CARDIOVASCULAR EVALUATION OF HYPERTENSIVE DISORDERS OF PREGNANCY BY ECHOCARDIOGRAPHY

Dushyant K Desai

Submitted in partial fulfilment of the requirements for the degree of Doctor of Medicine

Declaration

This doctoral thesis is my own unaided work. All echocardiographic and uterine Doppler flow velocity measurements were performed by myself.

.....
Dushyant K Desai

PUBLICATIONS SO FAR FROM THESIS

Desai DK, Moodley J, Naidoo DP

Echocardiography assessment of cardiovascular hemodynamics in normal pregnancy

Obstet Gynecol 2004; 104: 20-9

DEDICATION

This work is dedicated to my supervisor, Professor J Moodley, a dedicated teacher of obstetric medicine; my wife Jigna and children, Veeral and Bijal; and my co-supervisor and colleague of many years, Professor DP Naidoo.

ACKNOWLEDGEMENTS

- **Dr F Patel for supervising uteroplacental Doppler studies.**

- **Cunden Chetty for assistance with computer services while writing this thesis.**

- **Vanessa Tombe for assistance in typing/formatting this doctoral dissertation.**

ETHICS

This doctoral thesis has been approved by the Ethics Committee of the Nelson R Mandela School of Medicine, University of Kwa-Zulu Natal, Durban, South Africa.

ABSTRACT

Background:

Preliminary observations suggest that aberrations in maternal central hemodynamics and uterine artery Doppler velocimetry reflect the severity of hypertensive disorders of pregnancy. In addition, the precise changes of cardiac output in normal pregnancy, particularly in the third trimester, have remained controversial.

Aims and Objective:

To measure concomitantly Doppler echocardiographic maternal central hemodynamics and uterine artery Doppler velocimetry and evaluate their association with adverse feto-neonatal outcome in hypertensive pregnant women. To evaluate cardiac output longitudinally in the latter half of pregnancy in normal healthy women.

Design and Setting:

Prospective study conducted at the Obstetric Unit, King Edward VIII Hospital, Durban, South Africa. Study sample: forty (40) pregnant hypertensives without any prior therapy and a further group of pre-eclamptic women (n=22) treated with stat dose sodium gardinal and alpha-methyldopa were studied.

Results:

i) A trend to a higher cardiac output was seen in the hypertensives compared to the normotensives. Hypertensive women were of larger stature; there was no difference in cardiac index. Fetal birthweight correlated poorly with cardiac index in pre-eclamptic women (r =0.21). A better correlation was seen with uterine artery resistance index (r = -0.65) and systemic vascular resistance index (r = -0.49). Critical values for cardiac index

and systemic vascular resistance index to predict poor adverse feto-neonatal outcome with good predictive values were not identified.

ii) Pre-eclamptics treated with stat dose of sodium gardinal and/or methyldopa prior to echocardiography had a significantly lower systemic vascular resistance index and uterine artery resistance index compared to the untreated group. The lower systemic vascular resistance index in this treated cohort occurred from a combination of non-significant lower blood pressure and higher cardiac index.

iii) Compared to normotensive women, untreated pre-eclamptics had a significantly lower heart rate ($p< 0.001$), a higher stroke index ($p=0.018$) and no difference in resultant cardiac index ($p=0.452$).

iv) In gestational apoteinuric hypertensives presenting after 34 weeks gestation, maternal hemodynamics and uterine artery resistance index did not help define a higher risk group.

v) In chronic hypertensives pregnancies, left ventricular hypertrophy correlated with severity of blood pressure. Higher risk chronic hypertensives were better selected by proteinuria than maternal central hemodynamics or uterine artery resistance index.

vi) In normal pregnancy, maternal cardiac output peaked in early to mid third trimester and was maintained till term. Significant correlations were observed among maternal cardiac output, maternal body surface area and fetal birth weight.

Discussion:

i) This study shows that cardiac index and systemic vascular resistance index measured in the latter part of the second and third trimesters in hypertensive pregnant women were not associated with adverse fetal outcome. Large variations in cardiac index values were observed that restricted detection of satisfactory critical values for cardiac index and systemic vascular resistance index to predict adverse outcome.

ii) An improved correlation of uterine artery resistance index with maternal hemodynamics and fetal birthweight in pre-eclampsia supports the hypothesis that poor placentation does not allow for a normal increase in uterine blood flow.

iii) The poor correlation between uterine artery resistance index and maternal central hemodynamics, does not support the hypothesis that elevated cardiac output in hypertensive pregnancies (hyperdynamic disease model) occurs as a compensatory response to maintain adequate perfusion in a utero-placental bed with high resistance that did not decrease.

Table of contents

Chapter index

Chapter 1: Introduction and literature survey

Chapter 2: Aims and Methods

Chapter 3: Echocardiographic assessment of maternal cardiovascular hemodynamics in normal normotensive pregnancy

List of tables

Chapter 5: Focus on preeclampsia and its variants

Chapter 6: Gestational aproteinuric hypertension

Chapter 7: Chronic hypertension and superimposed pre-eclampsia on chronic hypertension

List of figures

CHAPTER 1

INTRODUCTION AND LITERATURE SURVEY

1.1 Background

Hypertension in pregnancy is associated with significant cardiovascular morbidity and mortality. It is the most common medical disorder complicating pregnancy with a reported incidence of 5-10% (Duley, 1992), and is an important cause of fetal and maternal morbidity and mortality. In his review on the subject, Bernheim (1997) stated that the practical management of hypertensive disorders of pregnancy and in particular pre-eclampsia require prudence, careful follow-up and prompt decision on the precise moment for delivery. The National Committee on Confidential Enquires into Maternal Deaths in South Africa (1998) reported that complications of hypertensive disorders of pregnancy accounted for 23% of maternal deaths. At King Edward VIII hospital, a tertiary teaching institution in Durban, South Africa, the setting for the current study, 18% of all admissions to the obstetric unit are hypertensive (Moodley, 1993).

Women with established hypertension carry a significant increase in feto-maternal risks compared to normotensive pregnant women. Kuzniar (1982) and Yang *et al,* (1996), described poor fetal outcome and fetal growth restriction in hypertensive women who had a markedly reduced cardiac index or elevated systemic vascular resistance, respectively. Nisell *et al* (1988) also made similar observations of maternal hemodynamics of a low cardiac output and high systemic vascular resistance being associated with birth of a small for gestational age infant. More recently, Xiong *et al,* (2002) in a large retrospective cohort study reported a significant association of pre-

eclampsia and gestational hypertension with both large for gestational age infants and low birth weight and small for gestational age infants, observations that highlight the heterogenous nature of hypertensive disorders of pregnancy.

Diagnosis of hypertension in pregnancy rests on detection of a persistently elevated blood pressure; levels for diagnosis and assessment of severity however, remain controversial, as blood pressure is a continuous variable with unimodal distribution The degree of impaired maternal cardiovascular adaptation in hypertensive pregnancies could potentially be used to risk stratify and identify hypertensive pregnancies at risk for adverse fetal outcome. This determines the need for some form of classification of both the type and severity of hypertension occurring during pregnancy.

1.2 Current classification of hypertensive disorders of pregnancy

1.2.1 Introduction

The current classification of hypertensive disorders of pregnancy is far from ideal as the exact aetiology of hypertensive disorders of pregnancy and in particular pre-eclampsia, is not known. Consequently there are numerous classifications in the literature that have varied from being simple, less specific and user friendly to complex, more specific and less user friendly (Brown *et al,* 1999).

Whatever classification is used, there is consensus that hypertension in pregnancy is defined either as a diastolic blood pressure of greater than or equal to 110mmHg on any one occasion or a diastolic blood pressure equal to or greater than 90mmHg on two consecutive occasions at least 4 hours apart. Proteinuria is defined either by a 24

hour urine collection or 2 clean-catch or catheter urine specimens collected 4 hours apart. The 24 hour urine collection should have ≥ 300mg protein or a spot urine sample should have 1+ protein or more on the reagent strip or the sulfosalicylic acid "cold" test.

1.2.2 Classification of hypertension outside pregnancy

There are similar problems in classifying hypertension outside pregnancy. Earlier staging of essential hypertension focussed primarily on blood pressure and its severity to identify at 'risk' groups. The limitations of these earlier classifications became evident as clinicians and researchers found that they fell short on prognostic risk stratification. The recent staging of hypertension outside pregnancy advised by international bodies of the Joint National Committee of Hypertension and World Health Organization include clinical variables that have improved risk stratification. Apart from severity of blood pressure, the current Joint National Committee (JNC 7) classification (Chobanian *et al*, 2003) includes an assessment of associated cardiovascular risks, presence of a cardiovascular event and target organ involvement.

The cardiovascular risk factors emphasized in the JNC staging include age, dyslipidaemia, diabetes mellitus, cigarette smoking, menopause status and family history of cardiovascular disease. Target organ involvement includes the presence of proteinuria, retinopathy, left ventricular hypertrophy and evidence of significant atherosclerosis. Left ventricular hypertrophy is now accepted as an independent risk factor for adverse outcome in these hypertensive patients, an observation that has stimulated research into detection of abnormalities of cardiac structure and function

by echocardiography and Doppler. Thus, the presently used staging of hypertension outside pregnancy is user-friendly and useful for the clinician as it carries important therapeutic and prognostic implications; it is however, not satisfactory in pregnancy where hypertension is often acute in onset, and except for proteinuria, not associated with the risk markers as a rule.

1.2.3 Current classification of hypertensive disorders of pregnancy

A classification must also find general acceptance so that the incidence and outcome of hypertensive disorders of pregnancy and the results of research in different centres can be compared and mutual understanding achieved. The classifications recommended by Davey and MacGillivray (1988) and that by the Australasian society for the study of hypertension in pregnancy (Brown *et al,* 2000) are acceptable as they combine the essential components of hypertension and proteinuria. These classifications are based largely on the physical signs of hypertension and proteinuria. The classifications recommended by the Australasian society for the study of hypertension in pregnancy (Brown *et al,* 2000) and Davey and MacGillivray (1988) have the following corresponding categories:

Australasian society	Davey and MacGillivray
Gestational hypertension	Gestational aproteinuric hypertension
Pre-eclampsia	Gestational proteinuric hypertension
Chronic hypertension	Chronic hypertension
Pre-eclampsia on chronic hypertension	Pre-eclampsia on chronic hypertension

1.2.4 Gestational hypertension

This is refers to hypertension that develops during pregnancy in a previously normotensive non-proteinuric woman. The term 'gestational' is intended to mean that the hypertension developed during pregnancy and disappears in the post-partum period. It is important to note whether the first occurrence of hypertension occurred antenatally, in labour or post partum.

Although useful this somewhat arbitrary definition of gestational hypertension in that it excludes women with proteinuric hypertension (pre-eclampsia) and women with preexisting hypertension, further more it embraces a heterogenous group of hypertensive pregnant women with varying prognosis. Also it is not a final diagnosis as it may overlap with pre-eclampsia (proteinuric hypertension). Saudan *et al,* (1998) found that approximately 17% of women (15% in a retrospective study and 26% in a prospective study) initially diagnosed with gestational hypertension develop pre-eclampsia.

Furthermore, many women diagnosed with gestational hypertension carry a good prognosis as borne out in the study of Bosio *et al,* (1999) that showed women with gestational aproteinuric hypertension may be 'closer' to normotensive pregnant women in risk and outcome than with women who have pre-eclampsia (gestational proteinuric hypertension). In addition, the clinical presentation of pregnant women with mild aproteinuric chronic hypertension is often similar to women with gestational aproteinuric hypertension as clinical evidence of hypertensive target organ involvement is often not present in the former especially when the disease is mild.

These observations highlight some of the limitations of an arbitrary category of gestational hypertension that make accurate differentiation and precise risk stratification difficult.

1.2.5 Pre-eclampsia (gestational proteinuric hypertension)

Pre-eclampsia is better called gestational proteinuric hypertension because the latter term is intended to mean that the hypertension with proteinuria developed during pregnancy and disappears in the postpartum period. Pre-eclampsia may be categorised as being either mild to moderate or severe. It is labelled as being severe if any one of the following is present:

i) Blood pressure ≥ 160/110mmHg on 2 occasions 4 hours apart.

ii) Proteinuria of ≥ 5g per 24 hours OR 3+/4+ on semi-quantitative assay

iii) Oliguria defined as ≤ 500cc urine output per 24 hours

iv) Pulmonary oedema or cyanosis

v) Thrombocytopaenia

vi) Cerebral or visual disturbances such as an altered consciousness, headache, scotoma or blurred vision

vii) Epigastric or right upper quadrant pain

viii) Impaired liver function of unclear aetiology

The absence of any of these features categorises the patient as having mild or mild-moderate pre-eclampsia. Although these features define a high risk cohort labelled as severe pre-eclampsia, it has limited usefulness in early diagnosis of severe pre-eclampsia as Redman and Roberts (1993) have importantly pointed out that a smooth

progression from mild pre-eclampsia to a severe form is often not seen. To add to the complexity of having an all encompassing classification, Brown & de Swiet (1999) in their review have stated that, while remaining a hallmark of pre-eclampsia, proteinuria should no longer be considered a 'sine qua non' for this disorder to be diagnosed.

1.2.6 Chronic hypertension and chronic hypertension with superimposed pre-eclampsia

Chronic hypertension in pregnancy is defined as the presence of non-proteinuric hypertension in women in whom a diagnosis of chronic hypertension was made before, during or after pregnancy. At a practical level a diagnosis of hypertension made before the 20^{th} week of gestation or persistent hypertension beyond 6 weeks postpartum is presumed to be chronic hypertension. The development of proteinuria in such women during pregnancy demands an increased surveillance for the development of superimposed pre-eclampsia, a diagnosis that is not secure without the other features of the pre-eclampsia syndrome.

Furthermore, although women labelled as chronic hypertension in pregnancy as a group are at increased risk of developing placental abruption, fetal growth restriction, prematurity and superimposed pre-eclampsia (Haddad *et al,* 1999), this risk is not uniform. The above risks are particularly increased in women who have severe hypertension, pre-existing renal disease and in those with hypertensive target organ damage. In addition, chronic hypertension usually implies established hypertension that warrants antihypertensive therapy; which itself, particularly with the use of

diuretics and beta-adrenergic blockers, is not without potential harm. A recent analysis by Ferrer *et al,* (2000) concluded that no study has as yet provided guidance on the benefits, consequences of therapies or monitoring strategies of chronic hypertension in pregnancy.

1.2.7 Unclassified hypertension

In this category are included all cases where essential clinical information is lacking or where the diagnosis is uncertain. This category helps ensure that the above categories of gestational aproteinuric hypertension, pre-eclampsia, chronic hypertension and superimposed pre-eclampsia on chronic hypertension are not confused. Such patients are then correctly classified at postpartum follow-up.

1.2.8 The need for continued refinement in classification of hypertensive disorders of pregnancy

Hypertension as a trait is also problematic as its classification as a blood pressure measure above 140/90 mmHg is arbitrary and its aetiology remains highly heterogeneous. In studies of hypertension, both in pregnant and non-pregnant settings, Peters *et al,* (1995) highlighted the limitation of using blood pressure as a distinguishing parameter because it exhibits great intra-individual variance.

The complexity of classifying hypertensive disorders of pregnancy becomes evident as Spaanderman *et al,* (2000) suggested that normotensive women with a history of pre-eclampsia should be considered as having latent hypertension. Despite the

limitations of M-mode echocardiographic study methods to evaluate maternal hemodynamics, Clapp *et al,* (1997) showed that cardiovascular adaptations during pregnancy may persist up to one year postpartum and that it may be enhanced by a subsequent pregnancy. These observations highlight potential limitation of grouping together primiparous and multiparous women and of using the postpartum period as baseline when evaluating maternal hemodynamics.

Higgins *et al,* (2001) point out that definitions of pre-eclampsia based solely on hypertension and proteinuria ignore the wide clinical variability, including the presence and severity of proteinuria in this syndrome. For instance, Saudan *et al,* (1998) have shown that women with gestational hypertension may progress to pre-eclampsia. In their review by Brown & de Swiet (1999) consider that proteinuria, while remaining a hallmark of pre-eclampsia, should no longer be considered a 'sine qua non' for this disorder to be diagnosed.

In the light of these drawback it is therefore not surprising that researchers have turned some of their focus to the maternal hemodynamic determinants of blood pressure (cardiac output and systemic vascular resistance) to risk stratify hypertensive pregnancies. Non-invasive evaluation of maternal central hemodynamics, cardiac structure and function together with simultaneous uteroplacental Doppler velocimetry evaluation offer an attractive option for improved understanding of the pathophysiology of hypertension in pregnancy and assist in the care of these patients. The literature survey focuses on the cardiovascular changes in normal and hypertensive pregnancy followed by an evaluation of echocardiographic-Doppler maternal central haemodynamics, uterine artery velocimetry and aims of this study.

1.3 Cardiovascular changes in normal pregnancy

1.3.1 Cardiac output

The precise changes of cardiac output in normal pregnancy have remained controversial. A meta-analysis of cross-sectional studies has revealed large ranges in cardiac output across studies (van Oppen *et al,* (1996). Despite numerous limitations of the above meta-analysis, pooled data from each trimester showed a tendency to higher cardiac output in the second trimester compared with the first and lower cardiac output in the third trimester compared to the second.

Van Oppen *et al,* (1996) also performed a meta-analysis of 6 longitudinal studies that had 2 or more cardiac output measurements during pregnancy. The authors found widely divergent changes in cardiac output between the second and third trimesters, with 2 studies showing an increase, 2 with no change, and 2 with a decrease. Both van Oppen *et al,* (1996) and Duvekot eand Peeters (1994) cited patient factors rather than technique as being responsible for the apparent divergent trends of cardiac output in the third trimester.

In their review Thornburg *et al,* (2000) reported that cardiac output peaks in the third trimester by approximately 50%. The peak has been reported to occur at gestations varying from 24 weeks to term in the review by van Oppen *et al,* (1996). Most of these studies of cardiac output in pregnancy were performed with subjects in the lateral position so that the effects of inferior vena caval compression are minimized and unlikely to account for the variability. However, most studies of maternal hemodynamics in normal pregnancy have reported measurement of cardiac output

rather than the stature-corrected measure of cardiac index and this may be a significant reason for the variable changes. The rise in cardiac output is generally accepted as being approximately 50% above pre-conception values but the relative contributions of heart rate and stroke volume remain unsettled. Cardiac output decreases in the early postpartum period and pre-conception values are reached around 6-12 weeks.

1.3.2 Heart rate, stroke volume and cardiac output

Although heart rate and stroke volume are the two major determinants of cardiac output, most studies of cardiac output in pregnancy have not paid particular attention to the effects of heart rate. The meta-analysis by van Oppen (1996) also did not focus on the influence of heart rate on cardiac output during pregnancy. In a study by Hennessy *et al,* (1996) of cardiac output measured by Doppler ultrasound, the authors showed a 32% increase in heart rate above baseline values. This maximal heart rate occurred at 32 weeks gestation corresponding to the time of peak cardiac output. Stroke volume however, continued to increase to a maximum at 36 weeks suggesting that the decline in cardiac output from 32 weeks is mediated by a decrease in heart rate.

In another longitudinal study, Mabie *et al* (1994) demonstrated an increase in cardiac output of 53% that occurred late in the third trimester; the peak occurring from an increase in stroke volume of 18% and an increase in heart rate of 29%. These varying contributions of heart rate and stroke volume to changes in cardiac output are not easily explained. Variations in autonomic control mechanisms in pregnant women

may explain some of the reported differences of heart rate effect on cardiac output. Blake *et al*, (2000) have reported reduced baroreceptor sensitivity for heart rate during normotensive pregnancy.

1.3.3 Blood pressure, cardiac output and systemic vascular resistance

Systolic, diastolic and mean blood pressure values begin to decline from the first trimester at approximately 8 weeks and continue to decline to reach their lowest towards the end of the second trimester after which there is a steady increase with a return to pre-pregnant blood pressure values at term or soon thereafter. Measuring muscle sympathetic nerve activity, Greenwood *et al,* (2001) showed that central sympathetic output was increased in the latter months of normal pregnancy; these findings suggest that a moderate increase in sympathetic hyperactivity in the latter months of normal pregnancy may help return of arterial pressure to non-pregnant levels. In addition, Greenwood *et al,* (2001) also noted that sympathetic output decreased to non-pregnant values after delivery; a change that occurred without significant change in blood pressure. This imprecise relationship between central sympathetic output and blood pressure in normotensive pregnant women is also supported in an earlier study by Ergman *et al*, (1999) who found no differences in neuropeptide Y, levels, modulator of vascular tone by the sympathetic nervous system, between normotensive and preeclamptic women.

As discussed in 1.3.1 cardiac output probably peaks by mid-third trimester; after this there is a steady decline to term. This corresponds to the systemic vascular resistance which reaches its lowest value at 28-32 weeks and increases steadily thereafter till term (van Oppen, 1996). Also Varga *et al,* (2000), have shown that the maximal

increase in glomerular filtration rate as a result of renal vasodilation precedes the maximal increase of cardiac output. They attributed the increase of cardiac output in the first trimester to a shunt effect of enhanced renal blood flow and in the second and third trimester to the shunt effect of the feto-placental unit and maternal kidneys. Noting that these observations support the "underfill hypothesis" in normal pregnancy, Carbillon *et al,* (2000) in their review stated that the adaptation of vascular tone in early pregnancy precedes and probably triggers blood volume and cardiac output increase.

1.3.4 Systemic vascular resistance and vasodilatory neurohormones

Thus the fall in systemic vascular resistance in normal pregnancy commences early in the first trimester and is related to changes in renal function and blood volume. The blood pressure is also diminished, a change noted especially during the second trimester. These changes are also associated with altered receptor responses to vasoconstrictor and vasodilatory neurohormones. Among the neuro-hormones regulating vascular homeostasis both in normal and hypertensive pregnancies, the renin-angiotensin system is important because of the known decrease in pressor responsiveness to angiotensin II in normal pregnancy. In a study of 7 normal pregnant volunteers Langer *et al,* (1998) showed that in the first trimester of normal pregnancy, active renin concentrations are elevated but angiotensin I, angiotensin II, and aldosterone levels remained at comparable postpartum levels. The highest activity of the renin angiotensin system, with increased levels of angiotensin I, angiotensin II, and aldosterone, was observed in the third trimester.

August *et al,* (1995) evaluated converting enzyme inhibition with captopril in normal pregnancy and concluded that activation of the renin-angiotensin system was responsible for maintained blood pressure. Merrill *et al,* (2002) showed that this is associated with a rise in plasma angiotensin II as well as a 51% increase in angiotensin(1-7), a bioactive component that has depressor, vasodilatory and antihypertensive actions. Angiotensin 1 – 7 is a novel counterregulator lacks the vasoconstrictor actions of angiotensin II; it has no central pressor effects, does not stimulate aldosterone and results in release of nitric oxide, bradykinin and prostacycline. In preeclamptics the level of angiotensin (1-7) is significantly reduced despite an increase in plasma angiotensin II levels.

Magness *et al,* (1994) have shown that the decreased pressor response to angiotensin II in normal pregnancy is not due to an increase in prostaglandin E_2, nor is it related to alterations in the balance ratio of prostacycline to thromboxane. In contrast there is evidence that angiotensin II evokes both a pressor and depressor effect and the latter effect could be mediated by angiotensin II – induced stimulation of prostacycline synthesis.

Endothelium-derived nitric oxide, a vasodilator, has also been reported to suppress vasoconstrictor reactivity and contributes to the fall in peripheral resistance in normal pregnancy. Using forearm blood flow responses Anumba *et al,* (1999) concluded however, that changes in vascular nitric oxide activity are unlikely to account for the increased vascular tone seen in pre-eclampsia. These observations are supported by Rajagopal *et al,* (2003) who found no differences in nitric oxide synthases by immunostaining in both normotensive and hypertensive pregnancies. Higher

concentrations of reproductive hormones such as progesterone and relaxin in early pregnancy have been described to be associated with lower systolic blood pressures in the second and third trimesters (Kristiansson *et al,* 2001). The vasodilator effect of endogenous calcitonin gene-related vasodilator on fetoplacental vascular tone could be mediated by a nitric oxide pathway (Dong *et al,* 2004).

Whatever the precise role of vasodilatory neurohormones in contributing to the reduced systemic vascular resistance in normal pregnancy it is clear that the renin angiotensin system has a principal role not only in regulating the vasodilation in normal pregnancy, but it also indicates the pathological vasoconstriction observed in pre-eclampsia.

1.3.5 Volume homeostasis and red cell mass

Plasma volume and total extracellular fluid volume are increased in normal pregnancy. The increase in plasma volume increase occurs from about the seventh week of gestation and increases gradually to a maximum at approximately 30 weeks and is maintained at this level till term. Brown *et al,* (1992) have reported that maximal increases 1200-1600ml corresponded to a 50% rise above pre-pregnancy levels. In addition, the authors also noted that both the maximum increment and the maximum plasma volume reached correlated positively with birth weight. These observations are consistent with the hypothesis that normal maternal cardiovascular adaptive responses are accompanied by increases in maternal cardiac output associated with an adequate plasma volume expansion and constitute a state of chronic volume overload (Katz *et al,* 1978).

One would expect that atrial distension or an increase in atrial pressure is the stimulus for atrial natriuretic secretion. However, atrial natriuretic peptide levels during pregnancy are essentially unchanged from pre-pregnant levels (Laragh, 1985). In a study of acute volume loading Nisell *et al,* (1992) did not demonstrate any increase in atrial natriuretic peptide concentration during late pregnancy as compared to the non-pregnant state. More recently, Maggioni *et al,* (2001) stated that in normal pregnancy, the relationship between atrial natriuretic peptide and arterial pressure and the renin-angiotensin system remains debatable. The authors also described elevated levels of atrial natriuretic peptide levels in normotensive pregnancy complicated by intrauterine growth restriction compared to normal normotensive pregnancy. It appears that during pregnancy atrial natriuretic peptide has negligible effects on plasma volume regulation and that volume homeostasis is the result of changes in various inter-dependent systems. The initial reduction in vascular tone leads to changes in plasma osmolality that probably results in resetting of volume and osmoreceptors. Thereafter, other volume regulating mechanisms such as the renin-angiotensin-aldosterone system, pregnancy hormones and atrial natriuretic peptides adapt to the increase in blood volume (Duvekot *et al,* 1994).

Plasma volume and red cell mass are closely related in pregnancy. The increase in total red cell mass varies from 17-40% (mean 24%) with a pattern that is similar to the increase in plasma volume (Brown *et al,* 1992). Whittaker *et al,* (1996) reported that both haemoglobin concentration and haematocrit show a steady decrease until late in the third trimester. These authors found no correlation between red cell indices and fetal outcome and suggested that the low haemoglobin noted in late pregnancy reflect

plasma volume changes rather than poor maternal nutrition or cardiovascular adaptation. Recently McMullin *et al,* (2003) showed that erythropoietin levels increased throughout normal pregnancy and they observed a significant relationship between erythropoietin levels and haemoglobin, ferritin, total iron binding capacity and folate. These observations support the hypothesis described by Donnelly (2003) that hematocrit regulation is mediated by the kidney acting as a "critmeter" that regulates the plasma volume and red cell mass.

1.3.6 Placental Implantation

In normal pregnancies the cytotrophoblast invades the endothelium and muscular tunica media of the maternal spiral arteries, resulting in transformation of these small muscular arterioles to large capacitance vessels of low resistance (Zhou *et al,* 1997). This process is dependent on the invasion of the interstitium and spiral arteries of the uterine wall by invasive extravillous trophoblast thereby creating a high flow-low resistance vessel (Naicker *et al*, 2003). This normal placental implantation is usually associated with the normal maternal cardiovascular adaptive changes characterised by an increase in cardiac output, stroke volume, heart rate, blood volume, renal blood flow and glomerular filtration and a reduction in systemic vascular resistance (Sibai *et al*, 1995). Defective placentation, that is so characteristic of hypertensive pregnancies, is associated with an attenuation or failure of this normal maternal cardiovascular adaptation (de Groot *et al*, 1996).

1.4 Cardiovascular changes in hypertensive pregnancy with focus on pre-eclampsia

1.4.1 Introduction

The aetiology of hypertensive disorders of pregnancy, in particular, pre-eclampsia, remains elusive despite significant knowledge gained about many of its biological characteristics and predictors. In his review of pre-eclampsia, Roberts (2000) attributed the primary pathophysiology in pre-eclampsia to reduced placental perfusion probably consequent upon abnormal implantation. Other major aetiological factors relate to maternal disorders that serve as predisposing factors and include conditions such as chronic hypertension, renal disease, diabetes and obesity.

In pre-eclampsia, trophoblastic implantation is abnormal or is limited to the decidual part of the vessels. Trophoblastic function is impaired and may include restricted invasive behaviour (Pijnenborg *et al,* 2000). The decidual portion of the spiral arteries does not undergo the normal pregnancy-induced remodelling that converts these vessels to high volume-low resistance conduits (de Groot *et al,* 1993). Histopathology of the placental bed in pre-eclamptic women shows the spiral and basal arteries to be more tortuous and have smaller calibre lumens and thicker walls (Starzyk *et al,* 1999). This failure of proper placentation in pre-eclamptic women may result in abnormal spatial anatomy of the placental bed. It is postulated that reduced placental perfusion interacts with maternal constitutional factors to generate the systemic pathophysiological milieu of pre-eclampsia (Roberts 2000).

In contrast to normal pregnancy, widespread injury to vascular endothelial cells is believed to result in an increased sensitivity to pressor agents causing vasospasm.

This endothelial injury and dysfunction has been described as the secondary pathophysiology in pre-eclampsia that results in disturbance in organ function of liver, heart, kidneys and brain. Recently, Anim-Nyame *et al,* (2003) measured circulating levels of vascular cell adhesion molecule-1, intercellular cell adhesion molecule–1, E-selectin and neutrophil elastase in pre-eclamptic women and showed impaired microvascular function related to alterations in endothelial cell and neutrophil activation.

Since hypertensive pregnancies comprise a highly heterogeneous group several other factors contribute to the pathogenetics. Furthermore the genetic component in such groups may elude detection in studies grouped by current criteria (Peters, 1995). As yet, the relative contributions of maternal and fetal genotypes are still unclear (Roberts, 2001). Other factors that play a pathogenetic role include immune mechanisms, genetic susceptibility, parity (either first order or high parities) and maternal age (teenagers and women of 35 years or greater), all of which may contribute to abnormal implantation of trophoblast.

The deficient placental implantation process is probably complete many weeks before hypertension becomes clinically apparent (Khong *et al,* 1986). Clinical disease in pre-eclampsia usually manifests much later, in the third trimester. However, less frequently, clinical disease occurs in the latter half of the second trimester, often referred to as early onset pre-eclampsia. These observations allude to the importance of evaluating subclinical changes in this latent or pre-clincal phase. A study of the time-course pattern of cardiovascular changes in normal pregnancy will allow for a more critical evaluation of cardiovascular hemodynamics in hypertensive disorders of

pregnancy. The hypothesis is that these adaptive changes may serve as a non-invasive 'window' to the presence and severity of the defective placentation that occurs in hypertensive pregnancies.

1.4.2 Latent (pre-clinical) phase

Symptomatic disease in pre-eclampsia is often preceded by a variable and often long pre-clinical period (latent phase). There are few studies of maternal cardiovascular hemodynamics in the latent phase of hypertensive disorders of pregnancy with most reports being limited to retrospective descriptions of changes in blood pressure. Although a study by Moutquin *et al,* (1985) found that a rise in blood pressure or elevated mean blood pressure in the second trimester was an early sign of pre-eclampsia, the value of such mid-trimester blood pressure screening remains limited by its low predictive value.

The work of Easterling *et al,* (1990) and Bosio *et al,* (1999) are the only reported studies of maternal hemodynamics in the latent phase of pre-eclampsia. In the Easterling *et al* (1990) study, cardiac output was studied prospectively in 98 nulliparous women using Doppler ultrasound. The authors noted that cardiac output was elevated throughout pregnancy in the 9 women who became pre-eclamptic. This study suggested that pre-eclampsia is characterised by a hyperdynamic circulation with a high cardiac output and challenged the generally accepted belief that pre-eclampsia is a disease of reduced cardiac output with high systemic vascular resistance. A limitation of this important study was that a large number of study patients had deficient observations in early and mid pregnancy. Furthermore baseline

demographics differed in that pre-eclamptic women were more obese and had higher body surface areas. In the second study in primigravida, Bosio *et al,* (1999) showed a similar hyperdynamic state in the latent phase but a change to low cardiac output and high vascular resistance in women who developed clinical pre-eclampsia.

1.4.3 Clinical phase

Almost 20 years ago, Phelan *et al,* (1982) studied women with pre-eclampsia and showed that all subjects had an elevated cardiac output and normal systemic vascular resistance. Subsequently in another invasive hemodynamic study of 49 women with severe pre-eclampsia, Mabie and Sibai (1989) also found most women had a high cardiac output and a normal to moderately elevated systemic vascular resistance.

Recent studies however are at variance with these findings. Visser and Wallenburg (1991) studied 87 women with early onset severe hypertension (gestational and chronic) and demonstrated a uniform pattern of low cardiac output and high systemic vascular resistance. The differences in observations were attributed to several factors that included small study numbers; variability in disease duration and severity; underlying medical problems; therapeutic intervention before hemodynamic monitoring and the absence of suitable control groups.

In a review on the subject Duvekot and Peeters (1994), pointed out that as yet there is no clear-cut central hemodynamic profile in hypertensive pregnancies, and that except in the setting of clinical cardiovascular decompensation, invasive hemodynamic

monitoring is not recommended as such techniques are not simple, quite inconvenient with unproven risk/benefit advantages in milder disease.

1.4.4 Heart rate –an important cardiac output variable

Heart rate is an important parameter directly affecting cardiac output. Yet, most studies of maternal cardiovascular hemodynamics in hypertensive disorders of pregnancy have given little attention to effects of heart rate on cardiac output. An early study by Kuzniar *et al,* (1982) demonstrated that the average heart rate during the third trimester in pre-eclampsia was lower than in the control group. This study has been criticised for averaging the heart rate of all visits in the third trimester with consequent loss in the power of study observations.

In a longitudinal study Easterling *et al,* (1990) demonstrated an elevated cardiac output in a predominantly obese pre-eclamptic group, which he attributed to an elevated heart rate, there being no differences in stroke volume between study and control groups. This study did not account for differences in body mass index at baseline. Scardo *et al,* (1996) corrected for effects of heart rate and showed an increased heart rate prevents the expected fall in cardiac output in severe pre-eclampsia. Using the stroke-systemic vascular resistance index, (heart rate x systemic vascular resistance index), they concluded that women with severe pre-eclampsia had a greater vasoconstricted state than milder cases of pre-eclampsia.

1.4.5 Volume homeostasis

An increase in capillary permeability leads to a redistribution of intravascular volume to interstitial fluid space in hypertensive pregnancies (Brown *et al,* 1992). As a result volume homeostasis is disturbed in hypertensive disorders of pregnancy, particularly in severe pre-eclampsia. As a result of the fluid shift plasma volume is reduced in pre-eclampsia but this fluid redistribution is not always clinically apparent as peripheral oedema. Recently Moran *et al,* (2003) demonstrated a reduced glomerular filtration rate and renal plasma flow in preeclamptics and showed that the glomerular dysfunction resolved postpartum. To what extent these changes in volume are compensated for by venoconstriction to maintain cardiac output is not clear Roberts (2000).

The onset and severity of plasma volume changes has received scant attention. Silver *et al,* (1998) showed that plasma volume is reduced in pre-eclampsia but is normal in women with non-proteinuric gestational hypertension, indicating that disease severity is an important factor in determining the magnitude of these changes. Furthermore, suboptimal plasma volume expansion (also referred to as contracted/reduced plasma volume) has been noted to occur early in the second trimester and changes in plasma volume have been reported to correlate with birth weight. Duvekot *et al,* (1995) noted that the reduction in plasma volume expansion occurred early in pregnancy in their study of women who developed fetal growth restriction. It therefore appears that the abnormal cardiovascular responses in plasma volume and cardiac output precede the fetal growth restriction that is detected in the latter half of pregnancy.

1.4.6 Maternal haemodynamics and fetal outcome

Pre-eclampsia increases the risk of intrauterine growth restriction and low birth weight Xiong *et al,* (1999). The relationship between foetal outcome and maternal cardiovascular hemodynamics has been studied non-invasively by echocardiography. Using M-Mode echocardiography alone Kuzniar *et al,* (1982), estimated hemodynamics in nineteen pre-eclamptic women and found a positive correlation between maternal cardiac output and infant birth weight. The three women in the study with the lowest cardiac index (cardiac output /body surface area) experienced stillbirth or neonatal death. This study is however, limited by its small sample size, a heterogeneous pre-eclamptic group (not stratified by severity of disease or gestation) and the use of M-mode echocardiography measurements.

Easterling *et al,* (1991) also assessed maternal hemodynamics in 76 women with hypertensive pregnancies presenting before 28 weeks of gestation. They concluded that hypertensive pregnancies characterised by a high systemic vascular resistance were associated with a poorer fetal outcome. This study was limited by its retrospective design; a heterogeneous hypertensive study group not stratified by disease severity and parity, and the sole inclusion of hypertensive pregnancies presenting before 28 weeks gestation.

A third study (Yang *et al,* (1996)) showed that maternal cardiac output was quite variable in pre-eclampsia but elevated systemic vascular resistance was associated with a higher incidence of small gestational age infants. Despite their limitations these studies do reflect the association between impaired maternal hemodynamics and adverse fetal outcome.

1.4.7 Vasoactive neurohormones and endothelial dysfunction in pre-eclampsia

The exact pathogenetic underlying activation of the renin-angiotensin system in pre-eclampsia remains incompletely understood. Whereas normal pregnancy is characterised by a reduced pressor sensitivity to infused angiotensin II, in pre-eclampsia an enhanced pressor activity to infused angiotensin II has been demonstrated to occur even before clinically manifest hypertension.

Langer *et al,* (1998), has confirmed earlier observations of a decrease in activity of the renin-angiotensin-aldosterone system in pre-eclampsia. The authors postulated that this decreased activation of the renin-angiotensin system could contribute to the diminished hemodynamic regulation seen in pre-eclampsia. Similar conclusions were drawn by Kalenga *et al,* 1996 and Brown *et al,* 1994 who showed that concentrations of angiotensin II, renin and aldosterone are reduced in pre-eclampsia compared to normal pregnancy. Furthermore, in a recent study Merrill *et al,* (2002) showed that levels of angiotensin-(1-7), a bioactive component of the renin-angiotensin system that has depressor and vasodilatory actions, were reduced in women with pre-eclampsia compared to normal pregnant women. Some of these apparent divergent observations of the circulatory renin-angiotensin system in hypertensive disorders of pregnancy may be explained in part by impaired functioning of a local renin-angiotensin system in the uteroplacental unit in pre-eclampsia patients (Baylis *et al,* 1998).

It has been postulated that reduced nitric oxide and an increase in peroxynitrite levels may account for many effects, including reduced prostacyclin production and alteration in the balance of thromboxane and prostacyclin favouring vasoconstriction and platelet aggregation (Lowe, 2000).

In a study of endothelial derived relaxing factor in normal and hypertensive pregnancy, Ashworth *et al,* (1999) showed that nitric oxide synthesis appears to mediate a greater proportion of the relaxation in pre-eclampsia than in normal pregnant women. Early studies (Seligman *et al,* (1994)) have demonstrated reduced levels of nitrate in pre-eclampsia although a recent study by Anumba *et al,* (1999) does not support a role for nitric oxide in the pathogenesis.

Also Slowinski *et al,* (2002) have reported that the endothelin system is activated in pre-eclampsia. However, the authors did not find a correlation between the elevated plasma levels of endothelin-1 and maternal blood pressure or urine protein excretion. Khedun *et al,* (2002) has also shown similar elevation in plasma endothelin-1 levels in black pre-eclamptic women compared to aproteinuric hypertensives and normotensives controls.

In contrast to normal pregnancy, atrial natriuretic peptide levels in pre-eclampsia are elevated. This appears paradoxical as this increase in atrial natriuretic peptide in pre-eclampsia subgroups was noted to occur in the setting of a contracted plasma volume (Spaanderman *et al*, 2001). These findings may be explained by the left ventricular structural adaptive changes to increased systolic blood pressure which has been

shown to correlate positively with plasma levels of both atrial natriuretic peptide and brain natriuretic peptide Borghi *et al,* (2000).

Although endothelial dysfunction is considered to underlie many of the clinical manifestation in preeclampsia, the precise biochemical pathways involved remain unclear. In a recent review, Shah (2005) suggested that angiotensin II mediated mechanisms can explain the vascular maladaptation with increased vasomotor tone and endothelial dysfunction seen in pre-eclampsia. A current hypothesis suggested in the review by Rodrigo *et al* (2005) indicates that oxidative stress is involved in the pathogenesis as placental and lipid peroxidation products of F2-isoprostanes and malondialdehyde are increased with activation of endothelial cells. Finally, Savvidou *et al* (2003) found that maternal endothelial function was impaired in women who eventually develop pre-eclampsia and that the maternal endothelial dysfunction occurs before the development of the clinical syndrome. Savvidou *et al* (2003) also showed that women with a high resistance placental circulation (at risk of pre-eclampsia) had raised levels of asymmetric dimethylarginine, an endogenous inhibitor of endothelial nitric oxide synthase.

1.4.8 Sympathetic activity and vagal baroreflex function

It appears that the increase in peripheral vascular resistance and blood pressure that characterise pre-eclampsia is mediated, at least in part, by an increase in sympathetic vasoconstrictor activity. There is evidence that sympathetic activity is augmented in pre-eclampsia and reverts to normal after delivery (Schobel *et al,* 1996). More recently, Greenwood *et al,* (2001) also showed that central sympathetic output was increased in normal pregnancy and increased to a greater extent in hypertensive

pregnant women. A similar pattern of changes in vagal baroreflex gain was reported by Silver *et al,* (2001) who found the normal reduction in baroreflex gain in pregnancy is further depressed in women with gestational hypertension and pre-eclampsia.

1.4.9 Electrolyte abnormalities

Various electrolyte abnormalities have been studied to explain regional and racial differences in the prevalence of hypertensive disorders of pregnancy. Dietary salt restriction and diuretic therapy have not reduced the incidence of pre-eclampsia (Steegers *et al,* 1991). In a meta-analysis by Bucher *et al,* (1996), calcium supplementation in pregnancy was noted to be effective in lowering blood pressure with a trend towards reducing the incidence of pre-eclampsia. Despite these observations, the authors state that the beneficial effects of calcium supplementation remain unproven.

1.4.10 Summary

The primary abnormality in hypertensive disorders of pregnancy and in particular pre-eclampsia, is defective placentation that is seen histologically as inadequate remodelling of the spiral arterioles. This results in reduced placental blood flow with resultant ischaemia to the fetus that probably commences at some point in the second trimester or later depending on the severity of the disease. Maternal cardiovascular diseases such as chronic hypertension, diabetes and renal disease are now recognised

as predisposing factors. Other factors such as age, parity, obesity and genetic susceptibility are helpful in defining risk groups.

The precise biochemical mediators responsible for the inadequate/abnormal maternal cardiovascular adaptation in hypertensive pregnancies still remain to be elucidated. The biochemical mediators include the renin-angiotensin system hormones, the sympathetic nervous system, atrial natriuretic peptides, prostaglandins, endothelins, nitric oxide and electrolyte abnormalities. In severe pre-eclampsia widespread maternal vascular endothelial dysfunction ensues, often with organ dysfunction and organ failure.

In normal pregnancy, the utero-placental circulation becomes maximally dilated with a fall in resistance, a change that seems necessary for fetal growth. Ramsay *et al,* (1994) in their study of the effects of glyceryl nitrate on the uterine artery suggested that endogenous nitric acid production is probably responsible for the adaptation of the maternal cardiovascular system to pregnancy.

The development of low resistance blood flow in the placental circulation occurs largely from anatomical transformation of trophoblastic invasion and loss of muscle layer in the spiral arterioles that may be influenced or directed by biochemically mediated vasomotor mechanisms. This anatomical transformation is striking at the level of the spiral arteries where a metamorphosis of small calibre spiral vessels into flaccid, distended uteroplacental arteries occurs (Pijnenborg *et al,* 1981).
The placental circulation is also unique in that the uterus loses its efferent innervation during pregnancy and both the placenta including the spiral arterioles and cord are not

innervated (Morizaki *et al,* 1989). Inappropriate changes in the efferent innervation of spiral arteries may be associated with impaired development of a low resistance placental bed in pre-eclamptic pregnancies. Non-invasive measurement of resistance in the uteroplacental circulation permits an evaluation of the placental circulation.

1.5 Uteroplacental Doppler velocimetry in hypertensive pregnancy

In recent times utero-placental blood flow using Doppler ultrasound (velocimetry) is being increasingly used to assist in predicting at risk hypertensive pregnancies. Serum urate, non-stress fetal cardiotocography and ultrasonic amniotic fluid volume estimation are still the classical measures that are used to predict fetal outcome and assist in therapeutic decisions. Although these tests have good negative predictive value, they are limited by a low sensitivity and low positive predictive value.

The uterine artery resistance index computed from flow velocity waveforms recorded at the level of the main uterine arteries reflects the downstream flow impedance in the whole uterine circulation (Maulik, 1995). Uterine artery Doppler studies have shown that in pregnancies complicated by pre-eclampsia and fetal growth restriction, there is a failure of uteroplacental resistance to decrease and accommodate the increased utero-placental blood flow, as is observed in normal healthy pregnancy (Harrington *et al,* 1991). The pathophysiology of the uterine Doppler velocimetry abnormalities are supported in part by histopathological placental studies by Pijnenborg *et al,* (1991 & 2001) who also stated that the placental changes seen in pre-eclampsia may also be associated or caused by the other forms of hypertension disorders of pregnancy. In

addition, it was noted that extent of failure of spiral artery remodelling did not carry a clear-cut correlation to clinical disease.

Studies evaluating the uteroplacental circulation using Doppler velocimetry have produced varying results regarding its predictive value (Bower *et al,* 1998). Yang *et al,* (1995) showed abnormal umbilical artery Doppler correlated with acute fetal distress whereas uterine artery Doppler was not beneficial in this respect. Aquilina *et al* (2001) used uterine artery Doppler at 20 weeks gestation as a screening test to predict pre-eclampsia found that uterine Doppler flow velocity alone was not a satisfactory predictor. An improved predictive potential was obtained when notching on uterine artery Doppler profile and serum inhibin A levels were included in the model.

In their study of uterine artery Doppler velocimetry and placental histopathology in preeclamptics with growth restriction, Sargol *et al,* (1999) showed that an elevated uterine artery resistance index (≥ 0.58) was associated with a higher prevalence of impaired trophoblast migration. Subsequently, Coleman *et al,* (2000) found that uterine artery resistance index of ≥ 0.70 at 24 weeks gestation was of value in predicting serious adverse outcome in women at high risk. Although lower uterine artery Doppler velocimetry cut-off values (resistance index ≥ 0.58) improved sensitivity, they were however associated with a reduced specificity and reduced positive predictive value.

All these studies did not combine uterine artery Doppler velocimetry with a measure of maternal central haemodynamics. Since uterine artery Doppler has the potential to

predict at risk hypertensive pregnancies, a combined evaluation of maternal central hemodynamics and concomitant uterine artery Doppler may define and predict at risk hypertensive pregnancies more accurately.

1.6 Doppler echocardiography for assessment of maternal central hemodynamics and aims of this thesis

The development of pre-eclampsia is thought to occur very early in pregnancy. The process probably starts with defective implantation and placentation followed by reduced placental perfusion and subsequent maternal endothelial dysfunction and organ dysfunction (Roberts, 2000). It is thus logical to anticipate that the more severe the impairment in trophoblast implantation and placental perfusion, the greater will be the extent to which a failure of the normal cardiovascular adaptation manifests. Abnormal maternal cardiovascular hemodynamics can thus be a good reflection of abnormalities in the fetus and/or placenta.

Many of the controversies of maternal hemodynamic profile in hypertensive pregnant women have arisen because of the limitation of invasive methods used to measure central hemodynamics. Furthermore, invasive Swan-Ganz catheter-measured hemodynamics requires considerable skill, is inconvenient, and is associated with potential hazard and a risk-benefit advantage that is as yet not proven.

Echocardiography on the other hand, is an excellent non-invasive method of assessing cardiac structure and function. Recent refinements in Doppler velocimetry techniques have enabled measurement of cardiac output with good accuracy. Doppler

echocardiography-derived cardiac output has been validated in pregnant subjects against the direct and "gold standard" invasive thermodilution technique (Easterling *et al,* 1987). It is presently accepted as an accurate, safe and repeatable non-invasive technique to measure maternal hemodynamics in hypertensive pregnancies, allowing correlation with changes in uterine artery Doppler velocimetry.

An accurate measure of maternal hemodynamics in hypertensive pregnancies will provide an improved understanding of the pathophysiology. Doppler echocardiography, a non-invasive modality, offers a safe measure of cardiovascular hemodynamics with good accuracy and also lends itself to serial measurement of hemodynamics without harm to mother or fetus. The altered maternal cardiovascular hemodynamics and uteroplacental Doppler velocimetry evaluation will contribute towards achieving a more precise definition of hypertensive disorders of pregnancy, help to better define high-risk pregnancies and thus allow for more appropriate use of available medical therapies.

CHAPTER 2

AIMS AND METHODS

2.1 Aims

This principal aim of this study was to document maternal central hemodynamics using Doppler echocardiography in women with hypertensive disorders of pregnancy. The second aim was to measure concomitantly, cardiac structure, function and uterine artery Doppler velocimetry and thereby evaluate associations between maternal central hemodynamics, uterine artery Doppler velocimetry, cardiac structural changes and feto-neonatal outcome in hypertensive disorders of pregnancy. The third aim was to evaluate longitudinally maternal central hemodynamics, cardiac structure and function by Doppler-echocardiography in normal normotensive pregnancy.

2.2 Setting

The study was conducted at the Obstetric Unit, King Edward VIII Hospital, Durban, South Africa. The unit is a tertiary referral centre for the greater Durban region and forms part of the academic teaching complex attached to the Faculty of Medicine, University of Natal. The maternity unit acts as a referral centre for at risk pregnancies. Patients are referred from the southern border of Kwa-Zulu Natal near the Port Shepstone area to an area extending far north as Empangeni. The hinterland extends about 50kms.

Women with hypertensive pregnancies were enrolled in the obstetric admission unit. Normal normotensive pregnant women were enrolled at the antenatal clinic attached to the obstetric unit; the study details of this normotensive control groups are discussed in Chapter 3.

2.3 Design

The study design was a prospective analytic study. Eligible hypertensive pregnant women presented either to satellite antenatal clinics or directly to the obstetric admission unit. Their blood pressure was recorded in the seated position, using a mercury sphygmomanometer. At the presenting antenatal unit, the attending obstetrician evaluated all pregnant women whose blood pressure was ≥140/90mmHg and verified the elevated blood pressure.

Women presenting to the obstetric admission unit with a blood pressure ≤ 160/110mmHg but meeting all inclusion and exclusion criteria were evaluated urgently at admission and had Doppler echocardiographic study prior to administration of antihypertensive therapy and are analysed as the untreated group of women with hypertension in pregnancy. Women presenting to satellite antenatal clinics and whose blood pressure was ≥ 160/110mmHg were immediately referred to the obstetric admission unit. Prior to referral, and at the discretion of the attending obstetrician, eighteen women were prescribed single dose of 1000mg methyl-dopa orally and sodium gardinal 200mg by the intramuscular route. A further four women

were given 1000mg methyl-dopa alone as a single oral dose. This treated group were analysed separately as a pre-eclampsia treatment group (n=22).

Hypertensive women whose blood pressure was ≥140/90mmHg but below 160/110mmHg, were asked to rest in a quieter area of the antenatal unit. The resident obstetrician reviewed women whose blood pressure remained elevated (≥140/90mmHg) 4 hours later and were eligible for the study. Women with sustained elevation in blood pressure were referred to the obstetric admission unit.

Upon arrival to the obstetric admission unit, the attending obstetrician assessed eligible participants. Maternal cardiovascular examination was performed in the ultrasound department attached to the obstetric admission unit. After informed consent was obtained, a comprehensive maternal echocardiographic examination was performed followed immediately by a Doppler velocimetry of the uterine and umbilical arteries. Blood pressure and heart rate were recorded during the echo study by an automated blood pressure measuring device (Critikon). The candidate (DK Desai) performed both the maternal echocardiographic-Doppler and utero-placental Doppler velocimetry studies.

2.4 Participants

All hypertensive pregnant women referred to the King Edward VIII Obstetric Unit during 1997-1998 were screened for participation in this study.

2.4.1 Inclusion criteria

All pregnant women who fulfilled criteria for the diagnosis of hypertension based on the classification of Davey and MacGillivray (1988) were eligible to enter the study. This classification required a diastolic blood pressure of ≥ 110mmHg on any one occasion or ≥ 90mmHg on two occasions at least 4 hours apart.

Women were eligible for enrolment and evaluation into a pre-eclampsia treatment group sub-study if echocardiography was performed within 6 hours of administration of sodium gardinal (200mg) by the intramuscular route and/or methyl-dopa 1000mg by the oral route. Institutional ethical approval was obtained and all participating women gave informed consent. In 10 normotensive participants, echocardiographic and Doppler study was repeated 2 hours apart. A single operator, the candidate (DK Desai) performed measurements on screen; this showed an intraobserver variability of 1.8% for echocardiographic-Doppler derived cardiac output.

2.4.2 Exclusion criteria

Women with the following medical and obstetric conditions were excluded from participating in this study.

General and medical conditions –

i) anaemia (haemoglobin < 10mg %)
ii) valvular heart disease
iii) myo-pericardial heart disease
iv) pulmonary parenchymal lung disease
v) renal insufficiency
vi) significant medical disorder
vii) unsatisfactory echocardiographic recording

Obstetric conditions –

i) complicated hypertensive crises e.g. cardiac failure
ii) imminent eclampsia
iii) antepartum haemorrhage
iv) in labour
v) prior parenteral dihydrallazine or magnesium sulfate therapy
vi) obvious fetal abnormality
vii) multiple pregnancy
viii) prior vasodilator therapy with hydrallazine or nifedipine.

2.5 Methods

2.5.1 Sample size of study

It was planned to recruit 60 hypertensive pregnant women with an aim of enrolling at least 20 women with pre-eclampsia and gestational hypertension and at least 20 women with chronic hypertension and chronic hypertension with superimposed pre-eclampsia. In addition, it was planned to study 30 normal normotensive women in a longitudinal study that would serve also as a control group. Normotensive women were enrolled in the second trimester (14-24 weeks gestation) and had serial echocardiographic studies at approximately 4 week intervals until delivery (Chapter 3).

2.5.2 Obstetric assessment

At enrolment, all women had an obstetric assessment by the admitting obstetric registrar whose assessment was verified by the duty consultant. All relevant clinical data were recorded to ensure inclusion and exclusion criteria were met. Gestational age was assessed clinically. All women had an obstetric ultrasound examination at

entry into the study to ensure accurate fetal gestation, exclude fetal abnormalities and to confirm a singleton pregnancy. A senior obstetric consultant determined the precise gestational age of the fetus at presentation utilizing clinical assessment, gestational age by dates assisted by ultrasound. The gestational age was thereafter followed by dates in the longitudinal study evaluating maternal central hemodynamics in normal normtensive pregnant women.

2.5.3 Echocardiography

All participants had a clinical assessment and examination by the author to rule out pre-existing heart disease. Enrolled women rested in the left lateral position with the assistance of a wedge for 10 minutes. The echocardiographic study was then performed over a period of 12-18 minutes on the Ultramark 9-HDI imaging system with a 2.5 MHz transducer (Scientific Medical System). Two-dimensional echocardiography facilitated accurate M-Mode recordings and colour flow mapping facilitated Doppler measurements according to standard criteria (Devereux, 1997). The procedure was carried out as follows:

An initial two-dimensional study in the standard parasternal long axis and short axis planes followed by the apical 4 chamber plane view was performed to evaluate cardiac structure and obtain a visual assessment of left ventricle contractile function (Fig 1). Two-dimensional imaging directed M-Mode studies at the level of aorta, left atrium, left ventricle and mid-position between the tips of the mitral valve leaflets and papillary muscle. Frozen M-Mode images on screen were used to measure chamber size and ventricular wall thickness (Fig 4). Pulsed Doppler flow across the mitral

valve was recorded just beyond tips of the mitral valve leaflets to obtain LV diastolic filling pattern.

For the cardiac output study, 3 estimates of the aortic annulus diameter were made in the parasternal long axis plane (Fig 2). The Doppler study was then performed using the apical 4 and 5 chamber views (Fig 3). Doppler measurements were then performed at the aortic annulus to obtain the best velocity-time profile from which screen measurements of velocity time integral were made.

The formulae for calculating maternal cardiac structural and functional and hemodynamic variables are listed in appendix 1. The following echo parameters were measured:

i) Structure and function of the left heart was studied in standard accepted views. Two-dimensional directed M-Mode views were used to measure left atrial and aortic root diameters and the ratio calculated.

ii) Two-dimensional directed M-Mode recordings of the left ventricle were made in the short axis view at a level just beyond the tips of the mitral valve leaflets. On screen measurements of the M-mode tracing was used to measure left ventricular (LV) cavity dimensions in systole and diastole, from which indices of LV contractile function (fractional shortening; ejection fraction; velocity of circumferential fibre shortening and LV end systolic wall stress) was computed. At least 2 M-mode tracings of the left ventricle was performed to ensure that cavity dimensions were within 2mm and of ventricular wall thickness was within 1mm of each other. A third trace was performed if the first two M-mode traces did not provide

satisfactory recordings and representative values of the left ventricle M-mode trace was obtained by consensus with a cardiology colleague.

iii) The LV wall thickness of the septum and posterior wall together with LV cavity size in diastole was used to calculate LV mass (grams) according to the formula of Devereux (1997). Left ventricular mass (g) was corrected for maternal size by dividing LV mass by body surface area (m^2) to obtain LV mass index (g/m^2). The LV mass was also corrected for height to obtain LV mass/height (g/m). The relative wall thickness ratio, a measurement to describe LV geometry and LV hypertrophy was derived from measurements of LV posterior wall thickness and LV internal diameter.

iv) LV diastolic filling velocities across the mitral valve were obtained by pulsed Doppler in the apical four chamber view; recordings were made at a position just distal to the mitral valve leaflets (fig 5). The results were recorded as early filling (E) velocity (m/sec), late filling velocity (A) and the E/A diastolic filling ratio was calculated.

v) LV Doppler cardiac output was obtained by standard accepted method as described by Ihlen *et al,* (1984) as follows: The cross sectional area was measured from the maximum systolic diameter at the level of the aortic annulus using 2-Dimensional echocardiography. Three (3) measurements were made and the average was accepted as representative cross sectional area at the aortic annulus. The velocity time integral measurement was performed in the apical - 5- chamber view at the level of the aortic valve

using pulsed Doppler. The best of 3 velocity time integral profile measurements were selected and measured; these were measured in the resting state with quiet breathing and after visualisation of at least 8-10 profiles on the screen to obtain a steady state.

LV Doppler-derived cardiac output was determined from the product of stroke volume (aortic cross sectional area X velocity time integral) and the average heart rate during the echo study. Systemic vascular resistance was derived from the cardiac output and mean BP and the systemic vascular resistance index obtained by correcting for body surface area. The LV ejection time, measured from the aortic velocity time integral profile was used to calculate velocity of circumferential fibre shortening, an index of LV contractile function.

vi) Heart rate and blood pressure (5-7 recordings) were measured by an automated blood pressure measuring device (Critikon) at intervals of 3 minutes during the echo study. Blood pressure was measured in the dependent arm and the average of 5-7 measurements of heart rate and blood pressure made during the Doppler echocardiographic study at 3 minute intervals was accepted as the representative measurements. These were used with echocardiographic Doppler determined stroke volume to derive cardiac output and systemic vascular resistance.

2.5.4 Uteroplacental Doppler velocimetry

Uteroplacental Doppler velocimetry was performed immediately after the maternal echocardiographic study with participants remaining comfortable in a slight left lateral position. The same imaging system (Ultramark 9-HDI) was used with a 3.5 MHz transducer. Colour flow mapping assisted in obtaining good uterine artery Doppler waveforms.

The examinations were performed by a single operator (DK Desai). Studies were performed whilst ensuring there were no gross fetal or breathing movements. Five consecutive waveforms with a clear outline were obtained. The peak systolic velocity and end diastolic velocity were measured on screen with a cursor. The resistance index for the right and left uterine arteries was calculated using mean values of peak systolic and end-diastolic velocities of 5 consecutive waveforms. The average of the computed right and left uterine artery resistance index was accepted as representative uterine artery resistance index (fig. 6). Ten normotensive women had repeat uterine Doppler velocimetry study measurement by the author and the senior obstetric ultrasonographer to validate technique and accuracy, this gave an interobserver variability of 3.8%

Umbilical artery Doppler velocimetry was performed using the same transducer as for uterine Doppler velocimetry studies. Colour flow mapping identification of the cord facilitated pulsed Doppler velocimetry of umbilical artery. At least 10 consecutive waveforms with a clear outline were obtained. The peak systolic velocity and end

diastolic velocity were measured on screen with a cursor. The umbilical artery pulsatility index was calculated using mean values of peak systolic and diastolic velocities of at least 5 consecutive waveforms (fig. 7).

2.6 Statistical Methods

All statistical comparisons were performed using the SPSS statistical Package version 11.0 and Sysstat software was used for regression analyses. The mean and standard deviation of measured cardiovascular parameters in the various hypertensive groups and categories were compared by independent samples non-parametric tests (Mann-Whitney U test or Kruskal-Wallis test). Cross tabulation (chi-squared test) was used for evaluation of non-continuous variables. Bivariate correlation and linear and multiple regression analyses were used to determine associations between measured maternal size, maternal cardiovascular variables, uterine artery resistance index and the various parameters reflecting adverse feto-neonatal outcome.

2.7 Analysis of results

All echocardiographic and Doppler velocimetry data were analysed where indicated according to hypertensive groups as listed below in section 2.7.1. Subgroup analyses were performed on data stratified by severity of proteinuria quantified as nil, mild to moderate (1^+ and 2^+ by dipstix testing) or severe proteinuria (3^+ and 4^+ by dipstix testing). Critical cut off values were sought for hemodynamic variables for cardiac index, systemic vascular resistance index; uterine artery resistance index and maternal size after detecting significant associations of measured parameter with adverse feto-neonatal outcome.

Neonatal outcome was determined as being adverse or non-adverse using criteria of fetal birth weight below the 10th centile; intrauterine death, fresh still birth, requirement of neonatal intensive support and neonatal death. Feto-neonatal outcome was classified as either adverse or non-adverse. The absolute fetal birth weight, gestational age at delivery and fetal birth weight centile (using charts of Altman & Chitty), were evaluated to determine if adverse feto-neonatal outcome could be represented a continuous variable of gestational age at delivery and/or fetal birth weight.

2.7.1 Classification of hypertensive groups

The hypertensive groups for comparative analysis are as listed below:

1) Gestational non-proteinuric hypertension (also referred to as gestational hypertension)
2) Gestational proteinuric hypertension (pre-eclampsia)
3) Chronic hypertension
4) Superimposed pre-eclampsia on chronic hypertension

2.7.2 Stratification by blood pressure

Patients were included in the study if they had a diastolic BP recording of $\geq$ 90mmHg on 2 occasions at least 4 hours apart or a single BP $\geq$ 160/110mmHg. This blood pressure at admission to the study was compared to blood pressure measured at echocardiography.

The blood pressure immediately prior to the echo study was measured in the left lateral position after a 10 minutes rest. Blood pressure and pulse rates were measured with automated blood pressure measuring device (Critikon) at 3 minutes intervals. The average of these recordings (5-7measurements) was used as representative blood pressure at echocardiography and used to stratify women into mild; moderate and severe hypertensive cateogories (Table 2.1).

Table 2.1 Staging of hypertensive group according to blood pressure levels

Stage severity		Blood pressure (mmHg)
Stage I	(mild)	< 140/90
Stage II	(moderate)	140/90 - 160/110
Stage III	(severe)	≥ 160/110

2.7.3 Stratification by proteinuria

Proteinuria status was assessed by repeated reagent strip (dipstix) testing of at least 2 specimens 4 hours apart or by a 24 hour urine protein where feasible. A negative or trace dipstix reading or a 24 hour urine protein of < 300mg was accepted as nil proteinuria. Dipstix testing of 1+/2+ protein or 300-1000mg protein in a 24 hour urine collection was accepted as mild or mild -moderate proteinuria. Dipstix testing of persistent 3+/4+ or ≥ 1000mg protein in a 24 hour urine collection was classified as severe proteinuria.

2.7.4 Stratification by treatment group

Preeclamptic women who were eligible to enter the study but who were prescribed treatment (n=22), in the form of single dose of sodium gardinal 200mg by the intramuscular route and 1000mg methyl-dopa by the oral route (n=18) and those who received 1000mg methyl-dopa orally alone (n=4), formed the treatment group and are evaluated separately to assess effects of initial stat therapy.

2.7.5 Stratification based on maternal haemodynamic variables

Maternal cardiovascular parameters of heart rate; stroke index; cardiac index and systemic vascular resistance index together with uterine artery resistance index were compared in the various hypertensive categories to establish if any association with adverse feto-neonatal outcome.

2.7.6 Adverse feto-neonatal outcome

Obstetric outcome was determined utilizing all information on feto-neonatal outcome that included occurrence of preterm delivery, intrauterine death and stillbirth, low fetal birth weight defined as birth weight below the 10^{th} centile, requiring neonatal ventilatory and intensive care and a complicated neonatal course and neonatal death. This allowed classifying feto-neonatal outcome into 2 categories of adverse or non-adverse feto-neonatal outcome.

CHAPTER 3

ECHOCARDIOGRAPHIC ASSESSMENT OF MATERNAL CARDIOVASCULAR HEMODYNAMICS IN NORMAL NORMOTENSIVE PREGNANCY

3.1 Introduction and aims

Normal pregnancy is accompanied by maternal cardiovascular adaptations that include an increase in cardiac output with a decline in blood pressure and systemic vascular resistance. However, the precise changes of cardiac output in normal pregnancy have remained controversial. In a meta-analysis of cross sectional studies by van Oppen *et al*, (1996) to evaluate a trend, the authors showed large ranges in cardiac output between studies. Despite numerous limitations of the above meta-analysis, pooling data from each trimester showed a tendency to a higher cardiac output in the second trimester compared to the first and a lower cardiac output in the third trimester compared to the second. This observation is supported by the Doppler echocardiographic study of Hennessy *et al,* (1996) which demonstrated a peak cardiac output at 32 weeks gestation of 49% that declined to a value of 21% at term.

Van Oppen *et al,* (1996) also performed a meta-analysis of 6 longitudinal studies that had 2 or more cardiac output measurements during pregnancy. The authors found widely divergent changes in cardiac output between the second and third trimesters with 2 studies showing an increase; 2 with no change and 2 with a decrease. Both van Oppen *et al,* (1996) and Duvekot and Peeters (1994) cited patient factors rather than

technique as being responsible for the apparent divergent trends of cardiac output in the third trimester.

Although Thornburg *et al,* (2000) in their review report that cardiac output peaks in the mid-third trimester by approximately 50%, the peaking of cardiac output has been reported to occur at gestations varying from 24 weeks to term. In addition, the relative contributions to cardiac output made by increases in heart rate and stroke volume have not been well addressed. Furthermore, most studies of maternal hemodynamics in normal pregnancy have reported measurement of cardiac output rather than a stature corrected measure of cardiac index. This study evaluates echocardiographic maternal central hemodynamics, cardiac structure and function and maternal stature in healthy pregnant women.

3.2 Methods

The study was conducted at the Obstetric Unit, King Edward VIII Hospital, Durban, South Africa. Healthy normotensive women with a singleton pregnancy who gave informed consent to participate in the study were selected and enrolled at the antenatal clinic. Women with a history of any medical disorder were excluded from the study. The University of Natal Ethics Committee granted ethical approval for the study and all participants gave informed consent.

At enrollment, the attending obstetrician performed an obstetric assessment together with clinical assessment of gestational age. Obstetric ultrasound examination was performed to obtain accurate fetal gestation; exclude fetal abnormalities and to confirm a singleton pregnancy. All participants had a clinical examination to rule out

pre-existing heart disease. Enrolled women rested in the left lateral position with assistance of a foam wedge for 10 minutes. Echocardiography studies were performed thereafter using the Ultramark 9-HDI imaging system with a 2.5 MZ transducer (Scientific Medical System). Two-dimensional echocardiography facilitated accurate M-Mode recordings and color flow mapping facilitated Doppler measurements according to standard criteria (Devereux, 1997). Ten normotensive participants at gestation 32-36 weeks had repeat echocardiographic study 2 hours apart to evaluate reproducibility; the mean percentage error for cardiac output was measured at 1.8 %. The procedure was carried out as described in Chapter 2 (section 2.5.3).

All statistical comparisons were performed using the SPSS version 11 statistical package. The primary comparative analyses of cardiovascular hemodynamic and structural variables in longitudinal study of normotensive healthy pregnant women were made using paired sample t-tests. Noting multiple paired t analyses, discussion is focused on highly significant differences ($p < 0.01$) as dictated by Bonferroni correction factor. Where appropriate, comparisons of average values between time periods were made either by independent samples t test or one-way analysis of variance and significance was set at $p < 0.05$. Cross tabulation (chi-squared test) was used for evaluation of non-continuous variables. Bivariate correlation and linear regression analyses were used to estimate relationships between measured cardiovascular variables. The hypertensive groups, given the smaller size, were compared by non-parametric methods using either Kruskal-Wallis or Mann-Whitney tests.

3.3 Results

3.3.1 Baseline Demographics

The group consisted of 35 women in whom a total of 160 echocardiographic studies were performed; 58 in 2nd trimester, 75 in 3rd trimester, and 27 postpartum as listed in Table 3.1. The baseline characteristics expressed as mean ±1SD at entry into the study are listed in table 3.2. Cardiac output in a subgroup of ten (10) women without missing visits are compared with the full cohort in Table 3.4.

Table 3.1 Patients studied at indicated gestational periods (n=35)

Gestational Period	Number of patients studied (%)
Second trimester – early (14-19 weeks)	n = 6 (17%)
- mid (20-23 weeks)	n = 23 (66%)
- late (24-27 weeks)	n = 29 (83%)
Third trimester - early (28-31 weeks)	n = 33 (94%)
- mid (32-36 weeks)	n = 28 (80%)
- late (37-40 weeks)	n = 14 (40%)
Post partum (6-12 weeks)	n = 27 (77%)

Table 3.2: Baseline characteristics of all participants (n=35)

	Mean (SD)
age (years)	23 ± 5
weight (kg)	67 ± 12
height (cm)	157 ± 5
body surface area (m^2)	1.68 ± 0.15
body mass index (kg/m^2)	27 ± 4
parity – number (%) nulliparous multiparous	 n = 22 (63%) n = 13 (37%)
gestation at delivery (weeks)	38 ± 2
caesarean section- number (%)	3 (9%)
birth weight (kg)	2.9 ± 0,6

3.3.2 Haemodynamic changes in cardiac output, heart rate and stroke volume

Table 3.3 details the haemodynamic changes in cardiac output and systemic vascular resistance with corresponding changes in heart rate, stroke volume and mean blood pressure. Cardiac output increased predominantly in the latter half of pregnancy and continued to increase and peak at term. However, statistically significant increases ($p<0.05$) were seen at time periods early third, late second and mid second trimester. Using postpartum value as baseline, a 46% increase in cardiac output was present. This maximal cardiac output occurred as a result of a 15% increase in heart rate and a

24% increase in stroke volume. This 24% increase in stroke volume was derived at Doppler-echocardiography by a 9% increase in velocity time integral at the aortic annulus and a 15% increase in aortic annulus cross-sectional area.

Heart rate showed a statistically non-significant decrease at late third trimester compared to mid third trimester. Although stroke volume increased till term, statistically significant increases were only noted in the late third and late second trimesters. A statistical maximal decrease in systemic vascular resistance was observed early in the third trimester; by comparison mean blood pressure showed a statistical increase after early third trimester.

Table 3.3: Longitudinal changes in normal pregnancy

Gestation (weeks)	Heart rate (beats/min)	Stroke volume (ml)	Cardiac output (l/min)	Mean blood pressure (mmHg)	Systemic vascular resistance (dyn.sec /cm^5)
14-19	75 ±8 (10%)	66±11 (-6%)	4.96 ±0.5 (4%)	74 ± 9 (-5%)	1214 ±163 (-9%)
20-23	76 ±9 (10%)	74 ±11 (6%)	5.60 ±0.8 (18%)	71 ± 6 (-9%)	1033 ±186 (-23%)
p	0.054	0.327	0.295	0.336	0.497
24-27	80 ±8 (16%)	75 ±11 (7%)	5.94 ±0.9 (25%)	70 ± 8 (-10%)	966 ±200 (-28%)
p	0.010*	0.133	0.009*	0.355	0.024*
28-31	80 ± 8 (16%)	77 ±11(10%)	6.18 ±0.9 (30%)	70 ± 7 (-10%)	923 ±140 (-31%)
p	0.489	<0.001*	<0.001*	0.317	0.014*
32-36	81 ±8 (17%)	80 ±13(14%)	6.42 ±0.9 (35%)	72 ± 6 (-8%)	917 ±139 (-31%)
p	0.383	0.202	0.156	0.010*	0.219
37-term	79 ±7 (15%)	87 ±17(24%)	6.94 ±1.8 (46%)	74 ± 7 (-5%)	902 ±202 (-32%)
p	0.098	0.048*	0.267	0.024*	0.250
Postpartum	69±11 (0%)	70 ±12 (0%)	4.75 ±0.7 (0%)	78 ± 9 (0%)	1336 ±218 (0%)
p	0.007*	<0.001*	<0.001*	0.008*	<0.001*$^+$

Data are presented as absolute mean ± one standard deviation (percent change from baseline).
Percent change from baseline is calculated by comparing mean value for the measured parameter to the postpartum value
P values (paired t test) indicate statistical change from preceding gestational period.
* Statistically significant.

3.3.3 Comparative analysis with subgroup (n=10) without missing visits

Table 3.4 shows the stroke volume and cardiac output in a subgroup of women (n=10) who had echocardiographic studies at all time periods from mid second trimester and are compared with that of the full group. The stroke volume and cardiac output between these groups are similar without any statistical differences. Paired t-testing shows similar trends and p-values at the various time periods in the subgroup and full group and thus validates conclusions drawn from the full study group who had missing visits. The p-values for cardiac output increases in the mid and late third trimester in the subgroup ($p=0.083$ and $p=0.156$ respectively) indicates that cardiac output probably peaks between early and mid third trimester and is maintained till term.

Table 3.4 Comparative longitudinal changes in full study group (n=35) and subgroup (n=10) without missing visits in the latter half of pregnancy

Gestation (weeks)	Stroke volume (ml		Cardiac output (L/min)	
	full group	subgroup	full group	subgroup
14-19	66±11 (-6%)	------	4.96 ±0.5 (4%)	-----
20-23	74 ±11 (6%)	70 ±13 (-3%)	5.60 ±0.8 (18%)	5.64 ±0.8 (12%)
p	0.327	------	0.295	-----
24-27	75 ±11 (7%)	69 ± 8 (-4%)	5.94 ±0.9 (25%)	5.68 ±0.8 (23%)
p	0.133	0.500	0.009*	0.276
28-31	77 ±11 (10%)	78 ±11 (8%)	6.18 ±0.9 (30%)	6.25 ±0.8 (36%)
p	<0.001*	0.007*	<0.001*	0.024*
32-36	80 ±13 (14%)	80 ±14 (11%)	6.42 ±0.9 (35%)	6.61 ±1.1 (43%)
p	0.202	0.253	0.156	0.083
37-term	87 ±17 (24%)	88 ±17 (22%)	6.94 ±1.8 (46%)	6.97 ±1.8 (51%)
p	0.048*	0.003*	0.267	0.156
Postpartum	70 ±12 (0%)	72 ±18 (0%)	4.75 ±0.7 (0%)	4.61 ±0.9 (0%)
P	<0.001*	<0.001*	<0.001*	<0.001*

Data are presented as absolute mean ± one standard deviation (percent change from baseline).
Percent change from baseline is calculated by comparing mean value for the measured parameter to the postpartum value.
P values (paired t test) indicate statistical change from preceding gestational period by using paired t tests.
t-test comparison of means of stroke volume and cardiac output for full group vs subgroup at each time period were not significant.
* Statistically significant.

3.3.4 Haemodynamics – cardiac output versus cardiac index

Tables 3.5 details changes in cardiac output and cardiac index together with weight and body surface area. It is noted that both cardiac output and cardiac index show similar statistical increases at the indicated time periods. Table 3.6 estimates relationships among cardiac output, cardiac index, and maternal stature variables in the early and mid third trimester and fetal birth weight. Significant correlations were noted between cardiac output with fetal birth weight and maternal stature variables as indicated. Linear regression analysis showed that in early and mid third trimesters, maternal weight best correlated with maternal cardiac output (r^2= 0.56 and 0.50 respectively).

Table 3.5: Longitudinal changes in normal pregnancy

Gestation (weeks)	Weight (kg)	Body surface area (m^2)	Cardiac output (l/min)	Cardiac index ($l/min/m^2$)
14-19	62 ± 12 (2%)	1.62 ± 0.14	4.96 ± 0.5 (4%)	3.09 ± 0.39 (4%)
20-23	64 ± 11 (5%)	1.65 ± 0.13	5.60 ± 0.8 (18%)	3.40 ± 0.46 (15%)
p	0.069	0.054	0.295	0.395
24-27	65 ± 11 (7%)	1.65 ± 0.14	5.94 ± 0.9 (25%)	3.63 ± 0.50 (22%)
p	<0.001*	<0.001*	0.009*	0.011*
28-31	67 ± 12 (10%)	1.68 ± 0.15	6.18 ± 0.9 (30%)	3.67 ± 0.35 (24%)
p	<0.001*	<0.001*	<0.001*	0.023*
32-36	69 ± 12 (13%)	1.70 ± 0.14	6.42 ± 0.9 (35%)	3.77 ± 0,41 (27%)
p	0.003*	0.004*	0.156	0.247
37-term	72 ± 14 (18%)	1.72 ± 0.17	6.94 ± 1.8 (46%)	4.00 ± 0.76 (35%)
p	<0.001*	<0.001*	0.267	0.388
postpartum	61 ± 3 (0%)	1.61 ± 0.17	4.75 ± 0.7 (0%)	2.97 ± 0.46 (0%)
p	<0.001*	<0.001*	<0.001*	<0.001*

Data are presented as absolute mean ± one standard deviation (percent change from baseline).
Percent change from baseline is calculated by comparing mean value for the measured parameter to the postpartum value
P values (paired t test) indicate statistical change from preceding gestational period.
* Statistically significant.

Table 3.6: Correlation of indices in normal pregnant women

	Cardiac output	Cardiac index	Fetal birth weight
cardiac output :early 3rd :mid 3rd	-----	------	0.52 p=0.008* 0.60 p=0.004*
cardiac index :early 3rd :mid 3rd	-----	-----	0.16 p=0.438 0.33 p=0.151
body surface area :early 3rd :mid 3rd	0.72 p<0.001* 0.64 p<0.001*	0.04 p=0.816 0.13 p=0.523	0.60 p=0.002* 0.63 p=0.002*
weight :early 3rd :mid 3rd	0.73 p<0.001* 0.66 p<0.001*	0.08 p=0.654 0.17 p=0.397	0.62 p=0.001* 0.60 p=0.004*
height :early 3rd :mid 3rd	0.34 p= 0.061 0.24 p=0.233	0.16 p=0.383 -0.08 p=0.694	0.45 p=0.023* 0.53 p=0.014*
body mass index :early 3rd :mid 3rd	0.69 p<0.001* 0.52 p=0.006*	0.15 p=0.424 0.09 p=0.642	0.52 p=0.008* 0.35 p=0.124

data are presented as *r* values
early 3rd = early third trimester (28-31 weeks gestation)
mid 3rd = mid third trimester (32-36 weeks gestation)
*statistically significant

3.3.5 Echocardiographic determinants of stroke volume

Table 3.7 details the changes in echocardiographic components of aortic velocity time integral and aortic cross sectional area that are used to compute stroke volume. A maximal increase in stroke volume of 24% at term was derived from a 9% increase in aortic velocity time integral and a 15% increase in aortic annulus cross sectional area.

Table 3.7: Longitudinal changes in normal pregnancy

Gestation (weeks)	Velocity time integral at aorta (cm)	Aortic cross sectional area (mm^2)	Stroke volume (ml)
14-19	21 ±3 (-4%)	320 ± 30 (0%)	66 ± 11 (-6%)
20-23 p value	23 ±3 (5%) 0.430	323 ± 39 (1%) 0.362	74 ± 11 (6%) 0.327
24-27 p value	23 ±3 (5%) 0.500	323 ± 40 (1%) 0.085	75 ± 11 (7%) 0.133
28-31 p value	23 ±3 (5%) 0.480	331 ± 47 (3%) 0.094	77 ± 11 (10%) < 0.001*
32-36 p value	23 ±3 (5%) 0.156	347 ± 37 (8%) 0.001*	80 ± 13 (14%) 0.202
37-term p value	24 ±3 (9%) 0.056	367 ± 63 (15%) 0.475	87 ± 17 (24%) 0.048*
postpartum p value	22 ±3 (0%) 0.011*	320 ± 37 (0%) 0.001*	70 ± 12 (0%) < 0.001*

Data are presented as absolute mean ± one standard deviation (percent change from baseline).
Percent change from baseline is calculated by comparing mean value for the measured parameter to the postpartum value
P values (paired t test) indicate statistical change from preceding gestational period.
* Statistically significant.

3.3.6 Cardiac structural and function changes

Table 3.8 shows changes in cardiac structure and function variables of left atrial size together with left atrial to aorta size ratio; LV early to late diastolic filling ratio; LV mass and LV mass index and LV systolic function reflected by fractional shortening percentage. Both the absolute left atrial size and left atrial size reflected by left atrial to aorta size ratio show a significant increase at term followed by a significant reduction postpartum. The LV diastolic filling of early to atrial filling ratio showed a decrease in the third trimester compared to postpartum.

Table 3.8 also shows significant increases in LV mass and LV mass index that are maximal at term. The mean LV mass index remained well below the arbitrary cut off level of 110g/m^2 to diagnose LV hypertrophy. Although not reflected in the tables, LV mass/height and LV mass/$height^{1.7}$ showed similar changes to LV mass index at the indicated gestational periods. A lower LV mass index at 14-19 weeks gestation compared to postpartum value (6-12 weeks) is noted and probably reflects that LV mass measured 6-12 weeks postpartum had not returned to normal pre-pregnant values; this limits an accurate assessment of extent of LV mass increase in our study. The increased LV mass was due both to an increased LV cavity size and wall thickness; both the LV cavity size and septal thickness at term were significantly larger than at postpartum. (4.8 ±0.3 versus 4.6 ±0.4cm; p=0.040 and 1.09 ±0.10cm versus 0.96 ±0.09cm; p=0.001respectively).

Table 3.8: Longitudinal echocardiographic changes in normal pregnancy.

Gestation (weeks)	Left atrium	Left atrium/ aorta ratio	LV filling ratio	LV mass (g)	LV mass index (g/m^2)	LV fractional shortening (%)
14-19	3.0 ± 0.2	1.18 ±0.12	2.1 ±0.6	102 ±16(15%)	63 ±10(-5%)	32 ±4
20-23	3.1 ± 0.6	1.34 ±0.28	2.1 ±0.4	127 ±18 (6%)	77 ±11 (4%)	34 ±4
p	0.391	0.428	0.495	0.038*	0.099	0.014*
24-27	3.2 ± 0.5	1.38 ±0.23	2.1 ±0.5	124 ±23 (3%)	75 ±12 (1%)	34 ±4
p	0.088	0.431	0.303	0.096	0.089	0.277
28-31	3.2± 0.5	1.35 ±0.23	2.0 ±0.6	131 ±24 (9%)	78 ±11 (5%)	34 ±4
p	0.171	0.335	0.067	0.210	0.376	0.032
32-36	3.2 ±0.5	1.37 ±0.23	1.8 ±0.3	139 ±30(16%)	81 ±13 (9%)	33 ±4
p	0.457	0.244	0.208	0.052	0.072	0.074
37-term	3.5 ±0.4	1.46 ±0.17	1.8 ±0.3	151±35(26%)	87 ±15(18%)	35 ±4
p	0.016*	0.006*	0.309	0.027*	0.048*	0.369
Postpartum	3.0 ±0.5	1.27 ±0.21	2.0 ±0.5	120 ±31 (0%)	74 ±16 (0%)	32 ±4
p	0.002*	0.005*	0.048*	0.001*	0.006*	0.130

Data are presented as absolute mean ± one standard deviation (percent change from baseline).
Percent change from baseline is calculated by comparing mean value for the measured parameter to the postpartum value
P values (paired t test) indicate statistical change from preceding gestational period.
* Statistically significant.

3.4 Discussion

Using 6-12 weeks postpartum as baseline, our study shows the expected increase in cardiac output in normal pregnancy of 46-51%. Approximately half of this increase occurred by 28 weeks gestation. Although we show a significantly higher cardiac output in the third trimester compared to the second, the increases of cardiac output between early, mid and late third trimesters were not statistically significant. A large variability in measured cardiac output at late third trimester, probably occurring from patient factors, did not allow for confident conclusions to be made of the precise changes in late third trimester. However, the data do show that cardiac output certainly peaks in early to mid third trimester and thereafter is maintained till term.

The literature has conflicting data on cardiac output changes during pregnancy, particularly in the third trimester. Although the meta-analysis of cross-sectional studies by van Oppen *et al,*(1996) showed a trend to a lower cardiac output in the third trimester compared to the second, the authors observed large ranges in cardiac output between the different studies that did not allow for any firm conclusions. In evaluating 6 longitudinal studies, van Oppen *et al,* (1996) found that cardiac output between the second and third trimesters plateaued, decreased or increased. Of these, the 4 studies with comparable techniques still showed striking differences in the course of cardiac output in the third trimester with Duvekot *et al,* (1993) showing a decrease of 11.5%; no change by Robson *et al,* (1989) and increases of 9.3% by Mabie *et al,* (1994) and 16.4% by Thomsen *et al,* (1993) .

Although design differences and measurement techniques between studies can explain some of the reported differences in maternal hemodynamics in normal pregnancy,

most researchers concur that patient factors rather than measurement error are largely responsible for discrepancies in reported studies. The longitudinal study by Robson *et al,* (1989) of 13 patients, cited as the only true longitudinal study in the van Oppen meta-analysis (1996), surprisingly showed a significant increase in cardiac output of 75% of peak value by 12weeks gestation that was followed by a very gradual rise to peak cardiac output occurring at 24-36 weeks and cardiac output being maintained thereafter till term. It is to be noted that after 16weeks gestation, the Robson study data did not show any statistically significant increase in cardiac output at any of the defined 4week time periods. It is also noted in an earlier M-mode echocardiographic study by Capeless *et al* (1989) that cardiac output increased greater than 50% by 8 weeks gestation using preconception values as baseline.

Our study shows a similar increase in mean cardiac output till term as described by Mabie *et al,* (1994) in their longitudinal study of 18 normotensive women. However, although the Mabie study showed a peak cardiac output at term, none of the increases in the comparative time periods (4weeks) were significant. In addition a similar wide variation in measured cardiac output at mid and late third trimester was also noted. In contrast, our study shows a statistically significant increase in cardiac output in early third trimester over late second trimester, data that clearly indicate that cardiac output at the very least peaks in early to mid third trimester. The increase in cardiac output in mid and late third trimester in our study, although not statistically significant, does indicate that at the very least, cardiac output in the mid and late third trimester is maintained.

The ability of our study to show a statistically significant increase in cardiac output at early to mid third trimester compared to the Robson and Mabie studies described above probably reflect differences in observed cardiac output increase in the first half of pregnancy. We did not directly measure cardiac output in early pregnancy but using postpartum values as baseline, our data show that 40% of peak cardiac output occurred at 24 weeks compared to the Robson and Mabie studies described above where >75% of peak cardiac output occurred by 24 weeks. These differences of a "predominantly early" versus a "predominantly late" increase in cardiac output in normal pregnancy are not easily explained. Although maternal body surface area and cardiac output increase expressed as a percentage in our study are similar to the study by Mabie *et al,* (1994), the peak cardiac index of 4.8 ± 0.8 l/min/m^2 in the Mabie study is higher than 4.0 ± 0.8 l/min/m^2 in our study. In addition, the mean birth weight in our study was 2.9 ± 0.6kg compared to 3.4 ± 0.6kg in the Mabie study. The above observations provide supportive evidence for a positive association between maternal cardiac output and fetal birth weight. In addition, they are hypothesis generating especially for comparative studies in different population groups where apparent normal maternal health and accepted normal fetal birth weights may not be so and simultaneous utero-placental evaluation may provide a more precise research definition of normal healthy pregnancy.

Most of the heart rate increase in our study (60%) probably occurred in the first trimester and that of stroke volume in the third trimester, since changes in heart rate in the second and third trimester were not significant. It therefore appears that the mild increase in cardiac output in early pregnancy is largely accounted for by an increase in

heart rate and the progressive increase in cardiac output thereafter in the latter half of pregnancy is due to an increase in stroke volume. The apparent bimodal peaking of stroke volume occurring initially in the second trimester probably occurs as a result of changes in heart rate described above. These observations are supported by the hypothesis of Carbillon *et al*, (2000) that adaptive changes in vascular tone in early pregnancy precedes and probably triggers blood volume and cardiac output increase.

The satisfactory association between maternal cardiac output and maternal body size in our study suggest that variations in cardiac output in normotensive pregnant women can be explained by differences in maternal stature and/or fetal birth weight. Van Oppen *et al*, (1995) showed a poor correlation between maternal cardiac output and body surface area whereas studies in children and obese adult participants indicate that variables such as cardiac output need correction for body stature to allow appropriate comparison between groups (de Simone *et al,* (1997)). The need for correction of cardiovascular variables for maternal size is highlighted in some early studies. Rosso *et al*, (1992) found that underweight mothers had lower birth weight babies compared to normal weight mothers and this corresponded with lower maternal plasma volume and cardiac output. Similarly, Carpenter *et al,* (1990) found that differences in maximal oxygen uptake during exercise in pregnant women were eliminated when measurements were corrected for maternal weight.

The poor correlation between cardiac output and body surface area in the van Oppen *et al,* (1995) study is not easily explained; possible reasons include the increased number of women (n=78) who had cardiac output measured by thoracic electrical

bioimpedence technique compared to only 10 women by the Doppler technique. Both groups in the van Oppen study had cardiac output increases of 88% and 92% of peak values by fifth and eight week gestation respectively; observations that do not make physiologic sense and Duvekot *et al,* (1993) suggested that this increase of cardiac output in early and mid first trimesters is probably mediated by an endocrine stimulus and hence not surprisingly, poorly related to maternal body surface area at this stage. It is also to be noted that the correlation of maternal cardiac output with maternal stature variables reported in our study were made, albeit more appropriately, only in the third trimester. Finally, the use of body surface area (DuBois and Dubois (1916)) to standardize maternal cardiovascular variables seems justified. Wang *et al,* (1992) in their study evaluating predictors of body surface area that included 60 women at gestation between 34-40 weeks, concluded that several body surface area formulas, including the Dubois formulas adequately predict measured body surface area over a wide range of patient population.

Differences in LV systolic function between studies may also explain some of the observed variation in measured cardiac output and hence heart rate and stroke volume. Normal pregnancy is associated with a significant drop in blood pressure and systemic vascular resistance index, a reflection of the reduced cardiovascular afterload and fall in uterine vascular resistance. Physiologically, an increase in preload and/or reduced afterload is often accompanied by an increase in left ventricular systolic function. Our study demonstrates that LV fractional shortening during pregnancy is preserved; findings that are similar to data of Robson *et al,* (1989) and Mabie *et al,* (1994). However, these observations are at variance to studies by Mone *et al,* (1996) who showed a transient fall in LV fractional shortening

during the third trimester and that of Schannwell *et al,* (2000) who also showed a reduction in left ventricular systolic function parameters of fractional shortening and velocity of circumferential fibre shortening that had a nadir at the first postpartum visit. Mone *et al,* (1996) and Schannwell *et al,* (2000) postulated that the reduced pre-load in the latter part of the third trimester probably contribute to a reversible fall in LV systolic function.

The study by Poppas *et al,* (1997) is of particular interest, in that they report a steady increase in cardiac output till term but without any *change* in LV contractility, measured both by load dependent parameter of fractional shortening and also by load independent indices of LV velocity of circumferential fibre shortening and LV systolic wall stress. As indicated, a limitation of LV fractional shortening and echocardiography derived ejection fraction are that they are sensitive to loading conditions, particularly preload and to a lesser extent, afterload. Group ethnic profile as a factor associated with LV contractility is also noted, as all participants in our study were Black-African. Desai *et al,* (1995) had previously reported a very high prevalence of peripartum cardiomyopathy in the same population group. Such differences in LV systolic function, although clinically small and transient, may explain some of the divergent trends in cardiac output in the third trimester.

In addressing a possible effect of parity on cardiac output changes in pregnancy, Clapp *et al,* (1997) in their M-mode echocardiographic study suggested that cardiovascular adaptation is enhanced by a subsequent pregnancy. In the study by van Oppen *et al,* (1996) that evaluated cardiac output in the third trimester by thoracic electric bioimpedence, the authors found a significant difference in mean cardiac

output between nulliparous and multiparous women. The number of participants in our study did not allow for any comparison in the hemodynamics between primiparous and multiparous normotensive pregnant women. It is possible that some of the differences in cardiac output between studies may be related to parity differences of study participants.

The variability of echocardiographic-doppler determined stroke volume and hence cardiac output depends largely on measurement of aortic annulus diameter and the computed aortic annulus cross sectional area. Data on appropriate and accurate measure of aortic annulus measurements are conflicting. In our study using a single operator and obtaining three measurements and using the average as representative measurement, the aortic annular measurement accounted for only 1.8% of the variation in measured cardiac output. Robson *et al,* (1987) have reported within subject (intraobserver) and temporal variation for Doppler derived cardiac output in pregnancy at <5%. A limitation however in our study is that reproducibility was tested only at 32-26 weeks gestation; this could potentially be different at other gestational periods. Furthermore a smaller number of subjects had echocardiographic evaluation in late third trimester, which probably limited a more precise and confident measure of changes between mid and latter portions of the third trimester where expected absolute changes are smaller.

Our study shows a significant increase in LV mass and LV mass index of 26% and 18% respectively using 6-12 weeks postpartum as baseline; observations that are similar to data of Mabie *et al,* (1994). However, reported increases in LV mass in pregnancy have been variable: it was 10% in a study of 14 normal pregnant women

by Poppas *et al,* (1997), 16% in a study of 33 normotensive women by Mone *et al,* (1996) and a 34% increase in left ventricular mass index by Schannwell *et al,* (2000). These variations in percentage increase in LV mass probably reflect differences in the precise timing of postpartum measurements. Robson *et al* (1987) have showed that although most of the haemodynamic parameters and to a lesser extent the structural cardiac changes return to pre-pregnant levels early in the pueperium, full return may take up to 24 weeks after delivery. Furthrmore, Mone *et al,* (1996) have indicated that it takes up to four weeks to develop a compensatory increase in LV mass to offset the increase in LV wall stress that accompanies elevation in ventricular pressures.

This study also shows that in normal pregnant women, there is an excellent correlation between LV mass and its stature corrected variables of LV mass index; LV mass/height or LV mass/height$^{1.7}$. An echocardiographic diagnosis of LV hypertrophy (LV mass index $\geq 110 g/m^2$) was noted in only 1 of 35 normotensive women at term. The data of this study thus supports the fact that although LV mass increases significantly in normotensive pregnancy, levels that define the presence of LV hypertrophy do not occur in most women.

Our study shows significant increases in LV mass in mid and late third trimester that correspond with small but statistically significant increases in mean blood pressure; a significant increase in left atrial size at term and non-significant decrease in LV diastolic filling parameter reflected by reduced LV early to atrial filling ratio. These observations may be of relevance as we have reported abnormalities in LV diastolic filling in pregnant women who presented with hypertensive crises complicated by pulmonary oedema (Desai *et al,* 1996). As it is also accepted that LV diastolic

dysfunction often precedes systolic dysfunction, differences in the degree of LV hypertrophy and diastolic filling could explain some of the reported small differences in LV contractility and cardiac output in the third trimester in normotensive pregnant women.

In conclusion, our study shows a significant increase in cardiac output at early third trimester that is maintained till term. Cardiac output increased predominantly in the latter half of pregnancy. We also show a significant correlation between cardiac output and maternal stature and birth weight. Comparative analyses of our data with that of Mabie *et al,* (1994) further support this association of maternal cardiac output, stature and fetal birth weight.

CHAPTER 4

MATERNAL HEMODYNAMICS IN HYPERTENSIVE DISORDERS OF PREGNANCY: COMBINED GROUP ANALYSIS

4.1 Introduction, aims and methods

Hypertensive disorders of pregnancy are not only an important cause of fetal and maternal morbidity and mortality, but are also the most common medical disorders complicating pregnancy (Duley, 1992). At King Edward VIII hospital (KEH), a tertiary teaching institution in Durban, South Africa, the setting for the current study, 18% of all admissions to the obstetric unit are hypertensive (Moodley, 1993). The National Committee on confidential enquires into maternal deaths in South Africa (2000) reported that complications of hypertensive disorders of pregnancy accounted for 23% of maternal deaths. This burden is highlighted in a comparative report by Mantel *et al,* (2002) which showed that maternal mortality ratios in South Africa was 12.3 times higher than that of the United Kingdom. In order to avoid adverse outcomes Bernheim (1997) stated that the practical management of hypertensive disorders of pregnancy requires prudence, careful follow-up and prompt decisions on the precise moment for delivery.

In studies by Kuzniar (1982) and Yang *et al,* (1996), the authors describe poor fetal outcome and fetal growth restriction in hypertensive women who had a markedly reduced cardiac index or elevated systemic vascular resistance respectively. In another study of invasive central hemodynamic in pre-eclampsia, Visser and Wallenburg (1991) emphasized that altered hemodynamics (elevated systemic

vascular resistance index) rather than the type of severity of hypertension was important in detecting at risk hypertensive pregnancies. A meta-analysis by Dadelszen *et al,* (2000) indicated that in addition to the hypertensive disease, treatment-induced falls in blood pressure may also be responsible for fetal growth restriction. It is possible that the cardiovascular haemodynamic maladaptation occurring in hypertensive pregnancies may serve as a measure of at risk pregnancies. .

Therefore all hypertensive patients were examined first as a combined group and later subdivided into individual groups. This section details the echocardiographic and uterine artery Doppler velocimetry evaluation of the combined and individual untreated hypertensive pregnant study groups compared to normotensive patients. Forty untreated hypertensive pregnant women (table 4.1) were compared with the 27 normotensive pregnant women who formed part of the longitudinally normotensive hemodynamic study as detailed in chapter 3. The enrolment, inclusion – exclusion criteria and echocardiographic and uterine Doppler flow velocimetry methods and statistical analysis are as described in chapter 2.

It is noted that during recruitment period of this study, guidelines for the initial care of hypertensive pregnant women prior to referral to the Obstetric Unit at King Edward VIII Hospital from satellite clinics were developed and enforced. The commencement of medical therapies such as alpha-methyldopa and /or sodium gardinal at satellite clinics as part of their initial care resulted in ineligibility for the study and resultant difficulty in recruitment and failure to reach the target study number of hypertensive pregnant women without prior medical therapies.

4.2 RESULTS

4.2.1 Demographics

The numbers in the individual groups are shown below.

Table 4.1 Hypertensive group demographics

	Number
Pre-eclampsia	n=10
Gestational aproteinuric hypertension	n=10
Chronic hypertension	n=10
Superimposed pre-eclampsia on chronic hypertension	n=10
Total	n=40

The demographic comparison of the combined hypertensive group shows that hypertensive pregnant women were of higher age, parity and had larger body size (body mass index and body surface area) compared to normotensives (Table 4.2). The chronic hypertensive and superimposed pre-eclampsia groups show a significantly larger maternal size than the pre-eclampsia and gestational hypertension groups (Table 4.3).

The mean blood pressure in the hypertensive cohort was significantly higher at entry into the study compared to blood pressure at echocardiography ($p < 0.001$) for the combined group. Blood pressure recordings in normotensive participants prior to echocardiography did not follow a similar time frame and are therefore not shown. Blood pressure in the full hypertensive cohort, showed that n=14 had severe hypertension and with the remaining n=26 having mild to moderate hypertension.

The lower birth weight in the hypertensive group is associated with a four week difference in gestation at delivery and occurred largely from a lower fetal birth weight and earlier gestation at delivery in the pre-eclampsia and superimposed pre-eclampsia groups. Feto-neonatal outcome was defined as adverse in 17 and non-adverse in the remaining 23 participants. Of the 17 defined as having an adverse outcome, 9 had fetal birth weight below the 10^{th} centile.

Of the twenty preeclamptic patients with proteinuria, eleven had $1^{+ \text{ or } 2^{+}}$ proteinuria and n=9 had $3^{+ \text{ or } 4^{+}}$ proteinuria or dipstix; the remaining twenty patients with gestational hypertension (n=10) and chronic hypertension (n=10) groups had nil or trace proteinuria.

Table 4.2 Demographics for combined hypertensive and normotensive groups

	Hypertensive group n = 40	Normotensive group n = 27	p value
Age (years)	28 ± 6	24 ± 5	0.001*
Parity: number (%) : para 0	5 (13%)	15 (56%)	
: >para 0	35 (87%)	12 (44%)	<0.001*
body mass index (kg/m^2)	34 ± 8	27 ± 4	<0.001*
body surface area (m^2)	1.81 ± 0.23	1.70 ± 0.14	0.057
height (cm)	156 ± 5	158 ± 5	0.063
weight (kg)	80 ± 18	69 ± 12	0.007*
gestation at evaluation (weeks)	31 ± 6	33 ± 1	0.466
systolic blood pressure at echocardiography (mmHg)	158 ± 26	102 ± 9	<0.001*
diastolic blood pressure at echocardiography (mmHg)	93± 15	56 ± 6	<0.001*
mean blood pressure at echocardiography (mmHg)	114 ± 18	71 ± 7	<0.001*
heart rate at echocardiography (beats/min)	77 ± 15	82 ± 8	0.175
gestation at delivery (weeks)	34 ± 5	38 ± 2	<0.001*
fetal birth weight (kg)	2.32 ± 0.97	3.01 ± 0.60	0.009*
systolic blood pressure at admission to study (mmHg)	165 ± 19	-----	-----
diastolic blood pressure at admission to study (mmHg)	105 ± 11	-----	-----
mean blood pressure at admission to study (mmHg)	125 ± 13	-----	-----

Data are presented as absolute mean ± one standard deviation
* Statistically significant, P values derived by Mann-Whitney U test.

Table 4.3 Demographic data of hypertensive participants

	pre-eclampsia n=10	gestational aproteinuric hypertension n=10	superimposed pre-eclampsia on chronic hypertension n=10	chronic hypertension n=10	p - value
age (years)	26 ± 7	27 ± 5	30 ± 6	31 ± 5	0.179
Parity: para 0 : para >0	n = 3 n = 7	n = 2 n = 8	n = 0 n = 10	n = 0 n = 10	
body surface area (m^2)	1.63 ± 0.14	1.78 ± 0.18	1.86 ± 0.13	1.96 ± 0.29	0.010*
body mass index (kg/m^2)	29 ± 5	33 ± 6	35 ± 6	38 ± 11	0.089
height (cm)	152 ± 5	155 ± 5	157 ± 6	160 ± 7	0.050*
weight (kg)	67 ± 13	80 ± 16	86± 13	97 ± 30	0.014*
gestation at evaluation (weeks)	31 ± 4	37 ± 3	29 ± 6	29 ± 8	0.024*
heart rate (beats/min)	67 ± 11	83 ± 10	79 ± 20	79 ± 15	0.060
systolic BP (mmHg) at echocardiography	166 ± 16	134 ± 19	179 ± 23	154 ± 22	0.001*
diastolic BP (mmHg) at echocardiography	96 ± 12	82 ± 10	104 ± 13	101 ± 6	0.014*
mean BP (mmHg) at echocardiography	119 ± 12	98 ± 16	129 ± 16	121 ± 8	0.003*
serum urate values (mmol/l)	0.36 ± 0.07	0.30 ± 0.08	0.35 ± 0.09	0.29 ± 0.07	0.308
platelet count (x 10^9/L)	207 ± 86	245 ± 52	188 ± 82	263 ± 73	0.081
gestation at delivery (weeks)	31 ± 4	37 ± 2	31 ± 5	35 ± 6	0.006*
birth weight (kg)	1.69 ± 0.91	3.02 ± 0.38	1.56 ± 0.91	2.77 ± 1.22	0.004*
p-value: mean BP at admission versus echocardiography	0.088	0.008*	0.046*	0.024*	------
systolic blood pressure at admission (mmHg)	168 ± 15	150± 15	182 ± 19	161± 13	0.003*
diastolic blood pressure at admission (mmHg)	107 ± 10	101 ± 10	112 ± 14	101 ± 6	0.032*
mean blood pressure at admission (mmHg)	126 ± 11	117 ± 12	136 ± 15	111 ± 14	0.006*

Data are presented as absolute mean ± one standard deviation

*Statistically significant, p values by Kruskal-Wallis one-way analysis of variance

4.2.2 Cardiac structure and function

Table 4.4 compares the echocardiographic data in the full hypertensive group with normotensives. The analysis of the individual hypertensive groups are shown in Table 4.5.

Compared to normotensive pregnant patients, hypertensive patients had a larger left atrial size but this difference existed only when left atrium to aorta size ratio was compared. There were no differences in atrial size between the hypertensive groups. The increased left ventricular mass index in the hypertensive cohort was associated with an increased septal thickness, higher relative wall thickness ratio and increased peak atrial filling veolocity. All hypertensive groups had a significantly higher left ventricle mass index compared to normotensives.

Higher left ventricular end systolic stress in the combined group was associated with preserved left ventricular contractile function indices, fractional shortening, ejection fraction, and velocity of circumferential fibre shortening with no differences in these indices between the hypertensive groups (table 4.5). The elevated left ventricular end systolic stress in the combined hypertensive group thus reflects the vasoconstricted state but without any impairment of left ventricle contractile function. Blood pressure (systolic, diastolic and mean) measured at echocardiography in the combined hypertensive cohort showed a good correlation with left ventricular hypertrophy as reflected by left ventricular mass index ($r = 0.45$).

Table 4.4 Cardiac structure and function- combined hypertensive and normotensive groups

	hypertensive group n=40	normotensive group n=27	p-value
LV internal diameter-diastole (cm)	5.00 ± 0.46	4.83 ± 0.34	0.093
LV internal diameter-systole (cm)	3.23 ± 0.41	3.23 ± 0.36	0.949
left atrium (cm)	3.7 ± 0.4	3.3 ± 0.6	0.009*
left atrial to aorta size ratio	1.38 ± 0.17	1.4 ± 0.3	0.482
LVseptal thickness (cm)	1.27 ± 0.26	0.99 ± 0.11	<0.001*
LV relative wall thickness ratio	0.28 ± 0.07	0.22 ± 0.04	<0.001*
LV mass (g)	212 ± 68	136 ± 26	<0.001*
LV mass index (g/m^2)	117 ± 32	79 ± 11	<0.001*
LV mass/height (g/m)	136 ± 41	86 ± 15	<0.001*
LV E/A (early to atrial) filling ratio	1.52 ± 0.65	1.76 ± 0.37	0.024*
LV peak E (early) filling(m/sec)	0.79 ± 0.16	0.82 ± 0.17	0.266
LV peak A (atrial) filling (m/sec)	0.57 ± 0.17	0.48 ± 0.09	0.047*
LV fractional shortening (%)	35 ± 5	33 ± 4	0.071
LV ejection fraction (%)	65 ± 6	62 ± 6	0.090
LV velocity of circumferential fibre shortening (circum/sec)	1.24 ± 0.23	1.18 ± 0.18	0.466
LV end systolic stress (dyn/cm^5)	93 ± 24	71 ± 17	<0.001*

Data are presented as absolute mean ± one standard deviation
* Statistically significant, p values derived by Mann-Whitney U test.

Table 4.5 Cardiac structure and function-hypertensive groups

	pre-eclampsia n=10	gestational aproteinuric hypertension n=10	superimposed pre-eclampsia on chronic hypertension n=10	chronic hypertension n=10	p - value
LV-internal diameter-diastole (cm)	4.84± 0.32	5.00 ± 0.29	5.04 ± 0.47	5.14 ± 0.68	0.424
LV internal diameter –systole (cm)	3.13 ±0.38	3.12 ± 0.30	3.33 ± 0.46	3.36± 0.48	0.474
left atrium (cm)	3.4 ± 0.4	3.8 ± 0.4	3.8 ± 0.5	3.8 ± 0.5	0.192
left atrial to aorta ratio	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	0.528
LV-septal thickness (cm)	1.2 ± 0.3	1.1 ± 0.2	1.5 ± 0.3	1.3 ± 0.2	0.009*
LV relative wall thickness ratio	0.25 ± 0.07	0.25 ± 0.03	0.32 ± 0.09	0.30 ± 0.06	0.035*
LV mass (g)	179 ± 59	177 ± 36	264 ± 63	233 ± 71	0.006*
LV mass index (g/m^2)	110 ± 35	99 ± 16	141 ± 27	119 ± 32	0.006*
% with LV-mass index ≥ $110 g/m^2$	40	20	90	70	
% with LV-mass index ≥$100 g/m^2$	60	50	100	80	
LV mass/height (g/m)	118 ± 39	114 ± 22	167 ± 38	146± 44	0.010*
LV-early to atrial diastolic filling ratio-(E/A)	1.67 ± 0.43	1.53 ± 0.40	1.28 ± 0.54	1.35 ± 0.55	0.255
LV fractional shortening (%)	36 ± 5	37 ± 5	34 ± 5	35 ± 4	0.387
LV ejection fraction (%)	64 ± 6	67 ± 6	63 ± 7	62 ± 6	0.345
LV –velocity of circumferential fibre shortening (circum/sec)	1.16 ± 0.16	1.34 ± 0.21	1.24 ± 0.34	1.23 ± 0.23	0.417
LV end systolic stress (dyn/cm^5)	98 ± 24	77 ± 16	105 ± 28	90 ± 22	0.100

Data are presented as absolute mean ± one standard deviation

* Statistically significant, P values by Kruskal-Wallis one-way analysis of variance

4.2.3 Maternal central hemodynamics and uterine Doppler velocimetry (Tables 4.6 and 4.7)

There were no differences in cardiac index between the individual hypertensive groups and normotensives. The elevated systemic vascular resistance index in the hypertensive group was thus largely a reflection of the elevated blood pressure. The higher stroke volume in the hypertensive group was associated with a trend to a lower heart rate and a larger maternal size as reflected by body surface area. The trend to a lower heart rate in preeclamptic cohort was associated with a higher stroke index but did not reach statistical significance.

The severity of hypertension and the severity of proteinuria were related to feto-neonatal outcome using chi-square analyses. Both the severity of blood pressure (classified as mild to moderate versus severe) ($p=0.041$) and the absence/presence of dipstix proteinuria showed good association with adverse/non-adverse feto-neonatal outcome ($p<0.001$).

Although both uterine artery resistance index and systemic vascular resistance index are elevated in the combined hypertensive group, the correlation between these variables was modest at $r = 0.44$. Uterine artery resistance index showed a better correlation with fetal birth weight and gestation at delivery ($r = -0.69$ and -0.67 respectively) compared to systemic vascular resistance index that gave correlation values with fetal birth weight and gestation at delivery of $r = -0.49$ and -0.55 respectively.

The hypertensive group (n = 40) was stratified by feto-neonatal outcome into two groups (Table 4.8). As expected, the adverse outcome group shows a significant lower fetal birth weight and earlier gestational age at delivery. The principal observations that characterised adverse feto-neonatal outcome cohort were the presence and severity of proteinuria, severity of hypertension, an elevated uterine artery resistance index and also of an elevated umbilical artery pulsatility index. There was no difference in the cardiac index between the adverse/non-adverse outcome groups but the systemic vascular resistance index was elevated in the adverse outcome group. The significantly lower heart rate in adverse outcome group was associated with a corresponding higher stroke index.

Stepwise multiple regression analysis using a model to evaluate predictors of adverse feto-neonatal outcome reflected that uterine artery resistance index indexed to maternal body surface area best predicted delivery gestational age ($r^2 = 0.634$). The model used quadratic analysis of variance co-variance where the square of the uterine artery resistance index is the co-variate and the study group is the factor. Maternal central hemodynamics showed only modest to poor correlations with adverse feto-neonatal outcome.

Table 4.6 Maternal central hemodynamics and uterine Doppler velocimetry in combined hypertensive and normotensive groups

	Hypertensive group n=40	Normotensive group n=27	p value
heart rate (beats/min)	77 ± 15	82 ± 8	0.175
mean blood pressure (mmHg)	115 ± 18	71 ± 7	<0.001*
stroke volume (ml)	89 ± 18	79 ± 12	0.038*
cardiac output (l/min)	6.76 ± 1.56	6.42 ± 0.90	0.424
systemic vascular resistance ($dyn.sec/cm^5$)	1447 ± 443	907 ± 135	<0.001*
body surface area (m^2)	1.81 ± 0.23	1.70 ± 0.14	0.057
stroke index (ml/m^2)	49 ± 10	46 ± 5	0.282
cardiac index ($l/min/m^2$)	3.72 ± 0.63	3.77 ± 0.44	0.908
systemic vascular resistance index ($dyn.sec/cm^5/m^2$)	2564 ± 680	1528 ± 236	<0.001*
Uterine artery resistance index	0.60 ± 0.12	0.46 ± 0.08	0.013*
umbilical artery pulsatility index	1.15 ± 0.37	1.10 ± 0.20	0.522

Data are presented as absolute mean ± one standard deviation
* Statistically significant, P values derived by Mann-Whitney U test.

Table 4.7 Maternal central hemodynamics and uterine Doppler velocimetry in hypertensive groups

	pre-eclampsia n=10	gestational aproteinuric hypertension n=10	superimposed pre-eclampsia on chronic hypertension n=10	chronic hypertension n=10	p - value
heart rate (beats/min)	67 ± 11	84 ± 9	79 ± 20	79 ± 15	0.060
stroke volume (ml)	86 ± 16	79 ± 15	92 ± 16	97 ± 24	0.241
cardiac output (l/min)	5.73 ± 1.21	6.69 ± 1.46	7.11 ± 1.58	7.49 ± 1.62	0.094
systolic blood pressure at echocardiography (mmHg)	166 ± 16	134± 19	179 ± 23	154± 22	0.001*
diastolic blood pressure at echocardiography (mmHg)	96 ± 12	82 ± 10	104 ± 13	90 ± 13	0.014*
mean blood pressure at echocardiography (mmHg)	119 ± 12	100 ± 16	129± 16	111 ± 14	0.003*
body surface area (m^2)	1.63 ± 0.14	1.78 ± 0.18	1.86 ± 0.13	1.96± 0.29	0.010*
stroke index (ml/m^2)	53 ± 8	45 ± 6	50 ± 9	50 ± 13	0.201
cardiac index ($l/min/m^2$)	3.51 ± 0.62	3.75 ± 0.62	3.82 ± 0.79	3.79 ± 0.53	0.727
systemic vascular resistance index (dyn.sec /cm^5/m^2)	2796 ± 574	2132 ± 523	2837± 812	2472 ± 601	0.079
uterine artery resistance index	0.67 ± 0.09	0.48 ± 0.07	0.67 ±0.12	0.58 ± 0.11	0.002*
Uterine artery resistance index standardised to maternal body surface area (/m^2)	0.42 ± 0.07	0.28 ± 0.04	0.36 ±0.06	0.31 ± 0.10	0.001*
umbilical artery pulsatility index	1.14 ± 0.41	0.92± 0.17	1.32 ± 0.37	1.30 ± 0.44	0.091
fetal birth weight (kg)	1.69 ± 0.91	3.02 ± 0.38	1.56 ± 0.91	2.77± 1.22	0.004*
fetal birth weight <10^{th} centile number (%)	3 (30%)	0 (0%)	5(50%)	1(10%)	-----

Data are presented as absolute mean ± one standard deviation.
*Statistically significant, P values by Kruskal-Wallis one-way analysis of variance.

Table 4.8 Combined hypertensive cohort (n=40) stratified by feto-neonatal outcome

	Adverse outcome n = 17	Non-adverse outcome n = 23	p value
Age (years)	28 ± 7	29 ± 6	0.753
parity-number (%):para 0 (n=16)	2 (12%)	3 (13%)	1.000
:para >0 (n= 16)	15 (88%)	20 (20%)	(chi-square)
body surface area (m^2)	1.73 ± 0.19	1.86 ± 0.24	0.085
proteinuria dipstix : nil/trace	3 (18%)	17 (74%)	0.001*
:1^{+} and 2^{+} (n=20)	8 (47%)	3 (13%)	(chi-square)
: 3^{+} and 4^{+} (n=12)	6 (35%)	3 (13%)	
gestation at evaluation (weeks)	27 ± 4	34 ± 6	< 0.001*
serum urate values (mmol/l)	0.36 ± 0.09	0.31 ± 0.07	0.201
systolic blood pressure at echocardiography (mmHg)	169 ± 26	151 ± 23	0.010*
diastolic blood pressure at echocardiography (mmHg)	98 ± 16	89 ± 14	0.080
LV mass index (g/m^2)	127 ± 34	110 ± 28	0.218
heart rate at echo (beats/min)	70 ± 16	82 ± 12	0.009*
stroke index (ml/m^2)	53 ± 11	47 ± 8	0.041*
cardiac index ($l/min/m^2$)	3.61 ± 0.58	3.80 ± 0.67	0.311
systemic vascular resistance index ($dyn.sec/cm^5/m^2$)	2781 ± 684	2395 ± 637	0.044*
uterine artery resistance index	0.68 ± 0.11	0.54 ± 0.10	0.001*
umbilical artery pulsatility index	1.33 ± 0.44	1.01 ± 0.23	0.008*
fetal birth weight (kg)	1.21 ± 0.58	3.04 ± 0.60	<0.001*
gestation at delivery (weeks)	29 ± 4	37 ± 3	<0.001*

Data are presented as absolute mean ± one standard deviation.
* Statistically significant, P values derived by Mann-Whitney U test.

4.3 Discussion

As a group the hypertensive patients in this study had a typical profile as seen in clinical practice. They were characterized by higher age, parity and body mass index and a higher systemic vascular resistance index. There was no difference in cardiac index between this combined hypertensive group normotensives patients.

These patients had a significantly lower fetal birth weight that correlated best with uterine artery resistance index ($r = -0.65$) and showed very modest correlations with systemic vascular resistance index ($r = -0.49$) and systolic and mean blood pressure ($r = -0.40$). The correlation of fetal birth weight with cardiac index was surprisingly poor ($r = 0.21$). Although severe hypertension at echocardiography recognized at risk hypertensive pregnancies, blood pressure alone did not correlate well with adverse feto-neonatal outcome.

An interesting observation was the significantly lower levels of blood pressure recorded at the time of echocardiography compared to that measured at entry into the study. This placebo effect probably reflects the more "pleasant" and quiet circumstances of the ultrasound laboratory compared the admission obstetric unit. Furthermore blood pressure measurements were taken in the recumbent as opposed to the sitting position in the laboratory. The fall in blood pressure could also include the presence of milder or possibly more labile hypertension, or even a "white coat" effect. The above observations call for a more standardized procedure for measuring blood pressure and evaluation of ambulatory blood pressure monitoring as well as personnel-free methods such as electronic blood pressure measurement.

Hypertensive women had significantly higher LV mass index with preserved contractility, characterized by a concentric increase in LV wall thickness and mass. Wall stress was still elevated indicating that these changes were still inadequate to offset this increased wall tension.

CHAPTER 5

FOCUS ON PRE-ECLAMPSIA AND ITS VARIANTS

5.1 Introduction, aims and methods

Pre-eclampsia-eclampsia complicates 3-5% of pregnancies and remains a leading cause of maternal and neonatal mortality worldwide (Duley, 1992). Pre-eclampsia is also termed gestational proteinuric hypertension, the presence of proteinuria being associated with an increased risk of fetal and maternal morbidity. This disease is progressive and in its advanced form leads to maternal renal failure, disseminated intravascular coagulation, liver failure, pulmonary oedema and death (Bolte *et al*, 2001). Although delivery cures progressive disease in pre-eclamptic women, it often results in delivery of a premature infant. Bernheim (1997) has stated that the management of pre-eclampsia requires prudence, careful follow up and prompt decisions on the precise moment for delivery. To this end, the clinician requires improved antenatal predictors to assist with management.

Although the aetiology of pre-eclampsia is not known, the primary pathophysiology is probably placental. Defective implantation and placentation is thought to result in reduced placental perfusion with ischaemia and subsequent maternal endothelial and organ dysfunction (Roberts, 2000). In an echocardiographic study of severe pre-eclamptic women, Yang *et al,* (1996) found that an elevated systemic vascular resistance index was associated with a higher prevalence of small for gestational age babies. These observations lend support to the view that the severity of pre-eclampsia may be stratified by measurement of maternal central hemodynamics. Doppler

echocardiography is safe in pregnancy and Doppler-derived cardiac output has been validated as an accurate measure of maternal hemodynamics by Easterling *et al,* (1990).

The elevated systemic vascular resistance seen in pre-eclamptic pregnancies is accompanied by varying degrees of increased resistance to flow in the uterine arteries. Sargol *et al,* (1999) showed that high uterine artery flow resistance was related to a reduced trophoblast migration into the myometrium and inadequate physiological changes in the spiral arteries not only in pre-eclamptic women but also in normotensive women with intrauterine growth restriction. Doppler velocimetry studies of the uterine arteries however, have produced varying results regarding its predictive value (Bower *et al,* 1998). Furthermore, most of these studies did not relate uterine artery Doppler velocimetry to maternal central hemodynamics.

In this chapter, participants with pre-eclampsia are compared with the other hypertensive groups. Since it has been well documented that pregnant women with gestational aproteinuric hypertension may progress to pre-eclampsia (Saudan *et al,* 1998) and since pre-eclampsia may complicate chronic hypertension in pregnancy these groups were compared with each other to elucidate any trend or gradation in haemodynamics and cardiac structural changes.

The enrolment, inclusion and exclusion criteria, echocardiographic and Doppler methods and statistical analysis are as described in Chapter 2. This study compares 10 women with pre-eclampsia without any prior anti-hypertensive therapy to 10 women with gestational hypertension and 10 women with superimposed pre-

eclampsia on chronic hypertension compared with ten normotensive gestation matched controls taken from the longitudinal echocardiographic study in normotensive pregnancy (Chapter 3).

In addition, a cohort of 22 pre-eclamptic women (referred to as treatment group preeclamptics) comprised of 18 women who received a single dose of methyl-dopa 1000mg orally and sodium gardinal 200mg by the intramuscular route and 4 women who received methyl-dopa 1000mg alone. This treatment group were evaluated by echocardiography and uterine Doppler velocimetry within 6 hours of having taken prescribed methyl-dopa and/or sodium gardinal. It is anticipated that evaluation of this larger cohort of preeclamptics (treated and untreated) will further contribute to an improved understanding of pre-eclampsia.

5.2 Results

5.2.1 Demographics (Tables 5.1 and 5.2)

Preeclamptic patients had a significantly smaller stature (body surface area and height) than the superimposed pre-eclampsia and gestational hypertension groups. Both pre-eclampsia and superimposed pre-eclampsia groups were associated with an earlier gestation at delivery while the gestational hypertensive participants presented closer to term.

Preeclamptic patients had a significantly lower heart rate and higher blood pressure at echocardiography than gestational hypertension groups. There was a trend to a lower blood pressure at echocardiography compared to the blood pressure measured at

inclusion into the study; this decrease in blood pressure reached statistical significance in the chronic hypertension and superimposed pre-eclampsia groups.

Table 5.1 Demographic data of pre-eclampsia, normotensive and gestational hypertensive groups

	pre-eclampsia n=10	normotensive n=27	p value: Pre-eclampsia versus normotensive group	gestational (aproteinuric) hypertension n=10	p – value: pre-eclampsia versus gestational hypertension
age (years)	26 ± 7	24 ± 5	0.346	27 ± 5	0.596
Parity : para 0 : > para 0	n = 3 (30%) n = 7 (70%)	n=15 (30%) n=12 (70%)	0.312 (chi-square)	n = 2 (20%) n = 8 (80%)	1.000 (chi-square)
body surface area (m^2)	1.63 ± 0.14	1.70 ± 0.14	0.111	1.78 ± 0.18	0.028*
body mass index (kg/m^2)	29 ± 5	27 ± 4	0.305	33 ± 6	0.058
height (cm)	152 ± 5	158 ± 5	0.001*	155 ± 5	0.149
weight (kg)	67 ± 13	69 ± 12	0.441	80 ± 16	0.019*
gestation at evaluation (weeks)	31 ± 4	33 ± 1	0.042*	37 ± 3	0.003*
heart rate (beats/min)	67 ± 11	82 ± 8	<0.001*	83 ± 10	0.002*
systolic BP (mmHg) at echocardiography	166 ± 16	102 ± 9	<0.001*	134 ± 19	0.002*
diastolic BP (mmHg) at echocardiography	96 ± 12	56 ± 6	<0.001*	82 ± 10	0.028*
mean BP (mmHg) at echocardiography	119 ± 12	82 ± 8	<0.001*	98 ± 16	0.006*
serum urate values (mmol/l)	0.36 ± 0.07	0.27 ± 0.06	0.134	0.30 ± 0.08	0.142
platelet count (x 10^9/L)	207 ± 86	259 ± 90	0.705	245 ± 52	0.481
gestation at delivery (weeks)	31 ± 4	38 ± 2	<0.001*	37 ± 2	0.003*
birth weight (kg)	1.69 ± 0.91	3.01 ± 0.60	0.001*	3.02 ± 0.38	0.007*
p-value: mean BP at admission versus echocardiography	0.088	--------	------	0.008*	------
systolic blood pressure at admission (mmHg)	168 ± 15	---------	<0.001*	150± 15	0.021*
diastolic blood pressure at admission (mmHg)	107 ± 10	---------	<0.001*	101 ± 10	0.176
mean blood pressure at admission (mmHg)	126 ± 11	----------	<0.001*	117 ± 12	0.091

Data are presented as absolute mean ± one standard deviation
* Statistically significant, P values derived by Mann-Whitney U test.

Table 5.2 Demographic data of pre-eclampsia and superimposed pre-eclampsia groups

	pre-eclampsia n=10	superimposed pre-eclampsia on chronic hypertension n=10	p - value Pre-eclampsia versus Superimposed pre-eclampsia
age (years)	26 ± 7	30 ± 6	0.161
Parity : para 0 : > para 0	n = 3 (30%) n = 7 (70%)	n = 3 (30%) n = 7 (70%)	0.210 (chi-square)
body surface area (m^2)	1.63 ± 0.14	1.86 ± 0.13	0.005*
body mass index (kg/m^2)	29 ± 5	35 ± 6	0.064
height (cm)	152 ± 5	157 ± 6	0.053
weight (kg)	67 ± 13	86 ± 13	0.015*
gestation at evaluation (weeks)	31 ± 4	29 ± 6	0.494
heart rate (beats/min)	67 ± 11	79 ± 20	0.241
systolic BP (mmHg) at echocardiography	166 ± 16	179 ± 23	0.150
diastolic BP (mmHg) at echocardiography	96 ± 12	104 ± 13	0.226
mean BP (mmHg) at echocardiography	119 ± 12	129 ± 16	0.185
serum urate values (mmol/l)	0.36 ± 0.07	0.35 ± 0.09	0.651
platelet count (x 10^9/L)	207 ± 86	188 ± 82	0.203
gestation at delivery (weeks)	31 ± 4	31 ± 5	0.939
birth weight (kg)	1.69 ± 0.91	1.56 ± 0.91	0.520
p-value: mean BP at admission versus echocardiography	0.088	0.046*	------
systolic blood pressure at admission (mmHg)	168 ± 15	182 ± 19	0.115
diastolic blood pressure at admission (mmHg)	107 ± 10	112 ± 14	0.130
mean blood pressure at admission (mmHg)	126 ± 11	136 ± 15	0.048*

Data are presented as absolute mean ± one standard deviation
* Statistically significant, P values derived by Mann-Whitney U test.

5.2.2 Cardiac structure and Function (Tables 5.3 and 5.4)

There were no differences in left ventricle diameters between the groups. Compared to preeclamptics and normotensive groups, patients with gestational hypertension and superimposed pre-eclampsia had larger atria but this was not evident when left atrial/aorta size ratios are compared. LV mass (and index) in pre-eclamptic participants was higher than normotensives but lower than that of superimposed pre-eclampsia group. This increased left ventricle mass in preeclamptic participants occurred from increased left ventricle wall thickness and was associated with a trend to a higher relative wall thickness ratio compared to normotensive participants. There were no differences in left ventricle diastolic filling rates between preeclamptics and normotensive groups but a trend to a lower left ventricle diastolic early to atrial filling ratio was noted in superimposed pre-eclampsia group. Left ventricle contractility indices reflected by load dependent indices (fractional shortening and ejection fraction) and less load dependent measure of velocity of circumferential fibre shortening were similar in preeclamptics and normotensive and superimposed pre-eclampsia groups. The elevated left ventricle systolic stress in the pre-eclampsia groups reflects the vasoconstricted state but with preserved left ventricle systolic function.

Table 5.3 Cardiac structure and function- pre-eclampsia, normotensives and gestational hypertension groups.

	pre-eclampsia n=10	normotensive n=27	p - value pre-eclampsia versus normotensive	gestational aproteinuric hypertension n=10	p - value pre-eclampsia versus gestational hypertension
LV-internal diameter-diastole (cm)	4.84 ± 0.32	4.83 ± 0.34	0.959	5.00 ± 0.29	0.289
LV internal diameter –systole (cm)	3.13 ± 0.38	3.23 ± 0.36	0.549	3.12 ± 0.30	0.970
left atrium (cm)	3.4 ± 0.4	3.3 ± 0.4	0.440	3.8 ± 0.4	0.028*
left atrial to aorta ratio	1.4 ± 0.2	1.4 ± 0.3	0.918	1.4 ± 0.2	0.290
LV-septal thickness (cm)	1.2 ± 0.3	1.0± 0.1	0.011*	1.1 ± 0.2	0.426
LV relative wall thickness ratio	0.25 ± 0.07	0.22 ± 0.04	0.174	0.25 ± 0.03	0.306
LV mass (g)	179 ± 59	136 ± 26	0.033*	177 ± 36	0.820
LV mass index (g/m^2)	110 ± 35	79 ± 11	0.002*	99 ± 16	0.520
% with LV-mass index ≥ $110 g/m^2$	40	0		20	
% with LV-mass index ≥$100 g/m^2$	60	0		50	
LV mass/height (g/m)	118 ± 39	86 ± 15	0.007*	114 ± 22	1.000
LV-early to atrial diastolic filling ratio-(E/A)	1.67 ± 0.43	1.76 ± 0.37	0.756	1.53 ± 0.40	0.473
LV fractional shortening (%)	36 ± 5	33 ± 4	0.192	37 ± 5	0.404
LV ejection fraction (%)	64 ± 6	62 ± 6	0.280	67 ± 6	0.324
LV –velocity of circumferential fibre shortening (circum/sec)	1.16 ± 0.16	1.18 ± 0.18	0.681	1.34 ± 0.21	0.069
LV end systolic stress (dyn/cm^5)	98 ± 24	71± 17	0.004*	77 ± 16	0.082

Data are presented as absolute mean ± one standard deviation; LV=left ventricle.
* Statistically significant, P values derived by Mann-Whitney U test.

Table 5.4 Cardiac structure and function- pre-eclampsia and superimposed pre-eclampsia groups

	pre-eclampsia n=10	superimposed pre-eclampsia on chronic hypertension n=10	p - value pre-eclampsia versus superimposed pre-eclampsia
LV-internal diameter-diastole (cm)	4.84 ± 0.32	5.04 ± 0.47	0.226
LV internal diameter –systole (cm)	3.13 ± 0.38	3.33 ± 0.46	0.307
left atrium (cm)	3.4 ± 0.4	3.8 ± 0.5	0.074
left atrial to aorta ratio	1.4 ± 0.2	1.4 ± 0.2	0.940
LV-septal thickness (cm)	1.2 ± 0.3	1.5 ± 0.3	0.015*
LV relative wall thickness ratio	0.25 ± 0.07	0.32 ± 0.09	0.053
LV mass (g)	179 ± 59	264 ± 63	0.007*
LV mass index (g/m^2)	110 ± 35	141 ± 27	0.013*
% with LV-mass index ≥ 110g/m^2	40	90	
% with LV-mass index ≥100 g/m^2	60	100	
LV mass/height (g/m)	118 ± 39	167 ± 38	0.008*
LV-early to atrial diastolic filling ratio-(E/A)	1.67 ± 0.43	1.28 ± 0.54	0.089
LV fractional shortening (%)	36 ± 5	34 ± 5	0.492
LV ejection fraction (%)	64 ± 6	63 ± 7	0.539
LV –velocity of circumferential fibre shortening (circum/sec)	1.16 ± 0.16	1.24 ± 0.34	0.850
LV end systolic stress (dyn/cm^5)	98 ± 24	105 ± 28	0.650

Data are presented as absolute mean ± one standard deviation.
* Statistically significant, P values derived by Mann-Whitney U test.

5.2.3 Maternal hemodynamics and uterine artery Doppler velocimetry (Table 5.5)

Evaluation of cardiac output and cardiac index between preeclamptic participants and the superimposed preeclampsia group show a significant lower cardiac output in preeclamptic women (p=0.049) but no differences in cardiac index. The larger body surface area in superimposed preeclampsia group (p= 0.005) compared to preeclamptic women is noted. The hypertensive participants as a group showed a fair positive correlation between cardiac output and body surface area (r =0.71), an association that remains but is less strong for the preeclampsia group alone at r = 0.58.

In pre-eclamptic women, fetal birth weight and gestation at delivery correlated best with uterine artery resistance index (r = -0.59). There is a significantly elevated uterine artery resistance index in the preeclampsia cohort compared to both normotensive and gestational hypertensive groups. Maternal body surface area also showed a modest correlation with fetal birth weight (r =0.50) and the uterine artery resistance index standardized to maternal body surface area showed an improved correlation with fetal birth weight (r = -0.70) in the preeclamptic groups an association that was also valid for the other hypertensive groups in this study.

In preeclamptic women, the correlation between fetal birthweight and maternal cardiac output, cardiac index and systemic vascular resistance were poor. In addition, it is noted that maternal haemodynamics reflected by systemic vascular resistance and its indexed value correlated poorly uterine artery resistance index.

Table 5.5 Maternal central hemodynamics and uterine Doppler velocimetry in pre-eclampsia, normotensive and gestational hypertension groups

	pre-eclampsia n=10	normotensive n=27	p - value pre-eclampsia versus normotensive	gestational aproteinuric hypertension n=10	p - value pre-eclampsia versus gestational hypertension
heart rate (beats/min)	67 ± 11	82 ± 8	<0.001*	84 ± 9	0.002*
stroke volume (ml)	86 ± 16	79 ± 12	0.238	79 ± 15	0.307
cardiac output (l/min)	5.73 ± 1.21	6.42 ± 0.90	0.116	6.69 ± 1.46	0.257
systolic blood pressure at echocardiography (mmHg)	166 ± 16	102 ± 9	<0.001*	134 ± 19	0.002*
diastolic blood pressure at echocardiography (mmHg)	96 ± 12	56 ± 6	<0.001*	82 ± 10	0.028*
mean blood pressure at echocardiography (mmHg)	119 ± 12	71 ± 7	<0.001*	100 ± 16	0.006*
body surface area (m^2)	1.63 ± 0.14	1.70 ± 0.14	0.011	1.78 ± 0.18	0.028*
stroke index (ml/m^2)	53 ± 8	46 ± 5	0.018*	45 ± 6	0.041*
cardiac index ($l/min/m^2$)	3.51 ± 0.62	3.78 ± 0.45	0.452	3.75 ± 0.62	0.545
systemic vascular resistance index (dyn.sec $/cm^5/m^2$)	2796 ± 574	1528 ± 236	<0.001*	2132 ± 523	0.016*
uterine artery resistance index	0.67 ± 0.09	0.46 ± 0.08	<0.001*	0.48 ± 0.07	0.001*
Uterine artery resistance index standardised to maternal body surface area ($/m^2$)	0.42 ± 0.07	0.31 ± 0.05	0.001*	0.28 ± 0.04	0.041*
umbilical artery pulsatility index	1.14 ± 0.41	1.10 ± 0.20	0.312	0.92 ± 0.17	0.091
fetal birth weight (kg)	1.69 ± 0.91	3.01 ± 0.61	<0.001*	3.02 ± 0.38	0.007*
fetal birth weight <10^{th} centile number (%)	3 (30%)	---	----	0 (0%)	---

Data are presented as absolute mean ± one standard deviation.
* Statistically significant, P values derived by Mann-Whitney U test.

Table 5.6 Maternal central hemodynamics and uterine Doppler velocimetry in hypertensive groups

	pre-eclampsia n=10	superimposed pre-eclampsia on chronic hypertension n=10	p - value
heart rate (beats/min)	67 ± 11	79 ± 20	0.241
stroke volume (ml)	86 ± 16	92 ± 16	0.472
cardiac output (l/min)	5.73 ± 1.21	7.11 ± 1.58	0.049*
systolic blood pressure at echocardiography (mmHg)	166 ± 16	179 ± 23	0.150
diastolic blood pressure at echocardiography (mmHg)	96 ± 12	104 ± 13	0.226
mean blood pressure at echocardiography (mmHg)	119 ± 12	129± 16	0.185
body surface area (m^2)	1.63 ± 0.14	1.86 ± 0.13	0.005*
stroke index (ml/m^2)	53 ± 8	50 ± 9	0.384
cardiac index ($l/min/m^2$)	3.51 ± 0.62	3.82 ± 0.79	0.326
systemic vascular resistance index ($dyn.sec/cm^5/m^2$)	2796 ± 574	2837± 812	0.880
uterine artery resistance index	0.67 ± 0.09	0.67 ±0.12	0.791
Uterine artery resistance index standardised to maternal body surface area ($/m^2$)	0.42 ± 0.07	0.36 ±0.06	0.049*
umbilical artery pulsatility index	1.14 ± 0.41	1.32 ± 0.37	0.369
fetal birth weight (kg)	1.69 ± 0.91	1.56 ± 0.91	0.520
fetal birth weight $<10^{th}$ centile number (%)	3 (30%)	5 (50%)	---

Data are presented as absolute mean ± one standard deviation.
* Statistically significant, P values derived by Mann-Whitney U test.

5.2.4 Evaluation of treated preeclamptics and combined preeclamptic groups (Tables 5.7 and 5.8)

Because of the possible effects of prior treatment on haemodynamic measurements these patients who received treatment were analysed separately. The treated pre-eclampsia group consisted of 22 participants who had been given a combination of sodium gardinal (200mg) by the intramuscular route and single dose of oral methyl-dopa 1000mg (n=18) or a single dose of oral methlydopa 1000mg alone (n=4) prior to echocardiography. The above therapy was prescribed at admission at the discretion of the attending obstetrician and the haemodynamic evaluation was performed within six hours of the administered medication.

Table 5.7 and 5.8 list the relevant demographic and echocardiographic data of treated, untreated and combined (untreated and treated) pre-eclampsia groups.

Table 5.7 lists and compares demographics data of untreated (n=10) and treated (n=22) preeclamptics and also that of the combined pre-eclampsia group (n=32) with normotensives (n=27). Body surface area and multiparity was higher in the treated group. There were no statistical differences in blood pressure and severity of proteinuria between the groups.

Cardiac output (Table 5.8) was higher in the treated pre-eclampsia group, but there were no differences in cardiac index ($p = 0.143$). A trend to a lower heart rate is noted in the untreated preeclamptic cohort but stroke index was similar for both groups. As expected, the systemic vascular resistance index was significantly lower in the treated pre-eclamptic group and this was associated with a significantly lower uterine

resistance index in treated patients probably due to the single dose of methyl-dopa and sodium gardinal at admission.

Maternal central hemodynamics showed poor correlation with both fetal birth weight and uterine artery resistance index. This poor correlation between maternal central hemodynamics and fetal birth weight remain when treated and untreated preeclamptics groups are evaluated separately. Systemic vascular resistance index showed the best correlation with uterine artery resistance index, (r =0.43).

Examined together, treated and untreated patients (combined preeclamptic group (n=32)) showed good correlation of uterine artery resistance and its indexed value with fetal birth weight (r = -0.71). This correlation remains unchanged when treated and untreated preeclamptics are evaluated separately.

The level of blood pressure, presence of severe proteinuria (3^{+} and 4^{+} on dipstix testing) and multiparity showed no significant association with adverse feto-neonatal outcome. (p = 0.683 for severe hypertension, p= 0.273 for severe proteinuria and p = 0.724 for multiparity) The associations remained similar when evaluated against low birth weight group defined by fetal birth weight below the 10^{th} centile.

5.2.5 Evaluation of preeclamptics stratified by adverse feto-neonatal outcome (Table 5.9)

Significant differences emerged when the combined (treated and untreated) group (n = 32) was stratified by feto-neonatal outcome into adverse and non-adverse outcome groups. Fetal birth weight and gestation of delivery were lower in the

adverse outcome group. There was a difference in maternal central hemodynamics between groups but the uterine artery resistance index was higher in the adverse outcome group. Both the uterine artery resistance and its standardized value corrected and correlated equally well with fetal birth weight ($r^2 = 0.51$). Adding variables of proteinuria, severity of hypertension, parity and systemic vascular resistance index to the regression model brought the predictive value of the model to $r^2 = 0.62$.

Table 5.7 Comparative demographics in untreated and combined pre-eclampsia groups

	untreated pre-eclampsia n=10	treated pre-eclampsia n=22	P value	combined pre-eclampsia n=32	Normo-tensive n=27	p value
body surface area (m^2)	1.63 ± 0.14	1.75 ± 0.14	0.019*	1.71 ± 0.15	1.70 ± 0.14	0.976
height (cm)	152 ± 5	156 ± 5	0.061	154 ± 5	158 ± 5	0.007*
weight (kg)	67 ± 0.13	76 ± 12	0.049*	73 ± 13	69 ± 12	0.357
parity : para 0 : para > 0	3 (30%) 7 (70%)	13 (59%) 9 (41%)	0.124 (chi-square)	16 (50%) 16 (50%)	15 (56%) 12 (44%)	0.670 (chi-square)
proteinuria $1^+/2^+$ $3^+/4^+$	6 (60%) 4 (40%)	14 (64%) 8 (36%)	0.84 chi-square	20 (63%) 12 (37%)	0 0	----
systolic BP (mmHg) at admission	168 ± 15	168 ± 13	0.917	168 ± 14	---	---
diastolic BP (mmHg) at admission	107 ± 10	114 ± 10	0.153	112± 11	---	---
mean BP (mmHg) at admission	126 ± 11	132 ± 10	0.355	130 ± 10	---	---
gestation at evaluation (weeks)	31 ± 4	33 ± 4	0.097	33 ± 4	33 ± 1	0.403
systolic BP (mmHg) at echocardiography	166 ± 16	155 ± 16	0.087	158 ± 16	102 ± 9	<0.001*
diastolic BP (mmHg)at echocardiography	96 ± 12	90 ± 9	0.172	92 ± 10	56 ± 6	<0.001*
mean BP (mmHg) at echocardiography	119 ± 12	112 ± 11	0.061	114 ± 12	71 ± 6	<0.001*
gestation at delivery (weeks)	31 ± 4	34 ± 4	0.029*	33 ± 4	38 ± 2	<0.001*
fetal birth weight (kg)	1.69 ± 0.91	2.10 ± 0.74	0.137	1.97 ± 0.80	3.01 ± 0.60	<0.001*
fetal birth weight $<10^{th}$ centile number (%)	3 (30%)	6 (27%)	0.874 (chi square)	9 (28%)	-----	----

Data are presented as absolute mean ± one standard deviation

* Statistically significant, P values derived by Mann-Whitney U test.

Table 5.8 Comparative hemodynamics and uterine artery velocimetry in treated and combined pre-eclampsia groups.

	untreated pre-eclampsia n=10	treated pre-eclampsia n=22	p value	combined pre-eclampsia n=32	normotensive n=27	p value
heart rate (beats/min)	67 ± 11	76 ± 12	0.103	76 ± 12	82 ± 8	0.005*
stroke index (ml/m^2)	53 ± 8	52 ± 7	0.903	52 ± 7	46 ± 5	0.001*
cardiac output (l/min)	5.73 ± 1.21	6.91 ± 1.29	0.034*	6.91 ± 1.29	6.42 ± 0.90	0.704
cardiac index ($l/min/m^2$)	3.51 ± 0.62	3.95 ± 0.67	0.143	3.95 ± 0.67	3.77 ± 0.44	0.879
LV ejection fraction (%)	64 ± 6	65 ± 7	0.476	65 ± 7	62 ± 6	0.017*
LV end systolic stress (dyn/cm^5)	98 ± 24	93 ± 32	0.542	93 ± 32	71 ± 17	0.001*
systemic vascular resistance index ($dyn.sec\ /cm^5/m^2$)	2796 ± 574	2332 ± 514	0.031*	2332 ± 514	1528 ± 236	* <0.001
uterine artery resistance index	0.67± 0.09	0.57 ± 0.11	0.015*	0.57 ± 0.11	0.46 ± 0.08	0.013*
Uterine artery resistance index standardised to maternal body surface area ($/m^2$)	0.42± 0.07	0.33 ± 0.06	0.003*	0.35± 0.08	0.31 ± 0.05	0.044*
umbilical artery pulsatility index	1.14 ± 0.41	1.26 ± 0.49	0.983	1.22 ± 0.46	1.10 ± 0.20	0.342

Data are presented as absolute mean ± one standard deviation.
* Statistically significant, P values derived by Mann-Whitney U test.

Table 5.9 Combined pre-eclamptic group (n=32) stratified by feto-neonatal outcome

	Adverse outcome n = 16	Non-adverse outcome n = 16	p value
Age	24 ± 6	25 ± 7	0.924
Parity-number (%):para 0 (n=16)	9 (56%)	7 (44%)	0.724(corrected chi-square)
:para >0 (n= 16)	7 (44%)	9 (56%)	
body surface area (m^2)	1.68 ± 0.14	1.74 ± 0.16	0.365
Proteinuria dipstix:1^{+} and 2^{+} (n=20)	8 (67%)	12 (60%)	0.273(corrected chi-square)
: 3^{+} and 4^{+} (n=12)	4 (34%)	8 (40%)	
gestation at evaluation (weeks)	30 ± 3	35 ± 3	0.001*
serum urate values (mmol/l)	0.35 ± 0.08	0.33 ± 0.06	0.699
systolic blood pressure at echocardiography (mmHg)	162 ± 17	155 ± 15	0.266
diastolic blood pressure at echocardiography (mmHg)	94 ± 12	90 ± 9	0.417
mean blood pressure at echocardiography (mmHg)	116 ± 12	113 ± 12	0.473
LV mass index (g/m^2)	117 ± 13	111 ± 10	0.336
heart rate at echo (beats/min)	70 ± 10	76 ± 13	0.131
stroke index (ml/m^2)	56 ± 7	50 ± 6	0.016*
cardiac index ($l/min/m^2$)	3.88 ± 0.6	3.74 ± 0.8	0.598
systemic vascular resistance index ($dyn.sec/cm^5/m^2$)	2456 ± 500	2499 ± 681	0.910
uterine artery resistance index	0.66 ± 0.10	0.55 ± 0.11	0.006*
umbilical artery pulsatility index	1.29 ± 0.50	1.15 ± 0.42	0.101
fetal birth weight (kg)	1.41 ± 0.33	2.53 ± 0.73	<0.001*
gestation at delivery (weeks)	31 ± 3	36 ± 3	0.001*

Data are presented as absolute mean ± one standard deviation.
* Statistically significant, P values derived by Mann-Whitney U test.

5.3 Discussion

The pre-eclamptic women in this study were of smaller stature compared to women with gestational hypertension and superimposed pre-eclampsia. There were no differences in cardiac index between groups. Similar to most studies on maternal hemodynamics, our study demonstrates a wide variation in cardiac index and systemic vascular resistance index values both in normotensive and hypertensive pregnancy groups that occurred largely from patient factors. This limited identification of a critical cardiac index or systemic vascular resistance index value with good discriminatory power to predict adverse fetal outcome.

The higher systolic and diastolic blood pressure in preeclamptic women compared to women with gestational hypertension was not accompanied by a similar statistical increase left ventricular mass index (Table 4.3). This suggests that the higher blood pressure in these groups allowed for a corresponding increase in left ventricular mass to occur. However there was a modest correlation between left ventricular mass index and systemic vascular resistance index ($r = 0.43$), and a better correlation with uterine artery resistance index ($r = 0.56$). This suggests that in addition to loading conditions non-haemodynamic factors such as activation of sympathetic and changes in renin-angiotensin systems may contribute to the development of left ventricular hypertrophy. The short duration of hypertension in pre-eclamptic women will also explain the modest correlation of maternal hemodynamics and development of LV hypertrophy. The increased left ventricular mass index in preeclamptic women was associated with an elevated left ventricular systolic wall stress but with preserved left ventricular systolic function.

Our data illustrate the limited benefit of maternal hemodynamics in defining at risk preeclamptic pregnancies as use of any arbitrary cut off value is only achieved at a cost of significant reduction in specificity and vise versa. The best predictor of an adverse feto-neonatal outcome in preeclamptic pregnancy was the uterine artery resistance index. The comparative review of our study with previously published research is discussed in Chapter 8, section 8.2.

CHAPTER 6

GESTATIONAL APROTEINURIC HYPERTENSION

6.1 Introduction, aims and methods

Gestational aproteinuric hypertension appears to carry a low risk of fetal and maternal morbidity. Bosio *et al,* (1999) showed that women with gestational aproteinuric hypertension may be 'closer' to normotensive pregnant women in risk and outcome than to women who have pre-eclampsia (gestational proteinuric hypertension).

It appears that the clinical presentation of pregnant women with gestational aproteinuric hypertension may be similar to women with mild aproteinuric chronic hypertension. Although evidence of hypertensive target organ involvement is often not present in the former, gestational hypertension does carry a significant risk. A recent study by Galanti *et al*, 2000 described significant adverse feto-neonatal outcome in women with gestational hypertension. Saudan *et al,* (1998) found that approximately 17% of women (15% in a retrospective study and 26% in a prospective study) initially diagnosed with gestational hypertension develop pre-eclampsia. The authors identified early gestation at presentation and history of prior miscarriage as variables that development to pre-eclampsia. These factors make accurate differentiation and risk stratification of women with gestational hypertension difficult. Antenatal predictors which help define risk in women with gestational hypertension more precisely may facilitate management pf these patients.

Therefore women with untreated gestational hypertension were compared with the normotensive control and mild chronic hypertensive groups, focussing on maternal

hemodynamics and uterine Doppler velocimetry. The rational, methods of enrolment, inclusion and exclusion criteria, echocardiographic and Doppler methods and analysis are as described in chapters 1 and 2. The study group comprised 10 women with untreated gestational hypertension and 10 with aproteinuric chronic hypertension compared with the control group normotensive pregnant women (n=27).

6.2 Results

6.2.1 Demographics

The women with gestational aproteinuric hypertension were similar in age and parity to the normotensive group (table 6.1) but with a significantly elevated body mass index compared to normotensives (p=0.003). In gestational hypertension women, the blood pressure at admission was elevated similar to chronic hypertensive participants. At echocardiography (performed within 6 hours of inclusion into the study) their blood pressure (systolic, diastolic and mean) was significantly lower than chronic hypertensive participants (p=0.008). Uterine artery resistance index measurements in gestational hypertensive women were similar to that of normotensive women but significantly lower than chronic hypertensive patients.

The later presentation of gestational hypertensive women is noted, the majority presenting after 34 weeks gestation. Two participants, who presented at gestational ages of 30 and 32 weeks had higher body mass index of 38 and 36 and were also of higher parity than the mean for the group. One of these women had an adverse feto-neonatal outcome. This participant had a body mass index of 38, parity of 6 and delivered at 35weeks with a fetal birth weight between 50^{th} to 90^{th} centiles. She required neonatal ventilatory support for 2 weeks.

Table 6.1 Demographic data of gestational hypertensive; normotensive and chronic hypertensive groups

	gestational (aproteinuric) hypertension n=10	normotensive n=27	p value: gestational hypertension versus normotensive	chronic hypertension n=10	p value: gestational versus chronic hypertension
age (years)	27 ± 5	24 ± 5	0.090	31 ± 5	0.088
Parity : para 0 : > para 0	n = 2 (20%) n = 8 (80%)	n=15 (30%) n=12 (70%)	0.120 (chi-square)	n = 0 n = 10	0.456 (chi-square)
body surface area (m^2)	1.78 ± 0.18	1.70 ± 0.14	0.211	1.96 ± 0.29	0.173
body mass index (kg/m^2)	33 ± 6	27 ± 4	0.003*	38 ± 11	0.545
height (cm)	155 ± 5	158 ± 5	0.090	160 ± 7	0.129
weight (kg)	80 ± 16	69 ± 12	0.030*	97 ± 30	0.131
gestation at evaluation (weeks)	37 ± 3	33 ± 1	0.002*	29 ± 8	0.050*
heart rate (beats/min)	84 ± 9	82 ± 8	0.493	79 ± 15	0.449
systolic BP (mmHg) at echocardiography	134 ± 19	102 ± 9	<0.001*	154 ± 22	0.053
diastolic BP (mmHg) at echocardiography	82 ± 10	56 ± 6	<0.001*	101 ± 6	0.139
mean BP (mmHg) at echocardiography	98 ± 16	82 ± 8	<0.001*	121 ± 8	0.069
serum urate values (mmol/l)	0.30 ± 0.08	0.27 ± 0.06	0.770	0.29 ± 0.07	0.833
platelet count ($x\ 10^9/L$)	245 ± 52	259 ± 90	0.850	263 ± 73	0.474
gestation at delivery (weeks)	37 ± 2	38 ± 2	0.130	35 ± 6	0.578
birth weight (kg)	3.02 ± 0.38	3.01 ± 0.60	1.000	2.77 ± 1.22	0.879
p-value: mean BP at admission versus echocardiography	0.008*	--------	------	0.024*	------
systolic blood pressure at admission (mmHg)	150± 15	---------	---------	161± 13	0.155
diastolic blood pressure at admission (mmHg)	101 ± 10	---------	---------	101 ± 6	0.904
mean blood pressure at admission (mmHg)	117 ± 12	----------	----------	111 ± 14	0.674

Data are presented as absolute mean ± one standard deviation

* Statistically significant, P values derived by Mann-Whitney U test.

6.2.2 Cardiac structure and function

There were no differences in left ventricle cavity dimensions between the groups (table 6.2). The left atrium and left ventricular mass index was significantly greater than that in normotensive patients but showed no differences from hypertensive women ($p = 0.09$).

Using 2 standard deviations above the mean LV mass index of normotensive ($>100g/m^2$) as cut off value to diagnose LV hypertrophy, half of the gestational hypertensive participants and 90% of chronic hypertensive women had left ventricular hypertrophy. These observations persisted when LV mass was corrected for LV mass/height. The correlation of LV mass index with LV diastolic filling abnormalities reflected by E/A filling ratio was modest at $r = -0.30$. Indices of LV contractility were significantly higher in gestational hypertensive women compared to normotensive patients.

Table 6.2 Cardiac structure and function- gestational hypertensives, normotensives and chronic hypertension groups.

	gestational (aproteinuric) hypertension n=10	normotensive n=27	p value: gestational hypertension versus normotensive	chronic hypertension n=10	p value: gestational versus chronic hypertension
LV-internal diameter-diastole (cm)	5.00 ± 0.29	4.83 ± 0.34	0.137	5.14 ± 0.68	0.496
LV internal diameter –systole (cm)	3.12 ± 0.30	3.23 ± 0.36	0.442	3.36± 0.48	0.325
left atrium (cm)	3.8 ± 0.4	3.3 ± 0.4	0.021*	3.8 ± 0.5	0.544
left atrial to aorta ratio	1.4 ± 0.2	1.4 ± 0.3	0.218	1.4 ± 0.2	0.130
LV-septal thickness (cm)	1.1 ± 0.2	1.0 ± 0.1	0.037*	1.3 ± 0.2	0.161
LV relative wall thickness ratio	0.25 ± 0.03	0.22 ± 0.04	0.174	0.30 ± 0.06	0.040*
LV mass (g)	177 ± 36	136 ± 26	0.003*	233 ± 71	0.037*
LV mass index (g/m^2)	99 ± 16	79 ± 11	0.003*	119 ± 32	0.070
% with LV-mass index ≥ $110 g/m^2$	20	0		70	
% with LV-mass index ≥$100 g/m^2$	50	0		80	
LV mass/height (g/m)	114 ± 22	86 ± 15	0.001*	146± 44	0.045*
LV-early to atrial diastolic filling ratio-(E/A)	1.53 ± 0.40	1.76 ± 0.37	0.208	1.35 ± 0.55	0.520
LV fractional shortening (%)	37 ± 5	33 ± 4	0.021*	35 ± 4	0.172
LV ejection fraction (%)	67 ± 6	62 ± 6	0.021*	62 ± 6	0.161
LV –velocity of circumferential fibre shortening (circum/sec)	1.34 ± 0.21	1.18 ± 0.18	0.081	1.23 ± 0.23	0.427
LV end systolic stress (dyn/cm^5)	77 ± 16	71± 17	0.338	90 ± 22	0.257

Data are presented as absolute mean ± one standard deviation; LV=left ventricle.
* Statistically significant, P values derived by Mann-Whitney U test.

6.2.3 Echocardiographic hemodynamics and uterine Doppler velocimetry

There were no differences in cardiac index between the groups and also no significant difference in systemic vascular resistance index. As mentioned, the lower systolic blood pressure in gestational hypertensives compared to chronic hypertensives just fell short of statistical significance ($p = 0.053$). The uterine artery resistance index was normal in both gestational hypertensive and normotensive women (0.46) but significantly elevated at 0.58 in chronic hypertensive women (Table 6.3).

Table 6.3 Maternal central hemodynamics and uterine Doppler velocimetry in gestational hypertensive, normotensive and chronic hypertensive groups.

	gestational (aproteinuric) hypertension n=10	normotensive n=27	p value: gestational hypertension versus normotensive	chronic hypertension n=10	p value: gestational versus chronic hypertension
heart rate (beats/min)	84 ± 9	82 ± 8	0.493	79 ± 15	0.449
stroke volume (ml)	79 ± 15	79 ± 12	0.891	97 ± 24	0.095
cardiac output (l/min)	6.69 ± 1.46	6.42 ± 0.90	0.745	7.49 ± 1.62	0.226
systolic blood pressure at echocardiography (mmHg)	134± 19	102 ± 9	<0.001*	154 ± 22	0.053
diastolic blood pressure at echocardiography (mmHg)	82 ± 10	56 ± 6	<0.001*	90 ± 13	0.139
mean blood pressure at echocardiography (mmHg)	100 ± 16	71 ± 7	<0.001*	111 ± 14	0.069
body surface area (m^2)	1.78 ± 0.18	1.70 ± 0.14	0.211	1.96± 0.29	0.173
stroke index (ml/m^2)	45 ± 6	46 ± 5	0.494	50 ± 13	0.343
cardiac index ($l/min/m^2$)	3.75 ± 0.62	3.78 ± 0.45	0.452	3.79 ± 0.53	0.650
systemic vascular resistance index (dyn.sec $/cm^5/m^2$)	2132 ± 523	1528 ± 236	0.002*	2472 ± 601	0.186
uterine artery resistance index	0.48 ± 0.07	0.46 ± 0.08	0.118	0.58 ± 0.11	0.034*
Uterine artery resistance index standardised to maternal body surface area ($/m^2$)	0.28 ± 0.04	0.31 ± 0.05	0.079	0.31 ± 0.10	0.691
umbilical artery pulsatility index	0.92± 0.17	1.10± 0.20	0.022*	1.30 ± 0.44	0.132
birth weight (kg)	3.02 ± 0.38	3.01 ± 0.61	1.000	2.77± 1.22	0.879
fetal birthweight $<10^{th}$ centile number (%)	0 (0%)	0 (0%)	----	1(10%)	---

Data are presented as absolute mean ± one standard deviation.
* Statistically significant, P values derived by Mann-Whitney U test.

6.3 Discussion

This study shows that women with gestational aproteinuric hypertension who presented after 34 weeks gestation have a good feto-neonatal outcome. Hemodynamic parameters did not help to further define a higher risk group. In fact the cardiac index and fetal outcome in these gestational hypertensive women was similar to normotensive participants. These observations are similar to a retrospective review by Xiong *et al,* (1999) who concluded that gestational hypertension did not significantly increase the risk of low birth weight. The above observations are also supported by findings in a larger multicentre, retrospective cohort study (Magee *et al,* 2003). These authors state that non-proteinuric chronic hypertension or gestational hypertension that presented before 34 weeks was associated with substantial adverse feto-neonatal outcome. This may explain the good outcome in our patients who presented late, at 37 weeks.

However it is apparent that gestational hypertension may include women with the pre-eclampsia syndrome who have not manifested proteinuria or developed the syndrome Saudan *et al,* (1998). This suggests that early gestational age at presentation itself recognizes a potentially higher risk group. Early detection of microalbuminuria or an elevated uterine artery resistance index may identify gestational hypertensive women at higher risk of disease progression.

A smaller sample size makes it difficult to adequately stratify gestational hypertensive women in this study by gestation at presentation. Analysis of an additional 6 women with gestational hypertension to the study (data not shown in results) who were prescribed a single dose of 1000mg methyl-dopa revealed similar conclusions as

above. Two women who presented before 34 weeks gestational age had a larger body mass index and higher parity. One of these delivered at 35 weeks without any evidence of fetal growth restriction but required neonatal ventilatory support and had a satisfactory outcome.

Weak correlations were noted between fetal birth weight and cardiac index ($r = 0.23$), systemic vascular resistance index ($r = 0.15$), mean blood pressure ($r = 0.24$) and uterine artery resistance index ($r = -0.21$). The above observations indicate that maternal hemodynamics and uterine artery resistance index did not help define a higher risk gestational hypertensive group presenting after 34 weeks gestation.

In our study the elevated blood pressure and systemic vascular resistance in gestational hypertensive women was associated with a significantly higher left ventricular mass index and suggests that the increased blood pressure in gestational hypertensive women is probably sustained. Bosio *et al,* (1999) described a hyperdynamic circulation of an elevated cardiac output and normal to near normal systemic vascular resistance index in gestational hypertensive women who had good feto-neonatal outcome. In our study cardiac index was unchanged and it was not associated with any depression in cardiac contractile function as reflected by ejection fraction and velocity of circumferential fibre shortening. This is in contrast to the study by Valensise *et al*, (2001) who reported a mildly depressed systolic function in these patients. The same group showed that left ventricular concentric geometry detected by echocardiography was independently associated with adverse feto-neonatal outcome (Novelli *et al*, (2003)). The important difference in the Novelli study is that gestational hypertension participants were diagnosed between 27 to 31

weeks. It is therefore not surprising that 54% of participants had echocardiographic left ventricular hypertrophy or concentric remodelling. This suggests that their hypertension was probably present from mid second trimester as it takes six weeks to show changes in LV mass. The high good negative predictive value of this (88%) supports our observations that absence of left ventricular hypertrophy in women with gestational hypertension is associated with a good feto-neonatal outcome. In our study the chronic hypertensives had larger left ventricular mass index ($p=0.070$) in keeping with high blood pressure. Haemodynamic parameters were similar in both groups.

In conclusion, this study shows that gestational hypertensive women who present close to term have a good perinatal outcome. Maternal hemodynamics and uterine artery Doppler velocimetry did not help to define a higher risk group among these women with gestational hypertension. The elevated blood pressure that was associated with a significant increase in left ventricular mass and a trend to LV hypertensive diastolic filling abnormalities suggest that these women with gestational hypertension presenting late in pregnancy have a similar clinical profile to mild chronic hypertension in pregnancy. This provides some supporting evidence that many women with gestational hypertension develop established hypertension in later life.

CHAPTER 7

CHRONIC HYPERTENSION AND SUPERIMPOSED PRE-ECLAMPSIA ON CHRONIC HYPERTENSION

7.1 Introduction, aims and methods

Pregnant women with chronic hypertension are at increased risk of developing placental abruption, fetal growth restriction, prematurity and superimposed pre-eclampsia (Haddad *et al,* 1999). This risk is particularly increased in pregnant women who have severe hypertension, in those with hypertensive target organ damage, in women who develop superimposed pre-eclampsia and also in women with prior renal disease (Livingston *et al*, 2003). A recent meta-analysis of studies of chronic hypertension in pregnancy by Ferrer *et al,* (2000) concluded that no study has as yet provided guidance on the benefits, consequences of therapies or monitoring strategies in this condition.

The diagnosis of superimposed pre-eclampsia on chronic hypertension tests the skills of the clinician. The Australasian society of the study of hypertension in pregnancy guidelines (2000) advise that in women with chronic hypertension, any sudden increases in proteinuria or hypertension should lead to increased surveillance for superimposed pre-eclampsia. This diagnosis is not secure without the development of other features that are associated with the pre-eclampsia syndrome. Therefore in the individual pregnant woman with chronic hypertension, a more precise risk assessment is necessary to assist the clinician towards correct decisions on management and delivery. This is especially important in the light of potential hazards of blood pressure lowering with antihypertensive medications. Recent studies emphasize that

the risk benefit of such therapies in chronic hypertensive pregnant women needs continued evaluation.

This study compares the haemodynamics in chronic hypertension and those with superimposed pre-eclampsia. The rationale for this study, methods of enrolment, inclusion and exclusion criteria, echocardiographic and uterine artery Doppler velocimetry methods and analyses are as described in chapters 1 and 2. Twenty women formed this group, 10 with chronic hypertension alone (no proteinuria) and 10 with superimposed pre-eclampsia (persistent proteinuria of $\geq$ 1+ on dipstix).

7.2 Results

7.2.1 Demographics (Table 7.1)

The patients in both groups had similar age, parity distribution, body habitus and gestational age at evaluation. A higher systolic ($p = 0,011$) and diastolic ($p = 0,024$) blood pressure at echocardiography was present in the superimposed pre-eclampsia group. In addition, the blood pressure at admission into the study was significantly higher than that measured at echocardiography in both chronic hypertensive groups. A lower fetal birth weight in the superimposed pre-eclampsia group was associated with a 4 week difference in gestation at delivery ($p = 0,052$). Also a significant lower platelet count was seen in the superimposed pre-eclampsia group ($p = 0,039$); the differences in serum urate level were not significant.

Table 7.1 Demographics of chronic hypertensive groups

	chronic hypertension n=10	Superimposed pre- eclampsia n = 10	p Value
age (years)	31 ± 5	30 ± 6	0.733
parity : number (%) : para 0 : > para 0	0 (0%) 10 (100%)	0 (0%) 10 (100%)	-----
body mass index (kg/m^2)	38 ± 11	35 ± 6	0.450
body surface area (m^2)	1.96 ± 0.29	1.86 ± 0.13	0.289
height (cm)	160 ± 7	157 ± 6	0.425
weight (kg)	97 ± 30	86 ± 13	0.496
systolic blood pressure at admission (mmHg)	161 ± 13	182 ± 19	0.011*
diastolic blood pressure at admission (mmHg)	101 ± 6	112 ± 14	0.024*
mean blood pressure at admission (mmHg)	121 ± 8	136 ± 15	0.015*
mean gestation at evaluation (weeks)	29 ± 8	29 ± 6	0.880
systolic blood pressure at echocardiography (mmHg)	154 ± 22	179 ± 23	0.018*
diastolic blood pressure at echocardiography (mmHg)	90 ± 13	104 ± 13	0.034*
mean blood pressure at echocardiography (mmHg)$^+$	113 ± 14	129 ± 16	0.025*
p-value: mean BP at admission versus echocardiography	0.024*	0.046*	------
heart rate at echocardiography (beats/min)	79 ± 15	79 ± 20	0.970
serum urate values (mmol/l)	0.29 ± 0.07	0.35 ± 0.09	0.270
platelet count (x 10^9/l)	263 ± 73	188 ± 82	0.039*
gestation at delivery (weeks)	35 ± 6	31 ± 5	0.052
fetal birth weight (kg)	2.8 ± 1.2	1.6 ± 0.9	0.021*
fetal birth weight < 10^{th} centile number (%)	1 (10%)	5 (50%)	-----

Data are presented as absolute mean ± one standard deviation

* Statistically significant; p values derived by Mann-Whitney U test.

7.2.2 Echocardiography - cardiac structure and function (Table 7.2)

There were no differences in ventricular and atrial dimensions between the groups. A larger septal wall thickness was noted in the superimposed pre-eclampsia group (p = 0,025) but the higher left ventricular (LV) mass index fell short of statistical significance. A significant proportion of women in both groups had echocardiographic LV hypertrophy (LV mass index $\geq 110 g/m^2$). Indices of LV contractility were similarly preserved in both groups.

Table 7.2 Echocardiographic cardiac structure and function

	chronic hypertension n=10	superimposed pre-eclampsia n=10	p Value
LV internal diameter in diastole (cm)	5.14 ± 0.68	5.04 ± 0.47	0.705
LV internal diameter in systole (cm)	3.36 ± 0.48	3.33 ± 0.46	0.880
left atrium (cm)	3.6 ± 0.5	3.8 ± 0.5	0.648
left atrial to aorta size ratio	1.4 ± 0.2	1.4 ± 0.2	0.733
LV septal thickness (cm)	1.3 ± 0.2	1.5 ± 0.3	0.025*
LV relative wall thickness ratio	0.30 ± 0.06	0.32 ± 0.09	0.621
LV mass (g)	233 ± 71	264 ± 63	0.364
LV mass index (g/m^2)	119 ± 32	141 ± 27	0.199
LV mass index ≥110g/m^2	n = 7	n = 9	-
LV early to atrial diastolic filling ratio	1.35 ± 0.55	1.28 ± 0.54	0.406
LV fractional shortening (%)	35 ± 4	34 ± 5	0.676
LV ejection fraction (%)	63 ± 6	63 ± 7	0.761
LV velocity of circumferential fibre shortening (circum/sec)	1.23 ± 0.23	1.24 ± 0.34	0.762
LV end systolic stress (dyn/cm^5)	90 ± 22	105 ± 28	0.199

Data are presented as absolute mean ± one standard deviation
* Statistically significant; p values derived by Mann-Whitney U test.

7.2.3 Maternal hemodynamics and uterine artery Doppler velocimetry

There were no differences in cardiac output or cardiac index between the groups (table 7.3). The higher systemic vascular resistance index in the superimposed pre-eclampsia group is thus largely a reflection of the higher blood pressure. There was no significant difference in measured uterine artery resistance index between the groups.

The correlation of systemic vascular resistance index with uterine artery resistance index for the combined groups was weak(r = 0.28). Systemic vascular resistance index (r = 0.45) correlated better with fetal weight but the best correlation was with uterine artery resistance index (r = 0,64).

Table 7.3 Hemodynamics Parameters

	Chronic hypertension n=10	Superimposed pre-eclampsia n=10	p Value
mean blood pressure (mmHg)	113 ± 14	129 ± 16	0.025*
body surface area (m^2)	1.96 ± 0.29	1.86 ± 0.13	0.289
heart rate (beats/min)	79 ± 15	79 ± 20	0.970
cardiac output (l/min)	7.49 ± 1.62	7.11 ± 1.58	0.520
stroke index (ml/m^2)	50 ± 13	50 ± 9	0.734
cardiac index ($l/min/m^2$)	3.79 ± 0.53	3.82 ± 0.79	0.910
systemic vascular resistance index ($dyn.sec/cm^5$)	2472 ± 601	2837 ± 812	0.450
uterine artery resistance index	0.58 ± 0.11	0.67 ±0.12	0.121
umbilical artery pulsatility index	1.30 ± 0.44	1.32 ± 0.37	0.874

Data are presented as absolute mean ± one standard deviation
* Statistically significant; p values derived by Mann-Whitney U test.

7.3 Stratification by presence of left ventricular hypertrophy

The data in both hypertensive groups (n = 20) were divided into those with and those without left ventricular hypertrophy (Table 7.4). The presence of left ventricular hypertrophy (LV mass index ≥ $110g/m^2$) was associated with a higher mean, systolic and diastolic blood pressure but with a non-significant higher systemic vascular resistance index, lower fetal birth weight and earlier gestation at delivery. Mean

blood pressure showed a good correlation with LV mass index (r = 0.53). Regression analyses identified gestation at presentation, severity of hypertension and presence of proteinuria as best associated with adverse feto-neonatal outcome.

Table 7.4 Comparative evaluation of chronic hypertension with left ventricular hypertrophy

	LV mass index ≥ 110g/m^2 n=15	**LV mass index <110g/m^2 n =5**	**p value**
systolic blood pressure at echocardiography (mmHg)	175 ± 23	143 ± 14	0.008*
diastolic blood pressure at echocardiography (mmHg)	101 ± 13	85 ± 13	0.073
mean blood pressure at echocardiography (mmHg)	126 ± 15	104 ± 13	0.013*
systemic vascular resistance index (dyn.sec/cm^5/m^2)	2811 ± 726	2184 ± 500	0.127
cardiac index (l/min/m^2)	3.77 ± 0.69	3.91 ± 0.61	0.541
gestation at delivery (weeks)	32 ± 6	35 ± 8	0.234
fetal birth weight (kg)	1.96 ± 1.2	2.8 ± 1.1	0.126
LV early to atrial diastolic filling ratio	1.28 ± 0.59	1.42 ± 0.30	0.407
uterine artery resistance index	0.63 ± 0.13	0.63 ± 0.11	0.920
umbilical artery pulsatility index	1.26 ± 0.40	1.52 ± 0.34	0.313

Data are presented as absolute mean ± one standard deviation
* Statistically significant; p values derived by Mann-Whitney U test.

7.4 Discussion

This study demonstrates a poorer feto-neonatal outcome in chronic hypertensive women who develop superimposed pre-eclampsia. These differences were not associated with any significant differences in maternal cardiovascular haemodynamics or uterine artery resistance index. Septal wall thickness was higher in the superimposed pre-eclampsia group (p=0.025).

Pregnant women with chronic hypertension have been described as having elevated maternal and fetal risks and greater fetal growth restriction (Haelterman *et al,* (1997) and Ferrer *et* al (2000). McCowan *et al,* (1996) however, noted that the risk was particularly high in chronic hypertensive women who had severe hypertension before 20 weeks gestation. Our study shows that at risk chronic hypertensive pregnancies were better associated with an early gestation at presentation (second trimester), severe hypertension of blood pressure ≥ 160/110mmHg and presence of proteinuria. Haddad *et al,* (1999) described increased complications only in women classified as higher risk (pre-existing cardiovascular and renal disease and target organ involvement) chronic hypertensives, in keeping with our findings of LV hypertrophy and proteinuria in the high risk group.

In conclusion, our study evaluating chronic hypertensive women show that early presentation (before 28 weeks gestation), persistent severe hypertension (BP ≥ 160/110mmHg) at initial presentation and proteinuria of 1+ or more by reagent strip testing identified at risk pregnancies.

CHAPTER 8

DISCUSSION

8.1 Introduction

The principal findings of this study are that cardiac index and to a lesser extent systemic vascular resistance measured in the latter part of the second and/or third trimesters in hypertensive women showed only modest to weak associations with adverse feto-neonatal outcome. There was a marginally stronger association between systemic vascular resistance index and adverse feto-neonatal outcome which largely reflected the severity of hypertension. In contrast, uterine artery resistance index measured by Doppler velocimetry showed a satisfactory association with adverse feto-neonatal outcome. In a multiple regression analysis as detailed in chapter 4, uterine artery resistance index was the best variable that identified an adverse feto-neonatal outcome.

The poor correlation between maternal cardiac index and adverse feto-neonatal outcome and/or fetal growth restriction (reflected by fetal birth weight below the 10^{th} centile), is not surprising. In a recent literature review Young *et al,* (2001) evaluated the clinical usefulness of both invasive and non-invasively measured maternal hemodynamics in pre-eclampsia. The authors concluded that the clinical impact of measuring maternal hemodynamics has yet to be demonstrated.

Similar to most studies on maternal hemodynamics, our study demonstrates a wide variation in cardiac index and systemic vascular resistance index values both in normotensive and hypertensive pregnancy groups that occurred largely from patient

factors. This limited the ability of variables of cardiac index or systemic vascular resistance index to be better associated with adverse feto-neonatal outcome.

Using fetal birthweight <1.8kg as an adverse outcome measure yielded sensitivity and specificity values of 39% and 73% for cardiac index < 3.5 l/min/m^2; 53% and 80% for systemic vascular resistance index value > 2500 dyn.sec/cm^5/m^2 and 53% and 87% for uterine artery resistance index ≥ 0.65 respectively. These data illustrate the limitations in predictive value of maternal hemodynamics in defining at risk hypertensive pregnancies as an improved sensitivity is achieved at a cost of reduced specificity and visa versa.

8.2 Prognostic value of haemodynamic studies

8.2.1 Maternal central haemodynamics, uterine Doppler velocimetry and feto-neonatal outcome

The pre-eclampsia syndrome is associated with a significant increase in maternal and perinatal morbidity and mortality. It has been recognized that the hypertension is just one manifestation of an underlying multifactorial and multisystem disorder that is often initiated early in pregnancy (Bolte *et al,* 2001). Presently used criteria to predict unfavourable outcome are inadequate in that they diagnose disease at a late stage (Zhang *et al,* 2001). An earlier detection of women with at risk hypertensive pregnancies is important as they may benefit from therapies aimed at beneficial prolongation of the pregnancy (Withagen *et al,* 2001). In an echocardiographic study of severe pre-eclamptic women, Yang *et al,* (1996) found that an elevated systemic vascular resistance index was associated with a higher prevalence of small for

gestational age babies. However, in a recent review Zhang *et al,* (2001) showed that the blood pressure alone has poor discriminatory value and that improved antenatal predictive tests are required to better define at risk pregnancies.

Defective implantation and placentation in hypertensive pregnancies is thought to result in reduced placental perfusion. This results in a failure of the normal maternal cardiovascular adaptation with subsequent maternal endothelial and organ dysfunction (Roberts, 2000).

Measurement of uterine artery Doppler velocimetry to predict adverse foetal outcome is limited by its low specificity and low positive predictive value (Coleman *et al,* 2000, Soregaroli *et al,* 2001). A refinement in uterine artery Doppler velocimetry is the notch index in the uterine artery waveform, which has improved predictive value but with a non-consistent benefit (Aquilina *et al* (2000), Aardema *et al* (2000). In a low risk study group defined as occurrence of pre-eclampsia and pre-eclampsia requiring delivery before 37 weeks. Aquilina *et al* (2001) found that adding the notching index and serum inhibin levels to a predictive model improved the predictive potential.

In another study Aardema *et al*, (2000) evaluated uterine artery velocimetry to predict recurrence of hypertensive disorder. The authors noted that although uterine artery velocimetry was unsatisfactory at predicting risk of recurrence of gestational hypertension and pre-eclampsia, it did show a satisfactory association with fetal growth restriction and adverse outcome. It appears that the varying risks of pregnant women in the above studies did not allow for confident evaluation of the potential

benefit of uterine artery Doppler velocimetry in hypertensive and/or at risk pregnancies.

A further confounding factor is that initial abnormal uterine artery velocimetry indices normalise later in pregnancy. Soregaroli *et al*, (2001), for instance, showed that approximately half of the study participants with abnormal uterine artery velocimetry at 24 weeks had normalisation of indices at 34 weeks gestation and this corresponded to a significant better feto-neonatal outcome than the group with persistently abnormal uterine artery waveforms.

In another study Valensise *et al*, (2001) described abnormalities in maternal diastolic function at 24 weeks gestation in a group of normotensive women who had abnormal uterine artery velocimetry with the waveform abnormality of bilateral notching. Fifty-eight (58) % of this cohort had normal feto-neonatal outcome. In the remaining pathological outcome group, 33% developed gestational hypertension and 8% had small for gestational age babies. As the abnormalities in maternal diastolic function were more prevalent in the pathological outcome group, the authors hypothesize that the abnormal placentation process reflected by abnormal uterine artery velocimetry results in maladaptation of the entire maternal cardiovascular system.

These studies provide plausible reasons to explain the modest to poor correlation between maternal central hemodynamics and uterine artery resistance index observed in our study. They also suggest that uterine artery velocimetry perhaps performed serially, remains a good diagnostic option.

Our study shows that the uterine artery resistance index measured at late second or early third trimesters, probably encompasses all the known risk variables such as severity and chronicity of hypertension, presence and severity of proteinuria, and possibly also bad obstetric history, multiparity, higher age, and maternal size. It proved to be the best single variable to correlate with adverse feto-neonatal outcome. These findings are supported by recent observations made by Frusca *et al*, (2003) in their retrospective study evaluating uterine artery velocimetry in women with gestational hypertension and pre-eclampsia. In a multivariate model that looked at presence of proteinuria, severity of hypertension and uterine artery velocimetry, the authors found that abnormal uterine velocimetry was the variable that was more frequently associated with adverse pregnancy outcome.

8.2.2. Limitations of maternal haemodynamics studies

Some of the difficulties of evaluating maternal central hemodynamics in hypertensive and/or at risk pregnancies are illustrated in the frequently cited studies of Easterling *et al,* (1999) and Bosio *et al,* (1999). The Easterling study was actually a retrospective review that used an elevated cardiac output of >7.4 l/min at 24 weeks gestation in normotensive and diabetic women to select women who may benefit from antihypertensive medication of atenolol. The implied message in the selection criteria is that an elevated cardiac output in the pre-clinical stage of hypertensive disorder of pregnancy is associated with the development of hypertension and associated risks and that the elevated cardiac output has a pathogenic role. The treatment component of the study aimed to support the hypothesis that appropriate treatment of the elevated cardiac output with anti-hypertensive medications will result in an improved feto-

neonatal outcome. One of several conclusions made by the authors was that a failure to adjust antihypertensive medication in response to an excessive drop in cardiac output or a corresponding increase in systemic vascular resistance was associated with an increased risk of fetal growth restriction. Apart from being a retrospective analysis, the arbitrary cut-off value for cardiac output (without stratifying for maternal size) and the inclusion of normotensive patients with a history of fetal growth restriction are significant limitations in this study.

The more conclusive work of Bosio *et al,* (1999) described an elevated maternal cardiac output in the pre-clinical period of normotensive women who developed hypertension later in pregnancy. Their data supports the hypothesis of a hyperdynamic disease model in women with pre-eclampsia and gestational aproteinuric hypertension. However, again this study did not correlate cardiac output to maternal body size (normalised BSA). Earlier studies have shown a poor correlation of maternal cardiac output with maternal body size, but in our study of normotensive pregnant there is women show a significant positive correlation between maternal cardiac output and maternal body size. In addition our study together with that of Bosio *et al*, (1999) show a very satifactory feto-neonatal outcome in women who present with gestational hypertension late in pregnancy. These patients have normal cardiac output with mildly elevated systemic vascular resistance late in pregnancy, supporting the concept that the elevated cardiac output in the pre-clinical phase of the disease is followed by a reduction in cardiac output in the clinical phase of disease (pre-eclampsia). This highlights the limitation of a single measure of cardiac output to risk stratify pre-eclamptic women. It can probably be stated that if increased cardiac index is indeed a feature of the initial stages of pre-eclampsia, then the results

of our study suggest that this does not persist into the clinical stage of the disease when cardiac index may be within the normal range but systemic vascular resistance index is high.

Our study evaluated women in the clinical phase of pre-eclampsia with the aim of providing more precise risk stratification. We show a trend to a lower cardiac output in a smaller sample of preeclamptic women compared to normotensives ($p = 0.116$) that corresponded to significant differences in feto-neonatal outcome. The lower cardiac output in our preeclamptic group compared to chronic hypertension with superimposed pre-eclampsia was not associated with a more adverse feto-neonatal outcome. Standardizing maternal cardiac output for maternal body size (body surface area) in our study revealed no differences in cardiac index among the hypertensive groups. These data suggest that, if indeed a reduced cardiac output is a marker of adverse feto-neonatal outcome, then there must be compensatory mechanisms, probably at uteroplacental level, to maintain satifactory fetal health. Our study thus provides supporting evidence for this hypothesis since there was poor correlation of maternal central hemodynamics compared to uterine artery velocimetry with adverse feto-neonatal outcome in hypertensive pregnancies.

The modest to poor correlation of maternal haemodynamic parameters with uterine artery resistance index, and the fact that the echocardiographic Doppler technique is labour and skills intensive – shows that risk stratifying hypertensive pregnancies by Doppler measurement of uterine artery resistance index is a more rewarding approach.

Yang *et al,* (1996), has shown that women with systemic vascular resistance index in the upper tertile had a higher incidence of small for gestational age babies. Similar to most studies of maternal hemodynamics in hypertensive pregnancies, the authors reported the limitations that arise as a result of a large variability in cardiac index. They observed that the pre-eclamptic sub-group had an elevated uterine artery resistance without a corresponding reduction in cardiac output or significant elevation of systemic vascular resistance index. This suggests that the relationship between regional uterine hemodynamics and maternal central hemodynamics is not linear in hypertensive pregnancies and it is likely that uteroplacental vasospasm occurs before systemic vasospasm. These authors hypothesized that an elevated cardiac output in these pre-eclamptic women reflected a hyperdynamic circulation that may be compensatory to maintain adequate perfusion in a high resistance utero-placental circulation.

Two studies using bioimpedance have evaluated the responses to volume expansion in pre-eclampsia. Siekmann *et al,* (1986) found that hypervolemic hemodilution with dextran in pre-eclampsia correlated with a rise in fetal blood flow velocity and flow volume and proposed that elevation in uteroplacental perfusion occurred as a result of an increase in maternal cardiac output. Subsequently Belfort *et al,* (1994) evaluated maternal hemodynamics by thoracic electrical bioimpedance and simultaneous uterine artery Doppler in five preeclamptics who received volume expansion followed by verapamil infusion. The authors noted widely varying changes in cardiac index but either unchanged or improved measurement in uterine artery velocimetry indices and the authors concluded that volume expansion could have limited benefits in such patients.

8.2.3 Clinical limitations: effects of treatment and maternal body habitus

Other factors that limit a precise evaluation of hemodynamics in hypertensive pregnancies include severity of disease at presentation, maternal body habitus and administration of sedative anti-hypertensive medication prior to measurements being made. Our study, similar to most others, confirms that hypertensive pregnant women are of larger stature than normotensive controls. In a recent review Broughton-Pipkin and Roberts (2000) suggest that obesity as a risk factor may in fact represent the metabolic syndrome and possibly an underlying genetic predisposition. The larger maternal stature and/or obesity in our study were reflected by a bigger weight, body surface area and body mass index of study participants with a trend to a smaller height than normotensive controls. Interestingly, this lower height in preeclamptics was statistically significant when compared to normotensive women.

Normotensive pregnant women in our study showed satisfactory positive correlations of maternal body surface area with maternal cardiac output measured in early and mid third trimester (r=0.72) and fetal birth weight (r= 0.60). The variations in cardiac output in normotensive pregnant women can thus be explained to a significant extent by differences in maternal size. There was a lower cardiac output in severe pre-eclamptic women compared to other hypertensive groups, but these differences were not significant when indexed for body surface area. Should maternal hemodynamic variables be standardized by correcting for body surface area? In a recent study there was a poor correlation between cardiac output and body surface area Oppen *et al,* (1995). Early invasive studies in hypertensive disorders of pregnancy reported standardized hemodynamic measurements of cardiac index rather than cardiac output.

We also describe an elevated cardiac output in gestational hypertensive participants compared to normotensives pregnant women, but these differences were not evident when cardiac output was standardized for body surface area. These findings imply that the elevated cardiac output reported early in pregnancy as a marker for subsequent development of hypertensive disease (Easterling *et al* (1999) and Bosio *et al* (1999) may in fact be recognising the risk related to obesity. Despite shortcomings when applied to pregnant women, it still remains necessary and logical to standardize maternal hemodynamic parameters for differences in body surface area or height; otherwise the effects of obesity would be obscured (de Simone *et al,* (1997).

Our study is limited by baseline differences in maternal body size and clinical severity of the disease as well as the treatment effect medication prior to measurement on hemodynamic parameters. Early invasive hemodynamic studies (Cotton *et al,* (1988)) showed that most pre-eclamptic participants had a hyperdynamic circulation with an elevated cardiac index. However, in addition to the inclusion of chronic hypertensives the pre-eclamptic women in Cotton's study received magnesium infusion prior to baseline measurements, introducing significant heterogenicity in the study groups.

The other large invasive hemodynamic study of Mabie *et al,* (1989) also demonstrated a hyperdynamic circulation with an elevated cardiac index in majority of their pre-eclamptic participants similar to the Cotton study. These findings were also complicated by effects of treatment, since approximately a third of the participants had received hydrallazine and almost half were in early labour, factors that likely

affected hemodynamic measurements. In both studies, intravenous fluid was also administered. This differed from the invasive study of Visser *et al,* (1991) in which intravenous fluid was not administered. Visser *et al,* (1991) pointed out that the marked disparity in haemodynamic studies in pre-eclamptic women, erroneously attributed to a variable hemodynamic expression of the disease, may in fact be related to administration of anti-hypertensive medication and/or intravenous fluids.

Such effects of treatment on maternal hemodynamics were reported in a study by Hung *et al,* (2000) who showed that preeclamptic women given methyl-dopa for five days had a significant reduction in retinal artery vascular resistance. In a small study assessing treatment effects in preeclamptic women, Scardo *et al,* (1999) reported a significant increase in cardiac index measured by thoracic electric bioimpedence in the group given non-dihydropyradine calcium antagonist, nifedipine, but no change in the group that was administered combined alpha-beta adrenergic blocking agent, labetalol. These differences in cardiac index occurred despite similar reductions in blood pressure, and, in part, were due to differences in heart rate; (an increase with nifedipine and a decrease with labetalol.

The contribution of heart rate to cardiac output was reported by Bolte *et al,* (1998) who attributed the increase in cardiac index to an increased heart rate in hypertensive pregnant women given dihydrallazine compared to group given the selective serotonin receptor blocker, ketanserin. Similarly, in their echocardiographic hemodynamic study of predominantly obese hypertensive pregnant women, Easterling *et al* (1990) attributed an elevated cardiac output to an increased heart rate. In another study of hemodynamics measured by thoracic electric bioimpedence in severe preeclamptics,

Scardo *et al,* (1996) also observed an increased heart rate but without any change in cardiac output. The authors therefore stated that the increased heart rate in their preeclamptics cohort prevented the expected fall in cardiac output.

Our study clearly demonstrates a significant lower heart rate in untreated preeclamptics with severe proteinuria compared to untreated gestational aproteinuric hypertensives (60 ± 11 versus 84 ± 9; $p=0.001$). Untreated preeclamptics with mild to moderate proteinuria had an intermediate heart rate of 72 ± 8. This lower heart rate was associated with a significantly higher stroke index resulting in little change in cardiac index. This is an important observation as pre-eclampsia has been described as a state of relative hypovolemia or failure of an adequate expansion of plasma volume and with some resultant hemoconcentration. However, the compensatory increase in stroke volume and preserved cardiac index and left ventricular systolic function indicate that there is probably an adequate preload reserve to allow for a compensatory increase in stroke volume, thereby maintaining maternal cardiac output.

This reduced heart rate in untreated pre-eclamptic women in our study supports early observations made by Kuzniar *et al,* (1982) in a M-mode echocardiographic study of pre-eclamptic women and in the important invasive hemodynamic study of Visser *et al,* (1991). At variance to our study, however Kuzniar *et al,* (1982) also showed a reduced stroke volume that was measured by the less accurate and unvalidated technique of M-mode echocardiography.

Differences of heart rate in pre-eclamptic women observed between studies can also be attributable to significant disease heterogenecity and maternal body size. For

instance, the Easterling study (1990) included women who were hypertensive prior to 20 weeks gestation and also included a milder category of hypertensive pregnant women defined by an increase in diastolic blood pressure of 15mmHg above baseline. It is unlikely variations in levels of aerobic conditioning as described in the non-pregnant setting could account for differences in heart rate. Wolfe *et al,* (1999) recently reported that aerobic conditioning had minimal effects on cardiovascular parameters in normotensive pregnant women. These effects are probably obscured by more powerful hemodynamics effects of pregnancy in the resting state.

Haemodynamic changes secondary to pharmacologic therapy may be an important determinant of cardiac index. In the setting of bradycardia, cardiac index is the normal pregnant state usually maintained by a compensatory increase in stroke index. In severe pre-eclampsia a significantly contracted plasma volume may attenuate this compensatory increase in stroke volume with a resultant fall in the cardiac index. It is worth nothing that treatment with B-adrenergic blocking agents may significantly lower heart rate to an extent whereby the compensatory increase in stroke volume may be inadequate to maintain a satisfactory cardiac output. This scenario explains the reduced cardiac output and associated fetal growth restriction in hypertensive women prescribed atenolol in the study by Easterling *et al,* (1999). This observation was further supported by the recent meta-analysis of Easterling *et al,* (2001) in which atenolol associated with a reduced incidence of pre-eclampsia but with fetal growth restriction that was attributed to inappropriate reduction in cardiac output with the drug. Similar observations were made by von Dadelszen *et al,* (2000) in a meta-analysis of randomised controlled trials evaluating pharmacological lowering of blood

pressure during pregnancy and feto-neonatal outcome. They concluded that treatment induced falls in maternal blood pressure could adversely affect fetal growth.

8.3 Blood pressure, maternal hemodynamics and feto-neonatal outcome

The finding that maternal central hemodynamics in this study showed only a modest to poor association with adverse feto-neonatal outcome indicating that these changes are secondary to the main pathology in the placenta. As there were no differences in cardiac index between the hypertensive and normotensives groups, the more modest elevation between elevated systemic vascular resistance index and adverse feto-neonatal outcome was largely a reflection of the severity of the measured blood pressure. While severe hypertension at echocardiography clearly recognized at risk hypertensive pregnancies; this higher risk cohort was often associated with the presence of proteinuria. Blood pressure alone had poor discriminatory value demanding better antenatal predictive tests to define at risk pregnancies Zhang *et al,* (2001).

An interesting observation in our study was that blood pressure measured at echocardiography performed soon after admission into the study was significantly lower than that measured at entry into the study. This placebo effect probably reflects the more "pleasant" circumstances of the ultrasound laboratory compared to that of the admission obstetric unit. Also the blood pressures were taken in the supine as opposed to the sitting position. Whatever the precise reason, it does demonstrate the variability in blood pressure measurements, and the importance of repeated readings.

It appears that participants who have an elevated but labile blood pressure that settles with time and/or bed rest probably have a milder disease process.

Any fall in blood pressure with more frequent blood pressure recordings may restage hypertensive pregnant women into lower risk categories and potentially improve risk stratification. This also dictates a more precise definition of procedures of measurement of blood pressure. In particular, methods that call for more frequent automated blood pressure recordings and or ambulatory blood pressure monitoring seem suited to provide a more accurate estimate of the hypertensive burden. Frequent measurements are more likely to remove the labile component in blood pressure measurements and thereby allow for a more accurate classification. For example, performing more frequent recordings at clinic, for example of 5-10 recordings over a 30 minute period and/or using ambulatory blood pressure measurements performed over periods varying from 6-24 hours in borderline and mild hypertension may identify the white coat hypertensive effect. This may help the clinician to avoid prescription of potentially harmful anti-hypertensive therapy to low risk pregnant women (Dadelszen *et al,* 2000).

Twenty-four hour ambulatory blood pressure study has significant prognostic value. There is a significant inverse relationship between mean daytime diastolic blood pressure and fetal birth weight; no association exists between day clinic assessment of blood pressure and fetal birth weight Waugh *et al,* (2000). Using ambulatory readings Hermida *et al*, (2002) described an improved stratification of women with gestational hypertension. Using hyperbaric index to describe the area of blood pressure excess above the upper limit of a time-specified tolerance interval they described

hypertensive categories that included detected and undetected gestational hypertension and white coat hypertension. A similar incidence of preterm delivery and fetal growth restriction was observed for both gestational hypertension categories compared to normotensive and white coat hypertensive groups.

Further support for use of ambulatory blood pressure comes from Penny *et al,* (1998) who found that daytime systolic and diastolic blood pressures predicted progression to severe pre-eclampsia (severe hypertension and/or proteinuria) better than obstetric clinic blood pressure measurements. In another recent study, Hermida *et al,* (2001) showed that 48 hour ambulatory blood pressure monitoring in normotensive and hypertensive pregnancies demonstrated the expected variability in blood pressure and defined proper reference limits that could be used in the early diagnosis of hypertensive pregnancies. However, Brown *et al,* (2001) recently reported that although 24 hour ambulatory blood pressure monitoring in mid-trimester identifies some women who may develop pre-eclampsia, the sensitivity is actually no better than other predictive tests even when women at higher risk are chosen.

The observations in our study, together with reported experience of ambulatory blood pressure measurement in hypertensive pregnancies, indicate that frequent blood pressure measurements performed in an appropriate setting provide a more accurate measure of the hypertensive burden with improved predictive potential.

8.4 Proteinuria, maternal hemodynamics and feto-neonatal outcome

Our study confirms the value of detecting the presence and severity of proteinuria by the reagent strip test to risk stratify hypertensive pregnancies. Stratifying hypertensive pregnant women by the presence of proteinuria clearly identified a higher risk group hypertensive pregnancies compared to hypertensive pregnancies without proteinuria. This was independent of the severity of blood pressure, systemic vascular resistance index and left ventricular hypertrophy, but was associated with an elevated uterine artery resistance index. As indicated in chapter 4 and section 8.1, multiple regression analysis for the entire hypertensive cohort showed uterine artery resistance index as the single variable that was best associated with adverse feto-neonatal outcome. Our data also concur with that of Scardo *et al*, (1996) who found that preeclamptic participants initially risk stratified by proteinuria did not show any differences in cardiac index.

Severe proteinuria was associated with a significantly higher mean uterine artery resistance index (0.67) compared to mild proteinuric pre-eclamptic women (0.56) and gestational aproteinuric hypertensive women (0.48). Similar findings have been reported in other studies (Soregaroli *et al,* (2001), Coleman *et al,* (2000) and McCowan *et al,* (2001)). Barton *et al,* (2001) also reported that the development of proteinuria in gestational hypertensive women was associated with earlier gestational age at delivery, lower fetal birth weight and higher incidence of small for gestational age newborns. He reported that 46% of women with mild gestational (aproteinuric) hypertension remote from term ultimately developed pre-eclampsia. These findings lend support to the concept that the elevated uterine artery resistance index parallels

the inadequate physiological changes in the spiral arteries that occur in women with intrauterine growth restriction and or pre-eclampsia.

Unlike hypertension outside pregnancy, our study showed a poor correlation between proteinuria and left ventricular hypertrophy. This again suggests that precise measures of proteinuria such as 24 hour urine protein excretion and/or blood pressure measurements (24 hour ambulatory blood pressure) are necessary to explore this association and to define more precise risk and stratification. For example, microalbuminuria (50-300mg/24 hours) in hypertensive pregnant women may identify mild disease at an earlier stage and thus allow for selection of hypertensive women who may benefit from closer monitoring. This is an area that provides scope for future research.

8.5 Maternal hemodynamics, left ventricular mass and systolic function

Left ventricular hypertrophy is now accepted as an important independent cardiovascular risk factor in hypertensives outside pregnancy, and is the result ov both hemodynamic and non-hemodynamic factors (neuro-humoral).

Our study however shows a modest to poor association of left ventricular mass index with maternal central hemodynamic in hypertensive pregnancies. Furthermore, women with pre-eclampsia were of smaller stature and had a significantly higher blood pressure than gestational aproteinuric hypertensive participants. Despite these differences in blood pressure at echocardiography, the left ventricular mass index and LV diastolic filling ratios were similar for both these groups. This suggests that the

higher blood pressure in pre-eclamptic women at presentation was probably of a shorter duration and did not allow for a corresponding increase in left ventricular mass or changes in left ventricular diastolic filling parameters.
This poor correlation of maternal hemodynamics to the severity of left ventricular hypertrophy is probably affected by a shorter duration of hypertension in the setting of pregnancy.

Similar to systemic vascular resistance index, uterine artery resistance index also showed a poor correlation with left ventricular mass index. The above is not unexpected as vasoconstriction is not the basic pathology in the uteroplacental circulation in these hypertensive pregnancies. An alternate explanation for the above may be the inherent limitations of less frequent clinic blood pressure measurements that probably provide a less accurate measure of the hypertensive burden. In addition, non-haemodynamic factors such as activation of sympathetic nervous system, alterations in angiotesin II vascular sensitivity (Fischer *et al,* 1999) and other humoral factors may contribute to the development of left ventricular hypertrophy with resultant poor correlation of maternal central hemodynamics and degree of left ventricular hypertrophy, as is described in hypertension outside pregnancy.

Although women with gestational aproteinuric hypertension in our study were identified as a low risk group with good outcome, their elevated blood pressure is probably persistent as echocardiographic evaluation of cardiac structure showed a significant increase in LV mass index, relative wall thickness ratio and changes in LV diastolic filling ratio compared to normotensive pregnant women, findings similar to

the cardiac structural changes recently reported by Valensise *et al,* (2001). The time frames in gestational aproteinuric hypertension (in pre-eclampsia) probably do not allow for development of significant left ventricular hypertrophy to impact on risk.

This explains why women with chronic hypertension in pregnancy had a significantly greater left ventricular mass index compared to women with gestational hypertension and pre-eclampsia in our study. Chronic hypertension is known to increase fetal and maternal risk significantly. Our data do show a (albeit non-significant) lower fetal birth weight, earlier gestation at delivery and a lower cardiac index in this group.

The echocardiographic structural changes we have described are similar to that reported by Vasquez Blanco *et al,* (2000) and Valensise *et al,* (2001) where most hypertensive women had a geometric pattern of eccentric left ventricular hypertrophy. In addition, all hypertensive groups had a significantly elevated left ventricular mass index compared to normotensives participants and this was not associated with any impairment of cardiac contractile function. Our data also show a significantly higher ejection fraction in chronic hypertensives compared to normotensives but no difference when less load dependent index of velocity of circumferential fibre shortening is compared suggesting little change in intrinsic myocardial contractility.

Our study is limited by the absence of parameters of systolic and diastolic function that are truly load and pressure independent. Nor did we correlate diastolic filling abnormalities with brain natriuretic peptide. Recent studies using tissue Doppler of the septal and lateral walls of the left ventricle reveal early changes in diastolic function while systolic function is preserved, findings that deserve study in

hypertensive pregnancy. Also the observations of preserved left ventricular systolic function in our study contrast with other studies by Valensise *et al,* (2001) and Borghi *et al,* (2000) who reported a reversible depression in systolic function reflected by left ventricular fractional shortening and ejection fraction, in such hypertensive pregnant groups. We have previously shown cardiac abnormalities on echocardiography in 16 consecutive women presenting with hypertensive crises in pregnancy complicated by pulmonary oedema (Desai *et al* 1996). The echocardiographic abnormalities included impaired systolic function in 4 women (25%) and abnormalities in left ventricular diastolic filling in the remainder.

A likely explanation for these apparent differences in left ventricular systolic function lies in the effect of loading conditions (Lang *et al*, (1991)) on left ventricular mechanics in pre-eclampsia. The authors concluded that intrinsic myocardial contractility is preserved when load is eliminated as a confounding variable. It is possible clinically small and subtle differences in left ventricular function may be detected by tissue Doppler studies.

Normotensive pregnancy is associated with a significant drop in blood pressure and systemic vascular resistance index, a reflection of the reduced cardiovascular afterload, partly in response to the increased cardiac output. Physiologically, an increase in preload and/or reduced afterload is often accompanied by an increase in left ventricular systolic function.

In our study systolic function was preserved through pregnancy. This contrasts with studies by Mone *et al,* (1996) who showed a transient fall in fractional shortening

during the third trimester. Similarly Schannwell *et al,* (2000) showed a reduction in fractional shortening and velocity of circumferential fibre shortening that had a nadir at the first postpartum visit. Differences in loading conditions probably explain these apparent differences in ejection fraction and velocity of circumferential fibre shortening.

Similar considerations pertain to pre-eclampsia. In an earlier study by Lang *et al,* (1991) evaluated left ventricular mechanics in preeclamptics during early labour and 4 weeks after delivery, and demonstrated that intrinsic left ventricular contractility was preserved and similar to control normotensive participants. The authors concluded that when load is eliminated as a confounding variable, the decrement in overall left ventricular performance in pre-eclampsia reflects a mechanically appropriate response to increased afterload rather than an abnormality in the ventricular contractile state. Again, these issues will also be better resolved when future studies focus on measuring load independent measures of left ventricular contractility and tissue Doppler studies.

8.6 Conclusion: maternal hemodynamics in hypertensive disorders of pregnancy

The principal findings in this study are that cardiac index and systemic vascular resistance measured in the latter part of the second and/or third trimesters in hypertensive women show only a modest to poor association with adverse feto-neonatal outcome.

In contrast, uterine artery resistance index measured by Doppler velocimetry showed a satisfactory association with adverse feto-neonatal outcome. In a multivariate model, uterine artery resistance index emerged as a single variable that had the best association with adverse feto-neonatal outcome. Addition of severity of hypertension, presence and severity of proteinuria did not influence the predicitive model to any significant extent. Uterine artery velocimetry and proteinuria status provided better risk stratification in hypertensive pregnancy.

There was a modest correlation of systemic vascular resistance index with uterine artery resistance index, the systemic vascular resistance index being largely a reflection of the blood pressure as cardiac index was similar between the hypertensive groups. Furthermore, less expertise is required in performing uterine artery velocimetry compared to maternal central hemodynamics, thus making the former more suitable for clinical risk stratification in hypertensive pregnancies.

Gestational hypertensives presenting after 34 weeks had a feto-neonatal outcome similar to normotensives and here knowledge of uterine artery velocimetry did not assist with further risk stratification. The cardiac index was not reduced and in fact similar to women with normotensive pregnancy. The elevated systemic vascular resistance index (largely a reflection of this elevated blood pressure) did not help to predict at risk pregnancies.

Finally, neither the haemodynamic parameters and severity of left ventricular hypertrophy nor the uterine artery resistance index helped to define risk in women with chronic hypertension.

8.7 Classification of hypertensive disorders of pregnancy

Comprehensive classifications of hypertensive disorders of pregnancy are limited by being less user-friendly to the clinician. Further such classifications have little value since they often create and recognize hypertensive groups that do not carry any adverse risk compared to normal pregnant women.

As an example, Levine *et al,* (2000) recently showed that 'normotensive' women whose hypertension was defined by a rise in diastolic BP of $\geq$ 15mmHg, did not have an adverse feto-neonatal outcome; an observation that highlights the shortcomings of evaluating blood pressure alone to predict at risk pregnancies. Zhang *et al,* (2001) also made observations that mild hypertension occurring for the first time in labour and isolated mild systolic hypertension were not associated with adverse feto-neonatal outcome. This problem was also observed in Easterling's echocardiographic study (1990) which included women whose blood pressure was defined by an elevation in diastolic blood pressure of 15mmHg, resulting in inclusion of a lower risk hypertensive group.

In another example, Spaanderman *et al,* (2000) observed differences in hemodynamics and volume homeostasis in women with a history of pre-eclampsia; the authors therefore proposed a category of latent hypertension for asymptomatic women with a history of pre-eclampsia. These observations are supported by Chambers *et al,* (2001) who showed that women with previous pre-eclampsia had

impaired endothelial function outside of pregnancy and this was reversed by folic acid.

The wide variation in hemodynamic measurements and prognosis in hypertensive disorders of pregnancy determine the need for a precise classification within the generally accepted broader hypertensive groups to allow for meaningful comparison between research studies. We therefore support comments of Higgins and de Swiet (2001) that research definitions for hypertensive disorders of pregnancy need to be more stringent as research studies are weakened if women without the disease are included. The caveat is that definitions for clinical purposes should be as safe as they are practical even though they are likely to include a considerable number of false positives.

Therefore, as a practical guide to the clinician, the results of this study support the use of the present classification of hypertensive disorders of pregnancy as a satisfactory initial step for risk stratification (step1) into gestational (aproteinuric) hypertension; pre-eclampsia (gestational proteinuric hypertension); chronic hypertension in pregnancy and chronic hypertension in pregnancy with superimposed pre-eclampsia. This step immediately utilizes information of proteinuria and hypertension. At step 2, this stratification is improved by incorporating gestational age and a measure of severity of proteinuria within the above hypertensive groups.

In the absence of severe hypertension and in the absence of chronic hypertension, an elevated level of uterine artery resistance index ≥ 0.65 is very likely to select out the higher risk hypertensive pregnancies (step 3). Finally as step 4, following on early

research by Kuzniar *et al* (1982); Yang *et al* (1996) and Nisell *et al* (1988), a measure of cardiac index of < 3.0 l/min/m^2 and/or systemic vascular resistance index > 2500 dyn.sec/cm^5/m^2 in this selected hypertensive pregnancy group may help to select hypertensive pregnancies at extremely high risk for adverse outcome in whom risk/benefit of allowing continuation or terminating pregnancy need to be made.

In conclusion, Brown *et al,* (1999) stated that without an agreed and acceptable classification of the hypertensive disorders of pregnancy, critical evaluation of studies from different research units would be extremely difficult. Lindheimer *et al,* 2001 also state in a review that a systematic attempt to accurately define and differentiate the various categories of hypertensive disorders is necessary so as to arm the clinician to better predict, prevent and improve the management of hypertensive disorders of pregnancy, in particular pre-eclampsia. The wide variability in measured maternal central hemodynamics in this and other studies reaffirm the importance of a precise and comprehensive definition of hypertensive participants in future studies that evaluate hemodynamics in hypertensive pregnancies.

8.8 Recommendations for future studies

Research in hypertensive disorders of pregnancy falls into 2 broad categories; the first category includes systematic attempts to accurately define and differentiate the various disorders of hypertension in pregnancy. The second include population studies to predict, prevent, and improve the management of women with hypertensive disorders of pregnancy. Continued research in both these areas is necessary to achieve improved maternal and feto-neonatal outcome. Research likely to result in clinical

benefit is particularly necessary as hypertensive disorders carry a 20-50% recurrence rate in the second pregnancy (Zhang *et al*, 2001). Our study evaluated echocardiographic maternal central hemodynamics and uterine artery velocimetry in hypertensive and normotensives pregnant women in an attempt to clarify the pathogenesis of hypertensive disorders in pregnancy from a haemodynamic with standpoint.

Future studies of maternal central hemodynamics in hypertensive pregnancies, where feasible, should incorporate a measure of biochemical markers that reflect volume homeostasis and renal function. Abnormal left ventricular geometry (concentric hypertrophy and remodelling) is now being increasingly recognised as a marker of higher risk hypertensive pregnancy. It is therefore of particular interest that Yasumoto *et al*, (2002) recently reported that in essential hypertention, decreased plasma and blood volume was associated with concentric remodelling.

To what extent genetic predispositions may be responsible for abnormalities in volume homeostasis and the maternal haemodynamic responses to therapeutic intervention is not clear. Spaanderman *et al,* (2001) for example explored the observation that many women with a history of pre-eclampsia have an underlying vascular or thrombophilic disorder. They found that pre-eclamptic women who were either hypertensive or without thrombophilia 5 months after delivery exhibited sub-optimal plasma volume expansion in their subsequent pregnancy. This was detected as early as seven weeks in the subsequent pregnancy and correlated inversely with circulating levels of alpha-atrial natriuretic peptide. This aspect of research becomes particularly important as it is being increasingly recognised that changes in maternal

renal function precede maternal cardiovascular changes of a decrease in systemic vascular resistance and an increase in cardiac output.

Also research into inflammatory markers and its associated endothelial dysfunction in pre-eclamptic women (Roberts *et al,* 2000) will elucidate the role of oxidant damage, endothelial dysfunction and its possible association with aberrations in maternal hemodynamics in hypertensive pregnant women. Carr *et al,* (2001) have demonstrated an interesting association of maternal hemodynamics and inflammatory markers in women at risk for pre-eclampsia.

More studies are also needed to explore traditional cardiovascular risk factors such as dyslipidaemia, obesity and insulin resistance that reflect the metabolic syndrome in normotensive and pre-eclamptic women of different population groups. This becomes especially important in the current epidemic of obesity and diabetes mellitus. In a recent epidemiological study Orskou *et al*, (2003) identified maternal overweight and obesity as one of the factors for delivering large for gestational age babies with its attendant risks. These maternal and fetal risks are likely to increase as Cundy *et al*, (2002) also reported the expected higher prevalence of hypertensive disorders of pregnancy in women with diabetes. Similarly, Kvetny *et al*, (2003) also reported a consistent higher body mass index in women with gestational hypertension and a higher prevalence of gestational hypertension in women with gestational diabetes mellitus. In a recent review Castro *et al*, (2002) in their review stressed the need for counselling of obese pregnant women and the need for specific guidelines for managing their pregnancy.

Research into the echocardiographic techniques used to measure stroke volume and diastolic dysfunction will help detect early changes in ventricular function. The Doppler echocardiographic technique is accurate and has been validated in pregnancy, but this technique requires extensive expertise and is labour intensive. Simplifying the above procedure by modifications in ultrasound techniques to perform automated cardiac output measurement was disappointing in a pilot study by Basdogan *et al,* (2000). Using thermodilution technique derived cardiac output as gold standard, the authors reported that automated Doppler echocardiography (in intensive care patients that included 5 pre-eclamptic women) underestimated measurements at higher levels of cardiac output. Despite these initial disappointing results, further studies of simplified Doppler echocardiographic measured cardiac output are necessary as there are subgroups of hypertensive pregnant women who require and benefit from intensive monitoring and control of central hemodynamics.

Ambulatory blood pressure monitoring permits a more accurate measure of the hypertensive load. This will allow for a closer evaluation, of systolic versus diastolic blood pressure, pulse pressure and its association with age in the hypertensive pregnancies. Similar to that described for hypertension outside pregnancy (Slotwiner *et al,* (2001)) ambulatory measurements also allow for a more precise measure of blood pressure load in pregnancy, described as the hyperbaric index. Such an approach is described by Hermida *et al*, (2002) and is likely to assist the clinician to make a more confident diagnosis of white coat hypertension and avoid potentially harmful antihypertensive medication. In addition it will also assist in diagnosing undetected hypertension in at risk patients in whom the diagnosis is not made by conventional office blood pressure measurements.

Studies of maternal central hemodynamics should also combine a measure of uterine artery resistance since concomitant maternal hemodynamics can be accompanied by parallel changes in uterine artery resistance. Research in this area will contribute to exploring the hypothesis of whether changes in maternal hemodynamics occur as a hemodynamic compensatory phenomenon to maintain uteroplacental perfusion, an avenue of research that will have particular significance in evaluating the risk/benefit of anti-hypertensive medications used in pregnancy. This area of research is also important as it may shed light on initial observations by Pijnenborg *et al,* (2000) which suggests that uterine hemodynamics may be a driving force for endovascular trophoblast migration in the placental bed.

It would also be interesting to see whether echocardiographic changes can be identified by biochemical markers such as brain natriuretic peptide as described by Borghi *et al,* (2000) who suggested that a measure of plasma natriuretic peptide helped differentiate pre-eclampsia from volume overload.

Finally our study also suggests that meaningful comparison of maternal hemodynamics is feasible only after standardization of these hemodynamic parameters by maternal stature that can be reflected either by body surface area or its variations. It is recommended that future studies of maternal hemodynamics and cardiac structure report both unstandardized and standardized measurements until consensus is reached. Continued research into the hypertensive diseases of pregnancy is necessary now more than ever before since hypertensive diseases of pregnancy seem to be associated in later life with diseases of hypertension (Wilson *et al*, (2003)).

A greater understanding and awareness of this association will lead to earlier diagnosis and management of such diseases.

Appendix-1

Formulae for calculation of left ventricle (LV) structure, function and hemodynamics

$$\text{LV-fractional shortening (\%)} = \frac{\text{LVID (d)} - \text{LVID (s)}}{\text{LVID (d)}} .100\% \quad \text{----------(1)}$$

*LVID (d) = left ventricle internal dimension in diastole

*LVID (s) = left ventricle internal dimension in systole

$$\text{LV- Ejection fraction (\%) (Teicholz)} = \frac{\text{LVV(d)} - \text{LVV (s)}}{\text{LVV (d)}} . 100\% \quad \text{----------(2)}$$

* LVV(d) = left ventricle volume in diastole

* LVD (s) = left ventricle volume in systole

and where LV volume is calculated by the Teichholz formula-

$$\text{LV Volume} = \left(\frac{7}{2.4 + D}\right) . (D)^3 \quad \text{--------(3)}$$

* D = LV minor axis dimension in diastole (cm)

LV – mean circumferential fibre shortening (circum/sec)

$$= \frac{\text{LV- fractional shortening}}{\text{LV-ejection time (seconds)}} \text{----------(4)}$$

LV – mass (g) =

$$= 1.04 [(\text{LVID(d)} + \text{LV septum(d)} + \text{LV pw (d)})^3 - [(\text{LVID (d)}^3] - 13.6 \text{----------(5)}$$

*LVID (d) = left ventricle internal dimension in diastole in cm
*LV-septum (d) = left ventricle septal thickness in diastole in cm
*LV-pw (d) = left ventricle posterior wall thickness in diastole in cm

$$\text{LV mass index } (g/m^2) = \frac{\text{LV mass (g)}}{\text{Body surface area } (m^2)} \text{ ----------(6)}$$

$$\text{LV-relative wall thickness ratio} = \frac{2.\ \text{LV pw}}{\text{LVID (d)}} \text{ ----------(7)}$$

* LVID (d) = left ventricle internal dimension in diastole in cm
* LV-pw (d) = left ventricle posterior wall thickness in diastole in cm

LV – Doppler stroke volume (ml) =

$$= \text{VTI}_{\text{aorta (m)}} \times \text{aortic annular area } (mm^2) \text{----------(8)}$$

VTI aorta (m) = velocity time integral at the level of aorta in meters

LV-end systolic wall stress (dyn./cm^5) =

$$= \frac{0.334.\ \text{Systolic blood pressure(mmHg).\ LVID(s)}}{(\ \text{LVpw (d)})\ .\ (\ 1 + \frac{\text{LVpw (d)}}{\text{LV ID (s)}}\ )} \text{ ----------(9)}$$

*LVID (s) = left ventricle internal dimension in systolic in cm
*LV-septum (d) = left ventricle septal thickness in diastole in cm
*LV-pw (d) = left ventricle posterior wall thickness in diastole in cm

$$\text{Uterine artery resistance index} = \frac{\text{peak systolic velocity} - \text{diastolic velocity}}{\text{systolic velocity}} \text{ ---(10)}$$

$$\text{Umbilical artery pulsatility index} = \frac{2\ (\text{systolic velocity} - \text{diastolic velocity})}{(\text{systolic velocity} + \text{diastolic velocity})} \text{ --(11)}$$

REFERENCES

Aardema MW, DeWolf BT, Saro MC, Ooserhof H, Fidler V, Aarnoudse JG. Quantification of the diastolic notch in the Doppler ultrasound screening of uterine arteries. *Ultrasound Obstet Gynecol* 2000; 16: 630-4.

Anim-Nyame N, Gamble J, Sooranna SR, Johnson MR, Sullivan MH, Steer PJ. Evidence of impaired microvascular function in preeclampsia: a non-invasive study. *Clin Sci (Lond)* 2003; 104: 405-12.

Anonymous. A review of maternal deaths in South Africa during 1998. National Committee on Confidential Enquiries into Maternal Deaths. *S Afr Med J* 2000; 90: 367-73.

Anumba DO, Robson SC, Boys RJ, Ford GA. Nitric oxide activity in the peripheral vasculature during normotensive and preeclamptic pregnancy. *Am J Physiol* 1999; 277: H848-54

Aquilina J, Barnett A, Thompson O, Harrington K. Comprehensive analysis of uterine artery flow velocity waveforms for the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2000; 16: 163-70.

Aquilina J, Thompson O, Thilaganathan B, Harrington K. Improved early prediction of pre-eclampsia by combining second-trimester maternal serum inhibin-A and uterine artery Doppler. *Ultrasound Obstet Gynecol* 2001; 17: 477-84.

Ashworth JR, Baker PN, Warren AY, Johnson IR. Mechanisms of endothelium-dependent relaxation in myometrial resistance vessels and their alteration in preeclampsia. *Hyperten Preg* 1999; 18: 57-71.

August P, Mueller FB, Sealey JE, Edersheim TG. Role of renin-angiotensin system in blood pressure regulation in pregnancy. *Lancet* 1995; 345: 896-7.

Barton JR, O'Brien JM, Bergauer NK, Jacues DL, Sibai BM. Mild gestational hypertension remote from term: progression and outcome. *Am J Obstet Gynecol* 2001: 184: 979-83.

Basdogan F, Visser W, Struijk PC, Jansen JR, Vletter WB, Wladimiroff JW, Lotgering FK. Automated cardiac output measurements by ultrasound are inaccurate at high cardiac outputs. *Ultrasound Obstet Gynecol* 2000; 15: 508-12.

Baylis C, Beinder E, Suto T, August P. Recent insights into the roles of nitric oxide and renin-angiotensin in the pathophysiology of preeclamptic pregnancy. *Sem Nephrol* 1998; 18: 208-30.

Belfort M, Akovic K, Anthony J, Saade G, Kirshon B, Miose K Jr. The effect of acute volume

expansion and vasodilation with verapamil on uterine and umbilical artery Doppler indices in severe pre-eclampsia . *J Clni Ultrasound* 1994; 22: 317-25.

Bernheim J. Hypertension in pregnancy. *Nephron* 1997; 76: 254-63.

Binder ND, Laird MR, Faber JJ. Interrelationships between the renin angiotensin system and uteroplacental blood flow--a recent perspective. *Reprod Fertil Dev* 1995; 7: 1437-42.

Blake MJ, Martin A, Manktelow BN, Armstrong C, Halligan AW, Panerai RB, Potter JF. Changes in baroreceptor sensitivity for heart rate during normotensive pregnancy and the puerperium. *Clin Sci (Lond)* 2000; 98: 259-68.

Bolte AC, van Eyck J, Strack van Schijndel RJ, van Geijn HP, Dekker GA. The haemodynamic effects of ketanserin versus dihydralazine in severe early-onset hypertension in pregnancy. *Br J Obstet Gynaecol* 1998; 105: 723-31.

Bolte AC, van Geijn HP, Dekker GA. Management and monitoring of severe preeclampsia. *Eur J Obstet Gynaecol Reprod Biol* 2001; 96: 8-20.

Borghi C, Esposti DD, Immordino V, Cassani A, Boschi S, Bovicelli L, Ambrosioni E. Relationship of systemic hemodynamics, left ventricular structure and function, and plasma natriuretic peptide concentrations during pregnancy complicated by preeclampsia. *Am J Obstet Gynecol* 2000; 183: 140-7.

Bosio PM, McKenna PJ, Conroy R, O'Herlihy C. Maternal central hemodynamics in hypertensive disorders of pregnancy. *Obstet Gynecol* 1999; 94: 978-84.

Bower S, Kingdom J, Campbell S. Objective and subjective assessment of abnormal uterine artery Doppler flow velocity waveforms. *Ultrasound Obstet Gynecol* 1998; 12: 260-4.

Broughton-Pipkin F, Baker PN. Angiotensin II has depressor effects in pregnant and nonpregnant women. *Hypertens* 1997; 30: 1247-52.

Broughton Pipkin F, Roberts JM. Hypertension in pregnancy. *J Hum Hypertens* 2000; 14: 705-24.

Brown MA, Mitar DA, Whitworth JA. Measurement of plasma volume in pregnancy. *Clin Sci (Lond)* 1992; 83: 29-34.

Brown MA, Zammit VC, Mitar DM. Extracellular fluid volumes in pregnancy-induced hypertension. *J Hypertens* 1992; 10: 61-8.

Brown MA, Reiter L, Rodger A, Whitworth JA. Impaired renin stimulation in pre-eclampsia. *Clin Sci (Lond)* 1994; 86: 575-81.

Brown MA, de Swiet M. Classification of hypertension in pregnancy. *Bailliere's Best Practice Research : Clin Obstet Gynaecol* 1999; 13: 27-39.

Brown MA, Hague WM, Higgins J, Lowe S, McCowan L, Oats J, Meek MJ, Rowan JA Walters BN, The Australasian Society of the Study of Hypertension in Pregnancy. The detection, investigation and management of hypertension in pregnancy: full consensus statement. *Aust N Z J Obstet Gynaecol* 2000; 40: 139-55.

Brown MA, Bowyer L, McHugh L, Davis GK, Mangos GJ, Jones M. Twenty-four-hour automated blood pressure monitoring as a predictor of preeclampsia. *Am J Obstet Gynecol* 2001; 185: 618-22.

Bucher HC, Guyatt GH, Cook RJ, Hatala R, Cook DJ, Lang JD, Hunt D. Effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia: a meta-analysis of randomized controlled trials. *JAMA* 1996; 275: 1113-7.

Capeless EL, Clapp JF. Cardiovascular changes in early phase of pregnancy. *Am J Obstet Gynecol* 1989; 161: 1449-53.

Carbillon L, Uzan M, Uzan S. Pregnancy, vascular tone, and maternal hemodynamics: a crucial adaptation. *Obstet Gynecol Surv* 2000; 55: 574-81.

Carpenter MW, Sady SP, Sady MA, Haydon B, Coustan DR, Thompson PD. Effect of maternal weight gain during pregnancy on exercise performance. *J App Physiol* 1990; 68: 1173-6.

Carr DB, McDonald GB, Brateng D, Desai M, Thach CT, Easterling TR. The relationship between hemodynamics and inflammatory activation in women at risk for preeclampsia. *Obstet Gynecol* 2001; 98: 1109-16.

Castro LC, Avina RL. Maternal obesity and pregnancy outcomes. *Curr Opin Obstet Gynecol* 2002; 14: 601-6.

Chambers JC, Fusi L, Malik IS, Haskard DO, De Swiet M, Kooner JS. Association of maternal endothelial dysfunction with preeclampsia. *JAMA* 2001; 285: 1607-12.

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil

S, Wright JT Jr, Roccella EJ. The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289: 2560-72.

Clapp III JF, Capeless E. Cardiovascular function before, during, and after the first and subsequent pregnancies. *Am J Cardiol* 1997; 80: 1469-73.

Coleman MA, McCowan LM, North RA. Mid-trimester uterine artery Doppler screening as a predictor of adverse pregnancy outcome in high-risk women. *Ultrasound Obstet Gynecol* 2000; 15: 7-12.

Cotton DB, Lee W, Huhta JC, Dorman KF. Hemodynamic profile of severe prenancy-induced hypertension. *Am J Obstet Gynecol* 1988; 158: 523-9.

Cundy T, Slee F, Gamble G, Neale L. Hypertensive disorders of pregnancy in women with Type 1 and Type 2 diabetes. *Diabet Med* 2002; 19: 482-9.

Davey DA, MacGillivray I. The classification and definition of the hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 1988; 158:892-8.

de Groot CJ, O'Brien TJ, Taylor RN. Biochemical evidence of impaired trophoblastic invasion of decidual stroma in women destined to have preeclampsia. *Am J Obstet Gynecol* 1996; 175: 24-9.

de Groot CJ, Taylor RN. New insights into the etiology of pre-eclampsia. *Ann Med* 1993; 25: 243-9.

de Simone G, Devereux RB, Daniels SR, Mureddu G, Roman MJ, Kimball TR, Greco R, Witt S, Contaldo F. Stroke volume and cardiac output in normotensive children and adults. Assessment of relations with body size and impact of overweight. *Circulation* 1997; 95: 1837-43.

de Swiet M. Maternal blood pressure and birthweight. *Lancet* 2000; 355: 81-2.

Delemarre FM, Didden MA, de Jong PA. Diurnal variation in angiotensin sensitivity in pregnancy. *Am J Obstet Gynecol* 1996; 174: 259-61

Desai DK, Moodley J, Naidoo DP, Bhorat I. Cardiac abnormalities in pulmonary oedema associated with hypertensive crises in pregnancy. *Br J Obstet Gynaecol* 1996; 103: 523-8.

Desai D, Moodley J, Naidoo D. Peripartum cardiomyopathy: experiences at King Edward VIII Hospital, Durban, South Africa and a review of the literature. *Trop Doct* 1995; 25: 118-23.

Devereux RB, Pini R, Aurigemma GP, Roman MJ. Measurement of left ventricular mass: methodology

and expertise. *J Hypertens* 1997; 15: 801-9.

Dong YL, Vegiraju S, Chauhan M, Gangula PR, Hankins GD, Goodrum L, Yallampalli C. Involvement of calcitonin gene-related peptide in control of human fetoplacental vascular tone. *Am J Physiol Heart Circ Physiol* 2004; 286(1): H230-9.

Donnelly S. Why is erythropoietin made in the kidney? The kidney functions as a "critmeter" to regulate the hematocrit. Adv Exp Med Biol. 2003; 543: 73-87

Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916; 17: 863-71.

Duley L. Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. *Br J Obstet Gynaecol* 1992; 99: 547-53.

Duvekot JJ, Cheriex EC, Pieters FA, Menheere PP, Peeters LH. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. *Am J Obstet Gynecol* 1993; 169: 1382-92.

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

Duvekot JJ, Cheriex EC, Pieters FA, Peeters LL. Severely impaired fetal growth is preceded by maternal hemodynamic maladaptation in very early pregnancy. *Acta Obsetet Gynecol Scand* 1995; 74: 693-7.

Easterling TR, Watts DH, Schmucker BC, Benedetti TJ. Measurement of cardiac output during pregnancy: validation of Doppler technique and clinical observations in preeclampsia. *Obstet Gynecol* 1987; 69: 845-50.

Easterling TR, Benedetti TJ, Schmucker BC, Millard SP. Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study. *Obstet Gynecol* 1990; 76: 1061-9.

Easterling TR, Benedetti TJ, Carlson KC, Brateng DA, Wilson J, Schmucker BS. The effect of maternal hemodynamics on fetal growth in hypertensive pregnancies. *Am J Obstet Gynecol* 1991; 165: 902-6.

Easterling TR, Brateng D, Schumucker B, Brown Z, Millard SP. Prevention of pre-eclampsia: a randomized trial of atenolol in hyperdynamic patients beofre onset of hypertension. *Obstet Gynecol* 1999: 93: 725- 33.

Easterling TR, Carr DB, Brateng D, Diederichs C, Schmucker B. Treatment of hypertension in pregnancy: effect of atenolol on maternal disease, preterm delivery, and fetal growth. *Obstet Gynecol* 2001; 98: 427-33.

Egerman RS, Andersen RN, Manejwala FM, Sibai BM. Neuropeptide Y and nitrite levels in pre-eclamptic and normotensive gravid women. *Am J Obstet Gynecol.* 1999; 181: 921-3.

Ferrer RL, Sibai BM, Mulrow CD, Chiquette E, Stevens KR, Cornell J. Management of mild chronic hypertension during pregnancy: a review. *Obstet Gynecol* 2000; 96: 849-60.

Fischer T, Heusser K, Schobel HP. Autonomes Nervensystem und Praeklampsie. *Zentralbl Gynakol* 1999; 121: 603-7.

Frusca T, Soregaroli M, Platto C, Enterri L, Lojacono A, Valcamonico A. Uterine artery velocimetry in patients with gestational hypertension. *Obstet Gynecol* 2003; 102: 136-40.

Galanti B, Kaihura CT, Ricci L, Bedocchi L, Rossi T, Benassi G, Benassi L. Perinatal morbidity and mortality in children born to mothers with gestational hypertension. *Acta Biomed Ateneo Parmense* 2000; 71; S361-5.

Greenwood JP, Scott EM, Stoker JB, Walker JJ, Mary DA. Sympathetic neural mechanisms in normal and hypertensive pregnancy in humans. *Circulation* 2001; 104 : 2200-4.

Haddad B, Sibai BM. Chronic hypertension in pregnancy. *Ann Med* 1999; 31: 246-52.

Haelterman E, Breart G, Paris-Llado J, Dramaix M, Tchobroutsky C. Effect of uncomplicated chronic hypertension on the risk of small-for-gestational age birth. *Am J Epidemiol* 1997; 145: 689-95.

Harrington KF, Campbell S, Bewley S, Bower S. Doppler velocimetry studies of the uterine artery in the early prediction of pre-eclampsia and intra-uterine growth retardation. *Eur J Obset Gynaecol Reprod Biol* 1991; 42: S14-20.

Hennessy TG, MacDonald D, Hennessy MS, Maguire M, Blake S, McCann HA, Sugrue DD. Serial changes in cardiac output during normal pregnancy: a Doppler ultrasound study. *Eur J Obstet Gynaecol Reprod Biol* 1996; 70: 117-22.

Hermida RC, Ayala DE, Iglesias M. Predictable blood pressure variability in healthy and complicated pregnancies. *Hypertension* 2001; 38: 736-41.

Hermida RC, Ayala DE. Prognostic value of office and ambulatory blood pressure measurements in

pregnancy *Hypertension* 2002; 40: 298-303.

Higgins JR, de Swiet M. Blood-pressure measurement and classification in pregnancy. *Lancet* 2001; 357: 131-5.

Hung JH, Yen MY, Pan YP, HSU LP. The effect of methyldopa on retinal artery circulation in pre-eclampic gravidae. *Ultrasound Obset Gynecol* 2000; 15: 513-9.

Ihlen H, Amlie JP, Dale J, *et al*. Determination of cardiac output by Doppler echocardiography. *Br Heart J* 1984; 51: 54-60.

Kalenga MK, Thomas K, de Gasparo M, De Hertogh R. Determination of renin, angiotensin converting enzyme and angiotensin II levels in human placenta, chorion and amnion from women with pregnancy induced hypertension. *Clin Endocrinol (Oxf)* 1996; 44: 429-33.

Katz R, Karliner JS, Resnik R. Effects of a natural volume overload state (pregnancy) on left ventricular performance in normal human subjects. *Circulation* 1978; 58: 434-41.

Khedun SM, Naicker T, Moodley J. Endothelin-1 activity in pregnancy. *J Obstet Gynaecol* 2002; 22: 590-3.

Khong TY, De Wolf F, Robertson WB, Brosens I. Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. *Br J Obstet Gynaecol* 1986; 93:1049-59.

Kristiansson P, Wang JX. Reproductive hormones and blood pressure during pregnancy. *Hum Reprod* 2001; 16: 13-17.

Kuzniar J, Piela A, Skret A, Szmigiel Z, Zaczek T. Echocardiographic estimation of hemodynamics in hypertensive pregnancy. *Am J Obstet Gynecol* 1982; 144:430-7.

Kvetny J, Poulsen HF. Incidence of gestational hypertension in gestational diabetes mellitus. *Arch Gynecol Obstet* 2003; 267: 153-7.

Lang RM, Pridjian G, Feldman T, Neuman T, Lindheimer M, Borow KM. Left ventricular mechanics in preeclampsia. *Am Heart J* 1991; 121: 1768-75.

Langer B, Grima M, Coquard C, Bader AM, Schlaeder G, Imbs JL. Plasma active renin, angiotensin I, and angiotensin II during pregnancy and in pre-eclampsia. *Obstet Gynecol* 1998; 91; 196-202.

Laragh JH. Atrial natriuretic hormone, the renin-aldosterone axis, and blood pressure-electrolyte

homeostasis. *New Engl J Med* 1985; 313:1330-40.

Levine RJ, Ewell MG, Hauth JC, Curet LB, Catalino PM, Morris CD, Choudhary G, Sibai BM. Should the definition of preeclampsia include a rise in diastolic blood pressure of $\geq$ 15 mmHg in association with proteinuria? *Am J Obstet Gynecol* 2000; 183: 787-92.

Lindheimer MD, Davison JM, Katz AI. The kidney and hypertension in pregnancy: twenty exciting years. *Semin Nephrol* 2001; 21:173-89.

Livingston JC, Maxwell BD, Sibai BM. Chronic hypertension in pregnancy. *Minerva Ginecol* 2003; 55: 1-13.

Lowe DT, Nitric oxide dysfunction in the pathophysiology of preeclampsia. *Nitric Oxide* 2000; 4 : 441–58.

Lund CJ, Donovan JC. Blood volume during pregnancy. Significance of plasma and red cell volumes. *Am J Obstet Gynecol* 1967; 98: 394-403.

Mabie WC, Ratts TE, Sibai BM. The central hemodynamics of severe preeclampsia. *Am J Obstet Gynecol* 1989; 161: 1443-8.

Mabie WC, DiSessa TG, Crocker LG, Sibai BM, Arheart KL. A longitudinal study of cardiac output in normal human pregnancy. *Am J Obstet Gynecol* 1994; 170: 849-56.

Magee LA, von Dadelszen P, Bohun CM, Rey E, El-Zibdeh M, Stalker S, Ross S, Hewson S, Logan AG, Ohlsson A, Naeem T, Thornton JG, Abdalla M, Walkinshaw S, Brown M, Davis G, Hannah ME. Serious perinatal complications of non-proteinuric hypertension: an international, multicentre, retrospective cohort study. *J Obstet Gynaecol Can* 2003; 25: 350-6.

Maggioni C, Lucini D, Antinozzi R, Pagani M. Circadian rhythm of ANP, aldosterone and PRA in normotensive IUGR. *J Hypertens* 2001; 19: 1659-64.

Magness RR, Cox K, Rosenfeld CR, Gant NF. Angiotensin II metabolic clearance rate and pressor responses in nonpregnant and pregnant women. *Am J Obstet Gynecol* 1994; 171:668-79.

Mantel GD, Moodley J. Can a developed country's maternal mortality review be used as the 'gold standard' for a developing country? *Eur J Obstet Gynaecol Reprod Biol* 2002; 100:189-95

Maulik D. Evidence of effectiveness and fetal investigation: trials and tribulations. *Ultrasound Obstet Gynecol* 1995; 6: 305-6.

McCowan LM, Buist RG, North RA, Gamble G. Perinatal morbidity in chronic hypertension. *Br J Obstet Gynaecol* 1996; 103:123-9.

McCowan LM, North RA, Harding JE. Abnormal uterine artery Doppler in small-for-gestational-age pregnancies is associated with later hypertension. *Aust N J Obstet Gynaecol* 2001; 41:56-60.

McMullin MF, White R, Lappin T, Reeves J, MacKenzie G. Haemoglobin during pregnancy: relationship to erythropoietin and haematinic status. *Eur J Haematol* 2003; 71: 44-50.

Merrill DC, Karoly M, Chen K, FerrarioCM, Brosnihan KB. Angiotensin(1-7) in normal and pre-eclamptics pregnancy. *Endocrine* 2002; 18: 239-45.

Mone SM, Sanders SP, Colan SD. Control mechanisms for physiological hypertrophy of pregnancy. *Circulation* 1996; 94: 667-72.

Moodley J. Coping with hypertension in pregnancy. *Afr Health* 1993; 15: 10-1.

Moran P, Baylis PH, Lindheimer MD, Davison JM. Glomerular ultrafiltration in normal and preeclamptic pregnancy. *J Am Soc Nephrol*. 2003; 14: 648-52.

Morizaki N, Morizaki J, Hayashi RH, Garfield RE. A functional and structural study of the innervation of the human uterus. *Am J Obstet Gynecol* 1989; 160: 218-28.

Moutquin JM, Rainville C, Giroux L, Raynauld P, Amyot G, Bilodeau R, Pelland N. A prospective study of blood pressure in pregnancy: prediction of preeclampsia. *Am J Obstet Gynecol* 1985; 151: 191-6.

Naicker T, Khedun SM, Moodley J, Pijnenborg R. Quantitative analysis of trophoblast invasion in pre-eclampsia. *Acta Obstet Gynecol Scand*. 2003; 82: 722-9.

Nisell H, Carlstrom K, Cizinsky S, Grunewald C, Nylund L, Randmaa I. Atrial natriuretic peptide concentrations and hemodynamic effects of acute plasma volume expansion in normal pregnancy and preeclampsia. *Obstet Gynecol* 1992; 79: 902-7.

Nisell H, Lunell NO, Linde B. Maternal hemodynamics and impaired fetal growth in pregnancy induced hypertension *Obstet Gynecol* 1988; 71: 163-6.

Novelli GP, Valensise H, Vasapollo B, Larciprete G, Altomare F, Di Peerro G, Casalino B, Galante A, Arduini D. Left ventricular concentric geometry as a risk factor in gestational hypertension. *Hypertension* 2003; 41: 469-80.

Orskou J, Henriksen TB, Kesmodel U, Secher NJ. Maternal characteristics and lifestyle factors and the risk

of delivering high birth weight infants. *Obstet Gynecol* 2003; 102: 115-20.

Penny JA, Halligan AW, Shennan AH, Lambert PC, Jones DR, deSwiet M, Taylor DJ. Automated, ambulatory, or conventional blood pressure measurement in pregnancy: which is the better predictor of severe hypertension? *Am J Obstet Gynecol* 1998; 178: 521-6.

Peters J. Molecular basis of human hypertension: the role of angiotensin. *Baillieres Clin Endocrinol Metab* 1995; 9: 657-78.

Phelan JP, Yurth DA. Severe preeclampsia. I. Peripartum hemodynamic observations. *Am J Obstet Gynecol* 1982; 144: 17-22.

Pijnenborg R, Bland JM, Robertson WB, Dixon G, Brosens I. The pattern of interstitial trophoblastic invasion of the myometrium in early human pregnancy. *Placenta* 1981; 2: 303-16.

Pijnenborg R, Anthony J, Davey DA, Rees A, tiltman A, Vercruysse L, Van Assche A. Placental bed spiral arteries in the hypertensive disorders of pregnancy. *Br J Obstet Gynaecol* 1991; 98: 648-55.

Pijnenborg R. Uterine haemodynamics as a possible driving force for endovascular trophoblast migration in the placental bed. *Med Hypoth* 2000; 55: 114-8.

Poppas A, Shroff SG, Korcarz CE, Hibbard JU, Berger DS, Lindheimer MD, Lang RM. Serial assessment of the cardiovascular system in normal pregnancy. Role of arterial compliance and pulsatile arterial load. *Circulation* 1997; 95: 2407-15.

Rajagopal M, Moodley J, Chetty R. Nitric oxide: does it have an etiological role in pre-eclampsia? *Acta Obstet Gynecol Scand.* 2003; 82: 216-9.

Ramsay B, De Belder A, Campbell S, Moncada S, Martin JF. A nitric oxide donor improves uterine artery diastolic blood flow in normal early pregnancy and in women at high risk of pre-eclampsia. *Eur J Clin Inves* 1994; 24: 76-8.

Redman CW, Roberts JM. Management of pre-eclampsia. *Lancet* 1993; 341: 1451-4.

Roberts JM. Preeclampsia: what we know and what we do not know. *Sem Perinatol* 2000; 24: 24-8.

Roberts JM, Cooper DW. Pathogenesis and genetics of pre-eclampsia. *Lancet* 2001; 357: 53-6.

Robson SC, Dunlop W, Moore M, Hunter S. Combined Doppler and echocardiographic measurement of cardiac output: theory and application in pregnancy. *Br J Obstet Gynaecol* 1987; 94: 1014-27.

Robson SC, Hunter S, Moore M, Dunlop W. Haemodynamic changes during the pueperium: a Doppler and

M-mode echocardiographic study. *Br J Obstet Gynaecol* 1987; 94: 1028-39.

Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol* 1989; 256: H1060-5.

Rodrigo R, Parra M, Bosco C, Fernandez V, Barja P, Guajardo J, Messina R. Pathophysiological basis for the prophylaxis of preeclampsia through early supplementation with antioxidant vitamins. *Pharmacology and Therapeutics* 2005; 107:177-197.

Rosso P, Donoso E, Braun S, Espinoza R, Salas SP. Hemodynamic changes in underweight pregnant women. *Obstet Gynecol* 1992; 95: 1837-43.

Sagol S, Ozkinay E, Oztekin K, Ozdemir N. The comparison of uterine artery Doppler velocimetry with the histopathology of the placental bed. *Aust N Z J Obstet Gynaecol* 1999; 39: 324-9.

Saudan P, Brown MA, Buddle ML, Jones M. Does gestational hypertension become pre-eclampsia? *Br J Obstet Gynaecol* 1998; 105: 1177-84.

Savvidou MD, Hingorani AD, Tsikas D, Frolich JC, Vallance P, Nicolaides KH. Endothelial dysfunction and raised plasma concentrations of asymmetric dimethylarginine in pregnant women who subsequently develop preeclampsia. *Lancet* 2003; 361: 1511-7.

Scardo J, Kiser R, Dillon A, Brost B, Newman R. Hemodynamic comparison of mild and severe preeclampsia: concept of stroke systemic vascular resistance index. *J Matern Fetal Med* 1996; 5: 268-72.

Scardo JA, Vermillion ST, Newman RB, Chauhan SP, Hogg BB. A randomized, double-blind, hemodynamic evaluation of nifedipine and labetalol in preeclamptic hypertensive emergencies. *Am J Obstet Gynecol* 1999; 181: 862-6.

Schannwell CM, Schoebel FC, Zimmermann T, Marx R, Plehn G, Leschke M, Strauer BE. Linksventridulare diastoliische Funktion in der normalen Schwangerschaft. Eine prospektive Untersuchung mittels M-mode-Echokardiographie und Doppler-Echokardiographie. [Left ventricular diastolic function in normal pregnancy. A prospective study using M-mode echocardiography and Doppler echocardiography]. *Dtsche Med Wochenschr* 2000; 125: 1069-73.

Schobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia -- a state of sympathetic

overactivity. *N Engl J Med* 1996; 335: 1480-5.

Seligman SP, Buyon JP, Clancy RM, Young BK, Abramson SB. The role of nitric oxide in the pathogenesis of preeclampsia. *Am J Obstet Gynecol* 1994; 171: 944-8.

Shah DM. Role of the renin-angiotensin system in the pathogenesis of preeclampsia. *Am J Renal Physiol* 2005; 288: 614-25

Sibai BM, Frangieh A. Maternal adaptation to pregnancy. *Curr Opin Obstet Gynecol* 1995; 7: 420-6.

Siekmann U, Heilmann L, Klosa W, Quaas L, Schillinger H. Simultaneous investigations of maternal cardiac output and fetal blood flow during hypervolemic hemodilution in preeclampsia--preliminary observations. *J Perinat Med* 1986; 14: 59-69.

Silver HM, Seebeck M, Carlson R. Comparison of total blood volume in normal, preeclamptic, and nonproteinuric gestational hypertensive pregnancy by simultaneous measurement of red blood cell and plasma volumes. *Am J Obstet Gynecol* 1998; 179: 87-93.

Silver HM, Tahvanainen KU, Kuusela TA, Eckberg DL. Comparison of vagal baroreflex function in nonpregnant women and in women with normal pregnancy, preeclampsia, or gestational hypertension. *Am J Obstet Gynecol.* 2001; 184 : 1189-95.

Slotwiner DJ, Devereux RB, Schwartz JE, Pickering TG, de Simone G, Roman MJ. Relation of age to left ventricular function and systemic hemodynamics in uncomplicated mild hypertension. *Hypertension* 2001; 37: 1404-9.

Slowinski T, Neumayer HH, Stolze T, Gossing G, Halle H, Hocher B. Endothelin system in normal and hypertensive pregnancy. *Clin Sci (Lond).* 2002; 103 : 448S-449S.

Soregaroli M, Valcamonico A, Scalvi L, Danti L, Frusca T. Late normalisation of uterine artery velocimetry in high risk pregnancy. *Eur J Obstet Gynaecol Reprod Biol* 2001; 95: 42-5.

Spaanderman ME, Ekhart TH, van Eyck J, Cheriex EC, de Leeuw PW, Peeters LL. Latent hemodynamic abnormalities in symptom-free women with a history of preeclampsia. *Am J Obstet Gynecol* 2000; 182: 101-7.

Spaanderman M, Ekhart T, van Eyck J, de Leeuw P, Peeters L. Preeclampsia and maladaptation to pregnancy: a role for atrial natriuretic peptide? *Kidney Int* 2001; 60: 1397-406.

Starzyk KA, Pijnenborg R, Salafia CM. Decidual and vascular pathophysiology in pregnancy

compromise. *Sem Reprod Endocrinol* 1999; 17: 63-72.

Steegers EA, Van Lakwijk HP, Jongsma HW, Fast JH, DeBoo T, Eskes TK, Hein PR (Patho)physiological implications of chronic dietary sodium restriction during pregnancy; a longitudinal prospective randomized study. *Br J Obstet Gynaecol* 1991; 98: 980-7.

Thomsen JK, Fogh-Andersen N, Jaszczak P, Giese J. Atrial natriuretic peptide (ANP) decrease during normal pregnancy as related to hemodynamic changes and volume regulation. *Acta Obstet Gynecol Scand* 1993; 72: 103-10.

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

Valensise H, Novelli GP, Vasapollo B, Di Ruzza G, Romanini ME, Marchei M, Larciprete G, Manfellotto D, Romaninic C, Galante A. Maternal diastolic dysfunction and left ventricular geometry in gestational hypertension. *Hypertension* 2001; 37: 1209-15.

Valensise H, Vasapollo B, Novelli GP, Larciprete G, Romanini ME, Arduini D, Galante A, Romanini C. Maternal diastolic function in asymtomatic pregnant women with bilateral notching of the uterine artery waveform at 24 weeks gestation: a pilot study. *Ultrasound Obstet Gynecol* 2001; 18: 450-5.

van Oppen AC, van der Tweel I, Duvekot JJ, Bruinse HW. Use of cardiac index in pregnancy: is it justified? *Am J Obstet Gynecol* 1995; 173: 923-8.

van Oppen AC, Stigter RH, Bruinse HW. Cardiac output in normal pregnancy: a critical review. *Obstet Gynecol* 1996; 87: 310-8.

van Oppen AC, van der Tweel I, Alsbach GP, Heethaar RM, Bruinse HW. A longitudinal study of maternal hemodynamics during normal pregnancy. *Obstet Gynecol* 1996; 88: 40-6.

Varga I, Rigo J, Jr., Somos P, Joo JG, Nagy B. Analysis of maternal circulation and renal function in physiologic pregnancies; parallel examinations of the changes in the cardiac output and the glomerular filtration rate. *J Matern Fetal Med* 2000; 9: 97-104.

Vazquez Blanco M, Grosso O, Bellido CA, Iavicoli OR, Bernsztein CS, Vega HR, Lerman J. Left ventricular geometry in pregnancy–induced hypertension. *Am J Hypertens* 2000; 13: 226-30.

Visser W, Wallenburg HC. Central hemodynamic observations in untreated preeclamptic patients. *Hypertension* 1991; 17: 1072-7

von Dadelszen P, Ornstein MP, Bull SB, Logan AG, Koren G, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. *Lancet* 2000; 355: 87-92.

Wang Y, Moss J, Thisted R. Predictors of body surface area. J Clin Anesth 1992; 4: 4-10.

Waugh J, Perry IJ, Halligan AW, De Sweit M, Lambert PC, Penny JA, Taylor DJ, Jones DR, Shennan A. Birth weight and 24-hour ambulatory blood pressure in nonproteinuric hypertensive pregnancy. *Am J Obstet Gynecol* 2000; 183: 633-7.

Whittaker PG, Macphail S, Lind T. Serial hematologic changes and pregnancy outcome. *Obstet Gynecol* 1996; 88: 33-9.

Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P, Smith WC. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ* 2003; 326: 845-52.

Withagen MI, Visser W, Wallenburg HC. Neonatal outcome of temporizing treatment in early-onset preeclampsia. *Eur J Obstet Gynaecol Reprod Biol* 2001; 94: 211-5.

Wolfe LA, Preston RJ, Burggraf GW, McGrath MJ. Effects of pregnancy and chronic exercise on maternal cardiac structure and function. *Can J Physiol Pharmacol* 1999; 77: 909-17.

Xiong X, Mayes D, Demianczuk N, Olson DM, Davidge ST, Newburn-Cook C, Saunders LD. Impact of pregnancy-induced hypertension on fetal growth. *Am J Obstet Gynecol* 1999; 180: 207-13.

Xiong X, Demianczuk NN, Saunders LD, Wang FL, Fraser WD. Impact of preeclampsia and gestational hypertension on birth weight by gestational age. *Am J Epidemiol* 2002; 155: 203-9.

Yang JM, Wang KG. Relationship between acute fetal distress and maternal-placental-fetal circulations in severe preeclampsia. *Acta Obstet Gynecol Scand* 1995; 74: 419-24.

Yang JM, Yang YC, Wang KG. Central and peripheral hemodynamics in severe preeclampsia. *Acta Obstet Gynecol Scand* 1996; 75: 120-6.

Yasumoto K, Takata M, Ueno H, Tomoda F, Inoue H. Relation of circulating blood volume to left ventricular geometry in essential hypertension. *Hypertens Res* 2002; 25: 703-10.

Young P, Johanson R. Haemodynamic, invasive and echocardiographic monitoring in the hypertensive parturient. *Best Pract Res Clin Obstet Gynaecol* 2001; 15: 605-22.

Zhang J, Klebanoff MA, Roberts JM. Prediction of adverse outcomes by common definitions of

hypertension in pregnancy. *Obstet Gynecol* 2001; 97: 261-7.

Zhou Y, Damsky CH, Fisher SJ. Preeclampsia is associated with failure of human cytotrophoblasts to mimic a vascular adhesion phentype. One cause of defective endovascular invasion in this syndrome? *J Clin Invest* 1997; 99: 2152-64.

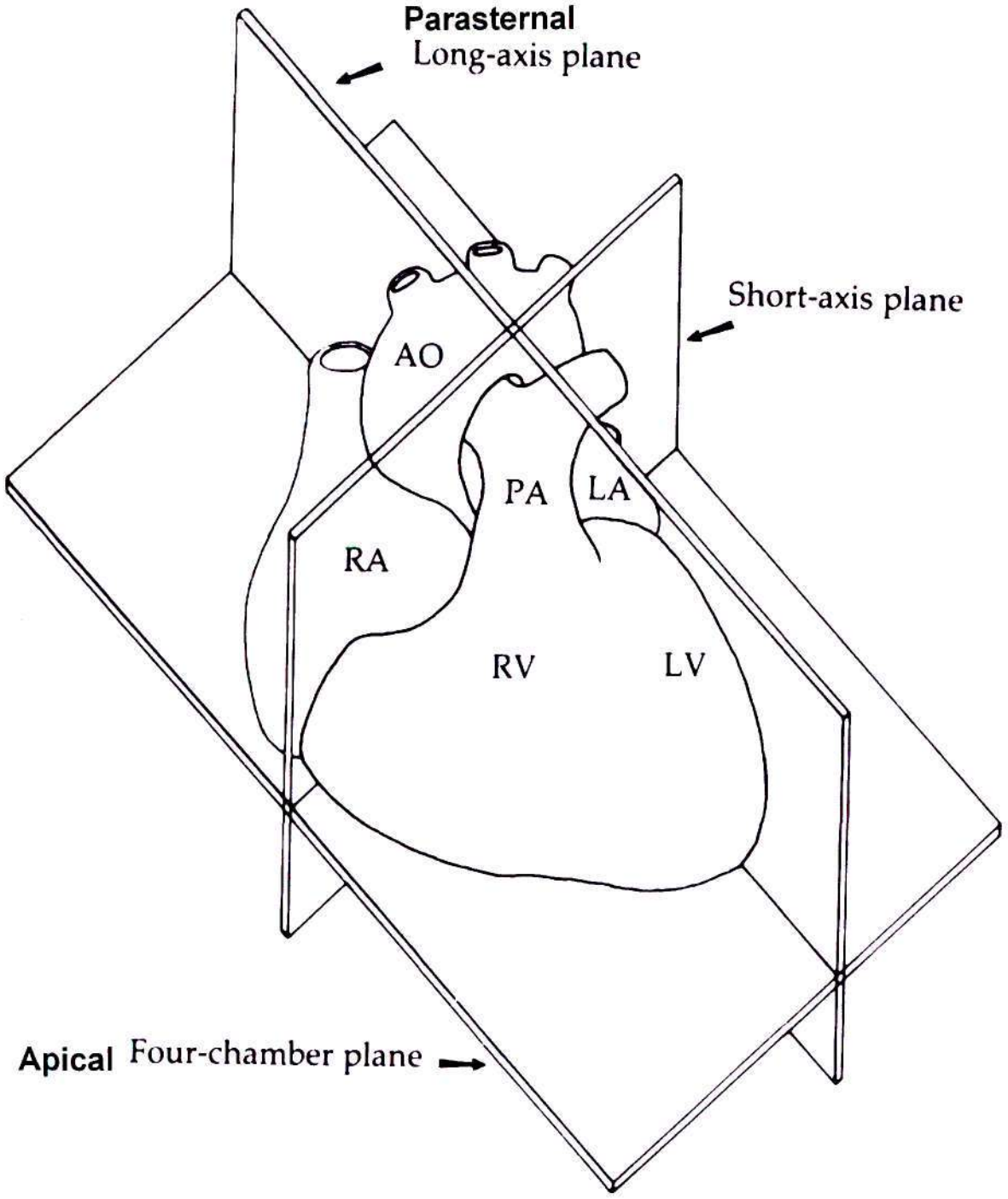

Figure 1

Echocardiographic planes

AO = aorta

PA = pulmonary artery

LA = left atrium

LV = left ventricle

RA = right atrium

RV = right ventricle

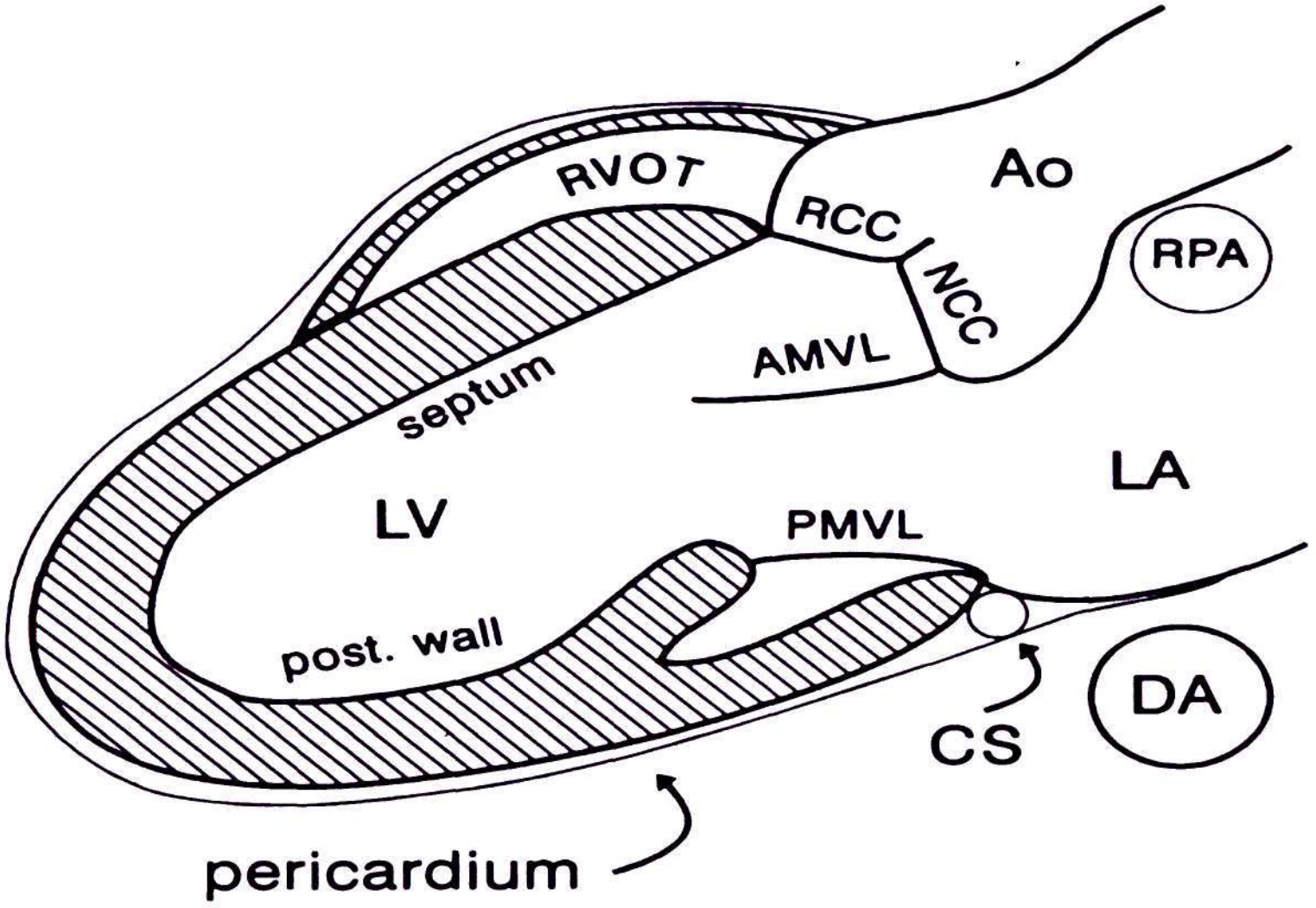

Figure 2 - Parasternal long axis view

AMVL = anterior mitral valve leafle, PMVL = posterior mitral valve leaflet, CS = coronary sinus

DA = descending aorta, RPA = right pulmonary artery, RVOT = right ventricle outflow tract

Post. Wall = posterior wall of left ventricle, LA = left atrium, LV = left ventricle

Ao = aorta, RCC = right coronary cusp of aortic valve, NCC = Non-coronary cusp of aortic valve

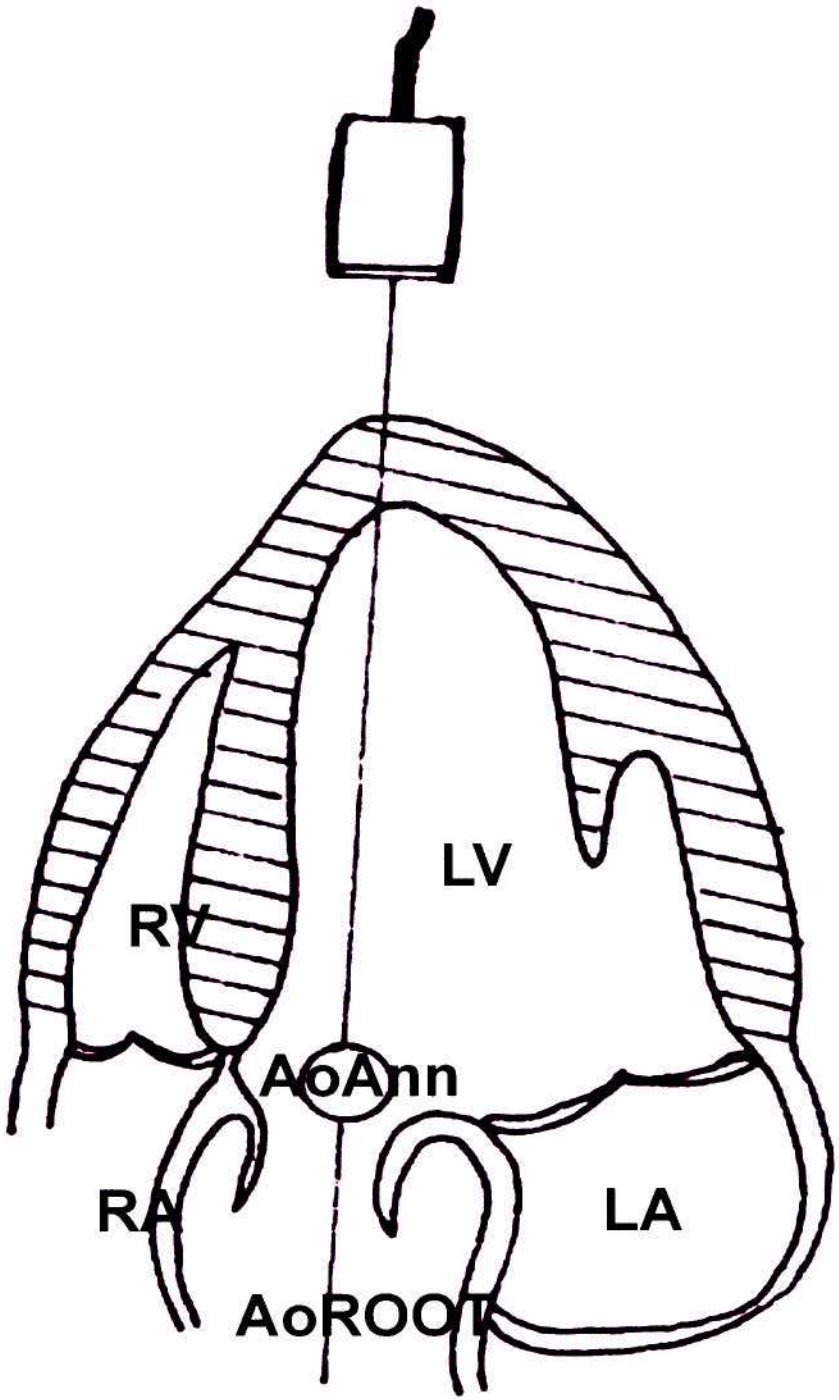

Figure 3

Apical 5 chamber view, doppler at LV outflow tract

AoAnn = aortic annulus

AoROOT = aortic root

LA = left atrium

LV = left ventricle

RA = right atrium

RV = right ventricle

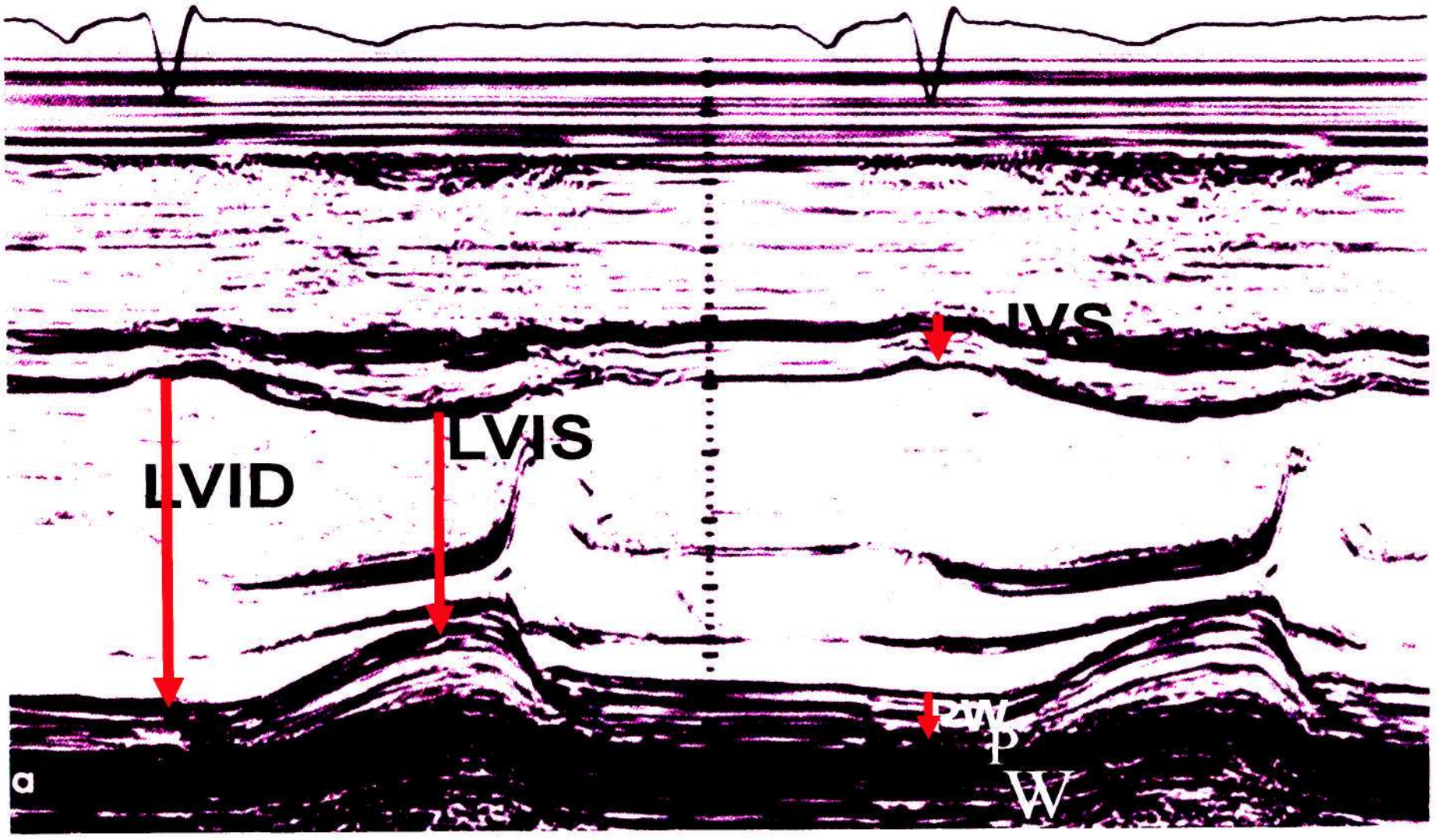

Figure 4 - M - mode echocardiographic study of the left ventricle

LVID = left ventricular internal dimension in diastole, LVIS = left ventricular internal dimension in systole

IVS = septum of the left ventricle, PW = posterior wall of the left ventricle

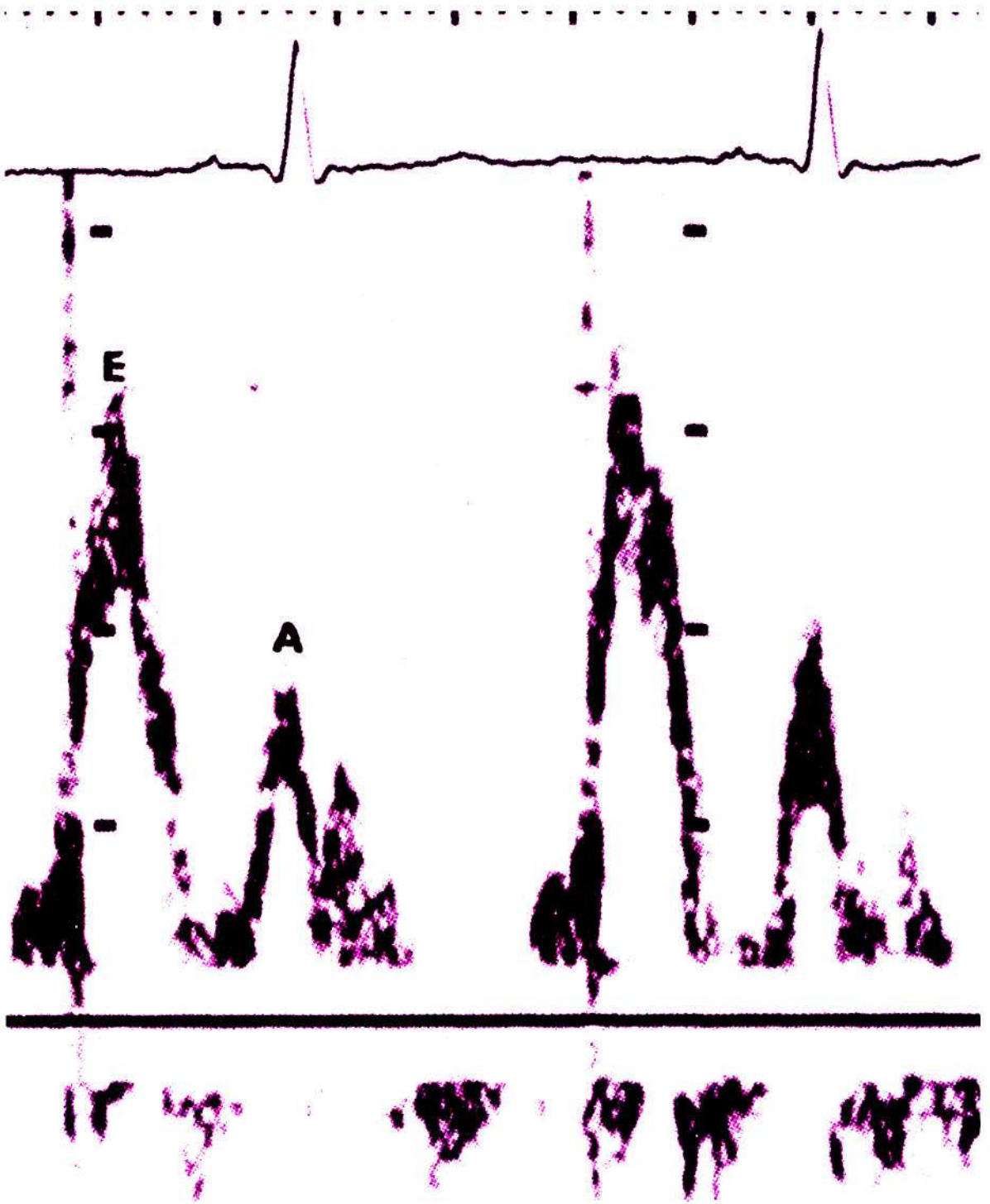

Figure 5

Left ventricle diastolic filling by pulsed doppler

E = peak early filling velocity

A = late (atrial) filling velocity

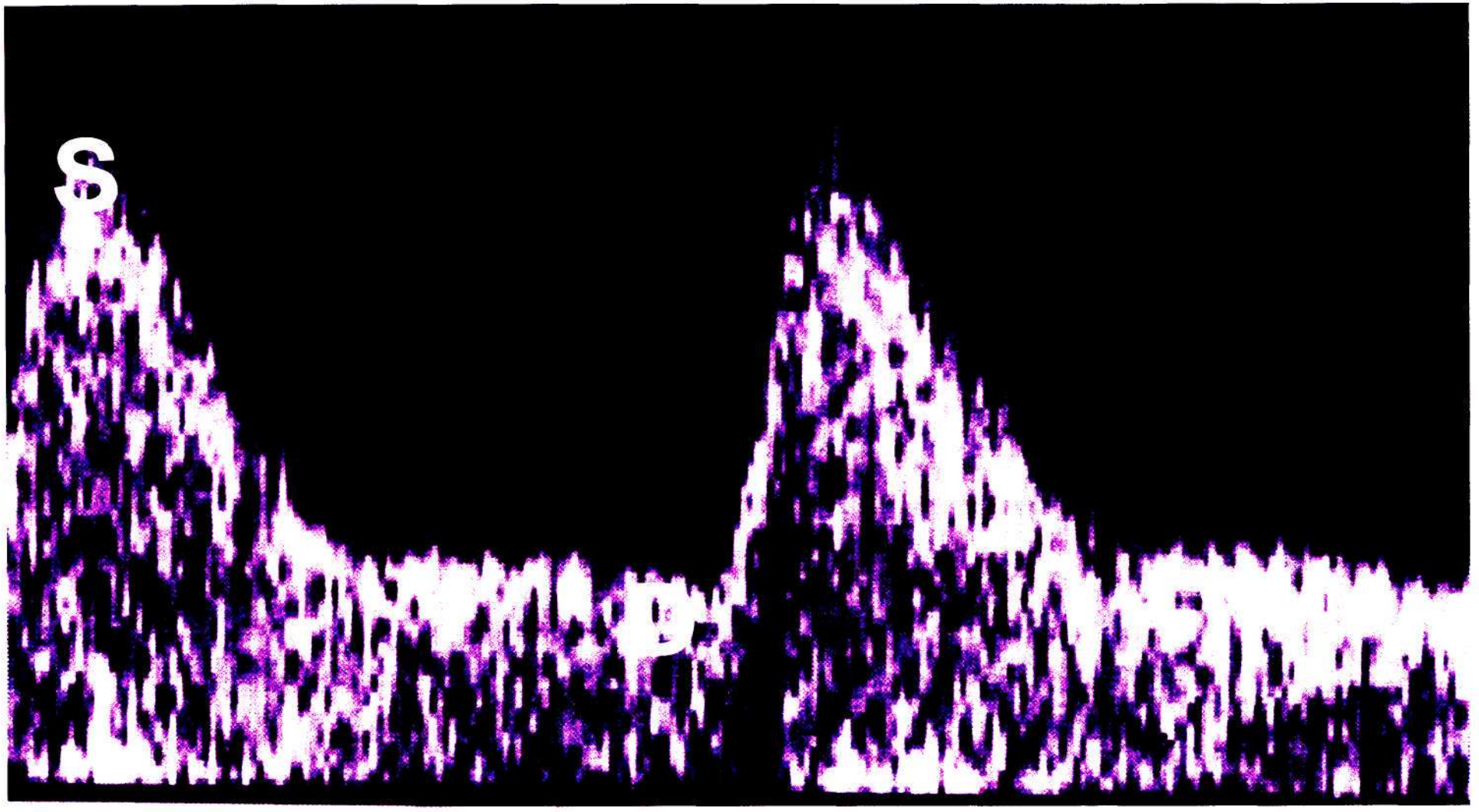

Figure 6(a) - Uterine artery Doppler velocimetry(Normal)

S = peak systolic velocity

D = end diastolic velocity

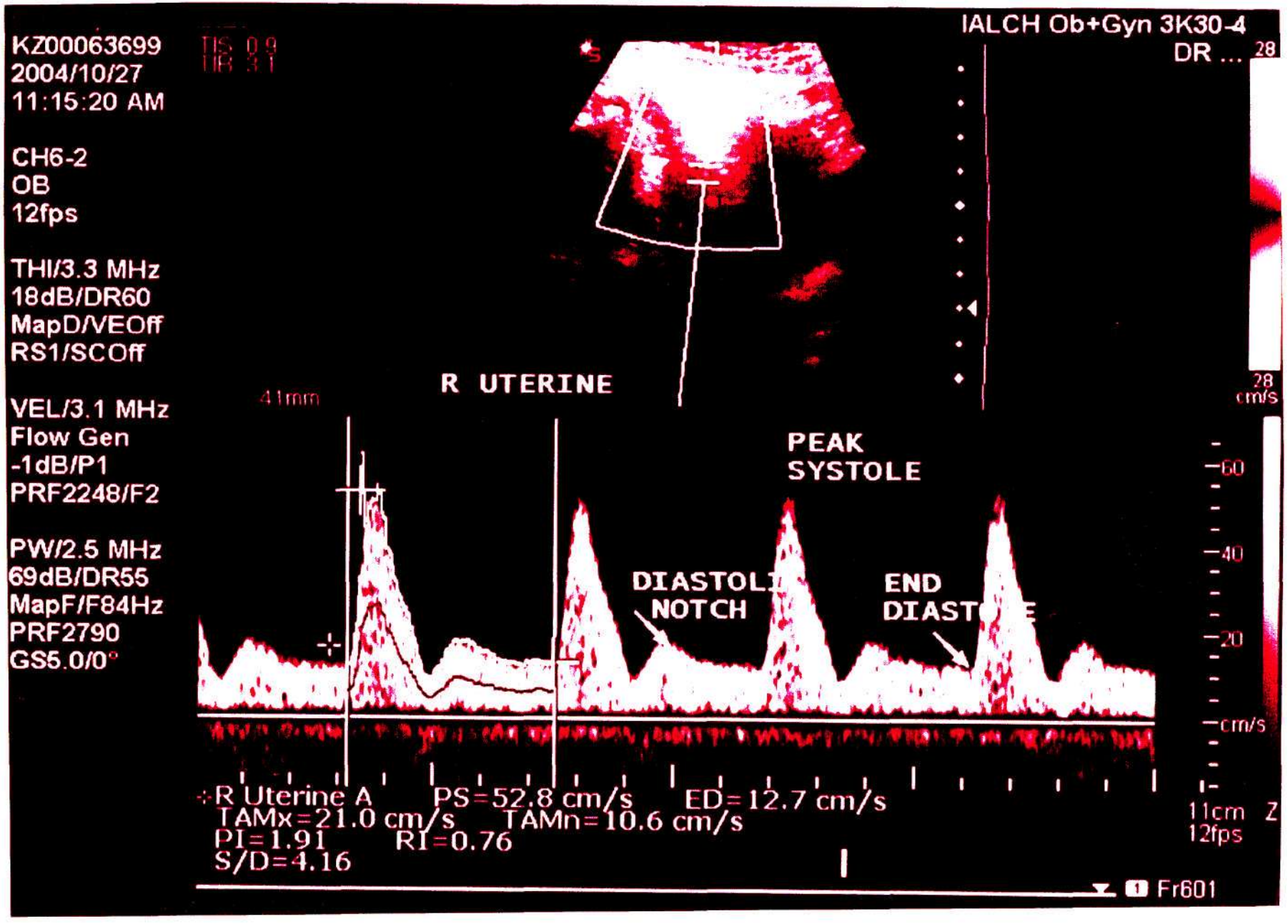

Figure 6(b) - Uterine artery Doppler velocimetry (Pre-Eclampsia)

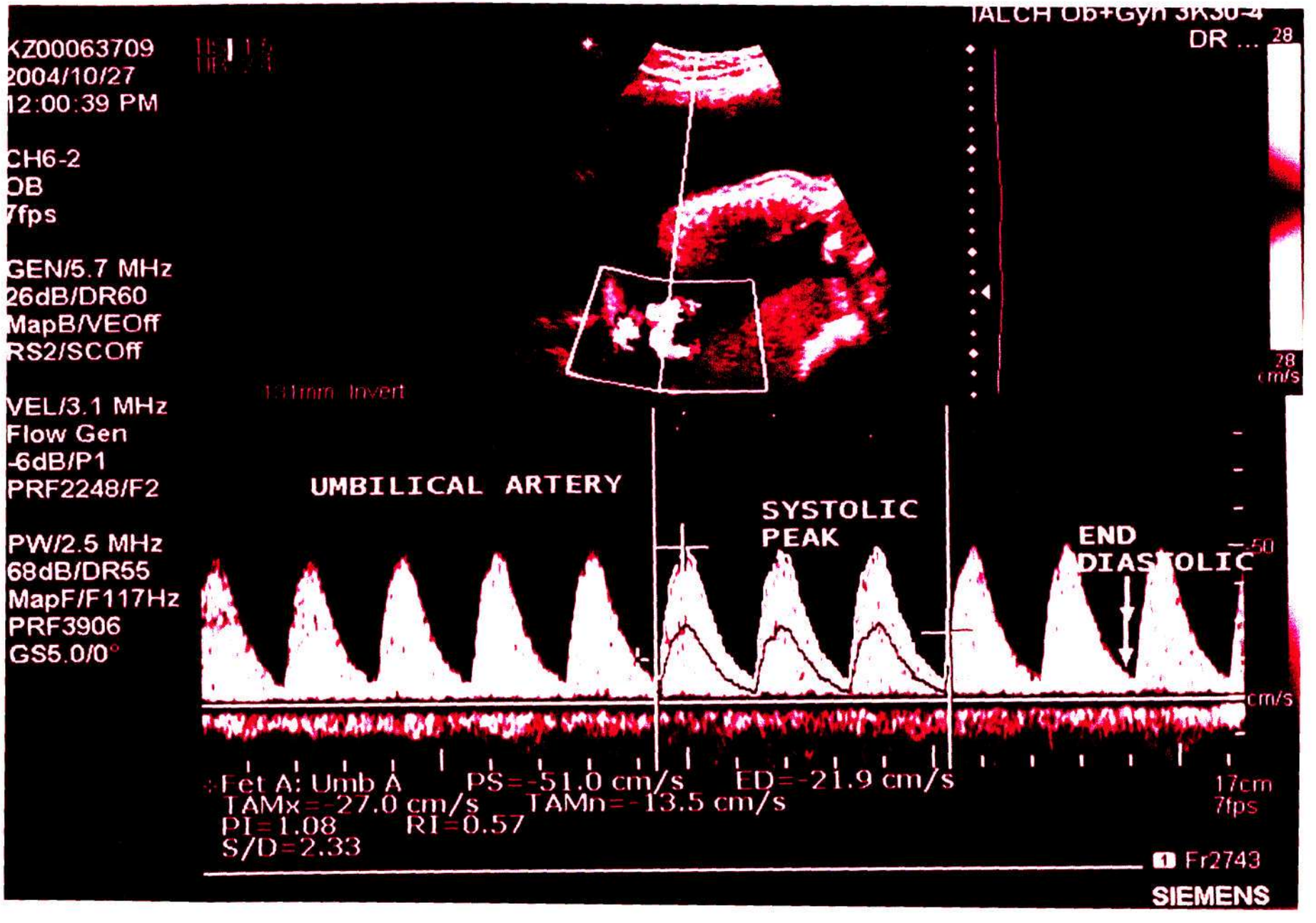

Figure 7 – Umbilical artery Doppler velocimetry (Normal)