(41) Freeman DJ, McManus F, Brown EA et al. Short- and long-term changes in plasma inflammatory markers associated with preeclampsia. *Hypertension* 2004;44:708-714.

(42) Austgulen R, Lien E, Vince G, Redman CW. Increased maternal plasma levels of soluble adhesion molecules (ICAM-1, VCAM-1, E-selectin) in preeclampsia. *Eur J Obstet Gynecol Reprod Biol* 1997;71:53-58.

(43) Greer IA, Dawes J, Johnston TA, Calder AA. Neutrophil activation is confined to the maternal circulation in pregnancy-induced hypertension. *Obstet Gynecol* 1991;78:28-32.

(44) Weinstein L. Syndrome of hemolysis, elevated liver enzymes, and low platelet count: a severe consequence of hypertension in pregnancy. *Am J Obstet Gynecol* 1982;142:159-167.

(45) Egerman RS, Sibai BM. HELLP syndrome. *Clin Obstet Gynecol* 1999;42:381-389.

(46) Joshi D, James A, Quaglia A, Westbrook RH, Heneghan MA. Liver disease in pregnancy. *Lancet* 2010;375:594-605.

(47) Goel A, Jamwal KD, Ramachandran A, Balasubramanian KA, Eapen CE. Pregnancy-related liver disorders. *J Clin Exp Hepatol* 2014;4:151-162.

(48) Sibai BM. Imitators of severe pre-eclampsia. *Semin Perinatol* 2009;33:196-205.

(49) McMinn JR, George JN. Evaluation of women with clinically suspected thrombotic thrombocytopenic purpura-hemolytic uremic syndrome during pregnancy. *J Clin Apher* 2001;16:202-209.

(50) Vesely SK, Li X, McMinn JR, Terrell DR, George JN. Pregnancy outcomes after recovery from thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Transfusion* 2004;44:1149-1158.

(51) Clark WF, Rock GA, Buskard N et al. Therapeutic plasma exchange: an update from the Canadian Apheresis Group. *Ann Intern Med* 1999;131:453-462.

(52) D'Angelo A, Fattorini A, Crippa L. Thrombotic microangiopathy in pregnancy. *Thromb Res* 2009;123 Suppl 2:S56-S62.

(53) Scully M, Hunt BJ, Benjamin S et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol* 2012;158:323-335.

(54) Tincani A, Bompane D, Danieli E, Doria A. Pregnancy, lupus and antiphospholipid syndrome (Hughes syndrome). *Lupus* 2006;15:156-160.

(55) Erkan D, Sammaritano L. New insights into pregnancy-related complications in systemic lupus erythematosus. *Curr Rheumatol Rep* 2003;5:357-363.

(56) Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. *N Engl J Med* 2002;346:752-763.

(57) Villa PM, Kajantie E, Raikkonen K et al. Aspirin in the prevention of pre-eclampsia in high-risk women: a randomised placebo-controlled PREDO Trial and a meta-analysis of randomised trials. *BJOG* 2013;120:64-74.

(58) Schramm AM, Clowse ME. Aspirin for prevention of preeclampsia in lupus pregnancy. *Autoimmune Dis* 2014;2014:920467.

(59) Abalos E, Duley L, Steyn DW, Henderson-Smart DJ. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cohcrane Database Syst Rev* 2001;2:CD002252.

(60) Website of the U.S. Food and Drug Administration. www.fda.com . 2010.
Ref Type: Internet Communication

(61) Gebruik van antihypertensiva tijdens de zwangerschap. www.bcfi.be/folia/2005/F32N01B.cfm. 2005.
Ref Type: Internet Communication

(62) Bortolus R, Ricci E, Chatenoud L, Parazzini F. Nifedipine administered in pregnancy: effect on the development of children at 18 months. *BJOG* 2000;107:792-794.

(63) Rubin PC, Butters L, Low RA, Reid JL. Atenolol in the treatment of essential hypertension during pregnancy. *Brit J Clin Pharmacol* 1982;14:279-281.

(64) Cooper WO, Hernandez-Diaz S, Arbogast PG et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006;354:2443-2451.

(65) Drugs in Pregnancy and Breastfeeding. www.safefetus.com/ . 2010.
Ref Type: Internet Communication

(66) Van Bortel LM, Duprez D, Starmans-Kool MJ et al. Clinical applications of arterial stiffness, Task Force III : recommendations for user procedures. *Am J Hypertens* 2002;15:445-452.

(67) Parati G, Stergiou GS, Asmar R et al. European Society of Hypertension Practice Guidelines for home blood pressure monitoring. *J Hum Hypertens* 2010.

(68) Atkins N, O'Brien. The dabl Educational Trust device equivalence procedure. *Blood Press Monit* 2007;12:246-249.

(69) Belz GG. Elastic properties and Windkessel function of the human aorta. *Cardiovasc Drugs Ther* 1995;9:73-83.

(70) Wang J, Xu J, Zhou C et al. Improvement of arterial stiffness by reducing oxidative stress damage in elderly hypertensive patients after 6 months of atorvastatin therapy. *J Clin Hypertens (Greenwich)* 2012;14:245-249.

(71) Van Bortel LM, Hoeks AP, Kool MJ, Struijker-Boudier HA. Introduction to large artery properties as a target for risk reduction by antihypertensive therapy. *J Hypertens Suppl* 1992;10:S123-S126.

(72) Nichols WW, Denardo SJ, Johnson BD, Sharaf BL, Bairey Merz CN, Pepine CJ. Increased wave reflection and ejection duration in women with chest pain and nonobstructive coronary artery disease: ancillary study from the Women's Ischemia Syndrome Evaluation. *J Hypertens* 2013;31:1447-1454.

(73) Baumbach GL, Heistad DD. Remodeling of cerebral arterioles in chronic hypertension. *Hypertension* 1989;13:968-972.

(74) Mitchell GF, van Buchem MA, Sigurdsson S et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility--Reykjavik study. *Brain* 2011;134:3398-3407.

(75) Laurent S. Arterial stiffness: intermediate or surrogate endpoint for cardiovascular events? *Eur Heart J* 2005;26:1152-1154.

(76) Basu P, Sen U, Tyagi N, Tyagi SC. Blood flow interplays with elastin: collagen and MMP: TIMP ratios to maintain healthy vascular structure and function. *Vasc Health Risk Manag* 2010;6:215-228.

(77) Evangelista A, Flachskampf FA, Erbel R et al. Echocardiography in aortic diseases: EAE recommendations for clinical practice. *Eur J Echocardiogr* 2010;11:645-658.

(78) Go OD, Safar ME, Smulyan H. Assessment of aortic stiffness by transesophageal echocardiography. *Echocardiography* 2014;31:1105-1112.

(79) Redheuil AB, Kachenoura N, Laporte R et al. Interobserver variability in assessing segmental function can be reduced by combining visual analysis of CMR cine sequences with corresponding parametric images of myocardial contraction. *J Cardiovasc Magn Reson* 2007;9:863-872.

(80) Lakatta EG. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part III: cellular and molecular clues to heart and arterial aging. *Circulation* 2003;107:490-497.

(81) Hofstra L, Willigers JM, Huvers FC et al. Short-term variation in the elastic properties of a muscular artery in humans. *Clin Sci (Lond)* 1994;86:567-574.

(82) van der Heijden-Spek JJ, Staessen JA, Fagard RH, Hoeks AP, Struijker Boudier HAJ, Van Bortel LM. Effect of age on brachial artery wall properties differs from the aorta and is gender dependent. A population study. *Hypertension* 2000;35:637-642.

(83) Sugawara J, Otsuki T, Maeda S et al. Effect of arterial lumen enlargement on carotid arterial compliance in normotensive postmenopausal women. *Hypertens Res* 2005;28:323-329.

(84) Laurent S, Cockcroft J, Van BL et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006;27:2588-2605.

(85) Kelly R, Fitchett D. Noninvasive determination of aortic input impedance and external left ventricular power output: a validation and repeatability study of a new technique. *J Am Coll Cardiol* 1992;20:952-963.

(86) Van Bortel LM, Balkestein EJ, van Der Heijden-Spek JJ et al. Non-invasive assessment of local arterial pulse pressure: comparison of applanation tonometry and echo-tracking. *J Hypertens* 2001;19:1037-1044.

(87) Chemla D, Hebert JL, Aptecar E et al. Empirical estimates of mean aortic pressure: advantages, drawbacks and implications for pressure redundancy. *Clin Sci (Lond)* 2002;103:7-13.

(88) Van Bortel LM, Balkestein EJ, van der Heijden-Spek JJ et al. Non-invasive assessment of local arterial pulse pressure : comparison of applanation tonometry and echo-tracking. *J Hypertens* 2001;19:1037-1044.

(89) Mourad JJ, Girerd X, Boutouyrie P, Safar M, Laurent S. Opposite effects of remodeling and hypertrophy on arterial compliance in hypertension. *Hypertension* 1998;31 (part 2):529-533.

(90) Meinders JM, Brands PJ, Willigers JM, Kornet L, Hoeks AP. Assessment of the spatial homogeneity of artery dimension parameters with high frame rate 2-D B-mode. *Ultrasound Med Biol* 2001;27:785-794.

(91) Korteweg DJ. Ueber die Fortpflanzungsgeschwindigkeit des Schalles in elastischen Röhren. *Annalen der Physik* 1880;241:525-542.

(92) Bramwell JC, Hill A. Velocity of transmission of the pulse-wave. *Lancet* 1922;199:891-892.

(93) Mitchell GF. Clinical achievements of impedance analysis. *Med Biol Eng Comput* 2009;47:153-163.

(94) Wagenseil JE, Mecham RP. Elastin in large artery stiffness and hypertension. *J Cardiovasc Transl Res* 2012;5:264-273.

(95) Baguet JP, Kingwell BA, Dart AL, Shaw J, Ferrier KE, Jennings GL. Analysis of the regional pulse wave velocity by Doppler: methodology and reproducibility. *J Hum Hypertens* 2003;17:407-412.

(96) Sugawara J, Hayashi K, Yokoi T, Tanaka H. Age-associated elongation of the ascending aorta in adults. *JACC Cardiovasc Imaging* 2008;1:739-748.

(97) Van Bortel LM, Laurent S, Boutouyrie P et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens* 2012;30:445-448.

(98) Huybrechts SA, Devos DG, Vermeersch SJ et al. Carotid to femoral pulse wave velocity: a comparison of real travelled aortic path lengths determined by MRI and superficial measurements. *J Hypertens* 2011;29:1577-1582.

(99) Westerhof N, Bosman F, De Vries CJ, Noordergraaf A. Analog studies of the human systemic arterial tree. *J Biomech* 1969;2:121-143.

(100) Stergiopulos N, Westerhof BE, Westerhof N. Total arterial inertance as the fourth element of the windkessel model. *Am J Physiol* 1999;276:H81-H88.

(101) Liang YL, Teede H, Kotsopoulos D et al. Non-invasive measurements of arterial structure and function: repeatability, interrelationships and trial sample size. *Clin Sci (Lond)* 1998;95:669-679.

(102) Cameron JD, Gatzka CD, Kingwell BA. Assessment of large artery function. *Coron Artery Dis* 2002;13:405-413.

(103) Hoeks AP, Brands PJ, Smeets FA, Reneman RS. Assessment of the distensibility of superficial arteries. *Ultrasound Med Biol* 1990;16:121-128.

(104) Chiu YC, Arand PW, Shroff SG, Feldman T, Carroll JD. Determination of pulse wave velocities with computerized algorithms. *Am Heart J* 1991;121:1460-1470.

(105) Chen CH, Ting CT, Nussbacher A et al. Validation of carotid artery tonometry as a means of estimating augmentation index of ascending aortic pressure. *Hypertension* 1996;27:168-175.

(106) Kips JG, Schutte AE, Vermeersch SJ et al. Comparison of central pressure estimates obtained from SphygmoCor, Omron HEM-9000AI and carotid applanation tonometry. *J Hypertens* 2011;29:1115-1120.

(107) Huntsman LL, Stewart DK, Barnes SR, Franklin SB, Colocousis JS, Hessel EA. Noninvasive Doppler determination of cardiac output in man. Clinical validation. *Circulation* 1983;67:593-602.

(108) Du BD, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. *Nutrition* 1989;5:303-311.

(109) Suleiman AB, Mathews A, Jegasothy R, Ali R, Kandiah N. A strategy for reducing maternal mortality. *Bull World Health Organ* 1999;77:190-193.

(110) 2015 Millenium Development Goals. 2010.
Ref Type: Internet Communication

(111) Hermida RC, Ayala DE. Prognostic value of office and ambulatory blood pressure measurements in pregnancy. *Hypertension* 2002;40:298-303.

(112) Dehaeck U, Thurston J, Gibson P, Stephanson K, Ross S. Blood pressure measurement for hypertension in pregnancy. *J Obstet Gynaecol Can* 2010;32:328-334.

(113) Chancellor J, Thorp JM, Jr. Blood pressure measurement in pregnancy. *BJOG* 2008;115:1076-1077.

(114) Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;34:2159-2219.

(115) Regitz-Zagrosek V, Blomstrom LC, Borghi C et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:3147-3197.

(116) Denolle T, Weber JL, Calvez C et al. Diagnosis of white coat hypertension in pregnant women with teletransmitted home blood pressure. *Hypertens Pregnancy* 2008;27:305-313.

(117) Bellomo G, Rondoni F, Pastorelli G, Stangoni G, Narducci P, Angeli G. Twenty four-hour ambulatory blood pressure monitoring in women with pre-eclampsia. *J Hum Hypertens* 1995;9:617-621.

(118) Bellomo G, Narducci PL, Rondoni F et al. Prognostic value of 24-hour blood pressure in pregnancy. *J Am Med Ass* 1999;282:1447-1452.

(119) Brown MA, McHugh L, Mangos G, Davis G. Automated self-initiated blood pressure or 24-hour ambulatory blood pressure monitoring in pregnancy ? *BJOG* 2004;111:38-41.

(120) Denolle T, Daniel JC, Calvez C, Ottavioli JN, Esnault V, Herpin D. Home blood pressure during normal pregnancy. *Am J Hypertens* 2005;18:1178-1180.

(121) Lo C, Taylor RS, Gamble G, McCowan L, North RA. Use of automated home blood pressure monitoring in pregnancy : is it safe ? *Am J Obstet Gynecol* 2002;187:1321-1328.

(122) Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol* 1989;256:H1060-H1065.

(123) Poppas A, Shroff SG, Korcarz CE et al. Serial assessment of the cardiovascular system in normal pregnancy. Role of arterial compliance and pulsatile arterial load. *Circulation* 1997;95:2407-2415.

(124) Gerretsen G, Huisjes HJ, Elema JD. Morphological changes of the spiral arteries in the placental bed in relation to pre-eclampsia and fetal growth retardation. *Br J Obstet Gynaecol* 1981;88:876-881.

(125) Curran-Everett D, Morris KG, Jr., Moore LG. Regional circulatory contributions to increased systemic vascular conductance of pregnancy. *Am J Physiol* 1991;261:H1842-H1847.

(126) Grindheim G, Estensen ME, Langesaeter E, Rosseland LA, Toska K. Changes in blood pressure during healthy pregnancy: a longitudinal cohort study. *J Hypertens* 2012;30:342-350.

(127) Macedo ML, Luminoso D, Savvidou MD, McEniery CM, Nicolaides KH. Maternal wave reflections and arterial stiffness in normal pregnancy as assessed by applanation tonometry. *Hypertension* 2008;51:1047-1051.

(128) Mahendru AA, Everett TR, Wilkinson IB, Lees CC, McEniery CM. A longitudinal study of maternal cardiovascular function from preconception to the postpartum period. *J Hypertens* 2014;32:849-856.

(129) Mahendru AA, Everett TR, Wilkinson IB, Lees CC, McEniery CM. Maternal cardiovascular changes from pre-pregnancy to very early pregnancy. *J Hypertens* 2012;30:2168-2172.

(130) Khalil A, Jauniaux E, Cooper D, Harrington K. Pulse wave analysis in normal pregnancy: a prospective longitudinal study. *PLoS One* 2009;4:e6134.

(131) Smith SA, Morris JM, Gallery ED. Methods of assessment of the arterial pulse wave in normal human pregnancy. *Am J Obstet Gynecol* 2004;190:472-476.

(132) Fujime M, Tomimatsu T, Okaue Y et al. Central aortic blood pressure and augmentation index during normal pregnancy. *Hypertens Res* 2012;35:633-638.

(133) Franz MB, Burgmann M, Neubauer A et al. Augmentation index and pulse wave velocity in normotensive and pre-eclamptic pregnancies. *Acta Obstet Gynecol Scand* 2013;92:960-966.

(134) Robb AO, Mills NL, Din JN et al. Influence of the menstrual cycle, pregnancy, and preeclampsia on arterial stiffness. *Hypertension* 2009;53:952-958.

(135) Wykretowicz M, Krauze T, Guzik P et al. Arterial stiffness, central hemodynamics and wave reflection in normal pregnancy and control nonpregnant women. *Eur J Obstet Gynecol Reprod Biol* 2011;159:49-52.

(136) Hughes AD, Park C, Davies J et al. Limitations of augmentation index in the assessment of wave reflection in normotensive healthy individuals. *PLoS One* 2013;8:e59371.

(137) Yuan LJ, Xue D, Duan YY, Cao TS, Zhou N. Maternal carotid remodeling and increased carotid arterial stiffness in normal late-gestational pregnancy as assessed by radio-frequency ultrasound technique. *BMC Pregnancy Childbirth* 2013;13:122.

(138) Mersich B, Rigo J, Jr., Besenyei C, Lenard Z, Studinger P, Kollai M. Opposite changes in carotid versus aortic stiffness during healthy human pregnancy. *Clin Sci (Lond)* 2005;109:103-107.

(139) Visontai Z, Lenard Z, Studinger P, Rigo J, Jr., Kollai M. Impaired baroreflex function during pregnancy is associated with stiffening of the carotid artery. *Ultrasound Obstet Gynecol* 2002;20:364-369.

(140) Savvidou MD, Kaihura C, Anderson JM, Nicolaides KH. Maternal arterial stiffness in women who subsequently develop pre-eclampsia. *PLoS One* 2011;6:e18703.

(141) Fabry IG, Richart T, Chengz X, Van Bortel LM, Staessen JA. Diagnosis and treatment of hypertensive disorders during pregnancy. *Acta Clin Belg* 2010;65:229-236.

(142) Snedecor GW, Cochram WG. *Statistical methods.* 7 ed. Iowa: University Press, 1980.

(143) Metoki H, Ohkubo T, Watanabe Y et al. Seasonal trends of blood pressure during pregnancy in Japan : the babies and their partens' longitudinal observation in Suzuki Memorial Hospital in Intrauterine Period study. *J Hypertens* 2008;26:2406-2413.

(144) Nama V, Antonios TF, Onwude J, Manyonda IT. Mid-trimester blood pressure drop in normal pregnancy: myth or reality? *J Hypertens* 2011;29:763-768.

(145) Alpert BS, Quinn DE, Friedman BA. A review of the latest guidelines for NIBP device validation. *Blood Press Monit* 2013;18:297-302.

(146) O'Brien E, Atkins N. A comparison of the British Hypertension Society and Association for the Advancement of Medical Instrumentation protocols for validating blood pressure measuring devices: can the two be reconciled? *J Hypertens* 1994;12:1089-1094.

(147) O'Brien E, Petrie J, Littler W et al. An outline of the revised British Hypertension Society protocol for the evaluation of blood pressure measuring devices. *J Hypertens* 1993;11:677-679.

(148) O'Brien E, Atkins N, Stergiou G et al. European Society of Hypertension International Protocol revision 2010 for the validation of blood pressure measuring devices in adults. *Blood Press Monit* 2010;15:23-38.

(149) Reinders A, Cuckson AC, Lee JT, Shennan AH. An accurate automated blood pressure device for use in pregnancy and pre-eclampsia: the Microlife 3BTO-A. *BJOG* 2005;112:915-920.

(150) Chung Y, de GA, Shennan A. Validation and compliance of a home monitoring device in pregnancy: microlife WatchBP home. *Hypertens Pregnancy* 2009;28:348-359.

(151) de GA, Beg Z, Gangji Z, Dorney E, Shennan AH. Accuracy of inflationary versus deflationary oscillometry in pregnancy and preeclampsia: OMRON-MIT versus OMRON-M7. *Blood Press Monit* 2009;14:37-40.

(152) Chung Y, de Greeff A, Shennan A. Validation and compliance of a home monitoring device in pregnancy : microlife WathBP home. *Hypertens Pregnancy* 2009;28:348-359.

(153) Loewenstein L, Naschitz JE. Use of automated home blood pressure monitoring in pregnancy. *Am J Obstet Gynecol* 2003;188:1662.

(154) Mancia G, Parati G. Ambulatory blood pressure monitoring and organ damage. *Hypertension* 2000;36:849-900.

(155) Altunkan S, Iliman N, Altunkan E. Validation of the Omron M6 (HEM-7001-E) upper arm blood pressure measuring device according to the International Protocol in elderly patients. *Blood Press Monit* 2008;13:117-122.

(156) Whiting PF, Weswood ME, Rutjes AW, Reitsma JB, Bossuyt PN, Kleijnen J. Evaluation of QUADAS, a tool for the quality assessment of diagnostic accuracy studies. *BMC Med Res Methodol* 2006;6:9.

(157) Staessen JA, Kuznetsova T, Roels HA, Emelianov D, Fagard R. Exposure to cadmium and conventional and ambulatory blood pressures in a prospective population study. Public Health and Environmental Exposure to Cadmium Study Group. *Am J Hypertens* 2000;13:146-156.

(158) Thijs L, Hansen TW, Kikuya M et al. The International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome (IDACO) : protocol and reseacrh perspectives. *Blood Press Monit*. In press.

(159) The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC), Mancia G, De Backer G et al. 2007 guidelines for the management of arterial hypertension. *Eur Heart J* 2007;28:1462-1536.

(160) Poon LC, Kametas NA, Pandeva I, Valencia C, Nicolaides KH. Mean arterial pressure at 11(+0) to 13(+6) weeks in the prediction of preeclampsia. *Hypertension* 2008;51:1027-1033.

(161) Regitz-Zagrosek V, Blomstrom LC, Borghi C et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:3147-3197.

(162) Macdonald-Wallis C, Silverwood RJ, Fraser A et al. Gestational-age-specific reference ranges for blood pressure in pregnancy: findings from a prospective cohort. *J Hypertens* 2015;33:96-105.

(163) Ting CT, Chen C-H, Chang M-S, Yin FCP. Short- and long-term effects of antihypertensive drugs on arterial reflections compliance and impedance. *Hypertension* 1995;26:524-530.

(164) Rurangirwa AA, Gaillard R, Steegers EA, Hofman A, Jaddoe VW. Hemodynamic adaptations in different trimesters among nulliparous and multiparous pregnant women; the Generation R study. *Am J Hypertens* 2012;25:892-899.

(165) Nadaud S, Philippe M, Arnal JF, Michel JB, Soubrier F. Sustained increase in aortic endothelial nitric oxide synthase expression in vivo in a model of chronic high blood flow. *Circ Res* 1996;79:857-863.

(166) Natoli AK, Medley TL, Ahimastos AA et al. Sex steroids modulate human aortic smooth muscle cell matrix protein deposition and matrix metalloptreinase expression. *Hypertension* 2005;46:1129-1134.

(167) Conrad KP. Maternal vasodilation in pregnancy: the emerging role of relaxin. *Am J Physiol Regul Integr Comp Physiol* 2011;301:R267-R275.

(168) Wilkinson IB, MacCallum H, Flint L, Cockeroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. *J Physiol* 2000;525:263-270.

(169) Macdonald-Wallis C, Lawlor DA, Fraser A, May M, Nelson SM, Tilling K. Blood pressure change in normotensive, gestational hypertensive, preeclamptic, and essential hypertensive pregnancies. *Hypertension* 2012;59:1241-1248.

(170) Elvan-Taspinar A, Franx A, Bots ML, Bruinse HW, Koomans HA. Central hemodynamics of hypertensive disorders in pregnancy. *Am J Hypertens* 2004;17:941-946.

(171) Segers P, Mahieu D, Kips J et al. Amplification of the pressure pulse in the upper limb in healthy, middle-aged men and women. *Hypertension* 2009;54:414-420.

(172) Weber T, Wassertheurer S, Hametner B et al. Reference values for central blood pressure. *J Am Coll Cardiol* 2014;63:2299.

(173) Cheng HM, Chen CH. The barriers to clinical application of non-invasively obtained central blood pressure. *Conf Proc IEEE Eng Med Biol Soc* 2013;2013:233-236.

(174) Wohlfahrt P, Krajcoviechova A, Seidlerova J, Mayer O, Filipovsky J, Cifkova R. Comparison of noninvasive assessments of central blood pressure using general transfer function and late systolic shoulder of the radial pressure wave. *Am J Hypertens* 2014;27:162-168.

(175) Ding FH, Fan WX, Zhang RY, Zhang Q, Li Y, Wang JG. Validation of the noninvasive assessment of central blood pressure by the SphygmoCor and Omron devices against the invasive catheter measurement. *Am J Hypertens* 2011;24:1306-1311.

(176) Costello BT, Schultz MG, Black JA, Sharman JE. Evaluation of a Brachial Cuff and Suprasystolic Waveform Algorithm Method to Noninvasively Derive Central Blood Pressure. *Am J Hypertens* 2014.

(177) Youn JC, Rim SJ, Park S et al. Arterial stiffness is related to augmented seasonal variation of blood pressure in hypertensive patients. *Blood Press* 2007;16:375-380.

(178) Simhan HN, Caritis SN. Prevention of preterm delivery. *N Engl J Med* 2007;357:477-487.

(179) ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologist. Number 43, May 2003. Management of preterm labor. *Obstet Gynecol* 2003;101:1039-1047.

(180) Caughey AB, Parer JT. Tocolysis with beta-adrenergic receptor agonists. *Semin Perinatol* 2001;25:248-255.

(181) de HR, Mol BW, Erwich JJ et al. Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study. *BMJ* 2009;338:b744.

(182) Shim JY, Park YW, Yoon BH et al. Multicentre, parallel group, randomised, single-blind study of the safety and efficacy of atosiban versus ritodrine in the treatment of acute preterm labour in Korean women. *BJOG* 2006;113:1228-1234.

(183) Shubert PJ. Atosiban. *Clin Obstet Gynecol* 1995;38:722-724.

(184) Chan J, Cabrol D, Ingemarsson I, Marsal K, Moutquin JM, Fisk NM. Pragmatic comparison of beta2-agonist side effects within the Worldwide Atosiban versus Beta Agonists study. *Eur J Obstet Gynecol Reprod Biol* 2006;128:135-141.

(185) Stergiotou I, Talbot F, Yoong W. The use of atosiban and ritodrine in external cephalic version. *Acta Obstet Gynecol Scand* 2007;86:927-929.

(186) Ferriols LR, Nicolas PJ, Alos AM. [Pharmacoeconomic assessment of two tocolysis protocols for the inhibition of premature delivery]. *Farm Hosp* 2005;29:18-25.

(187) Treatment of preterm labor with the oxytocin antagonist atosiban: a double-blind, randomized, controlled comparison with salbutamol. *Eur J Obstet Gynecol Reprod Biol* 2001;98:177-185.

(188) Effectiveness and safety of the oxytocin antagonist atosiban versus beta-adrenergic agonists in the treatment of preterm labour. The Worldwide Atosiban versus Beta-agonists Study Group. *BJOG* 2001;108:133-142.

(189) The oxytocin antagonist atosiban versus the beta-agonist terbutaline in the treatment of preterm labor. A randomized, double-blind, controlled study. *Acta Obstet Gynecol Scand* 2001;80:413-422.

(190) Roman MJ, Devereux RB, Kizer JR et al. High central pulse pressure is independently associated with adverse cardiovascular outcome the strong heart study. *J Am Coll Cardiol* 2009;54:1730-1734.

(191) McEniery CM, Yasmin, McDonnell B et al. Central pressure: variability and impact of cardiovascular risk factors: the Anglo-Cardiff Collaborative Trial II. *Hypertension* 2008;51:1476-1482.

(192) Avolio AP, Van Bortel LM, Boutouyrie P et al. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertension* 2009;54:375-383.

(193) Fabry I, De PP, Kips J, Vermeersch S, Van BL. Different effects of tocolytic medication on blood pressure and blood pressure amplification. *Eur J Clin Pharmacol* 2011;67:11-17.

(194) ACOG practice bulletin no. 127: Management of preterm labor. *Obstet Gynecol* 2012;119:1308-1317.

(195) Raju TN, Mercer BM, Burchfield DJ, Joseph GF, Jr. Periviable birth: executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Academy of Pediatrics, and American College of Obstetricians and Gynecologists. *Am J Obstet Gynecol* 2014;210:406-417.

(196) Goldenberg RL. The management of preterm labor. *Obstet Gynecol* 2002;100:1020-1037.

(197) Korenbrot CC, Aalto LH, Laros RK, Jr. The cost effectiveness of stopping preterm labor with beta-adrenergic treatment. *N Engl J Med* 1984;310:691-696.

(198) Myers ER, Alvarez JG, Richardson DK, Ludmir J. Cost-effectiveness of fetal lung maturity testing in preterm labor. *Obstet Gynecol* 1997;90:824-829.

(199) Romero R, Avila C, Brekus CA, Morotti R. The role of systemic and intrauterine infection in preterm parturition. *Ann N Y Acad Sci* 1991;622:355-375.

(200) Haas DM, Imperiale TF, Kirkpatrick PR, Klein RW, Zollinger TW, Golichowski AM. Tocolytic therapy: a meta-analysis and decision analysis. *Obstet Gynecol* 2009;113:585-594.

(201) Flenady V, Wojcieszek AM, Papatsonis DN et al. Calcium channel blockers for inhibiting preterm labour and birth. *Cochrane Database Syst Rev* 2014;6:CD002255.

(202) Caritis SN, Lin LS, Toig G, Wong LK. Pharmacodynamics of ritodrine in pregnant women during preterm labor. *Am J Obstet Gynecol* 1983;147:752-759.

(203) Caritis SN, Chiao JP, Moore JJ, Ward SM. Myometrial desensitization after ritodrine infusion. *Am J Physiol* 1987;253:E410-E417.

(204) Anotayanonth S, Subhedar NV, Garner P, Neilson JP, Harigopal S. Betamimetics for inhibiting preterm labour. *Cochrane Database Syst Rev* 2004;CD004352.

(205) Gyetvai K, Hannah ME, Hodnett ED, Ohlsson A. Tocolytics for preterm labor: a systematic review. *Obstet Gynecol* 1999;94:869-877.

(206) Lamont RF. The pathophysiology of pulmonary oedema with the use of beta-agonists. *BJOG* 2000;107:439-444.

(207) Golichowski AM, Hathaway DR, Fineberg N, Peleg D. Tocolytic and hemodynamic effects of nifedipine in the ewe. *Am J Obstet Gynecol* 1985;151:1134-1140.

(208) Papatsonis DN, Kok JH, van Geijn HP, Bleker OP, Ader HJ, Dekker GA. Neonatal effects of nifedipine and ritodrine for preterm labor. *Obstet Gynecol* 2000;95:477-481.

(209) Groome LJ, Goldenberg RL, Cliver SP, Davis RO, Copper RL. Neonatal periventricular-intraventricular hemorrhage after maternal beta-sympathomimetic tocolysis. The March of Dimes Multicenter Study Group. *Am J Obstet Gynecol* 1992;167:873-879.

(210) Weintraub Z, Solovechick M, Reichman B et al. Effect of maternal tocolysis on the incidence of severe periventricular/intraventricular haemorrhage in very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed* 2001;85:F13-F17.

(211) Palta M, Sadek M, Lim TS, Evans M, McGuinness G. Association of tocolytic therapy with antenatal steroid administration and infant outcomes. Newborn Lung Project. *Am J Perinatol* 1998;15:87-92.

(212) Witter FR, Zimmerman AW, Reichmann JP, Connors SL. In utero beta 2 adrenergic agonist exposure and adverse neurophysiologic and behavioral outcomes. *Am J Obstet Gynecol* 2009;201:553-559.

(213) Caritis SN, Simhan HN. Beta adrenergic agonists and neonatal outcome. *Am J Obstet Gynecol* 2010;203:e16-e17.

(214) Lemancewicz A, Laudanska H, Laudanski T, Karpiuk A, Batra S. Permeability of fetal membranes to calcium and magnesium: possible role in preterm labour. *Hum Reprod* 2000;15:2018-2022.

(215) Mizuki J, Tasaka K, Masumoto N, Kasahara K, Miyake A, Tanizawa O. Magnesium sulfate inhibits oxytocin-induced calcium mobilization in human puerperal myometrial cells: possible involvement of intracellular free magnesium concentration. *Am J Obstet Gynecol* 1993;169:134-139.

(216) Committee Opinion No. 573: Magnesium sulfate use in obstetrics. *Obstet Gynecol* 2013;122:727-728.

(217) Mercer BM, Merlino AA. Magnesium sulfate for preterm labor and preterm birth. *Obstet Gynecol* 2009;114:650-668.

(218) Macones GA, Sehdev HM, Berlin M, Morgan MA, Berlin JA. Evidence for magnesium sulfate as a tocolytic agent. *Obstet Gynecol Surv* 1997;52:652-658.

(219) Twickler DM, McIntire DD, Alexander JM, Leveno KJ. Effects of magnesium sulfate on preterm fetal cerebral blood flow using Doppler analysis: a randomized controlled trial. *Obstet Gynecol* 2010;115:21-25.

(220) Schanler RJ, Smith LG, Jr., Burns PA. Effects of long-term maternal intravenous magnesium sulfate therapy on neonatal calcium metabolism and bone mineral content. *Gynecol Obstet Invest* 1997;43:236-241.

(221) Bashuk RG, Krendel DA. Myasthenia gravis presenting as weakness after magnesium administration. *Muscle Nerve* 1990;13:708-712.

(222) Mueksch JN, Stevens WA. Undiagnosed myasthenia gravis masquerading as eclampsia. *Int J Obstet Anesth* 2007;16:379-382.

(223) Conde-Agudelo A, Romero R, Kusanovic JP. Nifedipine in the management of preterm labor: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2011;204:134-20.

(224) Caritis SN. Treatment of preterm labour. A review of the therapeutic options. *Drugs* 1983;26:243-261.

(225) Cornette J, Duvekot J, Roos-Hesselink J, Hop W, Steegers E. Maternal and fetal haemodynamic effects of nifedipine in normotensive pregnant women. *BJOG* 2010.

(226) Ferguson JE, Dyson DC, Schutz T, Stevenson DK. A comparison of tocolysis with nifedipine or ritodrine: analysis of efficacy and maternal, fetal, and neonatal outcome. *Am J Obstet Gynecol* 1990;163:105-111.

(227) Guclu S, Saygili U, Dogan E, Demir N, Baschat AA. The short-term effect of nifedipine tocolysis on placental, fetal cerebral and atrioventricular Doppler waveforms. *Ultrasound Obstet Gynecol* 2004;24:761-765.

(228) Guclu S, Gol M, Saygili U, Demir N, Sezer O, Baschat AA. Nifedipine therapy for preterm labor: effects on placental, fetal cerebral and atrioventricular Doppler parameters in the first 48 hours. *Ultrasound Obstet Gynecol* 2006;27:403-408.

(229) Mari G, Kirshon B, Moise KJ, Jr., Lee W, Cotton DB. Doppler assessment of the fetal and uteroplacental circulation during nifedipine therapy for preterm labor. *Am J Obstet Gynecol* 1989;161:1514-1518.

(230) Feldman S, Karalliedde L. Drug interactions with neuromuscular blockers. *Drug Saf* 1996;15:261-273.

(231) Carles G, Helou J, Alassas N, Dallah F, Ibrahim N. [Complications of association magnesium sulfate with nicardipine during preeclampsia: report of 2 cases]. *Gynecol Obstet Fertil* 2012;40:614-616.

(232) O'Brien WF. The role of prostaglandins in labor and delivery. *Clin Perinatol* 1995;22:973-984.

(233) Chandrasekharan NV, Dai H, Roos KL et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. *Proc Natl Acad Sci U S A* 2002;99:13926-13931.

(234) Sadovsky Y, Nelson DM, Muglia LJ et al. Effective diminution of amniotic prostaglandin production by selective inhibitors of cyclooxygenase type 2. *Am J Obstet Gynecol* 2000;182:370-376.

(235) King J, Flenady V, Cole S, Thornton S. Cyclo-oxygenase (COX) inhibitors for treating preterm labour. *Cochrane Database Syst Rev* 2005;CD001992.

(236) Hayes E, Moroz L, Pizzi L, Baxter J. A cost decision analysis of 4 tocolytic drugs. *Am J Obstet Gynecol* 2007;197:383-386.

(237) Niebyl JR, Blake DA, White RD et al. The inhibition of premature labor with indomethacin. *Am J Obstet Gynecol* 1980;136:1014-1019.

(238) Abou-Ghannam G, Usta IM, Nassar AH. Indomethacin in pregnancy: applications and safety. *Am J Perinatol* 2012;29:175-186.

(239) Cordero L, Nankervis CA, Gardner D, Giannone PJ. The effects of indomethacin tocolysis on the postnatal response of the ductus arteriosus to indomethacin in extremely low birth weight infants. *J Perinatol* 2007;27:22-27.

(240) Van Den Veyver IB, Moise KJ, Jr. Prostaglandin synthetase inhibitors in pregnancy. *Obstet Gynecol Surv* 1993;48:493-502.

(241) Phaneuf S, Asboth G, MacKenzie IZ, Melin P, Lopez BA. Effect of oxytocin antagonists on the activation of human myometrium in vitro: atosiban prevents oxytocin-induced desensitization. *Am J Obstet Gynecol* 1994;171:1627-1634.

(242) Phaneuf S, Asboth G, Carrasco MP et al. The desensitization of oxytocin receptors in human myometrial cells is accompanied by down-regulation of oxytocin receptor messenger RNA. *J Endocrinol* 1997;154:7-18.

(243) Goodwin TM, Valenzuela G, Silver H, Hayashi R, Creasy GW, Lane R. Treatment of preterm labor with the oxytocin antagonist atosiban. *Am J Perinatol* 1996;13:143-146.

(244) Papatsonis D, Flenady V, Cole S, Liley H. Oxytocin receptor antagonists for inhibiting preterm labour. *Cochrane Database Syst Rev* 2005;3:CD004452.

(245) Romero R, Sibai BM, Sanchez-Ramos L et al. An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. *Am J Obstet Gynecol* 2000;182:1173-1183.

(246) de Heus R, Mol BW, Erwich JJ et al. Adverse drug reactions to tocolytic treatment for preterm labour : prospective cohort study. *BMJ* 2009;338:b744.

(247) Greig PC, Massmann GA, Demarest KT, Weglein RC, Holland ML, Figueroa JP. Maternal and fetal cardiovascular effects and placental transfer of the oxytocin antagonist atosiban in late-gestation pregnant sheep. *Am J Obstet Gynecol* 1993;169:897-902.

(248) Valenzuela GJ, Craig J, Bernhardt MD, Holland ML. Placental passage of the oxytocin antagonist atosiban. *Am J Obstet Gynecol* 1995;172:1304-1306.

(249) Wex J, Connolly M, Rath W. Atosiban versus betamimetics in the treatment of preterm labour in Germany : an economic evaluation. *BMC Pregnancy Childbirth* 2009;9:23.

(250) Ferriols Lisart R, Nicolas Pico J, Alos Alminana M. [Pharmacoeconomic assessment of two tocolysis protocols for the inhibition of premature delivery.]. *Farm Hosp* 2005;29:18-25.

(251) Dong YL, Fang L, Gangula PR, Yallampalli C. Regulation of inducible nitric oxide synthase messenger ribonucleic acid expression in pregnant rat uterus. *Biol Reprod* 1998;59:933-940.

(252) Duckitt K, Thornton S, O'Donovan OP, Dowswell T. Nitric oxide donors for treating preterm labour. *Cochrane Database Syst Rev* 2014;5:CD002860.

(253) Smith GN, Walker MC, Ohlsson A, O'Brien K, Windrim R. Randomized double-blind placebo-controlled trial of transdermal nitroglycerin for preterm labor. *Am J Obstet Gynecol* 2007;196:37-38.

(254) Lees CC, Lojacono A, Thompson C et al. Glyceryl trinitrate and ritodrine in tocolysis: an international multicenter randomized study. GTN Preterm Labour Investigation Group. *Obstet Gynecol* 1999;94:403-408.

(255) Bisits A, Madsen G, Knox M et al. The Randomized Nitric Oxide Tocolysis Trial (RNOTT) for the treatment of preterm labor. *Am J Obstet Gynecol* 2004;191:683-690.

(256) Flenady V, King J. Antibiotics for prelabour rupture of membranes at or near term. *Cochrane Database Syst Rev* 2002;CD001807.

(257) Hutzal CE, Boyle EM, Kenyon SL et al. Use of antibiotics for the treatment of preterm parturition and prevention of neonatal morbidity: a metaanalysis. *Am J Obstet Gynecol* 2008;199:620-628.

(258) de HR, Mulder EJ, Visser GH. Management of preterm labor: atosiban or nifedipine? *Int J Womens Health* 2010;2:137-142.

(259) Brown RG, MacIntyre DA. Calcium channel blockers are effective as first line for tocolysis in the management of preterm labour. *Evid Based Med* 2014.

(260) Haram K, Mortensen JH, Morrison JC. Tocolysis for acute preterm labor: does anything work. *J Matern Fetal Neonatal Med* 2015;28:371-378.

(261) Hammers AL, Sanchez-Ramos L, Kaunitz AM. Antenatal exposure to indomethacin increases the risk of severe intraventricular hemorrhage, necrotizing enterocolitis, and periventricular leukomalacia: a systematic review with metaanalysis. *Am J Obstet Gynecol* 2014.

(262) Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. *BMJ* 2012;345:e6226.

(263) Wojcieszek AM, Stock OM, Flenady V. Antibiotics for prelabour rupture of membranes at or near term. *Cochrane Database Syst Rev* 2014;10:CD001807.

(264) Lamont RF. The pathophysiology of pulmonary oedema with the use of beta-agonists. *BJOG* 2000;107:439-444.

(265) Alouini S. Adverse reactions to tocolytics. No to beta agonists for tocolysis. *BMJ* 2009;338:b1502.

(266) Van Bortel LM, Duprez D, Starmans-Kool MJ et al. Clinical applications of arterial stiffness, Task Force III: recommendations for user procedures. *Am J Hypertens* 2002;15:445-452.

(267) Tsatsaris V, Carbonne B, Papatsonis D, Goffinet F. Nifedipine versus ritodrine for suppression of preterm labor; a meta-analysis. *Acta Obstet Gynecol Scand* 2000;79:618-619.

(268) Papatsonis DN, van Geijn HP, Ader HJ, Lange FM, Bleker OP, Dekker GA. Nifedipine and ritodrine in the management of preterm labor: a randomized multicenter trial. *Obstet Gynecol* 1997;90:230-234.

(269) Rasmussen BB, Larsen LS, Senderovitz T. Pharmacokinetic interaction studies of atosiban with labetalol or betamethasone in healthy female volunteers. *BJOG* 2005;112:1492-1499.

(270) Gerris J, Thiery M, Bogaert M, De SA. Randomized trial of two beta-mimetic drugs (ritodrine and fenoterol) in acute intra-partum tocolysis. *Eur J Clin Pharmacol* 1980;18:443-448.

(271) Vanmolkot FH, Van Bortel LM, de Hoon JN. Altered arterial function in migraine of recent onset. *Neurology* 2007;68:1563-1570.

(272) Bos WJ, Verrij E, Vincent HH, Westerhof BE, Parati G, van Montfrans GA. How to assess mean blood pressure properly at the brachial artery level. *J Hypertens* 2007;25:751-755.

(273) Kelly R, Hayward C, Avolio A, O'Rourke M. Noninvasive determination of age-related changes in the human arterial pulse. *Circulation* 1989;80:1652-1659.

(274) Rietzschel ER, De Buyzere ML, Bekaert S et al. Rationale, design, methods and baseline characteristics of the Asklepios Study. *Eur J Cardiovasc Prev Rehabil* 2007;14:179-191.

(275) Chen CH, Ting CT, Nussbacher A et al. Validation of carotid artery tonometry as a means of estimating augmentation index of ascending aortic pressure. *Hypertension* 1996;27:168-175.

(276) Millasseau SC, Patel SJ, Redwood SR, Ritter JM, Chowienczyk PJ. Pressure wave reflection assessed from the peripheral pulse: is a transfer function necessary? *Hypertension* 2003;41:1016-1020.

(277) Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. *J Physiol* 2000;525 Pt 1:263-270.

(278) Wilkinson IB, Cockcroft JR, Webb DJ. Pulse wave analysis and arterial stiffness. *J Cardiovasc Pharmacol* 1998;32 Suppl 3:S33-S37.

(279) Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;55:1318-1327.

(280) Papatsonis DN, van Geijn HP, Bleker OP, Ader HJ, Dekker GA. Hemodynamic and metabolic effects after nifedipine and ritodrine tocolysis. *Int J Gynaecol Obstet* 2003;82:5-10.

(281) Goodwin TM, Valenzuela G, Silver H, Hayashi R, Creasy GW, Lane R. Treatment of preterm labor with the oxytocin antagonist atosiban. *Am J Perinatol* 1996;13:143-146.

(282) Goodwin TM, Millar L, North L, Abrams LS, Weglein RC, Holland ML. The pharmacokinetics of the oxytocin antagonist atosiban in pregnant women with preterm uterine contractions. *Am J Obstet Gynecol* 1995;173:913-917.

(283) Moutquin JM, Sherman D, Cohen H et al. Double-blind, randomized, controlled trial of atosiban and ritodrine in the treatment of preterm labor: a multicenter effectiveness and safety study. *Am J Obstet Gynecol* 2000;182:1191-1199.

(284) Cekici L, Valipour A, Kohansal R, Burghuber OC. Short-term effects of inhaled salbutamol on autonomic cardiovascular control in healthy subjects: a placebo-controlled study. *Br J Clin Pharmacol* 2009;67:394-402.

(285) Smulyan H, Mukherjee R, Sheehe PR, Safar ME. Cuff and aortic pressure differences during dobutamine infusion: a study of the effects of systolic blood pressure amplification. *Am Heart J* 2010;159:399-405.

(286) Waring WS, Sinclair HM, Webb DJ. Effects of salbutamol and glyceryl trinitrate on large arterial stiffness are similar between patients with hypertension and adults with normal blood pressure. *Br J Clin Pharmacol* 2006;62:621-626.

(287) Husslein P, Quartarolo JP. Review of clinical experience with atosiban and the Tractocile Efficacy Assessment Survey in Europe (TREASURE) study protocol. *Int J Clin Pract* 2003;57:121-127.

(288) Papatsonis D, Flenady V, Cole S, Liley H. Oxytocin receptor antagonists for inhibiting preterm labour. *Cochrane Database Syst Rev* 2005;CD004452.

(289) Bos WJ, Verrij E, Vincent HH, Westerhof BE, Parati G, van Montfrans GA. How to assess mean blood pressure properly at the brachial artery level. *J Hypertens* 2007;25:751-755.

(290) Mahieu D, Kips J, Rietzschel ER et al. Noninvasive assessment of central and peripheral arterial pressure (waveforms): implications of calibration methods. *J Hypertens* 2010;28:300-305.

(291) Hayward CS, Kraidly M, Webb CM, Collins P. Assessment of endothelial function using peripheral waveform analysis: a clinical application. *J Am Coll Cardiol* 2002;40:521-528.

(292) O'Rourke MF. Mechanical principles. Arterial stiffness and wave reflection. *Pathol Biol (Paris)* 1999;47:623-633.

(293) Leduc L, Wasserstrum N, Spillman T, Cotton DB. Baroreflex function in normal pregnancy. *Am J Obstet Gynecol* 1991;165:886-890.

(294) Vesalainen RK, Ekholm EM, Jartti TT, Tahvanainen KU, Kaila TJ, Erkkola RU. Effects of tocolytic treatment with ritodrine on cardiovascular autonomic regulation. *Br J Obstet Gynaecol* 1999;106:238-243.

(295) Nichols WW, O'Rourke MF. Mc Donald's Blood Flow in Arteries: Theoretical, Experimental, and Clinical Principles. 2005.

(296) Van Bortel LM, Mahieu D, De Backer T. Measurement of central aortic blood pressure. In: Laurent S, Cockroft J, eds. Central aortic blood pressure. ed. Neuilly-sur-Seine Cedex, France: Elsevier Masson SAS; 2008;35-40.

(297) Segers P, Mahieu D, Kips J et al. Amplification of the pressure pulse in the upper limb in healthy, middle-aged men and women. *Hypertension* 2009;54:414-420.

(298) Benedetti TJ. Maternal complications of parenteral beta-sympathomimetic therapy for premature labor. *Am J Obstet Gynecol* 1983;145:1-6.

(299) Hosenpud JD, Morton MJ, O'Grady JP. Cardiac stimulation during ritodrine hydrochloride tocolytic therapy. *Obstet Gynecol* 1983;62:52-58.

(300) Tsatsaris V, Carbonne B, Cabrol D. Atosiban for preterm labour. *Drugs* 2004;64:375-382.

(301) Schneider KT, Deckardt R. The implication of upright posture on pregnancy. *J Perinat Med* 1991;19:121-131.

(302) Dennedy MC, Houlihan DD, McMillan H, Morrison JJ. Beta2- and beta3-adrenoreceptor agonists: human myometrial selectivity and effects on umbilical artery tone. *Am J Obstet Gynecol* 2002;187:641-647.

(303) Lantelme P, Mestre C, Lievre M, Gressard A, Milon H. Heart rate: an important confounder of pulse wave velocity assessment. *Hypertension* 2002;39:1083-1087.

(304) Duvekot JJ, Peeters LL. Maternal cardiovascular hemodynamic adaptation to pregnancy. *Obstet Gynecol Surv* 1994;49:S1-14.

(305) Gimpl G, Fahrenholz F. The oxytocin receptor system: structure, function, and regulation. *Physiol Rev* 2001;81:629-683.

(306) Mitchell BF, Schmid B. Oxytocin and its receptor in the process of parturition. *J Soc Gynecol Investig* 2001;8:122-133.

(307) Dawes M, Chowienczyk PJ, Ritter JM. Effects of inhibition of the L-arginine/nitric oxide pathway on vasodilation caused by beta-adrenergic agonists in human forearm. *Circulation* 1997;95:2293-2297.

(308) Anumba DO, Ford GA, Boys RJ, Robson SC. Stimulated nitric oxide release and nitric oxide sensitivity in forearm arterial vasculature during normotensive and preeclamptic pregnancy. *Am J Obstet Gynecol* 1999;181:1479-1484.

(309) Bussen SS, Sutterlin MW, Steck T. Plasma renin activity and aldosterone serum concentration are decreased in severe preeclampsia but not in the HELLP-syndrome. *Acta Obstet Gynecol Scand* 1998;77:609-613.

(310) Noori M, Donald AE, Angelakopoulou A, Hingorani AD, Williams DJ. Prospective study of placental angiogenic factors and maternal vascular function before and after preeclampsia and gestational hypertension. *Circulation* 2010;122:478-487.

(311) Simmons LA, Hennessy A, Gillin AG, Jeremy RW. Uteroplacental blood flow and placental vascular endothelial growth factor in normotensive and pre-eclamptic pregnancy. *BJOG* 2000;107:678-685.

(312) Anton L, Brosnihan KB. Systemic and uteroplacental renin--angiotensin system in normal and pre-eclamptic pregnancies. *Ther Adv Cardiovasc Dis* 2008;2:349-362.

(313) Wex J, Connolly M, Rath W. Atosiban versus betamimetics in the treatment of preterm labour in Germany: an economic evaluation. *BMC Pregnancy Childbirth* 2009;9:23.

(314) Shubert PJ. Atosiban. *Clin Obstet Gynecol* 1995;38:722-724.

(315) Moussa HN, Arian SE, Sibai BM. Management of hypertensive disorders in pregnancy. *Womens Health (Lond Engl)* 2014;10:385-404.

(316) Feldman DM. Blood pressure monitoring during pregnancy. *Blood Press Monit* 2001;6:1-7.

(317) Manning DM, Kuchirka C, Kaminski J. Miscuffing: inappropriate blood pressure cuff application. *Circulation* 1983;68:763-766.

(318) Marks LA, Groch A. Optimizing cuff width for noninvasive measurement of blood pressure. *Blood Press Monit* 2000;5:153-158.

(319) Parati G, Mendis S, Abegunde D et al. Recommendations for blood pressure measuring devices for office/clinic use in low resource settings. *Blood Press Monit* 2005;10:3-10.

(320) Bailey RH, Bauer JH. A review of common errors in the indirect measurement of blood pressure. Sphygmomanometry. *Arch Intern Med* 1993;153:2741-2748.

(321) Stewart MJ, Padfield PL. Measurement of blood pressure in the technological age. *Br Med Bull* 1994;50:420-442.

(322) Villar J, Repke J, Markush L, Calvert W, Rhoads G. The measuring of blood pressure during pregnancy. *Am J Obstet Gynecol* 1989;161:1019-1024.

(323) Avni B, Frenkel G, Shahar L, Golik A, Sherman D, Dishy V. Aortic stiffness in normal and hypertensive pregnancy. *Blood Press* 2010;19:11-15.

(324) Mosca L, Benjamin EJ, Berra K et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol* 2011;57:1404-1423.

(325) Oliver-Williams CT, Heydon EE, Smith GC, Wood AM. Miscarriage and future maternal cardiovascular disease: a systematic review and meta-analysis. *Heart* 2013;99:1636-1644.

(326) Takase B, Goto T, Hamabe A et al. Flow-mediated dilation in brachial artery in the second half of pregnancy and prediction of pre-eclampsia. *J Hum Hypertens* 2003;17:697-704.

(327) Haas DM, Imperiale TF, Kirkpatrick PR, Klein RW, Zollinger TW, Golichowski AM. Tocolytic therapy: a meta-analysis and decision analysis. *Obstet Gynecol* 2009;113:585-594.

(328) Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2006;CD004454.

(329) Ahmed KT, Almashhrawi AA, Rahman RN, Hammoud GM, Ibdah JA. Liver diseases in pregnancy: diseases unique to pregnancy. *World J Gastroenterol* 2013;19:7639-7646.

(330) Verdonk K, Visser W, van den Meiracker AH, Danser AH. The renin-angiotensin-aldosterone system in pre-eclampsia: the delicate balance between good and bad. *Clin Sci (Lond)* 2014;126:537-544.

(331) Steyn DW, Odendaal HJ, Hall DR. Diurnal blood pressure variation in the evaluation of early onset severe pre-eclampsia. *Eur J Obstet Gynecol Reprod Biol* 2008;138:141-146.

(332) Fukushima T, Berumen M, Vargas N, Zadeh N, Hon EH. The effects of cardiovascular dynamics monitoring in the outpatient management of pregnancy hypertension. *Am J Obstet Gynecol* 2002;186:1207-1213.

(333) Pickering TG, Hall JE, Appel LJ et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 2005;45:142-161.

(334) Cnossen JS, Morris RK, Ter RG et al. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. *CMAJ* 2008;178:701-711.

(335) Niiranen TJ, Jula AM, Kantola IM, Kahonen M, Reunanen A. Home blood pressure has a stronger association with arterial stiffness than clinic blood pressure: the Finn-Home Study. *Blood Press Monit* 2009;14:196-201.

(336) Neilson JP, West HM, Dowswell T. Betamimetics for inhibiting preterm labour. *Cochrane Database Syst Rev* 2014;2:CD004352.

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Curriculum Vitae

Isabelle Fabry was born on May 30th, 1979 in Hasselt. She received undergraduate education (Latin-Greek) at the Humaniora Virga Jesse in Hasselt from 1991 until 1995, and at the Sint-Jozefcollege in Herentals from 1995 till 1997. In 1997 she started her medical education at the University Hasselt and later on at the Ghent University. In 2005 she obtained her medical degree with great distinction. Subsequently, she started her training in Internal Medicine at Ghent University Hospital. Simultaneously she worked as a co-investigator at the Drug Research Unit Ghent where she experienced the succession of phase I and II-trials. She used this experience in her PhD-fellowship at the Clinical Pharmacology Department at the Heymans Institute. Under the supervision of Prof. Dr. Lucas Van Bortel she learned non-invasive measurements to unravel the cardiovascular system. In 2010 she left the Heymans Institute to resume her clinical training with a special interest for Respiratory Medicine. She became a Pulmonologist at the end of 2014.

In the past few years she attended several courses on ICH-GCP and local, European and international legislation, data and time management, teaching, antibiotics policy, clinical pharmacology/pharmacotherapy and internal medicine. During her PhD-fellowship, she participated the Pharmacotherapy and the Artery Working Group at the Heymans Institute.

At January 1st 2015 she started her fellowship in Thoracic Oncology under the supervision of Prof. Dr. Veerle Surmont and Prof. Dr. Karim Vermaelen at the Department of Respiratory Medicine at Ghent University Hospital, headed by Prof. Dr. Guy Joos.

In January 2016 she will join the staff of the Department of Respiratory Medicine at the AZ Sint Jan Brugge-Oostende, Campus Henri Serruys.

Isabelle is living together with Sam Vander Eecken, Orthopaedic Surgeon/Micro-surgeon at AZ ZENO (Knokke-Blankenberge). She is the mother of Louis (°2007), Lucas (°2010) and Julie (°2013).

Isabelle has special interests in music.

A1-Publications as first author:

The influence of tocolytic drugs on cardiac function, large arteries, and resistance vessels.

Fabry IG, De Paepe P, Kips JG, Van Bortel LM; Eur J Clin Pharmacol. 2011 Jun;67(6):573-80. Epub 2011 Apr 15.

Different effects of tocolytic medication on blood pressure and blood pressure amplification.

Fabry I, De Paepe P, Kips J, Vermeersch S, Van Bortel L; Eur J Clin Pharmacol. 2011 Jan;67(1):11-7. Epub 2010 Nov 16.

Diagnosis and treatment of hypertensive disorders during pregnancy.

Fabry IG, Richart T, Cheng X, Van Bortel LM, Staessen JA.; Acta Clin Belg. 2010 Jul-Aug;65(4):229-36.

A1-Publication as co-author:

The use of diameter distension waveforms as an alternative for tonometric pressure to assess carotid blood pressure.

Kips J, Vanmolkot F, Mahieu D, Vermeersch S, Fabry I, de Hoon J, Van Bortel L, Segers P.; Physiol Meas. 2010 Apr;31(4):543-53. Epub 2010 Mar 5.

Oral Presentations

Hemodynamics in Breastfeeding

Arterial Meeting 01/2007, Heymans Instituut Gent

The form factor (FF) of pressure waveforms in a young population: difference between men and women;

Dries Mahieu UGent, ISABELLE FABRY UGent, Floris Vanmolkot, Jan de Hoon and Lucas Van Bortel UGent - ARTERY RESEARCH (2008) – Presented on Artery 2008

Influence of tocolytics on central and peripheral hemodynamics.

Oral presentation on the Spring Meeting of the Belgian Society of Fundamental and Clinical Physiology and Pharmacology 07/03/2009 and on the Arterial Meeting 07/04/2009, Heymans Institute Ghent and on the Joint Meeting of the Dutch and Belgian Hypertension Committee.

Effects of tocolytical medications on the peripheral and central hemodynamics of healthy non-pregnant women.

ISABELLE FABRY UGent, Peter De Paepe UGent and Lucas Van Bortel UGent - Presented on annual meeting Belgian Hypertension Committee 2009

Diagnostic Thresholds for the Office and Self-Measured Blood Pressure During Pregnancy

Oral presentation on the meeting of the Belgian Hypertension Committee, 10/2010

Hypertension in Pregnancy - Current Management

Oral presentation on the meeting of the Belgian Hypertension Committee, 10/2011

Should self-measured blood pressure be the standard follow-up during pregnancy?

Oral presentation on the meeting of the Belgian Hypertension Committee, 02/2011

Posters

Factors influencing the use of continuous positive airway pressure (CPAP); a literature study

ISABELLE FABRY UGent, Lucas Van Bortel UGent, Dirk Pevernagie UGent. – Presented on the Joint Meeting of the Czech and Belgian Hypertension Commitee 2006

The form factor (FF) of pressure waveforms in a young population: difference between men and women;

Dries Mahieu UGent, ISABELLE FABRY UGent, Floris Vanmolkot, Jan de Hoon and Lucas Van Bortel UGent - Presented on Artery 2008

Influence of tocolytics on central and peripheral hemodynamics

ISABELLE FABRY UGent, Peter De Paepe UGent, Lucas Van Bortel UGent – Presented on EACPT 2008

Effects of tocolytical medications on the peripheral and central hemodynamics of healthy female volunteers

ISABELLE FABRY UGent, Peter De Paepe UGent and Lucas Van Bortel UGent - Presented on Artery 2009

Effects of tocolytical medication on blood pressure and blood pressure amplification;

ISABELLE FABRY UGent, Peter De Paepe UGent and Lucas Van Bortel UGent - Presented on Artery 2009

The influence of tocolytic drugs on cardiac function, large arteries, and resistance vessels

ISABELLE FABRY UGent, Peter De Paepe UGent, Jan Kips UGent and Lucas Van Bortel UGent – Presented on ESH 2010

Different effects of tocolytic medication on blood pressure and blood pressure amplification

ISABELLE FABRY UGent, Peter De Paepe UGent, Jan Kips UGent, Sebastian Vermeersch UGent and Lucas Van Bortel UGent– Presented on ESH 2010

Reference values for Office and Self-measured blood pressure during pregnancy.

ISABELLE FABRY UGent, Tom Richart, Lutgarde Thijs, Jan Staessen and Lucas Van Bortel UGent – Presented on ESH 2011