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Faculty of Health Sciences
Department of Clinical Medicine

Dynamic functional assessment of maternal hemodynamics in human pregnancy

Åse Lillian Vårtun
A dissertation for the degree of Philosophiae Doctor – September 2016

HELSE NORD

UNIVERSITY OF TROMSØ

Cover photo

My grandfather built this house in 1917 with his hard work. I grew up at this farm. I compare myself to the old house and the pine tree in the backyard trying to stand firmly to reach my goal.

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Tromsø, September 2016

Åse Lillian Vårtun

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LIST OF ABBREVIATIONS

ACI	Acceleration index
BMI	Body mass index
BSA	Body surface area
CI	Cardiac index
CO	Cardiac output
CVP	Central venous pressure
DBP	Diastolic blood pressure
EDV	End-diastolic volume
HELLP	Hemolysis Elevated Liver enzymes Low Platelets
HR	Heart rate
ICG	Impedance cardiography
IUGR	Intrauterine growth restriction
IVC	Inferior vena cava
MAP	Mean arterial pressure
LVET	Left ventricular ejection time
LWCI	Left ventricular work-index
PAOP	Pulmonary arterial occlusion pressure
PE	Pre-eclampsia
PEP	Pre-ejection period
PI	Pulsatility index
PLR	Passive leg raising
PSV	Peak systolic velocity
SBP	Systolic blood pressure
SD	Standard deviation
SI	Stroke index
SV	Stroke volume
STR	Systolic time ratio
SVR	Systemic vascular resistance
SVRI	Systemic vascular resistance index
TFC	Thoracic fluid content
UtA	Uterine artery
UtA PI	Uterine artery pulsatility index
UtA RI	Uterine artery resistance index
VI	Velocity index

ABSTRACT

Introduction

Static parameters of maternal cardiovascular function have been studied well using a variety of methods. However, studies on dynamic assessment of maternal cardiovascular function are scarce. Gestational age related serial changes in maternal preload reserve have not been studied, and there is a need to establish normal reference intervals for functional hemodynamic parameters during pregnancy. Furthermore, how functional hemodynamics may be affected in high-risk pregnancies and whether it could be used to predict pregnancy complications has not been properly explored.

Objectives

The aim of this thesis was to investigate maternal functional hemodynamics in normal pregnancies and in pregnancies at risk of developing placental dysfunction disorders.

The main objectives were:

A. To investigate functional hemodynamic response to passive leg raising (PLR) in healthy pregnant women at 22-24 weeks of gestation and compare with non-pregnant women.
B. To investigate cardiovascular response to PLR in healthy pregnant women and establish longitudinal reference ranges for the second half of pregnancy.
C. To compare cardiac function, systemic hemodynamics and preload reserve among women with increased and normal uterine artery pulsatility index (UtA PI) at 22-24 weeks of gestation.

Methods

Systemic hemodynamics and cardiac function were evaluated during rest and after PLR to assess cardiovascular response to a change in preload using noninvasive impedance cardiography (ICG). Utero-placental circulation in pregnant women was evaluated using Doppler ultrasonography.

In a prospective cross-sectional study, 108 low-risk pregnant women (22-24 weeks of gestation) and 54 non-pregnant women (in the follicular phase of menstrual cycle) were examined to investigate differences in functional hemodynamics in response to PLR.

In a longitudinal study, cardiovascular function was serially assessed at baseline and after PLR at approximately 4-weekly intervals in 98 healthy pregnant women during 20-41 weeks of gestation to establish normal reference ranges for maternal functional hemodynamics.

In another prospective cross-sectional study, functional hemodynamics and utero-placental circulation were assessed in 620 unselected pregnant women during 22-24 gestational weeks to

investigate whether pregnant women at increased risk of developing placental dysfunction disorders as identified by abnormal UtA PI have a different functional hemodynamic profile compared to low-risk women.

Results

PLR caused significant changes in the majority of hemodynamic variables both in pregnant (at 22-24 weeks of gestation) and non-pregnant women. The hemodynamic response to PLR was similar in both groups with similar trend and magnitude of change (Δ %). Approximately, 15% of pregnant women and 11% of non-pregnant women increased their stroke volume (SV) above 10% after 90s of PLR. For the cardiac output (CO) the proportion was 13% and 18.5%, respectively.

The effect of modified preload caused by PLR on cardiac function and hemodynamics varied by gestation, and varied among individual pregnant women at different gestations. There was no significant association between the gestational age and % change in SV and heart rate (HR) from baseline to PLR. During PLR there was an increase in SV from 20^{+0} to 31^{+6} weeks of gestation, but later in gestation the SV was slightly decreased by PLR. The CO decreased after 24 weeks in response to PLR. The HR, blood pressure and cardiac contractility decreased by PLR throughout the second half of pregnancy. In response to PLR, the systemic vascular resistance (SVR) was reduced until 32 weeks, and then it slightly increased until term.

The mean arterial pressure (MAP) and SVR were significantly higher at baseline among pregnant women with high mean UtA PI compared to controls. 28.6% of women with high UtA PI developed pregnancy complications compared to 9.5% in the control group. However, the functional hemodynamic response to PLR was not different between groups. The SV increased significantly (4-5%) following PLR in both groups. whereas cardiac output remained unchanged.

Conclusions

Maternal hemodynamics is different in healthy pregnant women compared to non-pregnant women. In healthy pregnancies, the physiological response to PLR was not modified at 22-24 weeks of gestation.

Longitudinal reference ranges for maternal functional hemodynamics were established for the second half of pregnancy. Healthy pregnant women appear to have limited preload reserve, especially in the third trimester, and might be vulnerable to fluid overload and cardiac failure.

The functional hemodynamic profile of pregnant women with high UtA PI at 22-24 weeks was similar to that of controls, suggesting that its assessment is unlikely to improve the value of UtA Doppler in predicting pregnancy complications.

LIST OF ORIGINAL PAPERS

Paper I

Effect of passive leg raising on systemic hemodynamics of pregnant women: A dynamic assessment of maternal cardiovascular function at 22-24 weeks of gestation. *PLoS One. 2014 Apr 14;9(4):e94629.*

Paper II

Maternal functional hemodynamics in the second half of pregnancy: A longitudinal study. *PLoS One. 2015 Aug 10;10(8):e0135300.*

Paper III

Static and functional hemodynamic profiles of women with abnormal uterine artery Doppler at 22-24 weeks of gestation. *PLoS One. 2016 Jun 16;11(6):e0157916.*

1 INTRODUCTION

Measurements of heart rate (HR), stroke volume (SV), cardiac output (CO), mean arterial pressure (MAP), central venous pressure (CVP) and systemic vascular resistance (SVR) are generally used to assess maternal systemic hemodynamics. Non-invasive methods, such as Doppler echocardiography, impedance cardiography (ICG) and cardiac magnetic resonance imaging (cMRI) are often used to evaluate cardiovascular function, and have in many clinical situations replaced the more invasive methods that require cardiac catheterization. With the development and validation of noninvasive techniques it has become easier to perform repeated measurements and longitudinal studies during pregnancy. Methods that allow continuous measurement and monitoring of cardiovascular function over a time period are more useful in clinical settings. Although static measures of cardiovascular function are reasonably well studied during pregnancy, dynamic assessment of cardiovascular function has rarely been performed to assess physiological changes that occur with advancing gestation and to evaluate the role of functional hemodynamics in the prediction, diagnosis and management of pregnancy complications.

2 CARDIOVASCULAR PHYSIOLOGY

The cardiovascular system, which consists of the heart and the blood vessels, transports oxygen and nutrients to cells and tissues of the body, and removes carbon dioxide and waste products. The cardiac function is the ability of the heart to pump blood into the aorta and the pulmonary arteries resulting in adequate tissue perfusion required to meet metabolic demands of different organs. The cardiac cycle consists of two phases: diastole, when the ventricles relax and are filled with blood, and systole when the ventricles contract and pump blood into the systemic and pulmonary circulation. The total cardiac cycle can be divided into four different phases/periods: isovolumic ventricular relaxation and ventricular filling (rapid filling, slow filling and atrial contraction) constituting the *diastole*, and isovolumic ventricular contraction and ejection constituting the *systole*. The cardiac cycle is generally assumed to start with atrial contraction (P-wave on electrocardiogram) and end when the slow filling of the ventricle ends. Dynamic changes in myocardial motion (deformation) and ventricular pressure occur during the cardiac cycle. Changes in ventricular volume occur except during the isovolumic phases.

2.1 Factors affecting cardiac function

Cardiac function can be described by the ventricular pressure-volume changes that occur during the cardiac cycle and the time intervals of different phases/periods of the cardiac cycle. Cardiac function is affected by several intrinsic and extrinsic factors. The SV is the difference between the ventricular end-systolic volume (ESV) and the end-diastolic volume (EDV). The ejection fraction (EF), calculated as: EF=SV/EDV x 100 %, is a widely used parameter describing systolic function of the heart. CO is the product of SV and HR. SVR is calculated as: MAP-CVP/CO.

Myocardial Contractility

The heart consists of cardiac muscle fibers made up of two types of cardiac muscle cells, cardiomyocytes and cardiac pacemaker cells. The atria and ventricles consist of about 99% of cardiomyocyte cells, and each cell contains specialized myofibrils (sarcomeres), which are the contractile units of the muscle cells. These cells have the intrinsic ability to shorten and to lengthen the muscle fibers. The cardiac muscle contracts as a response to impulses (action potential) from the pacemaker cells (1%), which constitute the conducting system distributed throughout the heart.

Sympathetic and parasympathetic nerve fibers innervate the cardiac muscle cells (and the conducting system) coordinating contraction and relaxation of the cardiac muscle tissue to obtain an efficient pumping action of the heart. However, heart can pump efficiently even without any nerve supply or cardiac pacing (such as following cardiac transplantation) maintaining the CO and balance between systemic and pulmonary circulation.

Sympathetic stimulation by norepinephrine and epinephrine stimulates the cardiac muscle to contract faster and stronger. Sympathetic stimulation over a longer time period can cause cardiac hypertrophy, an increase of the ventricles wall thickness. There are two types of cardiac hypertrophy, eccentric and concentric hypertrophy. Eccentric hypertrophy results from e.g. aerobic training and pregnancy, and is caused by an increase of blood volume returning to the heart (volume overload) resulting in new sarcomeres in series by lengthening rather than thickening of the muscle. The ability of the heart to expand by receiving greater volume of blood enables the ventricle to generate greater forces. Concentric hypertrophy results from disease as a response to pressure overload, such as chronic hypertension. This results in an increase of the cardiac muscle mass that causes cardiac stiffness, but not the heart's ability to pump blood.

2.2 Preload

Preload is described as the wall stress of the ventricle by initial stretching of the cardiac myocytes just prior to contraction depending on the amount of blood returning into the ventricle [1]. Preload determines end-diastolic sarcomere length and therefore, the force of contraction. In an intact heart the length of sarcomeres, myofibrils, cannot be measured. However, the end-diastolic pressure (EDP) and the EDV are related to the degree of stretching of the myocytes, and can be used to describe preload.

The venous blood pressure, the circulating blood volume and the rate of venous return affect preload. The two main body "pumps" affect venous return:

1. The respiratory pump, where the intra-thoracic pressure is decreased during inspiration with an increase in the abdominal pressure followed by squeezing of the abdominal veins and increase of blood flow towards the right atrium.

2. The skeletal muscle pump, where the surrounding muscles squeeze the veins and pump blood back towards the heart.

Changes in venous compliance affect preload. Increased venous compliance (e.g. during spinal anesthesia) reduces preload, and a decrease in venous compliance (e.g. due to hemorrhage leading to vasoconstriction) results in an improved venous return and an increase in preload.

The EDP of the left ventricle correlates with left atrial pressure, which can be indirectly measured as pulmonary capillary wedge pressure (PCWP) using pulmonary artery catheterization (Swan-Ganz catheter).

The EDV is another surrogate for preload. The main factor determining the EDV is the ventricular filling time. The faster the heart rate, the shorter is the filling time, leading to a reduced EDV. Sympathetic stimulation of the venous system increases the venous return to the heart and the ventricular filling. An opposite response occurs by parasympathetic stimulation.

The ventricular wall stress can be expressed based on Laplace's law as: Wall stress = (pressure x radius)/2 x wall thickness. Preload can be calculated using echocardiography as: (LVEDV x LVEDR)/2*h*, where LVEDV is left ventricle end diastolic volume. LVEDR is left ventricle end diastolic radius (at the ventricle's midpoint) and *h* is thickness of the ventricle.

2.3 Afterload

Afterload is the load the ventricular myocardium faces during active force development, and it determines the degree of myocardial fiber shortening. In order to open the aortic and pulmonary valves, the pressure in the left and the right ventricle must be greater than the systemic and the pulmonary pressures, respectively. The SVR reflects the afterload of the cardiovascular system

and it is the main determinant of myocardial oxygen consumption. SVR represents the force or pressure the ventricle must overcome to eject blood into the aorta [2]. The pressure is assessed by measurement of the gradient between the beginning of the circuit (MAP) and the end (CVP). This value is then divided by the volume of blood flow i.e. CO. SVR = 1333.22 x (MAP-CVP)/CO. A conversion factor of 1333.22 is used to adjust the value into the units of force for SVR as dyne.s.cm^{-5} (1 mmHg = 1333.22 dynes.cm^{-2} and ml = cm^{3}). This can be simplified to: SVR, dyne.s.cm^{-5} = 80 (MAP, mmHg – CVP, mmHg)/CO, l/min. Some researchers have reported SVR as total peripheral vascular resistance (PVR or TVR) calculated as 80x(MAP/CO) mmHg/ml disregarding the CVP which is normally quite low [3] [4]. Normal SVR is 800-1200 dynes.s.cm^{-5}. An increase in afterload caused by, e.g. systemic hypertension or aortic valve disease, is followed by a decreased SV and CO.

Frank-Starling mechanism

The Frank-Starling mechanism was established from studies performed by Otto Frank and Ernest Starling in the late 19th and early 20th century. Frank observed that the strength of the ventricular contraction increased when the ventricle was stretched. Starling found that increased venous return to the heart and increased left ventricular EDP (LVEDP) resulted in an increase of SV.

The Frank-Starling mechanism (also called Starling's law of the heart) refers to the ability of the heart to change its contractility and stroke volume in response to changes in venous return and ventricular filling pressure. The force of ventricular contraction is directly proportional to the initial length of muscle fiber. During exercise increased volume of blood returns to the heart that causes an increase of venous return and end-diastolic volume resulting in stretching of the heart muscle. Thus, the more the ventricular muscle is stretched the more forceful is the ventricular contraction (within certain limits). The distension of the ventricle leads to greater ejection pressure and increased ventricular contractility, which will increase the SV and the CO due to increased preload (end-diastolic volume). An opposite effect occurs with a reduction in the velocity of fiber shortening and the velocity of ejection of blood resulting in reduced CO and SV [1].

2.4 Vascular physiology

The vascular system includes the systemic and the pulmonary circulation. In the adults under physiological conditions there is a balance between systemic and pulmonary circulations, i.e. pulmonary blood flow (Qp) = systemic blood flow (Qs). The blood volume and blood pressure

are the main determinants of end-diastolic volume (EDV), SV and CO. Approximately 70% of the total blood of the systemic circulation is stored in the venous system [5] and serves as a reservoir of blood. Veins are more compliant compared to arteries having the ability to accommodate changes in blood volume by being more distensible. Venous compliance is defined as; $\Delta V / \Delta P$, where ΔV is the change in volume of blood within a vein (or venous system) and ΔP is the change of intravenous distending pressure [5].

2.5 Factors affecting blood flow

Blood flows from high pressure to low-pressure regions. Blood flow (Q) = Pressure (P)/Resistance (R). Vascular resistance is determined by two factors; a) blood viscosity (ŋ) and b) blood vessel size [the length (L) and radius (r)], and it can be determined using the following formula: $R= (ŋ\ L/r^4) \times (8/\pi)$ or $R = 8L\eta/\pi r^4$. According to Poiseuille's law $Q = \pi r^4\ (P1-P2)/8L\eta$. Blood viscosity increases with increasing hematocrit of the blood. This can have an important effect on the resistance to flow in certain conditions. The most important determinant of changes in resistance is the radius of the blood vessel. If the radius increases two-fold, the resistance decreases sixteen-fold, resulting in sixteen-fold increase of flow at a constant pressure.

The major sites of resistance to flow are the arterioles participating in the regulation of arterial blood pressure. In low-resistance vessels, blood flows to organs with little loss in pressure. They act as pressure reservoir for maintaining blood flow during ventricular relaxation.

3 CARDIOVASCULAR ADAPTATION TO PREGNANCY

Pregnancy causes significant changes in the cardiovascular system by alteration in maternal cardiac function and hemodynamics [2, 6-9]. A century ago Lindhard showed that pregnant women have higher cardiac output (CO) than non-pregnant women [10]. Since then several studies on maternal hemodynamics have been performed using invasive and non-invasive methods (Tables 1, 2 and 3). Many of these studies have shown variable results depending on their study design, methodology and the position of the participant during examination [6].

Table 1. Studies on maternal hemodynamics in normotensive women using invasive methods.

No of participants	Study design	Method	Position	Gestation (weeks)	CO (L/min) range	SVR (dyne s/cm^5) range	MAP (mmHg) range	SV (ml) range	HR (beats/min) range	Author
1	L	Fick	Sitting	23-40	5.2-5.5					Lindhard (1915) [10]
68	C	Fick	Not described	6-40	4.29-4.60					Hamilton (1949) [11]
84	C	Fick	Not described	12-40	6.2-5.7					Palmer (1949) [12]
46	C	Fick	Not described	14-40	6.53-5.53	986-1244		70-58	99-96	Bader *(1955) [13]*
46	C	Fick	Not described	14-40	6.53-5.53	986-1244		70-58	99-96	Rose (1956) [14]
30	L	Dye	Not described	8-43	7.01-6.19			91-79	77.55-78.86	Walters (1966) [15]
5	L	Fick	Lateral	11-37	6.10-6.26		81.6-86.2	75.6-75.8	81.4-84.2	Lees (1967) [16]
11	L	Dye	Left lateral	20-40	6.9-5.7			94.5-69.0	73.4-83.2	Ueland (1969) [17]
10	C	Dye	Left lateral	36-39				95.5	78.2	Milsom (1983) [18]
10	C	TD	Left lateral	36-38	6.2	1210	90.3		83	Clark (1989) [19]
20	L	Fick	Sitting	8-40	3.8-4.6[#]			50 - 50	83-87[#]	Spätling (1992)[#] [20]

Dye, dye dilution and TD, thermodilution. C, cross sectional and L, longitudinal. CO, cardiac output; SVR, systemic vascular resistance; MAP, mean arterial pressure; SV, stroke volume and HR, heart rate. Hemodynamic parameters from cross sectional studies presented as mean values. [#]Spätling: value estimated from figure (box and whisker plot) given in manuscript.

Table 2. Studies on maternal hemodynamics in normotensive women using echocardiography.

No of participants	Study design	Position	Gestation (weeks)	CO (L/min) range	SVR (dyne s/cm^5) range	MAP (mmHg) range	SV (ml) range	HR (beats/min) range	Author
13	C	Left lateral	13-23	6.05			74.1	84.5	Rubler (1977) [21]
15			24-32	6.15			72.3	84.9	
12			40	5.88			69.7	85.1	
19	L	Left lateral	12-38	5.71-8.56		68-66	75-97	77-88	Katz (1978) [22]
18	C	Semi-recumbent	3.Tr	6.6	996	76.8	81.5	82.7	Easterling (1987) [23]
16	L	Left lateral	10-38	4.3-5.5	1519.9-1328.7	76.9-79.6	58.5-63.6	75-87.9	Mashini (1987) [3]
14	C	Left lateral	10-13	5.6	1143	76.3	78.6	71.4	Easterling (1988) [24]
16		Left lateral	35-40	6.7	988	76.1	82.1	83.6	
8	L	Left lateral	8-24	5.2-5.7	969-930	62-67	79-81	68-73	Capeless (1989) [25]
13	L	Left semi-lateral	5-38	5.40-7.22	1213-966	80.3-86	68.6-83.6	79-87	Robson (1989) [26]
20	L	Left lateral	15-35	6.13-7.25	1328-1151	97-100	77.3-83.0	74-82	Bolter (1990) [27]
16	C	Supine	24-36	8.41	821	76.71	95.79	83.8	Droste (1992) [28]
10	L	Semi-left lateral	5-35	5.24-5.78	1252-1257	90-91	74-68	76-85	Duvekot (1993) [29]
40	L	Left lateral	20-38	6.48-7.54					Thomsen (1993) [30]
18	L	Left lateral	8-39	6.7-8.5	1008-829	84-88	85-98	80-88	Mabie (1994) [31]
26	L	Left lateral	24-40	5.0-5.7	1360-1302	83-91	60-71	86-82	Hennessy (1996) [32]
30	L	Left-lateral	8-38	5.90-6.91	1080-946	80-82	92-96	64-72	Clapp (1997) [33]
34	L	Left lateral	10-38	5.8-7.35	1076.1-818.2	75.6-78.0	82.4-96.6	71.6-78.3	Geva (1997) [34]
76	L	Left lateral	15-36	5.0-5.8	1027-941	59-62	66-70	75-82	Gilson (1997) [35]
14	L	Left lateral	12-31	6.8-7.9	885-743	71-70	95-99	70-80	Poppas (1997) [36]
37	L	Left lateral	10-34	4.6-6.0	1485-1143	83-82	62-71	74-87	Mesa (1999) [37]
43	L	Semi-recumbent	12-33	5.6-6.6	1188-1023	79.6-79.9	67-77		Valensise (2000) [38]
13	L	Left lateral	10-34	6.75-6.85	1037-912	81.5-75.9	81.9-78.6	81.6-87.2	Del Bene (2001)[#] *[39]*
46	L	Not described	9-33	4.5-6.7	1386-895	85.1-82.6	64-76	71-89	Schannwell (2002) [40]
35	L	Left lateral	14-37	4.96-6.94	1214-902	74-74	66-87	75-79	Desai (2004) [41]
41	C	Lateral	28-31	6.75	949	78	77	87	Valensise (2006) [42]
104	C	Left lateral	11-38	6.34	995.39	76.47	79.60	79.87	Bamfo (2007) [43]
26	C	Left lateral	20-36	6.1	1088	79.5	73.6	84.3	Bamfo (2007) [44]

Table 2. Continuation.

Study design	No of participants	Position	Gestation (weeks)	CO (L/min) range	SVR (dyne s/cm^5) range	MAP (mmHg) range	SV (ml) range	HR (beats/min) range	Author
17	C	Left lateral	33-38	7.31	932.63	82.09	89.78	82.64	Bamfo (2007) [45]
16	L	Left lateral	12-34	5.6-5.7			81-75	70-78	Rang (2007) [46]
2352[§]	C	Left lateral	11-13±6	5.6	1190.8	83.3	73.5	76.0	Turan (2008)[§&] [47]
2337[&]				5.2	1253.7	83.3	70.5	75.0	
1119	C	Lateral	24	6.61	990	80	83	80	Valensise (2008) [48]
429	C	Lateral	24	6.57	1009	80	82	80	Vasapollo (2008) [49]
17	C	Left lateral	13-40	5.8-6.7	2062-1858	78-80	80-88	73-77	Abdullah (2012) [50]
26	C	Left lateral	≥ 32	5.8	993		74		Burlingame (2013) [51]
63	L	Left lateral	14-36	5.7-6.0	15-14.5	82.8-84.8	78-75	73-80	Estensen (2013) [52]
105	C	Left lateral	20-23	5.6	1067	80	72	81	Melchiorre (2013) [53]
29	C	Left lateral	37	5.6			79.4	71.8	McIntyre (2015) [54]
109	C	Left lateral	11-14	5.7	1059	77	76	75	Melchiorre (2016) [55]
105			20-23	5.9	1093	79	78	76	
102			28-32	6.4	977	83	80	82	
96			37-39	6.8	1000	83	83	79	

C, cross sectional and L, longitudinal. CO, cardiac output; SVR, systemic vascular resistance; MAP, mean arterial pressure; SV, stroke volume and HR, heart rate. Hemodynamic parameters from cross sectional studies presented as mean or median values. [#]Del Bene: SV calculated as left ventricular end-diastolic volume – left ventricular end-systolic volume. [§&]Turan: § = parous women and & = nulliparous women.

Table 3. Studies on maternal hemodynamics in normotensive women using impedance cardiography.

No of participants	Study design	Position	Gestation (weeks)	CO (L/min) range	SVR dyne s/cm^5) range	MAP (mmHg) range	SV (ml) range	HR (beats/min) range	Author
30	C	Left lateral	16-38	7.45			94.22	80.9	Lechner (1978) [56]
19	L	Left lateral	8-40	6.8 -5.0			90-65		Atkins (1981) [57]
14	L	Supine	15-40	7.2-6.6		82-90	103-86	71-76	Myhrman (1982) [58]
20	C	Left lateral 45°	36-40	6.6	869.0	70.8	93.2	71	Milsom (1984) [59]
49	L	Left lateral	5-41	5.32-4.55	1341-1912		67.3-54.2	79-84	Heilmann (1993)[#] [60]
50	L	Sitting	10-42	7.26-6.37	966-1118	87-86	85-70	87-92	van Oppen (1996) [61]
18	C	Left lateral	37	7.07	827.75	71.5	80	84.06	San-Frutos (2005) [62]
100	C	Left lateral	36-39	6.8			79.7	86.1	Tamás (2007) [63]
20	L	Not described	10 - >30	6.91-5.76	918.40-1244.00	78-86	92.53-65.31	74-88	Moertl (2009) [64]
53	L	Supine 45°	22-40	5.5-5.8	1112-1179	78-87	74-70	75-82	Flo (2010) [7]
103	C	Lateral	38	6.10	1103.27	88.05	65.13	95.25	Jia (2010) [65]
48	L	Left lateral	12-35	6.7-5.9		74.5-80.6	89.6-71.3	75.9-84.7	Moertl (2012) [66]
26	C	Left lateral	≥ 32	6.4	921		84		Burlingame (2013) [51]
28	L	Supine 45°	12-36	7.0-7.0	911-946		89.5-79.1	81-90	D'Silva (2014) [67]
32	C	Supine 45°	22-24	6.12	1020.63	80.23			Flo (2014) [68]
13	C	Supine	38	7.6		95	84	95	Gyselaers (2014) [69]
23	C	Supine lateral tilt	20-27	6.7	824	76.6	77.8	87.7	Morris (2014) [70]
23			28-33	6.6	1020.6	78.0	74.0	90.2	
21			34-40	5.6	1164	82.0	64.2	89.8	
218	C	Standing	12	7.1		85	75	94	Oben (2014) [71]
108	C	Supine 45°	22-24	6.61	938.61	78.88	84.16	81.17	Vårtun (2014)[*]
22	C	Standing	37	7.3		99.5	77.5	97	Gyselaers (2015) [72]
47	C	Supine 45°	39	7.8	893	84	98	80	Marques (2015) [73]
29	C	Left lateral	37	6.1			83.1	74.2	McIntyre (2015) [54]
98	L	Supine 45°	20-40	6.58-7.11	956.73-971.22	80.10-86.56	82.97-81.68	82.13-90.37	Vårtun (2015)[**]
557	C	Supine 45	22-24	6.26	993.34	78.66	80.73	79.91	Vårtun (2015)[***]

C, cross-sectional study and L, longitudinal study. PLR, passive leg raising. CO, cardiac output; SVR, systemic vascular resistance; MAP, mean arterial pressure; SV, stroke volume and HR, heart rate. [#]Heilman: CO calculated from SV and HR given in the manuscript. [*]Vårtun: paper I; [**]Vårtun: paper II and [***]Vårtun: paper III.

In early pregnancy there is a significant fall in mean arterial pressure (MAP) and SVR. These alterations are also shown in the mid-luteal phase even before pregnancy occurs [74]. As a response to the fall in SVR, the CO, HR and SV increase already from 5 to 8 weeks of gestation [6, 25, 29, 33, 75-77]. Circulating blood volume increases by approximately 50%. The increase in plasma volume is larger than the increase in the red cell mass resulting in a physiological hemodilution [8, 75, 77-79]. Hytten and Paintin observed a gradual increase in plasma volume reaching a plateau of 1250 ml above non-pregnant level in the third trimester [75]. Pirani et al found a 40 % increase in plasma volume from 2635 ml at around 12 weeks to 3700 ml at 30-34 weeks among 56 primigravidae [79]. Similar observations were made by others reporting an increase in plasma volume from gestational weeks 6-8 until 28-30 weeks [9, 80]. The cardiovascular responses in early pregnancy result in decreased afterload and increased preload persisting until approximately the end of the second trimester. Thereafter, the hemodynamic variables remain relatively stable or fall slightly until term [6, 26, 81, 82]. Failure to increase plasma volume is probably involved in the development of complications such as pre-eclampsia (PE) and intrauterine growth restriction (IUGR) [83]. The maternal cardiovascular changes and adaptations during pregnancy are necessary to maintain adequate utero-placental perfusion, which is essential to supply the growing fetus with oxygen and nutrition [2, 9, 82].

3.1 Blood pressures

The ability to perfuse the maternal organs and the feto-placental unit depends on the maternal blood pressure, which is the product of CO and SVR [2]. MAP represents the average blood pressure during the cardiac cycle, and is calculated as DBP + (SBP-DBP)/3, where DBP is diastolic blood pressure and SBP is systolic blood pressure. Maternal blood pressure decreases by approximately 10% at 7-8 weeks of gestation reaching the lowest value (nadir) at gestational weeks 16-20 [26, 33, 77]. Other reports have shown that the blood pressure and the SVR fall to a nadir at 22-24 weeks of gestation [7, 33, 81]. DBP decreases significantly until 20 gestational weeks, then rises progressively towards term, whereas SBP is relatively constant until 36 weeks of gestation [26]. Clark et al observed no significant difference in MAP between pregnant women at 36-38 weeks of gestation and non-pregnant women 11-13 weeks postpartum [19].

During early pregnancy, the hormonal milieu is changed with an elevation of progesterone level and secretion of local mediators such as prostaglandins and nitric oxide (NO) exerting a vasodilatating effect on the arterial and venous vasculature [29, 81]. The atrial compliance is increased leading to a decrease in SVR to accommodate for the increased blood volume [84].

Chapman et al found that arterial vasodilation stimulates activation of renin-angiotensin-aldosterone system resulting in a decrease of SVR [74].

3.2 Heart rate

The heart rate increases from about 5 weeks of gestation [6, 29] throughout pregnancy as a compensatory response to the decrease in SVR [6, 26, 29, 31]. In a longitudinal study, Mabie et al found an increase in HR by 29% from the first to the third trimester [31]. Hunter and Robson, and Flo et al report a maximum increase of HR at 32 and 34 weeks, respectively, with a slight decrease towards term [6, 7]. Mahendru et al made similar observations, and they found a significant increase of HR until the third trimester by about 13 beats per minute [82]. The HR was significantly higher among multiparous women compared to nulliparous women, and HR reversed to pre-pregnancy level at 14-17 weeks after delivery [82]. Clapp and Capeless found that the heart rate returned to baseline level at 12 weeks postpartum [33].

3.3 Stroke volume

The SV increases from eight to 20 weeks of gestation to approximately 20-30% above the non-pregnant values [6, 25, 29, 33]. Clapp and Capeless observed a maximum increase in SV to 97 ml at 24 weeks [33]. During the third trimester of pregnancy, the SV is relatively stable or slightly lower towards term [6, 29, 33].

3.4 Cardiac output

CO increases by 40-50% above non-pregnant values from 5 weeks of gestation reaching maximum at 28-32 gestational weeks [6, 13, 17, 26, 29]. The increase in CO is approximately 1.5 L above the pre-pregnancy values [11], resulting from an increase in HR and SV [6, 33, 34, 81]. There are conflicting observations regarding changes in CO from the second half of pregnancy until term. Some authors have reported a steady state [6, 33] whereas others report a steady increase towards term [22]. In a longitudinal study, Flo et al found that CO increased significantly from 5.5 L/min at 22 weeks to 5.8 L/min at 34 weeks of gestation with no further change until term [7]. Others have found a decrease of CO in the second half of normal pregnancies until term [13, 29, 34]. The variation in absolute values of CO may be explained by inter-individual differences among pregnant women, maternal position during investigation, study design and method used to measure the CO [22, 85-87]. In addition, several studies have estimated changes of CO using postpartum values at various time intervals to represent non-pregnant values [52].

Clapp et al investigated 30 healthy women before pregnancy, throughout gestation and 12, 24 and 52 weeks postpartum [33]. They found significant differences between pre-pregnancy CO and lower CO values in pre-pregnancy state compared to postpartum [33]. The observed reduction of CO during investigation in the supine position in late pregnancy may result from compression of inferior vena cava by the enlarged uterus causing reduced venous return to the heart [88, 89]. Approximately 5% of women experience hypotension in the flat supine position during late gestation with symptoms of dizziness, headache or nausea [88].

3.5 Systemic vascular resistance

SVR is affected by changes in blood volume, vessel diameter and viscosity of the blood, all of which are affected by pregnancy. A study from Robson et al has shown a progressive fall of SVR by 34% from early pregnancy (5 weeks) to 20 gestational weeks in accordance with reduction in the DBP [26]. They observed a small increase of SVR towards term [26]. Other studies have reported similar reduction of SVR from six gestational weeks, reaching a nadir between 14 and 24 weeks of gestation, followed by an increase to pre-pregnancy values towards term [7, 13, 19, 29, 33, 81, 90]. Flo et al demonstrated an increase of SVR from gestational weeks 22 until term [7]. The plasma volume increases in pregnancy, but the CVP and the pulmonary capillary occlusion pressure (PAOP) remain unchanged [19]. This might be a result of reduced SVR and ventricular dilatation due to increased end-diastolic volume (preload).
Summary of results of CO, SVR, MAP, SV and HR from previously published studies are presented in Table 1, 2, 3 and 4.

Table 4: Studies on maternal hemodynamics in normotensive women at different body positions using invasive and noninvasive methods.

No of participants	Study design	Method	Position	Gestation (weeks)	CO (L/min) range	SVR (dyne /cm^5) range	MAP (mmHg) range	SV (ml) range	HR (beats/min) range	Author
5	L	Fick	Lateral	11-37	6.10-6.26					Lees (1967) [16]
			Supine		6.06-5.31					
11	L	Dye	Supine	20-40	6.4-4.5			88.3-52.2	74.4-85.5	Ueland (1969) [17]
			Lateral		6.9-5.7			94.5-69.0	73.4-83.2	
			Sitting		5.9-5.2			73.6-57.8	83.4-89.4	
12	C	Echo	Left lateral	40	5.88			69.7	85.1	Rubler (1977) [21]
			Supine		4.63			54.6	86.3	
19	L	Echo	Left lateral	12-38	5.71-8.56		68-66	75-97	77-88	Katz (1978) [22]
			Supine		6.21-8.01		73-79	82-87	76-92	
30	C	ICG	Standing	16-38	7.36			80.28	96.5	Lechner (1978) [56]
			Supine		6.90			85.54	83.5	
			Left lateral		7.45			94.22	80.9	
14	L	ICG	Supine	15-40	7.2-6.6		82-90	103-86	71-76	Myhrman (1982) [58]
			Left lateral		6.2-5.3			89-78	70-68	
			Right lateral		6.2-5.9			89-83	70-71	
10	C	ICG	Left lateral	36-39				83.8	78.2	Milsom (1983) [91]
			Right lateral					71.7	84.5	
			Supine					68.8	87.0	
10		Dye	Left lateral	36-39				95.5		
			Right lateral					84.7		
			Supine					74.5		
10	C	ICG	Left lateral 45°	36-40	6.6	869.0	70.8	93.2	71	Milsom (1984) [59]
			Supine		5.5	1335.5	87.2	75.5	73	
			Right lateral 45°		5.9	1143.2	82.7	82.3	73	
			Lithotomy		5.9	1150.7	82.0	84.0	71	
			Standing		7.1	1000.8	86.7	89.9	79	

Table 4: Continuation.

No of participants	Study design	Method	Position	Gestation (weeks)	CO (L/min) range	SVR (dyne s/cm^5) range	MAP (mmHg) range	SV (ml) range	HR (beats/min) range	Author
14	C	Echo	Left lateral	10-13	5.6	1143	76.3	78.6	71.4	Easterling (1988) [24]
			Sitting		4.4	1552	80.9	53.3	82.9	
			Standing		3.8	1730	80.0	39.9	97.1	
16	C		Left lateral	35-40	6.7	988	76.1	82.1	83.6	
			Sitting		5.7	1213	80.6	66.5	87.1	
			Standing		5.0	1367	81.1	51.3	100.3	
16		Echo	Supine	24-36	8.41	821	76.71	95.79	83.8	Droste (1992) [28]
			Standing		6.22	1157	85.84	65.17	95.0	
13	L	Echo	Standing	10-34	5.84-6.66	1301-1079	89.1-87.6	57.6-61.9	100.8-109.0	Del Bene (2001)* [39]
			Left lateral		6.75-6.85	1037-912	81.5-75.9	81.9-78.6	81.6-87.2	
			Standing		5.60-6.80	1299-1031	86.6-84.1	59.4-69.4	93.9-98.0	
100	C	ICG	Supine	36-39	6.7			71.2	95.5	Tamás (2007) [63]
			Left lateral		6.8			79.7	86.1	
20	C	ICG	Supine 45°	32-35	5.9			72.1	86.0	Flo (2010) [7]
			Left lateral		5.6			75.9	77.0	
			Supine 45°	36-39	5.5			72.0	79.0	
			Left lateral		5.4			74.5	73.1	
6	C	CMR	Supine	20	6.5			76.0	80.5	Rossi (2011) [92]
			Left lateral		6.5			90.9	72.3	
8			Supine	32	5.6			71.2	80.8	
			Left lateral		6.9			94.8	75.2	
26	C	ICG	Left later	≥ 32	6.4	921		84		Burlingame (2013) [51]
			Seated 60º		6.1	1050		78		
28	L	ICG	Supine 45°	12-36	7.0-7.0	911-946		89.5-79.1	81-90	D'Silva (2014) [67]
			Standing		7.0-7-6	1002-940		75.7-77.6	94-99	
			Supine 45°	26-28	7.4	860		86.0	88	
			Standing		7.8	872		81.3	98	

Table 4: Continuation.

No of participants	Study design	Method	Position	Gestation (weeks)	CO (L/min) range	SVR (dyne s/cm^5) range	MAP (mmHg) range	SV (ml) range	HR (beats/min) range	Author
108	C	ICG	Supine 45°	22-24	6.61	938.61	78.88	84.16	81.17	Vårtun (2014)*
			PLR 45°		6.62	894.72	75.32	85.74	78.72	
47	C	ICG	Supine 45°	39	7.8	893	84	98	80	Marques (2015) [73]
			PLR 45°		7.7	906	85	98	78	
			PLR left lateral		7.8	913	86	101	77	
			PLR right lateral		7.6	960	88	99	77	
14	L	CMR	Left lateral	12-36	5.8-6.3#		76-80	81-84#	70-74	Nelson (2015)# [93]
			Supine		5.5-5.7#			81-72#	69-80	
98	L	ICG	Supine semi-recumbent	20-40	6.58-7.11	956.73-971.22	80.10-86.56	82.97-81.68 84.11-80.68	82.13-90.37	Vårtun (2015)**
			PLR 45°		6.54-6.73	906.22-976.59	75.52-83.29		79.59-85.32	
557	C	ICG	Supine semi-recumbent	22-24	6.26	993.34	78.66	80.73	79.91	Vårtun (2015)***
			PLR 45°		6.31	941.61	75.88	83.33	77.67	

Dye, dye dilution; Echo, echocardiography; ICG, impedance cardiography and CMR, cardiac magnetic resonance. C, cross-sectional and L, longitudinal. PLR, passive leg raising. CO, cardiac output; SVR, systemic vascular resistance; MAP, mean arterial pressure; SV, stroke volume and HR, heart rate. Hemodynamic parameters from cross sectional studies given as mean or median values. *Del Bene: SV calculated as left ventricular end-diastolic volume – left ventricular end-systolic volume. #Nelson: values estimated from the figures (graphs) given in the article. *Vårtun: paper I; **Vårtun: paper II and ***Vårtun: paper III.

3.6 Cardiac function in pregnancy

Pregnancy causes structural changes of the heart induced by altered preload, afterload and HR [81]. The increased blood volume following a rise in venous return and venous filling leads to an increased stretching of cardiac muscle fibers before contraction. The left ventricle (LV) mass and wall thickness increase from 12 weeks of gestation until the third trimester [22, 26]. The structural changes of the LV cause alteration of the heart's position. The elevated diaphragm due to the enlarged gravid uterus pushes the heart upwards and rotates it forwards [94, 95]. Echocardiographic studies using Doppler have shown that the LV wall is thickened and the cardiac mass increased during pregnancy [22, 26, 96]. Robson et al observed a progressive increase in both LV mass and thickness from gestational weeks 12-38 by 52% and 28% above pre-pregnancy values, respectively [26]. Kametas et al report similar results; they found 52% increase in LV mass, and LV end-diastolic and end-systolic diameters increased by 12% and 20%, respectively [97]. In addition, they found a 40% increase in left atrial diameter, 12% increase in LV end-diastolic diameter, and a 20% increase in LV end-systolic diameter during gestation compared to non-pregnant. Simmons et al found in their study among normotensive women that the LV wall thickness increased by 11% during pregnancy [96]. Similar results were reported by Estensen et al, who observed a slight increase in LV wall thickness from the second to the third trimester [52]. They found an increase of 23% in LV EDV with a decrease of 11% in LV EF indicating that the LV contractility is reduced during normal pregnancy. Other studies report different results regarding to the heart's contractility during pregnancy. Mone et al and Geva et al also report decreased cardiac contractility during pregnancy [34, 98]. Two other studies report increased cardiac contractility during pregnancy [21, 35]. Clark et al observed that pregnancy is not associated with hyperdynamic LV function [19], and recently Melchiorre et al showed that the remodeling of the heart with a hypertrophy of the LV maintains the performance of the LV and the myocardial oxygenation in pregnancy [84].

Analysis of systolic time intervals such as the left ventricular ejection time (LVET) and the pre-ejection period (PEP) provide information about the function of the left ventricle and the cardiac performance. LVET and PEP represent the duration of left ventricular ejection (mechanical systole) and the phase of isovolumetric ventricular contraction time (electrical systole), respectively [71]. The systolic time ratio (STR) is defined as the ratio of PEP and LVET (STR = PEP/LVET). Burg et al found that PEP decreased from the first to the second trimester [99]. Thereafter, they observed an increase towards term. LVET decreased throughout pregnancy. Katz et al observed similar reduction of LVET [22]. Liebson et al found that PEP increased and

LVET decreased during gestation [100]. These two variables relating to the systolic time intervals indicate decreased cardiac contractility among normotensive women during pregnancy. All three studies showed an increase in LVET during postpartum period. Burg et al and Liebson et al report contrasting results regarding PEP in postpartum period, showing an increase and a decrease, respectively [99, 100]. Estensen et al observed reduction of LV contractility during normal pregnancy due to reduced LVET and ejection fraction compared to 6 months postpartum [52]. Their findings suggest that pregnancy induces a larger load on the cardiovascular system than previous studies have assumed. Other variables have been used to describe cardiac contractility and systolic function using impedance cardiography, such as the acceleration index (ACI), the velocity index (VI), and left ventricle work index (LCWI) representing cardiac work [51, 65, 69, 71].

3.7 Utero-placental circulation

The left and right uterine arteries originate from the internal iliac arteries, supply the uterus and form anastomoses with the respective ovarian arteries. The uterine arteries branch into arcuate arteries, then into radial arteries, and finally into spiral arteries penetrating the outer and middle thirds of the myometrium [101, 102]. Approximately 80 % of the total utero – placental blood flow comes from the uterine arteries [103].

Development of placenta starts with the trophoblast cell lineage 4-5 days after conception. As pregnancy advances, the trophoblast cells further differentiate into specialized subtypes such as multinucleated syncytiotrophoblasts and mononuclated cytotrophoblasts [104, 105]. Following this, a fluid-filled space occurs within the syncytiotrophoblast layers forming a large lacuna that surrounds the embryo. The syncytium enables invasion and implantation into the interstitium of the endometrium (decidual stroma), thereby establishing direct contact with the maternal blood cells [104]. Thereafter, the cytotrophoblast cells differentiate into villous structures as chorionic villi protruding into the intervillous space [104]. The chorionic villi continue to grow throughout the pregnancy causing an increase in placental mass and surface, to secure adequate exchange of gases, nutritional substrates and metabolic waste products between the fetus and the mother [106]. The extravillous trophoblast cells invade and replace the endothelial and muscular layer of the maternal spiral arteries [102, 104]. Following this, the spiral arteries open into the intervillous space allowing the maternal blood flow to the fetus. The trophoblast invasion is complete at 18-20 weeks of gestation [107]. Physiological changes resulting from spiral artery remodeling by the trophoblast cells and subsequent vasodilatation cause increased artery diameter and reduced vascular resistance [103, 105, 108].

3.8 Utero-placental Doppler indices

Indices related to the blood flow of the uterine arteries (UtA) such as pulsatility index (PI), resistance index (RI) and systolic /diastolic ratio (S/D) have been used to predict risk of adverse pregnancy outcomes such as PE, IUGR, and placental abruption. These indices are calculated from the Doppler derived blood flow velocity waveforms of the UtA and increased values of these indices have been implied to be surrogate measures of increased uterine vascular resistance [109]. Diastolic notching in the early diastolic phase of the cardiac cycle in the UtA waveform is another indirect sign of reduced blood flow and increased UtA vascular resistance [110]. An increase of UtA PI or RI, and unilateral or bilateral notching may indicate an increased risk of developing pregnancy complications [111]. However, UtA notching may be a normal finding in the first trimester before the utero-placental circulation is fully established [112].

Several studies have used Doppler ultrasonography in the evaluation of UtA blood flow pattern to obtain information about the utero-placental circulation [113, 114]. The reduction in impedance to flow in the UtA during pregnancy reflects trophoblastic invasion of the spiral arteries and their conversion into low-resistance vessels [115]. Campbell et al were the first to report the use of Doppler ultrasonography of the UtA to identify risk of pregnancy complications [116]. There are discrepancies between studies regarding the value of UtA Doppler indices in predicting pregnancy outcomes. This might be due to differences in measurement techniques, the definition of abnormal blood flow velocity waveform pattern and cut off values of indices used [117]. Previous studies have used different cut-offs or percentiles values of PI or RI together with or without bilateral notches for screening women for the risk of developing pregnancy complications. Papageorghiou et al found that 2.2% of pregnant women developed PE with a mean UtA PI >1.6 (95% percentile), and the presence of bilateral notches were highly associated with high PI when examined during 22-24 weeks of gestation [118]. Rizzo et al found that 4.7 % of pregnant women at 20-24 weeks with mean PI >1.63 and bilateral notches developed PE [119]. Abnormal uterine artery blood flow is a good predictor of early-onset PE, but has limited value in predicting late-onset PE [120]. Measurements performed in the second or third trimesters have a higher predictive value than those performed in early pregnancy. Among women with pre-existing cardiac disease a higher incidence of abnormal UtA flow is found, as the utero-placental flow probably depends on maternal cardiac performance [121].

4 PLACENTAL DYSFUNCTION DISORDERS

Placental dysfunction can cause miscarriage, hypertensive pregnancy disorders, gestational diabetes, intra-uterine growth restriction and fetal death. These conditions have long-term consequences for the mother and her offspring.

4.1 Hypertensive disorders

The hypertensive disorders of pregnancy include gestational hypertension, pre-existing chronic hypertension, PE and eclampsia [122].

4.2 Gestational hypertension

Gestational hypertension is characterized by an increase of maternal SBP and DBP ≥ 140/90 mmHg, measured at least two times 4-6 hours apart after 20 weeks of gestation [123-126]. Blood pressure ≥ 140/90 mmHg before 20 weeks of gestation is defined as chronic or pre-existing hypertension, and the risk of adverse pregnancy outcome is increased [124, 127]. Blood pressure ≥ 160/110 mmHg for at least 6 hours is considered to be severe hypertension [128].

4.3 Pre-eclampsia

PE is a complication affecting 2-8% of pregnant women worldwide, and is characterized by new onset of hypertension with proteinuria after 20 weeks of gestation [123, 129]. Proteinuria is defined as urine protein concentration of 300 mg/L or more (≥1+ on dipstick) at least on two occasions and 4-6 hours apart [123, 124]. PE can affect several organs including kidney, liver, brain and the clotting system [42, 106, 124, 130-132]. The disorder is a major cause of maternal and perinatal morbidity and mortality [42, 106, 123, 124, 130, 133]. Maternal deaths from pre-eclampsia and eclampsia account for up to 15% of maternal mortality, and it is 100 to 200 times higher in developing countries (Africa and Asia) than developed countries (Europe and North America) [130, 134]. The rate of PE in developed countries vary from 1.4% to 4%, and the overall risk of developing PE in Norway is 3.6% [135, 136].

PE causes changes in maternal hemodynamics. The SVR is increased and CO is often lowered compared to normotensive pregnancy [53, 90]. The pathogenesis of PE is currently thought to arise from placental dysfunction affecting the maternal endothelium resulting in systemic vascular complications [106, 131, 137]. Several acute maternal complications can evolve following PE including eclamptic fits, stroke, placental abruption, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), pulmonary edema, liver hemorrhage or rupture, renal failure and death [134]. Neonatal complications from PE include preterm delivery, IUGR, hypoxia, neurologic injury and perinatal death depending on gestational age

and severity of the disease [123]. Pre-eclampsia is a heterogeneous condition, and term PE probably includes different diseases. Early-onset PE is defined as onset before 34 weeks of gestation, and late PE when the condition is diagnosed after 34 gestational weeks [48]. Early-onset PE is often associated with placental abnormality due to insufficient utero-placental blood flow. IUGR, premature delivery, and severe maternal morbidity are associated with the early-onset form of PE [48, 106, 125, 131, 138, 139]. Late-onset PE is considered to be superimposed upon a pre-existing maternal cardiovascular condition such as high blood pressure, diabetes or various organ diseases [140]. Approximately 80 % of PE worldwide, is late onset PE associated with an appropriately grown baby [138]. A previous study by Valensise et al observed significantly higher CO and lower TVR among women with late onset PE compared to early onset PE [48]. Risk factors for developing PE are previous PE, pre-existing hypertension, primiparity, maternal age < 18 or > 40 years, multiple pregnancy, renal or rheumatic disease, obesity and a family history of hypertensive disorders of pregnancy [120, 123, 131, 141, 142]. However, more than 50% of the women who develop PE have no risk factors in their history, and many women with risk factors mentioned above do not develop the disorder. Women developing PE are at increased risk of cardiovascular diseases (CVD) later in life, and additional risk factors such as high levels of cholesterol, glucose and abdominal obesity increase the remote risk for CVD further [132, 143-145]. The causes of PE are unknown, and currently there are no precise criteria for prediction or prevention of PE [106, 123, 131, 139]. Early identification of women at risk for developing PE is crucial to assure adequate antenatal care and eventually prophylactic treatment [146]. Delivery and removal of the placental tissue is the only definite cure [137].

4.4 Intrauterine growth restriction

A fetus or neonate is defined as small for gestational age (SGA) when the (estimated) weight is below a certain percentile, usually the < 10^{th} percentile [147]. The majority of these babies are healthy and only constitutionally small. During pregnancy they will generally grow appropriately although in the lower percentiles [4].

IUGR is characterized also by low birth weight, most commonly defined as weight < the 10% percentile. These fetuses have failed to reach their genetically determined growth potential. There is often asymmetric growth with an abdominal size that is smaller compared to the size of the head, and the fetal growth is slower than expected. Mostly, IUGR is caused by placental insufficiency and the umbilical (and/or UtA) Dopplers are usually abnormal [113].

5 METHODS OF ASSESSING MATERNAL CARDIOVASCULAR FUNCTION

Different methods have been used to investigate systemic hemodynamics and cardiac function in pregnant women, and to monitor critically ill patients. Two basic categories are available, invasive and non-invasive methods. In clinical settings both methods are used. Non-invasive methods are more appropriate for research purposes among especially in healthy pregnancies.

5.1 Invasive methods

5.1.1 Fick principle

The Fick principle was first described and developed by Adolf Eugen Fick in 1870 and used for the assessment of CO. The method has been described as the "gold standard" for determination of CO, based on oxygen consumption by an organ by calculating the difference between the arterial (A) and the venous (V) oxygen content.

Oxygen is the most commonly used marker in the determination of CO. The oxygen consumed over time is calculated from measurement of oxygen concentration of venous and arterial blood using the Fick's equation; $VO_2 = (CO \times C_A) - (CO \times C_V)$, where VO_2 is oxygen consumption in ml of pure gaseous oxygen per minute, C_A is oxygen concentration of arterial blood, C_V is oxygen concentration of mixed venous blood. From these measurements cardiac output can be calculated as; $CO = VO_2 / (C_AO_2 - C_VO_2)$, where $(C_AO_2 - C_VO_2)$ is the arteriovenous oxygen content difference [148, 149]. Among critically ill patients who are hemodynamically unstable, and need breathing assistance, expired air measurement and arterial blood sampling are necessary for the determination of CO. It is one of the most accurate techniques when the CO is low, but requires repeated measurements, and is not very practical in clinical and research settings.

5.1.2 Dye indicator dilution

During the 1890's, Stewart introduced an indirect method for determination of CO [150]. Later Hamilton refined this technique. The technique is based on injection of a known amount of an indicator dye into one site of the circulatory system, and the measurement of the concentration of the dye at another site after certain time intervals. Then a dilution curve of the dye can be constructed, from the concentration of the dye obtained at different time intervals. Cardiac output is calculated from the time-concentration plot by using the equation: $CO = (I \times 60)/(C \times t)$, where I is the amount of dye injected (mg), 60 is conversion factor from seconds to minutes, C is the mean concentration of dye (mg/L) during curve duration, t is time during curve duration

in seconds [151]. This method is more accurate when the CO is high. The drawbacks of this method are the need for multiple blood samples and a device for measuring of the concentration of the indicator.

5.1.3 Thermodilution

The thermodilution technique to measure CO was first described in the 1950's [152]. In the 1970's this method was shown to be reliable and reproducible by Swan and Ganz using a temperature sensing pulmonary artery catheter (PAC), known as the Swan-Ganz catheter. The method is based on the indicator dilution principle measuring temperature change of the indicator as heated or cooled fluid. A solution with known temperature is injected rapidly into the pulmonary artery via a catheter. This provides direct access to the right heart. The temperature of the blood is measured downstream at a known distance in the pulmonary artery by a thermistor bead embedded in the same catheter. CO is determined from a time-temperature change curve using the modified Stewart-Hamilton equation; CO = (Ta-Tb) x VI x K /$\int$dT/dt, where Ta is the temperature before injection, Tb is the temperature after injection, VI is the volume of the injected substance, K is a constant, and dT/dt is the change in temperature per change in time [148]. Calculation of CO from a measured time-temperature curve shows reproducible values, as the degree of temperature change is directly proportional to the CO. A slow temperature change indicates a low CO; a rapid shift of temperature indicates a high CO, and averaging repeated measurements improves the accuracy of the method. Swan-Ganz thermodilution method is a useful tool for clinicians and it is used in the assessment and guide management of critically ill patients. The method is referred to as the clinical "gold standard" method of hemodynamic monitoring when new technologies are compared and validated.

5.2 Noninvasive methods

Noninvasive methods are simpler to use and constitute less risk compared with the invasive methods. Such techniques offer assessment of absolute values as well as trend analysis of cardiac output and other hemodynamic variables.

5.2.1 Impedance cardiography

The ICG technique, also referred to as thoracic electrical bioimpedance, has been used for the last 50 years to measure hemodynamic and cardiovascular variables [153, 154]. This technique is based on changes in the thoracic impedance during the cardiac cycle. The method measures SV and other cardiovascular parameters including cardiac contractility directly [51, 81, 155]. The basic principles of ICG were established in Russia during the 1940s, and improved during

the 1960s when it was used to measure CO among astronauts in a space program. In 1966 Kubicek et al. introduced the four-electrode impedance system using aluminum band electrodes applied around the abdomen and neck as the cylinder model to calculate SV from the original equation [156, 157] as: $SV = p \times L^2 / Z_0^2 \times (dZ/dt)_{max} \times LVET$, where p is a constant for the electrical resistivity of blood, L represents the mean distance between the two inner electrodes (cm), Z_0 is the basic impedance between the two inner electrodes (ohms), $(dZ/dt)_{max}$ is the maximum value of the first derivative of the impedance waveform and LVET is the LV ejection time [155, 156].

Later, Sramek modified Kubiceks' equation considering the chest as a truncated cone [158], and proposed a new formula to calculate SV as: $SV = (0.17 \times H)^3 / 4.2 \times (dZ/dt)_{max} / Z_0 \times LVET$, where the constant L in the above equation is approximated as 17 % of the height (cm) in a normal adult. Bernstein further modified the equation by adding a weight correction factor, δ, representing the modified ratio of the observed weight to the so-called ideal weight [159]. This modification would determine a more correct volume of the thorax [153, 156, 159] as follows: $SV = \delta \times (0.17 \times H)^3 / 4.2 \times (dZ/dt)_{max} / Z_0 \times LVET$.

The ICG technology has recently been improved further by more advanced data processing and software [51, 153, 155, 156, 160]. ICG is painless, without risk, operator independent, and has the ability to obtain continuous hemodynamic data and allows evaluation of trends and changes of cardiovascular variables over time by performing repeated measurements [51, 153, 160].

5.2.2 Bioreactance

Bioreactance is a new noninvasive technique similar to ICG using an electrical current of low amplitude with known frequency applied on the chest between two leads [161]. This technique is based on detection of the relative phase shifts (frequency shifts) between the two leads, the applied current and the received signal, which is created due to changes in the blood volume of the aorta [162]. The advantage of this technique is that the frequency modulations and phase shifts are independent of the distance between the applied and detected signal. The SV is proportional to the product of ventricular time (VET), the maximum phase shift $(d\phi/dt_{max})$ and a constant of proportionality is C [161, 162]: $SV = VET \times d\phi/dt_{max} \times C$. There are only few published studies with small sample sizes using this method.

5.2.3 Echocardiography

Echocardiography combined with Doppler ultrasound has been in use since the 1980s for investigation of hemodynamics and cardiac function. This method is widely used in the diagnosis and management of patients with cardiac diseases as well as in clinical research [38,

163]. For measuring the CO, the diameter of the aorta is measured at the aortic valve level, and the aortic cross-sectional area (CSA) is calculated as: $CSA = \pi (D/2)^2$, where D is the diameter of the aorta [76, 164]. Transthoracic Doppler ultrasound is used to measure blood flow velocity at the aortic valve during systole, and the time velocity integral is measured (VTI) [23, 161]. Then the SV is determined from the formula: CSA x VTI. CO is calculated as SV x HR. Measurement of CO with echocardiography correlates well compared with the invasive "gold standards" i.e. thermodilution and Fick methods by a correlation coefficient of 0.91 and 0.93, respectively [23, 76]. Lee et al found that the correlation between echocardiography and thermodilution performed among pregnant women was 0.94 for CO and 0.86 for SV [165]. Easterling et al observed a correlation coefficient of 0.92 between different operators for CO measurements ([166]. A study by Robson et al shows a high reproducibility of 3.1-3.7% within patient [76]. One limitation of Doppler echocardiography is that it does not provide continuous hemodynamic measurements [161]. Another limitation is that Doppler echocardiography is operator-dependent, and requires a trained operator to obtain correct measurements of the vessel diameter and the blood flow velocity [164]. However, Doppler ultrasonography is not very difficult to learn, and it is a useful tool in studying hemodynamics, as well as identifying and monitoring heart diseases in clinical settings [161, 164].

5.2.4 Cardiac magnetic resonance

The cardiac magnetic resonance imaging (CMRI) is a method that is increasingly used for the diagnosis of cardiac disease and evaluation of the cardiovascular system [167, 168]. The CMRI technique is based on strong magnetic fields and radio waves converting echoes from released energy into images, and combining sequences of electrocardiography (ECG) at each stage of the cardiac cycle from multiple cardiac cycles displaying cardiovascular function as cine imaging loops [168]. Assessment of cardiac blood flow can be performed in a single scan with good image quality compared to transthoracic echocardiography (TTE), which requires several assumptions for evaluation of systemic hemodynamics [93].

Until now, few studies have been published using the CMRI in the evaluation of maternal hemodynamics and cardiac function during pregnancy [92, 93, 169]. Ducas et al found good correlation between the CMRI and TTE measured SV and CO among women in the third trimester, but reporting consistently lower values for TTE compared to CMRI [169].

The advantage of CMRI is the fast imaging combined with good quality images. Safety, accuracy and reproducibility of CMRI are comparable to echocardiography [169]. Investigation using CMRI requires an experienced and skilled operator and expensive equipment and

repeated measurements may not be practical. However, this non-invasive method can be useful in the assessment of pregnant women with pre-existing or suspected cardiac disease or pregnancy complications.

5.2.5 Gas re-breathing technique

Investigation and assessment of CO can also be performed using the gas re-breathing technique [170]. This method is used for measuring effective pulmonary blood flow (Q_{EP}) that in the absence of intrapulmonary shunt flow is equivalent to CO [170]. The system consists of an accurate infrared photo acoustic gas analyzer continuously analyzing gas concentrations of the ventilator. It is a closed system including a mouthpiece with a three-way respiratory valve and a re-breathing bag that is connected to the gas analyzer. The re-breathing bag contains a gas mixture of blood-insoluble gas, N_2O, and O_2 in N_2. The software of the gas analyzer calculates the Q_{EP} from the rate of uptake of N_2O into the blood. Then CO is determined according to the formula as: CO = Q_{EP} + shunt flow, where the shunt flow is based on shunt fraction of O_2 content in arterial and mixed venous blood samples. This method might be useful in assessing patients with cardiovascular diseases such as pulmonary hypertension and heart diseases as well as for cardiovascular research [170].

5.3 Functional hemodynamics

Previous studies evaluating cardiac function and systemic hemodynamics in different maternal body positions show differences both between methods and between studies using the same equipment (Tables 1-3). Variation in results from studies among pregnant women may reflect factors such as: inaccurate description of body position during examinations, differences in study design, gestational age, methods used and small number of participants. Some researchers describe the position just as left, right lateral or supine without precisely describing if the upper part of the body is elevated or flat during examination (Figure 1).

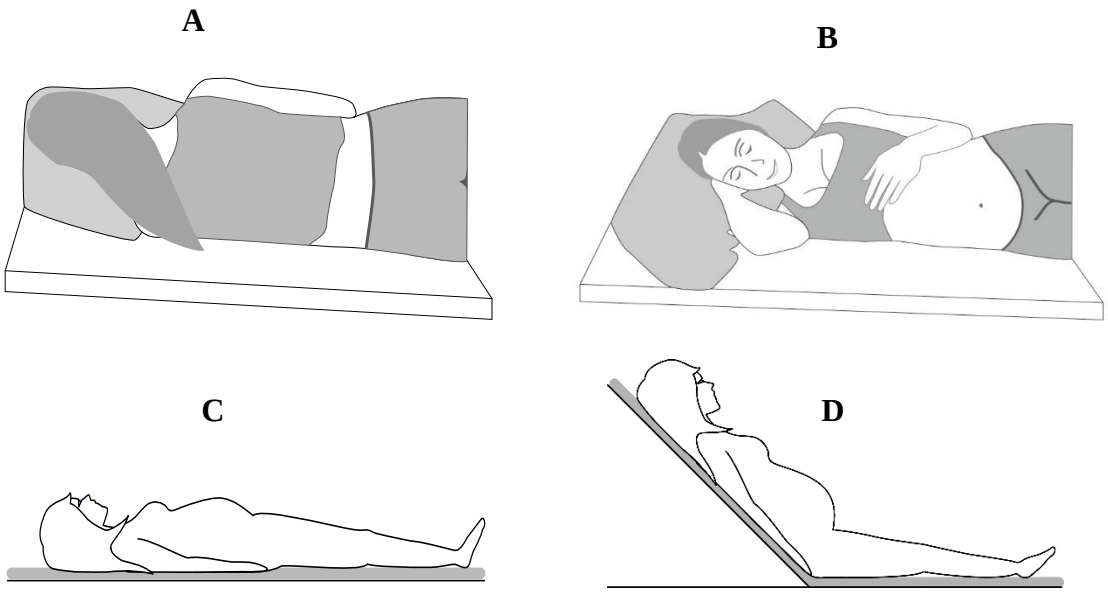

Figure 1. Different maternal positions during examination of cardiac function and systemic hemodynamics, left lateral (A), right lateral (B), supine flat (C), and supine semi-recumbent (D).

Static measurements of hemodynamic variables are not sufficient to understand maternal cardiovascular adaptation in pregnancy. Therefore, investigations in different body positions (functional hemodynamics) have also been performed to evaluate the physiological cardiovascular response (Table 4). Functional hemodynamics in pregnant women may also be important to identify and monitor complications during pregnancy. Static measures of hemodynamic variables among critically ill patients have shown limitations in response to fluid therapy when change in SV was used to assess fluid responsiveness [171]. Fluid responsiveness is generally defined as a 10-15% increase in CO or SV [161]. Dynamic measurements perform better in evaluating fluid responsiveness (preload reserve) helping to unmask hypovolemia [161, 171].

Katz et al found a significant increase in SV from the first to the third trimester in the lateral position, but not in the supine position [22]. Lees et al on the other hand, reported a reduction in SV measured in the supine position compared to the lateral position in the late third trimester of pregnancy [172]. This difference between positions might be due to pressure of the gravid uterus on the inferior vena cava with a subsequent reduction of venous return. Using ICG, Myhrman et al measured 14% and 20% decrease in CO during early and late pregnancy, respectively when changing maternal position from supine to left or right lateral [58]. Milsom et al found a decrease of 17% in CO by posture change from lateral (45°) to supine [59]. Some other studies report no changes of CO during postural change in late pregnancy [7, 63]. Burlingame et al observed a decrease of CO as well as SV, and an increase of SVR by changing from left lateral to seated (60º) position in the third trimester [51]. Katz et al observed that

LVET was reduced throughout pregnancy, from first trimester to term, measured with echocardiography in the left lateral decubitus as well as in the supine position [22]. Change of body position from the supine to the standing posture may affect the cardiovascular system due to gravitational effect leading to decreased venous return as blood pools in the vessels of the lower part of the body. This leads to a reduction in blood pressure, which is followed by an activation of the baroreflex receptors to maintain pressure by increasing vascular tone and SVR. Easterling et al observed that the maternal CO decreased by 1.7-1.8 L/min both in early and late gestation with increasing orthostatic stress by changing body position from the left lateral recumbent to sitting and then to the standing positions [24]. Both HR and SVR increased by the change of body position [24].

Recently, several investigators have used passive leg raising (PLR) as a dynamic test to predict fluid responsiveness (preload reserve), particularly in intensive care units [173, 174]. PLR induces changes of CO and SV independent of breathing conditions. This method may be useful for assessing volume status and fluid responsiveness in pregnant women. It has been shown to be useful in monitoring fluid management in oliguric women suffering from severe preeclampsia [175].

6 AIMS OF THE STUDY

The aim of this thesis was to investigate maternal functional hemodynamics in normal pregnancies and in pregnancies at risk of developing placental dysfunction disorders.

The main objectives were:

1. To investigate functional hemodynamic response to PLR in healthy pregnant women at 22-24 weeks of gestation and compare with non-pregnant women.
2. To investigate cardiovascular response to PLR in healthy pregnant women and establish longitudinal reference ranges for the second half of pregnancy.
3. To compare cardiac function, systemic hemodynamics and preload reserve among women with increased and normal UtA PI at 22-24 weeks of gestation.

7 MATERIAL AND METHODS

7.1 Ethical approval

The studies were approved by the Regional Committee for Medical and Health Research Ethics - North Norway (Ref. nr.5.2005.1386. Date of approval: 12.03.2010 (Paper I). Ref. nr.2010/575-2. Date of approval: 10.02.2010 (Paper II). Ref. nr.5.2005.1386 and 2010/586 (Paper III).

7.2 Study design

The studies were prospective and observational. The cross-sectional studies (article I and III) were performed in the second trimester during 22-24 weeks of gestation. The longitudinal study (article II) was carried out on pregnant women from 20 weeks of gestation until term and examinations were performed at approximately 4-weekly intervals.

7.3 Study population

The study population consisted of 54 non-pregnant women of reproductive age and 826 pregnant women.

7.4 Non-pregnant women

Healthy non-pregnant women of reproductive age were recruited from among the nursing, administrative and laboratory staff of the hospital and the university. They were asked to attend for hemodynamic assessment during the follicular phase between day 5 and 10 of the menstrual cycle. Exclusion criteria were women with a previous history of pregnancy complications or with a known disease, and those on regular medication. Examinations were performed in a non-fasting state.

7.5 Pregnant women

The pregnant women attending the antenatal clinic at the University Hospital of North Norway for routine ultrasound screening at 17-20 weeks of gestation were recruited to the study. They were informed about the study and invited to participate if they were aged >18 years, had a singleton pregnancy and the ultrasound scan did not show any fetal or placental abnormality. Multiple gestation and inability to communicate in Norwegian or English were exclusion criteria. Additionally, in study I and II, only women with low risk pregnancy were included and those with a previous history of PE, gestational diabetes, IUGR and preterm delivery were excluded. Examinations of the participants were performed during 8:00 to 14:00 hours in a quiet room with ambient temperature maintained at approximately 22 degree Celsius.

8 METHODS

8.1 Anthropometry

Height was measured in centimeters using an altimeter (Charder Electronic Co, Taichung City, Taiwan). Body weight was determined by weighing the woman on a precision scale (Soehnle, Leifheit AG, Nassau, Germany) in light clothing without shoes. The weight was recorded to in kilograms. Body mass index was calculated as: weight/height^2 and the body surface area (BSA) was calculated as: BSA = 0.007184 × height $^{0.725}$ × weight $^{0.425}$.

8.2 Impedance cardiography

Cardiac function and systemic hemodynamic variables were measured using ICG (Philips Medical Systems, Androver, MA, USA) together with a sphygmomanometer cuff placed on left arm connected to the ICG instrument. Height and weight of the participants were inserted in the machine before measurements were performed. The CVP and PAOP were preset to 4 and 8 mmHg, respectively. Measurements were performed at baseline and after PLR. The participants were instructed not to move and speak during the measurements. Four pairs of sensors were used for assessing ICG signals, and applied on the body shown in Figure 2.

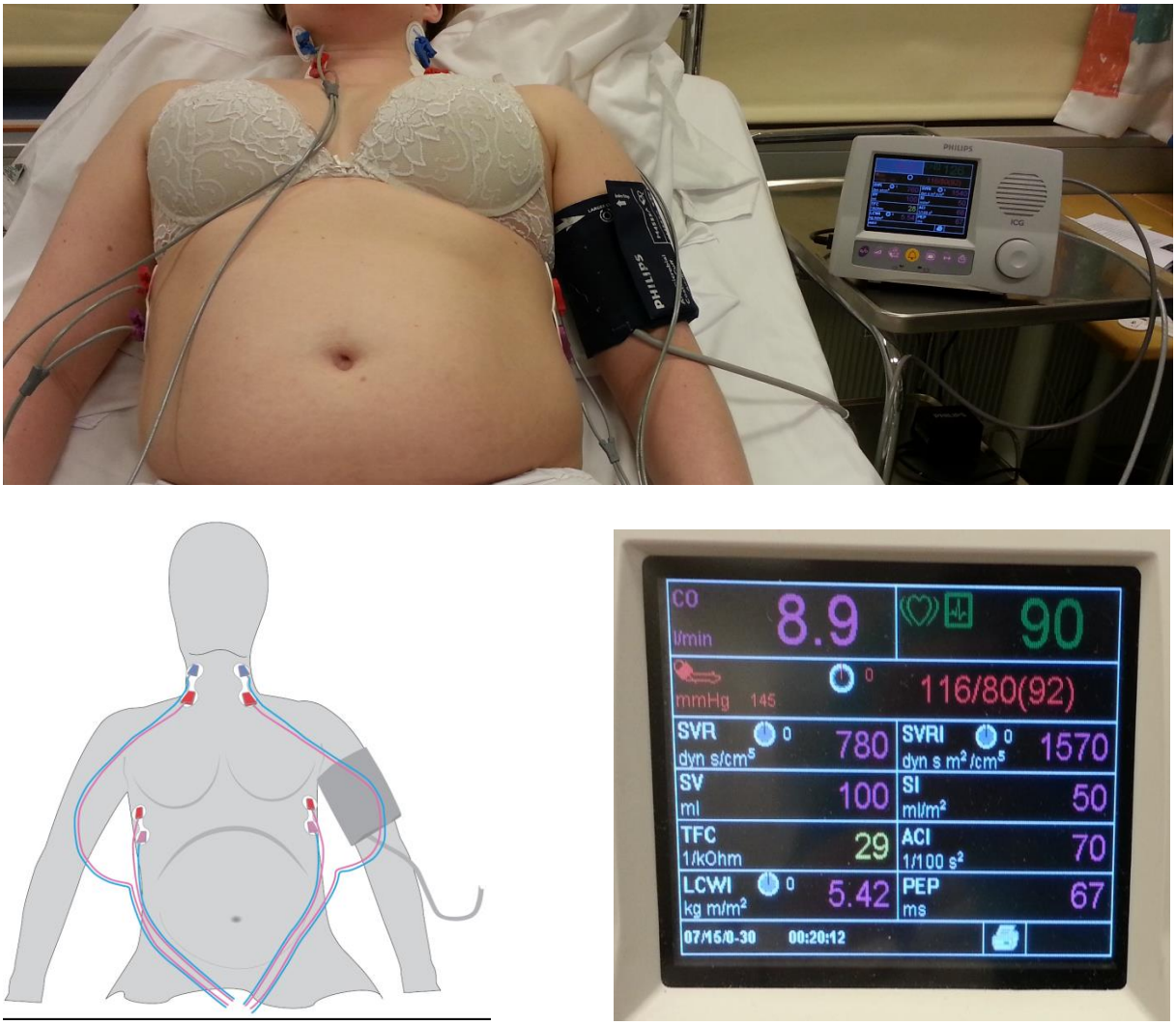

Figure 2. Assessment of maternal cardiac function and systemic hemodynamics using impedance cardiography (ICG) in a women at 29 weeks of gestation (upper) and a schematic representation showing placement of ICG sensors (four outer, purple and blue, electrodes transmit the current and four red inner electrodes detect the impedance signals).
The blood pressure cuff is placed on the left arm. The measured variables are continuously displayed on the ICG screen (lower right).

Two pairs of sensors were placed vertically on each side of the thorax at the anterior axillary line, whereas the other two pairs were placed on each side of the neck. The outer electrodes on the sensor are electrodes transmitting current through the chest to the aorta with the least resistance. The inner electrodes of the sensor are voltage electrodes measuring impedance signals that change as blood volume and velocity is changes with each heartbeat. Impedance changes together with electrocardiogram (ECG) and blood pressure measurements are used for the calculation of the systemic hemodynamic parameters.

The measurements were performed after approximately 10 minutes of rest in a supine recumbent position on an electronically steerable bed with the upper part of the bed at a 45° tilt (Figure 3A). Thereafter the upper part of the bed was lowered to a flat supine position and PLR was achieved by elevating both legs to a 45° tilt (Figure 3B).

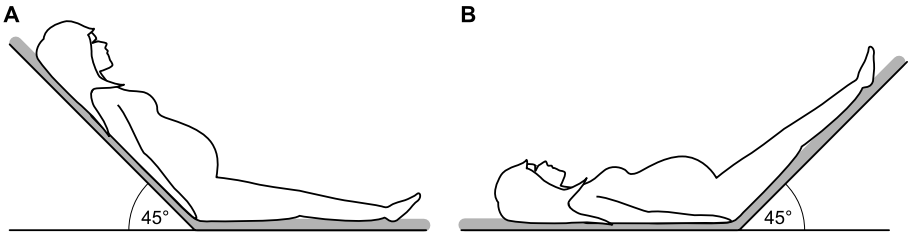

Figure 3. The position of the study participant during the assessment of systemic hemodynamics. A) Baseline measurement after 10 minutes of rest. B) Measurement after 90 seconds of passive leg raising.

The cardiac function and hemodynamic parameters (CO, HR, SBP, DBP, MAP, SVR, systemic vascular resistance index (SVRI), SV, stroke index (SI), TFC, ACI, LCWI, LVET and PEP) were continuously measured as displayed on the screen (Figure 2). Cardiac index (CI) was calculated as: CI = CO/BSA.

LVET is the interval from the opening to the closing of the aortic valve, called the mechanical systole. PEP is the time interval from the beginning of the electrical stimulation of the ventricles to the opening of the aortic valve, called the electrical systole. Systolic time ratio (STR) is the ratio of electrical systole to mechanical systole: (PEP/LVET) x100 in percent. Acceleration index (ACI) reflects the maximum acceleration of blood flow in the aorta during systole. Velocity index (VI) is the peak velocity of blood flow in the aorta during systole. Left ventricular work index (LWCI) is the left cardiac work normalized to body surface area (BSA). BSA is calculated as: 0.0136 x (MAP-PAOP) x SV. Thoracic fluid content (TFC) is an indicator of the chest fluid status, denoted as 1/kOhm.

8.3 Doppler ultrasonography of uterine arteries

The blood flow velocity waveforms were obtained from the maternal UtAs using Acuson Sequoia 512 ultrasound system (Mountain View, CA, USA) with a 2.5-6 MHz curvilinear transducer. Doppler ultrasonography was performed keeping the exposure to ultrasound energy low according to the ALARA (as low as reasonably applicable) principle [176]. During examination the pregnant women were lying in a semi-recumbent position to avoid compression

of inferior vena cava by the gravid uterus. Color-directed pulse-wave Doppler was used for visualizing the UtAs. Blood velocity waveforms were recorded (Figure 4) from both UtAs (left and right) proximal to the apparent crossover with the external iliac artery. Three to six uniform Doppler velocity waveforms were recorded and online measurements of velocities were performed. UtA PI was calculated as: (peak systolic velocity – end-diastolic velocity)/time-averaged maximum velocity. Values of three successive cardiac cycles were averaged and recorded. The PI values of the left and the right UtA was averaged and used for statistical analysis. Presence of bilateral or unilateral diastolic notch was also recorded.

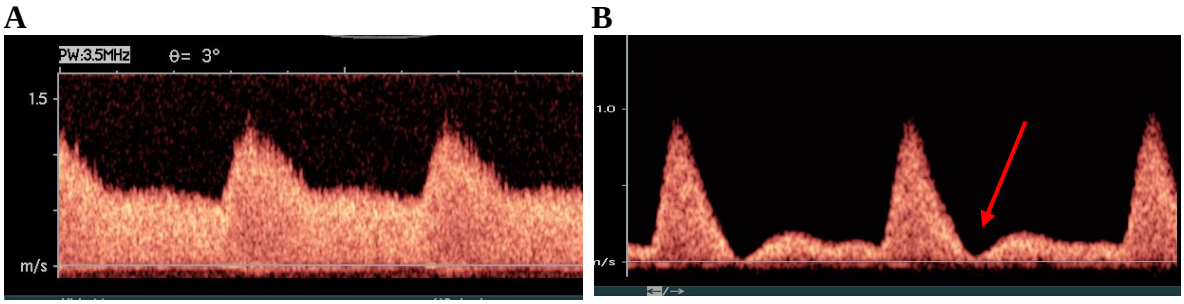

Figure 4. Pulsed-wave Doppler images showing blood velocity waveforms of the uterine arteries (UtA). Normal UtA blood flow velocity waveform (A), and abnormal UtA blood flow velocity waveform with diastolic notch indicated by the red arrow (B).

8.4 Outcome measures

The participants had standard follow up during pregnancy and the course and outcome of pregnancy including information on the neonate was recorded in electronic medical records. The outcome data were obtained from all the participants. Information on any complications arising during pregnancy, mode of delivery, gestational age, birth weight, Apgar score, umbilical artery pH and base excess, and placental weight was recorded. In addition, information on neonatal outcome was also obtained.

8.5 Statistical analysis

The IBM Statistical Software for Social Sciences for Windows (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis of cross-sectional data. Independent samples t-test was used for analysis of difference between groups. Continuous variables are presented as mean±standard deviation or median (range). Categorical variables are presented as n (%). Differences in proportions between groups were analyzed using chi-squared test. Comparison between baseline measurements and measurements obtained after PLR on the same individuals in each group was performed using paired sample t-test.

The Statistical Analysis Software, version 9.3 (SAS Institute INC., Cary, NC, USA) was used for statistical analysis of the longitudinal data. The number of study participants required to establish normal reference intervals was estimated to be approximately 100 based on the assumption that 20 observations per gestational week (i.e. a total of 400 observations between 20-40 weeks) would be sufficient to calculate reference intervals with adequate precision [177]. Each variable was checked for normality. Logarithmic or power transformations were performed to achieve normal distribution as required. Fractional polynomials were used to obtain best fitting curves in relation to gestational age accommodating for nonlinear association. Multilevel regression modeling using proc mixed in SAS was used to investigate gestational age associated changes in functional hemodynamics and estimate the reference percentiles accounting for possible dependency between repeated measures [178, 179]. Individual observations were fitted as a linear function for the fractional polynomial term of time, i.e. the gestational age. A random intercept term for each individual and a random slope were included for the fractional polynomial term of gestational age. Statistical significance was set to a p-value of <0.05.

9 SUMMARY OF RESULTS

9.1 Paper I

Functional hemodynamic measurements may be more informative than just the static measures of cardiovascular function. We investigated functional hemodynamic response to 45° of PLR using impedance cardiography. A total of 108 healthy pregnant women were examined cross-sectionally at 22-24 weeks of gestation using ICG and compared with 54 non-pregnant women. Parameters describing cardiac function and systemic hemodynamics were obtained at baseline and 90 seconds after PLR. Percent change in the value of measured variables from baseline to PLR represented the preload reserve.

Static measurements of systemic hemodynamics and cardiac function at baseline were different between pregnant and non-pregnant women. The CO and SV were observed to be 27.6% and 5.1% higher, respectively among healthy pregnant women, whereas the MAP and SVR were 6.9% and 27.3% lower, respectively compared to healthy non-pregnant women.

The variables describing cardiac contractility (ACI, VI, PEP, LVET) and work (LCWI) were statistically different between pregnant and non-pregnant women ($p=0.050$ to <0.001).

PLR led to significant changes in the majority of hemodynamic parameters compared to baseline in both pregnant and non-pregnant women with similar trends. The SV increased by

2.15% (p=0.042) in pregnant women and by 2.44% (p=0.018) in non-pregnant women as a result of PLR, but the CO did not increase significantly in both groups. PLR caused a significant reduction in MAP and SVR ($p<0.001$ and $p<0.005$).

We observed a reduction of cardiac contractility and work as assessed by ACI, VI, PEP and LCWI in both groups during PLR. The duration of ventricular ejection during systole represented by the LVET was significantly increased by PLR.

The physiologic response to PLR was similar among pregnant and non-pregnant women. Less than 15% of the pregnant women were found to be preload responsive (i.e. had >10% increase in SV or CO in response to PLR) in the second trimester of pregnancy at 22-24 weeks.

9.2 Paper II

There are only a few studies with small sample size that have investigated hemodynamic responses to postural changes in healthy pregnant women (Table 4). We investigated maternal systemic hemodynamics at baseline and cardiovascular response to PLR serially during the second half of pregnancy. A total of 98 healthy pregnant women were examined approximately at 4-weekly intervals during 20^{+1} – 40^{+5} weeks of gestation (441 observations) and gestational age specific longitudinal reference ranges (graphs and percentile charts) were constructed (Figures 3 and 4 and Tables S2-S13). The variables describing maternal cardiovascular function were significantly associated with gestational age, except for CI and SVR. We found an increase of CO from 6.3 L/min at 20 weeks to 7.0 L/min at 37 weeks, remaining stable thereafter until term. The SV decreased from 83 ml at 20 weeks to 78 ml at term, the HR increased progressively during the second half of pregnancy, and the SVR remained stable.

Maternal cardiovascular response to PLR was also significantly associated with gestational age. We observed a 1.2% reduction in CO at 24 weeks and 5.4% reduction at term compared to baseline values following 90 seconds of PLR. Whilst PLR led to an insignificant but small increase in SV from 20^{+1} to 31^{+6} weeks, thereafter the SV was slightly lowered by PLR compared to baseline until term. The SVR was also significantly altered by PLR showing a decrease until 31^{+6} weeks, and a slight increase thereafter until term. Our study showed that healthy pregnant women have limited preload reserve especially in the third trimester. We have established gestational age specific longitudinal reference ranges of maternal systemic hemodynamics (Tables S2-S13) and functional hemodynamic response to PLR during the second half of pregnancy (Figures 3 and 4, and Tables 5-16 in Appendix).

9.3 Paper III

UtA Doppler velocity waveforms with PI and/or presence of early diastolic notching have been used to identify women at risk of developing pregnancy complications such as PE and IUGR. This has been shown to be a useful screening test especially in high-risk populations of pregnant women. However, this is not an effective screening tool in low-risk pregnancies. As many women who develop placental dysfunction disorders may have underlying cardiovascular predisposing factors, combining UtA Doppler with functional hemodynamic assessment might improve the predictive value of UtA Doppler. We examined 620 pregnant women at 22-24 weeks of gestation using Doppler ultrasound to measure UtA PI and ICG to assess maternal systemic hemodynamics and cardiac function. Functional hemodynamic response to PLR was also evaluated by performing ICG at baseline in a supine semi-recumbent position and during PLR and pregnant women with increased UtA PI (mean PI ≥1.16), were compared to those with normal UtA PI (mean PI <1.16).

We observed that 17.5% of women with abnormal UtA PI developed PE compared to 3.8% of controls. The CO, SV and HR were not different between groups, but at baseline the SVRI and MAP were significantly higher in the abnormal PI group compared to controls. The cardiovascular response to PLR was similar in both groups at 22-24 weeks of gestations. The PLR led to slightly higher increase of SV among pregnant women with high UtA PI compared to women with normal UtA PI (3.4 ml versus 2.6 ml). We found 26.3% of women with high UtA PI to be preload responsive (i.e. increased SV by >10% following PLR) compared to 23.1% of women with normal UtA PI (p=0.656).

10 DISCUSSION

Assessing maternal hemodynamics can be useful in identifying women at risk of developing pregnancy complication as well as monitoring women with severe disease. However, static measures of cardiovascular function may not provide sufficient insight into changes in maternal hemodynamics occurring during pregnancy. Studies presented in this thesis were performed to investigate maternal functional hemodynamics to better understand the physiological cardiovascular adaptations that take place during the course of normal pregnancy and maternal functional hemodynamic profile in pregnancies at increased risk developing placental dysfunction disorders.

10.1 Preload reserve in pregnancy

We found no differences in the magnitude or trend of response to PLR between non-pregnant women and healthy pregnant women at 22-24 gestational weeks. Our study showed that less than 15% of healthy pregnant women were preload responsive at 22-24 weeks of gestation, and the results were not significantly different compared to non-pregnant women. Volume depletion has been shown to increase preload reserve during PLR [180]. However, preload reserve seems to be low in well-hydrated individuals. Furthermore, increased circulating blood volume in pregnancy may cause an attenuation of baroreflex activity and increased tolerance of orthostatic stress [181].

In the longitudinal study we found that PLR led to a small, but insignificant increase in SV during $20^{+0} – 31^{+6}$ gestational weeks. Thereafter the SV actually decreased in response to PLR until term. We found significant decrease in CO from 24 weeks of gestation to term. The decrease in CO in response to PLR during the third trimester is in concordance with the observations made by Marques et al in a cross-sectional study at term [73]. Paradoxically, the PLR resulted in a reduction in cardiac contractility in the second half of pregnancy, and reduced cardiac contractility could be one possible explanation for the decreased preload reserve after 32 gestational weeks. We observed an increase in SVR after 32 weeks in spite of reduced blood pressure, indicating reduced ability of the heart to increase CO towards the end of pregnancy.

We compared preload functional hemodynamic response to PLR between pregnant women with normal and abnormal UtA PI. Functional hemodynamic variables did not differ significantly between groups. However, we found different trends in LCWI and VI in the response to PLR, indicating that women with abnormal UtA PI may be volume depleted compared to those with normal UtA PI. Pregnant women who subsequently develop early onset PE are known to have lower CO and higher SVR [48, 182]. We found that pregnant women with high UtA PI have significantly higher MAP and SVR, and lower SV and CO compared to women with normal UtA PI. There are only few published studies evaluating cardiovascular function during postural changes, and no other longitudinal studies assessing response to PLR during pregnancy to compare our results. Further studies are needed to validate our findings.

10.2 Cardiac contractility in pregnancy

The PEP and LVET, STR, VI, ACI and LCWI provide information of ventricular systolic function. The trend of change in these variables indicates that the contractility of the left ventricle was not altered by PLR both in pregnant and non-pregnant women. Our results during the second half of pregnancy showed a reduction in ACI and VI, prolongation of PEP, and

shortening of LVET at baseline with advancing gestational age (Paper II). This may reflect decreased contractility of the left ventricle in the third trimester of pregnancy in accordance with other reports [34, 52].

Women with high UtA PI had lower values of ACI and VI compared to women with normal UtA PI. The physiological response to PLR was not significantly different between the groups with regards to the parameters of cardiac contractility and work, but the VI and LCWI changed in opposite directions; PLR led to a small increase in LCWI and VI in women with high UtAPI, and a decrease in the normal UtA PI group. Overall our results do not indicate that the pregnant women with high UtA PI have overt cardiac dysfunction. However, larger studies are needed to confirm our findings.

10.3 Static measures of maternal systemic hemodynamics

The CO was significantly higher among pregnant women at 22-24 weeks compared to non-pregnant women (Paper I), which is in accordance with the study by Droste et al [28]. Tables 1-3 gives an overview of previously published studies performed using different methods showing differences in the absolute values of CO and SV reported previously. CO has been shown to increase from early pregnancy plateauing at mid- gestation and then decreasing toward term, or increasing throughout pregnancy [22]. A recent meta-analyses of 39 studies concluded that CO increases during pregnancy peaking in the early third trimester [183]. Invasive methods such as dye dilution [17] appear to show higher CO in left-lateral position compared to supine. Echocardiographic studies performed in left-lateral position (Table 2) show an increase of CO from 5.24 L/min at 5 weeks [29] to 8.5 L/min at term [31]. Only nine longitudinal studies applying ICG method to investigate maternal hemodynamics have been published previously, which report variable findings (CO is stable, increases or decreases with advancing gestational age). In our longitudinal study, we found that the CO increased from 6.58 L/min to 7.11 L/min from 20 weeks of gestation to term (Paper II).

10.4 Functional hemodynamics in pregnancy

Maternal position may affect hemodynamics especially in late pregnancy. However, few studies have investigated cardiovascular response to postural changes in pregnancy and the reports vary in their findings. Some studies report higher values of SV and CO in left lateral compared to supine or standing position [22, 24], whilst others found no difference between supine and left lateral position at 36-39 weeks [7]. The adaptive cardiovascular response to active postural changes in pregnancy is complex and affected by the activity as well as mechanical (e.g.

pressure of gravid uterus on the inferior vena cava), gravitational (e.g. pooling of blood in the lower body in a standing position) and autonomic (e.g. baroreflex response to decreased aortic pressure on standing from a supine position) factors. These have to be taken into account when interpreting the findings of functional hemodynamic investigations during pregnancy based on position changes. PLR causes an increase in venous return to the heart without changing other physiological variables and allows evaluating cardiovascular response to an increase in preload. However, the amount of autotransfusion effected by PLR can not be readily assessed and individual responses may vary.

10.5 Validity of the studies

All examinations were performed in a standardized manner with the women in a supine semi-recumbent position to avoid compression of the inferior vena cava by the gravid uterus. Regarding the validity of methods used to investigate hemodynamics, use of noninvasive methods, such as ICG and Doppler ultrasonography, is important in studies on pregnant women where repeated measurements are necessary.

ICG is a risk free, noninvasive method that provides continuous assessment of multiple parameters of the cardiovascular function in a single session. The method has been used for the last 50 years [154]. Several studies have investigated the validity of ICG in clinical and research settings. Although some concerns have been expressed regarding the validity using ICG in pregnancy [66], recent studies have demonstrated its accuracy, reliability and repeatability to be good [7, 51, 155, 184]. Masaki et al and Clark et al have reported an excellent correlation (0.91 and 0.915), respectively between CO measured by ICG and thermodilution in complicated and healthy pregnancies, respectively [86, 185]. Other validation studies between ICG and invasive methods have been performed using band electrodes instead of the currently used spot electrodes, but report good correlation between measured parameters in healthy pregnancies [91, 186].

Several studies have used the ICG monitor, BioZ, with refined technology and compared with echocardiography in pre-eclamptic women and healthy pregnant women during the third trimester and report good agreement and correlation between methods [51] [187]. The ICG has been shown to be reliable in identifying women with severe forms of PE, stratifying pregnant women with various forms of hypertensive disorders [188]. Villacorte et al investigated 31 patients (58% men) using ICG and CMRI and found a good agreement between methods for determining CO (r=0.79) and SV (r=0.88) [189].

Tomsin et al report a good correlation ($r \geq 0.80$) comparing cardiac contractility parameters and TFC by position change in healthy and pre-eclamptic women using the third generation device [184]. Burlingame et al showed that ICG has the ability to detect small changes in maternal SV associated with change of position from left lateral to supine semi-recumbent [51], whereas echocardiography lacked the sensitivity to detect small changes in EF as the latter method cannot assess hemodynamics continuously.

Although ICG is a relatively operator independent it requires attention to the details of the technique to obtain accurate hemodynamic measurements. These include correct positioning of the ICG electrodes to obtain correct signals [185]. The participant should not move during measurements, as an uncontrolled motion during examination may influence the results. Additionally, some conditions, such as heart disease with pulmonary edema, morbid obesity etc., may cause changes in baseline thoracic impedance. However, none of the participating women in our studies had such conditions. The ICG technology is user friendly, with a portable device, which is simple to use both in clinical and research settings. The use of ICG does not require special skills, as compared to Doppler echocardiography. Additionally, with ICG it is possible to obtain continuous measurements of cardiovascular variables, which makes it suitable for detecting trends over time.

All ICG examinations were performed by a single operator (ÅV) and in the same room with stable temperature using the same electronically steerable bed and the same ICG device. The participants were told not to speak or move during the examinations. We performed a repeatability study in 20 pregnant women at different gestational ages showing good reproducibility of SV, HR, CO and SVR measured by ICG.

Doppler ultrasonography of the UtA is a widely used method in clinical practice and has been shown to have a reasonable good reproducibility [190]. All the doctors who performed examinations were appropriately trained and had several years of experience in this methodology.

Regarding internal validity, it could be argued that the recruitment of non-pregnant women (in study I) from among the hospital and university staff might have caused some selection bias. However, as all pregnant women residing in the area attend the same hospital for the second trimester routine ultrasound examination the pregnant population should be representative of the source population.

Regarding external validity, our study population had a fairly homogeneous ethnic and socioeconomic background and we believe that our sample population is representative of the White European population. However, our findings, especially the reference ranges for the

static and functional parameters of cardiovascular function may not be generalizable to other multiethnic populations.

10.6 Limitations of the study

There are some limitations of our study. We did not examine the participants before pregnancy, in the first trimester or postpartum to evaluate changes from the pre-pregnancy state until after delivery. In Norway first trimester ultrasound is not offered as a routine investigation, therefore recruitment of the women to the study in early pregnancy is difficult. Additionally, we did not obtain blood samples from all the participants to evaluate possible relevant biochemical markers of cardiovascular function, which might have added more information to our study.

11 CONCLUSIONS

We studied functional hemodynamics in healthy pregnant women and women at increased risk of developing placental dysfunction disorders. Maternal hemodynamics was found to be different in healthy pregnant women compared to non-pregnant women. In healthy pregnancies, the physiological response to PLR was not modified at 22-24 weeks of gestation.

Longitudinal reference ranges for maternal functional hemodynamics were established for the second half of pregnancy. Healthy pregnant women appear to have limited preload reserve, especially in the third trimester, and might be vulnerable to fluid overload and cardiac failure.

The functional hemodynamic profile of pregnant women with high UtA PI at 22-24 weeks was similar to that of controls, suggesting that its assessment is unlikely to improve the value of UtA Doppler in predicting pregnancy complications.

12 FUTURE PERSPECTIVES

Future studies on maternal hemodynamics and cardiac function aiming at prediction of pregnancy complications could include measurement of biomarkers sensitive in identifying subtle cardiovascular dysfunction. Investigations of pregnant women during the first trimester and postpartum would add important knowledge about maternal cardiovascular adaptation in pregnancy.

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APPENDIX

Tables 5-16

Table 5. Longitudinal reference ranges of preload reserve for maternal stroke volume (ml) during second half of pregnancy.

Gestation (weeks)	Percentile						
	2.5th	5th	10th	50th	90th	95th	97.5th
20	-19.9	-16.3	-12.2	2.3	16.7	20.8	24.4
21	-20.2	-16.6	-12.5	2.0	16.4	20.6	24.1
22	-20.4	-16.9	-12.8	1.7	16.2	20.3	23.8
23	-20.7	-17.1	-13.0	1.5	15.9	20.0	23.6
24	-20.9	-17.4	-13.2	1.2	15.7	19.8	23.4
25	-21.1	-17.6	-13.5	1.0	15.5	19.6	23.2
26	-21.3	-17.8	-13.6	0.8	15.3	19.4	23.0
27	-21.5	-17.9	-13.8	0.7	15.1	19.2	22.8
28	-21.7	-18.1	-14.0	0.5	15.0	19.1	22.6
29	-21.8	-18.2	-14.1	0.3	14.8	18.9	22.5
30	-22.0	-18.4	-14.3	0.2	14.7	18.8	22.3
31	-22.1	-18.5	-14.4	0.1	14.5	18.6	22.2
32	-22.2	-18.7	-14.5	-0.1	14.4	18.5	22.1
33	-22.3	-18.8	-14.7	-0.2	14.3	18.4	22.0
34	-22.4	-18.9	-14.8	-0.3	14.2	18.3	21.8
35	-22.5	-19.0	-14.9	-0.4	14.1	18.2	21.7
36	-22.6	-19.1	-15.0	-0.5	14.0	18.1	21.6
37	-22.7	-19.2	-15.1	-0.6	13.9	18.0	21.5
38	-22.8	-19.3	-15.2	-0.7	13.8	17.9	21.5
39	-22.9	-19.4	-15.2	-0.8	13.7	17.8	21.4
40	-23.0	-19.4	-15.3	-0.8	13.6	17.7	21.3

Table 6. Longitudinal reference ranges of preload reserve for maternal heart rate (/min) during second half of pregnancy.

Gestation (weeks)	Percentile						
	2.5th	5th	10th	50th	90th	95th	97.5th
20	-17.7	-15.2	-12.4	-2.5	7.5	10.3	12.7
21	-17.7	-15.3	-12.4	-2.5	7.4	10.3	12.7
22	-17.8	-15.3	-12.5	-2.6	7.4	10.2	12.6
23	-17.8	-15.4	-12.6	-2.6	7.3	10.1	12.6
24	-17.9	-15.4	-12.6	-2.7	7.3	10.1	12.5
25	-18.0	-15.5	-12.7	-2.8	7.2	10.0	12.4
26	-18.0	-15.6	-12.8	-2.8	7.1	9.9	12.4
27	-18.1	-15.7	-12.9	-2.9	7.0	9.8	12.3
28	-18.2	-15.8	-12.9	-3.0	6.9	9.7	12.2
29	-18.3	-15.9	-13.0	-3.1	6.8	9.7	12.1
30	-18.4	-16.0	-13.1	-3.2	6.7	9.5	12.0
31	-18.5	-16.1	-13.3	-3.3	6.6	9.4	11.9
32	-18.6	-16.2	-13.4	-3.4	6.5	9.3	11.8
33	-18.8	-16.3	-13.5	-3.6	6.4	9.2	11.6
34	-18.9	-16.5	-13.6	-3.7	6.2	9.1	11.5
35	-19.0	-16.6	-13.8	-3.8	6.1	8.9	11.4
36	-19.2	-16.7	-13.9	-4.0	6.0	8.8	11.2
37	-19.3	-16.9	-14.1	-4.1	5.8	8.6	11.1
38	-19.5	-17.1	-14.3	-4.3	5.6	8.4	10.9
39	-19.7	-17.2	-14.4	-4.5	5.4	8.3	10.7
40	-19.9	-17.4	-14.6	-4.7	5.3	8.1	10.5

Table 7. Longitudinal reference ranges of preload reserve for maternal cardiac output (L/min) during second half of pregnancy.

	Percentile						
Gestation (weeks)	2.5th	5th	10th	50th	90th	95th	97.5th
20	-18.3	-15.3	-11.8	1.0	14.1	17.9	21.3
21	-18.9	-15.9	-12.4	0.3	13.5	17.3	20.6
22	-19.4	-16.4	-12.9	-0.2	12.9	16.7	20.0
23	-19.9	-16.9	-13.4	-0.7	12.4	16.2	19.5
24	-20.3	-17.3	-13.9	-1.2	11.9	15.7	19.0
25	-20.7	-17.8	-14.3	-1.6	11.5	15.3	18.6
26	-21.1	-18.1	-14.6	-2.0	11.1	14.9	18.2
27	-21.4	-18.5	-15.0	-2.4	10.7	14.5	17.8
28	-21.7	-18.8	-15.3	-2.7	10.4	14.1	17.4
29	-22.0	-19.1	-15.6	-3.0	10.0	13.8	17.1
30	-22.3	-19.4	-15.9	-3.3	9.7	13.5	16.8
31	-22.6	-19.6	-16.2	-3.6	9.4	13.2	16.5
32	-22.8	-19.9	-16.4	-3.9	9.2	12.9	16.2
33	-23.0	-20.1	-16.6	-4.1	8.9	12.7	16.0
34	-23.2	-20.3	-16.9	-4.3	8.7	12.5	15.7
35	-23.4	-20.5	-17.1	-4.5	8.5	12.2	15.5
36	-23.6	-20.7	-17.3	-4.7	8.3	12.0	15.3
37	-23.8	-20.9	-17.4	-4.9	8.1	11.8	15.1
38	-24.0	-21.0	-17.6	-5.1	7.9	11.6	14.9
39	-24.1	-21.2	-17.8	-5.3	7.7	11.5	14.7
40	-24.3	-21.4	-17.9	-5.4	7.5	11.3	14.6

Table 8. Longitudinal reference ranges of preload reserve for maternal mean arterial pressure (mmHg) during second half of pregnancy.

	Percentile						
Gestation (weeks)	2.5th	5th	10th	50th	90th	95th	97.5th
20	-14.7	-13.1	-11.3	-5.6	-0.5	0.9	2.1
21	-14.3	-12.7	-11.0	-5.3	-0.2	1.1	2.3
22	-14.0	-12.5	-10.7	-5.1	-0.0	1.3	2.5
23	-13.8	-12.2	-10.5	-4.9	0.2	1.5	2.7
24	-13.6	-12.0	-10.3	-4.7	0.3	1.7	2.9
25	-13.4	-11.9	-10.1	-4.6	0.5	1.9	3.0
26	-13.3	-11.7	-10.0	-4.4	0.6	2.0	3.1
27	-13.2	-11.6	-9.9	-4.3	0.8	2.1	3.3
28	-13.1	-11.5	-9.8	-4.2	0.9	2.2	3.4
29	-13.0	-11.4	-9.7	-4.1	1.0	2.3	3.5
30	-12.9	-11.3	-9.6	-4.0	1.1	2.4	3.6
31	-12.8	-11.3	-9.5	-3.9	1.2	2.5	3.7
32	-12.8	-11.2	-9.5	-3.9	1.2	2.6	3.8
33	-12.7	-11.2	-9.4	-3.8	1.3	2.7	3.9
34	-12.7	-11.1	-9.4	-3.7	1.4	2.8	3.9
35	-12.6	-11.1	-9.3	-3.7	1.4	2.8	4.0
36	-12.6	-11.0	-9.3	-3.6	1.5	2.9	4.1
37	-12.6	-11.0	-9.2	-3.6	1.6	2.9	4.1
38	-12.5	-11.0	-9.2	-3.5	1.6	3.0	4.2
39	-12.5	-10.9	-9.2	-3.5	1.6	3.0	4.2
40	-12.5	-10.9	-9.2	-3.5	1.7	3.1	4.3

Table 9. Longitudinal reference ranges of preload reserve for maternal mean systemic vascular resistance (dyne s/cm^5) during second half of pregnancy.

	Percentile						
Gestation (weeks)	2.5th	5th	10th	50th	90th	95th	97.5th
20	-23.9	-21.7	-18.9	-7.3	6.4	10.6	14.4
21	-22.7	-20.4	-17.6	-6.2	7.1	11.2	14.9
22	-21.7	-19.4	-16.6	-5.3	7.9	12.0	15.5
23	-21.0	-18.7	-15.8	-4.4	8.7	12.8	16.4
24	-20.4	-18.1	-15.2	-3.7	9.6	13.6	17.2
25	-20.0	-17.7	-14.7	-3.0	10.4	14.5	18.2
26	-19.8	-17.3	-14.3	-2.5	11.2	15.4	19.1
27	-19.5	-17.1	-14.0	-1.9	12.0	16.3	20.0
28	-19.4	-16.9	-13.8	-1.5	12.7	17.1	20.9
29	-19.3	-16.7	-13.6	-1.0	13.4	17.8	21.8
30	-19.2	-16.6	-13.4	-0.6	14.1	18.6	22.6
31	-19.2	-16.5	-13.3	-0.3	14.7	19.3	23.3
32	-19.2	-16.5	-13.2	0.0	15.3	19.9	24.1
33	-19.1	-16.4	-13.1	0.3	15.8	20.5	24.8
34	-19.1	-16.4	-13.0	0.6	16.3	21.1	25.4
35	-19.1	-16.4	-12.9	0.8	16.8	21.7	26.0
36	-19.2	-16.3	-12.9	1.1	17.2	22.2	26.6
37	-19.2	-16.3	-12.8	1.3	17.6	22.6	27.1
38	-19.2	-16.3	-12.8	1.5	18.0	23.1	27.6
39	-19.2	-16.3	-12.7	1.6	18.4	23.5	28.0
40	-19.2	-16.3	-12.7	1.8	18.7	23.9	28.5

Table 10. Longitudinal reference ranges of preload reserve for maternal thoracic fluid content (1/kOhm) during second half of pregnancy.

	Percentile						
Gestation (weeks)	2.5th	5th	10th	50th	90th	95th	97.5th
20	-9	-7	-5	4	15	19	22
21	-9	-7	-5	4	15	18	22
22	-9	-7	-5	4	15	18	21
23	-9	-7	-5	4	15	18	21
24	-9	-8	-5	4	15	18	21
25	-9	-8	-5	4	14	18	21
26	-10	-8	-5	4	14	18	21
27	-10	-8	-6	3	14	18	21
28	-10	-8	-6	3	14	18	21
29	-10	-8	-6	3	14	17	20
30	-10	-8	-6	3	14	17	20
31	-10	-8	-6	3	14	17	20
32	-10	-8	-6	3	14	17	20
33	-10	-8	-6	3	14	17	20
34	-10	-8	-6	3	13	17	20
35	-10	-8	-6	3	13	17	20
36	-10	-8	-6	3	13	17	20
37	-10	-8	-6	3	13	16	19
38	-10	-9	-6	2	13	16	19
39	-10	-9	-6	2	13	16	19
40	-10	-9	-7	2	13	16	19

Table 11. Longitudinal reference ranges of preload reserve for maternal acceleration index (1/100 s^2) during second half of pregnancy.

	Percentile						
Gestation (weeks)	2.5th	5th	10th	50th	90th	95th	97.5th
20	-37	-33	-27	-2	31	42	51
21	-38	-33	-27	-2	30	41	50
22	-38	-34	-28	-3	29	40	49
23	-39	-34	-28	-4	29	39	49
24	-39	-34	-29	-4	28	38	48
25	-39	-35	-29	-5	27	38	47
26	-40	-35	-30	-5	27	37	46
27	-40	-35	-30	-6	26	36	46
28	-40	-36	-30	-6	25	36	45
29	-40	-36	-31	-7	25	35	44
30	-41	-36	-31	-7	24	34	44
31	-41	-37	-31	-7	24	34	43
32	-41	-37	-31	-8	23	33	43
33	-41	-37	-32	-8	23	33	42
34	-41	-37	-32	-8	22	33	42
35	-42	-37	-32	-9	22	32	41
36	-42	-38	-32	-9	22	32	41
37	-42	-38	-33	-9	21	31	41
38	-42	-38	-33	-10	21	31	40
39	-42	-38	-33	-10	21	31	40
40	-42	-38	-33	-10	20	30	39

Table 12. Longitudinal reference ranges of preload reserve for maternal velocity index (1/1000s) during second half of pregnancy.

	Percentile						
Gestation (weeks)	2.5th	5th	10th	50th	90th	95th	97.5th
20	-34	-30	-26	-7	15	21	27
21	-34	-30	-26	-7	15	21	27
22	-34	-31	-26	-7	15	21	27
23	-35	-31	-26	-7	15	21	27
24	-35	-31	-26	-7	15	21	27
25	-35	-31	-26	-7	15	21	27
26	-35	-31	-26	-7	15	21	27
27	-35	-31	-26	-7	15	21	27
28	-35	-31	-26	-7	15	21	27
29	-35	-31	-26	-7	15	21	27
30	-35	-31	-26	-7	15	21	27
31	-35	-31	-26	-7	15	22	27
32	-35	-31	-26	-7	15	22	28
33	-35	-31	-27	-7	15	22	28
34	-36	-32	-27	-7	15	22	28
35	-36	-32	-27	-7	15	22	28
36	-36	-32	-27	-7	15	22	28
37	-37	-32	-27	-7	15	22	29
38	-37	-33	-28	-8	16	23	29
39	-37	-33	-28	-8	16	23	29
40	-38	-33	-28	-8	16	23	30

Table 13. Longitudinal reference ranges of preload reserve for maternal pre-ejection period (ms) during second half of pregnancy.

	Percentile						
Gestation (weeks)	2.5th	5th	10th	50th	90th	95th	97.5th
20	-43	-39	-34	-14	9	17	24
21	-41	-37	-33	-13	11	19	26
22	-40	-36	-31	-11	13	21	28
23	-39	-35	-30	-9	16	23	30
24	-38	-33	-28	-7	18	25	32
25	-36	-32	-27	-6	20	27	35
26	-35	-31	-26	-4	21	29	37
27	-34	-30	-24	-3	23	31	38
28	-33	-29	-23	-1	25	33	40
29	-32	-28	-22	-0	26	34	41
30	-32	-27	-22	1	27	35	43
31	-31	-27	-21	1	28	36	43
32	-31	-26	-21	2	28	36	44
33	-31	-26	-21	2	28	37	44
34	-31	-27	-21	1	28	36	44
35	-32	-27	-21	1	27	36	43
36	-32	-28	-22	-0	26	34	42
37	-33	-29	-23	-2	24	33	40
38	-35	-30	-25	-3	22	30	38
39	-36	-32	-27	-6	20	28	35
40	-38	-34	-29	-8	16	24	31

Table 14. Longitudinal reference ranges of preload reserve for maternal left ventricular ejection time (ms) during second half of pregnancy.

	Percentile						
Gestation (weeks)	2.5th	5th	10th	50th	90th	95th	97.5th
20	-21.9	-17.9	-13.1	5.1	25.2	31.2	36.4
21	-21.8	-17.8	-13.1	5.0	24.8	30.7	35.9
22	-21.7	-17.8	-13.1	4.9	24.5	30.3	35.4
23	-21.6	-17.7	-13.1	4.7	24.2	29.9	35.0
24	-21.6	-17.7	-13.1	4.6	23.9	29.6	34.7
25	-21.6	-17.7	-13.1	4.4	23.6	29.3	34.3
26	-21.6	-17.8	-13.2	4.3	23.4	29.1	34.1
27	-21.6	-17.9	-13.3	4.1	23.2	28.8	33.8
28	-21.7	-18.0	-13.4	4.0	23.0	28.7	33.6
29	-21.9	-18.1	-13.5	3.8	22.9	28.5	33.5
30	-22.0	-18.2	-13.7	3.7	22.8	28.4	33.4
31	-22.2	-18.4	-13.9	3.6	22.7	28.3	33.3
32	-22.4	-18.7	-14.1	3.4	22.6	28.3	33.3
33	-22.7	-18.9	-14.3	3.3	22.6	28.3	33.3
34	-23.0	-19.2	-14.6	3.1	22.6	28.3	33.4
35	-23.3	-19.5	-14.8	3.0	22.6	28.4	33.5
36	-23.6	-19.8	-15.1	2.8	22.6	28.5	33.7
37	-24.0	-20.1	-15.4	2.7	22.7	28.6	33.9
38	-24.4	-20.5	-15.8	2.6	22.8	28.8	34.1
39	-24.8	-20.9	-16.1	2.4	22.9	29.0	34.4
40	-25.3	-21.3	-16.5	2.3	23.0	29.2	34.7

Table 15. Longitudinal reference ranges of preload reserve for maternal systolic time ratio (%) during second half of pregnancy.

Gestation (weeks)	Percentile						
	2.5th	5th	10th	50th	90th	95th	97.5th
20	-51	-47	-42	-19	13	24	35
21	-50	-46	-41	-17	16	27	38
22	-49	-45	-39	-15	19	30	41
23	-48	-43	-38	-13	21	33	44
24	-47	-42	-37	-11	24	36	47
25	-46	-41	-35	-9	26	38	50
26	-45	-40	-34	-8	29	41	53
27	-44	-39	-33	-6	31	43	55
28	-43	-38	-32	-5	33	45	57
29	-42	-37	-31	-3	34	47	59
30	-41	-37	-30	-2	36	49	61
31	-41	-36	-30	-2	37	50	62
32	-41	-36	-29	-1	38	51	63
33	-41	-36	-29	-1	38	51	63
34	-41	-36	-30	-1	37	50	62
35	-41	-36	-30	-2	36	49	61
36	-42	-37	-31	-3	35	48	60
37	-43	-38	-32	-5	33	45	57
38	-44	-39	-33	-7	30	42	54
39	-46	-41	-35	-9	26	39	50
40	-47	-43	-37	-12	22	34	45

Table 16. Longitudinal reference ranges of preload reserve for maternal left ventricular work index (Kg m/m^2) during second half of pregnancy.

	Percentile						
Gestation (weeks)	2.5th	5th	10th	50th	90th	95th	97.5th
20	-26.4	-23.2	-19.4	-5.9	8.2	12.2	15.7
21	-26.5	-23.3	-19.5	-6.0	7.9	11.9	15.4
22	-26.5	-23.4	-19.7	-6.2	7.7	11.7	15.2
23	-26.7	-23.5	-19.8	-6.4	7.4	11.4	14.9
24	-26.8	-23.7	-20.0	-6.6	7.3	11.2	14.7
25	-27.0	-23.8	-20.1	-6.7	7.1	11.1	14.5
26	-27.2	-24.1	-20.3	-6.9	6.9	10.9	14.4
27	-27.5	-24.3	-20.6	-7.1	6.8	10.8	14.3
28	-27.8	-24.6	-20.8	-7.3	6.7	10.8	14.3
29	-28.1	-24.9	-21.1	-7.5	6.7	10.7	14.3
30	-28.5	-25.2	-21.4	-7.6	6.6	10.7	14.3
31	-28.8	-25.6	-21.7	-7.8	6.6	10.7	14.4
32	-29.3	-25.9	-22.1	-8.0	6.6	10.8	14.5
33	-29.7	-26.4	-22.4	-8.2	6.6	10.9	14.6
34	-30.2	-26.8	-22.8	-8.3	6.6	11.0	14.7
35	-30.7	-27.2	-23.2	-8.5	6.7	11.1	14.9
36	-31.2	-27.7	-23.6	-8.7	6.8	11.2	15.1
37	-31.7	-28.2	-24.0	-8.9	6.9	11.4	15.4
38	-32.3	-28.7	-24.5	-9.1	7.0	11.6	15.7
39	-32.9	-29.2	-24.9	-9.2	7.1	11.8	16.0
40	-33.5	-29.8	-25.4	-9.4	7.2	12.1	16.3