THE SENSITIVITY OF UTERINE ARTERY SPECTRAL DOPPLER SCREENING IN PREDICTING PRE-ECLAMPSIA AND FOETAL GROWTH RESTRICTION

A dissertation submitted to the Faculty of Health Sciences, University of Johannesburg, as fulfilment for the Master's degree in Radiography: by

Yasmin Casmod

Supervisor: 20/6/12

Date

Co-supervisor: 01/06/2012

Date

ACKNOWLEDGEMENTS

I would like to express my sincere appreciation to the following:

- The almighty God-without you I would not have had the strength to pursue this study. I am most grateful for your guidance
- My family-(My parents and siblings)-you have supported me every step of the way. Thank you for all your love and support.
- My supervisor Mrs B Van Dyk-thank you for your support encouragement, care and most of all thank you for your patience.
- My co supervisor Professor Nicolaou- Thank you for your expert knowledge and professional advice
- The staff of the Ultrasound/X-Ray departments at Rahima Moosa Mother and Child hospital in particular Ms Lucille Israel-thank you for your continuous motivation.
- The management at Rahima Moosa Mother and Child Hospital-thank you for allowing me to carry out the study.

ABSTRACT

Monitoring the growth and wellbeing of the foetus is a major purpose of antenatal care. The use of diagnostic ultrasound to assess foetal wellbeing has become an important part of prenatal care in both low and high risk pregnancies.

Pre-eclampsia and foetal growth restriction (FGR) remains important causes of maternal and perinatal mortality and morbidity. Pre-eclampsia is characterised by an abnormal vascular response to placentation and is a multisystem disorder of unknown cause specific to pregnancy which affects the health of both mother and fetus.

Prep-eclampsia complicates between 2 and 8 % of all pregnancies and is the second most common cause of maternal deaths in the developing world.

The aim of this study was to assess the sensitivity of uterine artery spectral Doppler screening in the prediction of pregnancies with a high risk of developing pre-eclampsia or FGR before the clinical onset of the disease.

The research objectives were to:

1) Determine the sensitivity of first and second trimester uterine artery spectral Doppler assessment in predicting pre-eclampsia or FGR
   Identify associations between normal and abnormal uterine artery Doppler waveforms and pregnancy outcomes.
2) Determine the most effective Doppler indices
3) Develop ultrasound management guidelines

The data was statistically analyzed to determine the sensitivity of uterine artery Doppler screening.

In this study uterine artery Doppler screening performed well in the risk assessment of the most severe cases of pre-eclampsia and FGR. A larger prospective multicenter trial in South Africa is long overdue and therefore a follow-up study to assess Doppler as a screening tool in a high risk population, as per the guidelines formulated

CONTENTS

CONTENTS PAGE

CHAPTER 4: RESULTS

CHAPTER 5: DISCUSSION

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

LIST OF TABLES

LIST OF FIGURES/IMAGES/GRAPHS

LIST OF ANNEXURES:

CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

Monitoring the growth and wellbeing of the foetus is a major purpose of antenatal care. A key aim of antenatal care is to identify and manage the proportion of pregnancies at risk for complications. There is evidence that antenatal care enhances the outcome of pregnancy as measured by perinatal morbidity and mortality (Kurdi *et al.*, 1998).

Pre-eclampsia (PET) and foetal growth restriction (FGR) remains important causes of maternal and perinatal mortality and morbidity. Pre-eclampsia is a multisystem disorder of unknown cause specific to pregnancy which affects the health of both mother and foetus. Pre-eclampsia is associated with the highest maternal and foetal mortality and morbidity of all pregnancy complications with the highest incidence of serious adverse outcomes occurring in developing countries (Villar *et al.*, 2003).

Maternal complications include the HELLP syndrome, eclampsia, coagulopathy, cerebrovascular accident and death.

Newborns affected by foetal growth restriction are at increased risk for hypertension, cardiovascular disease and diabetes later in life (McLeod, 2008:727).

The introduction of diagnostic ultrasound has been one of the great medical advances in recent decades. The use of diagnostic ultrasound to assess foetal wellbeing has become an important part of prenatal care in both low and high risk pregnancies. The use of ultrasound has in particular improved the clinical care in pregnancy and expanded the research potential and understanding of normal and abnormal foetal development (Salvesen *et al.*, 1999).

Defective trophoblastic invasion is associated with subsequent development of preeclampsia and FGR.

Trophoblastic invasion is detectable by uterine artery Doppler measurements and precedes clinical manifestations.

1.2 THE RESEARCH QUESTION

In the developing world, hypertensive disorders represent the second most common cause of maternal death as well as perinatal foetal mortality and morbidity (Papageorghiou *et al.*, 2006 : 594). The lack of diagnosing the above conditions before the clinical onset of the disease is of great concern. Hence it prompted the researcher to investigate the use of uterine artery spectral Doppler analysis as a screening tool in order to predict pre-eclampsia and FGR before the clinical onset of the disease.

1.3 MOTIVATION FOR THE STUDY

Pre-eclampsia is a heterogeneous disorder with variable maternal and foetal manifestations. Pre-eclampsia occurs in about 3 % of pregnancies with a recurrence risk ranging from 7, 5 % to 65 % (Fratelli *et al.*, 2008). Defective trophoblastic invasion is associated with subsequent development of pre-eclampsia and foetal growth restriction.

Direct assessment of trophoblastic invasion in human pregnancy is not possible, however the use of Doppler ultrasound permits noninvasive evaluation of the uteroplacental circulation (Hamedi *et al.*, 2005).

Due to the high risk pre-eclampsia carries it may be beneficial to ascertain the predictive value of uterine artery spectral Doppler analysis for pre-eclampsia. Uterine artery Doppler waveform screening may enable caregivers to identify and target patients at higher risk for close monitoring and intervention with prophylactic therapy.

1.4 RESEARCH AIM

The aim of this study is to assess the sensitivity of uterine artery spectral Doppler screening in the prediction of pregnancies with a high risk of developing pre-eclampsia or FGR before the clinical onset of the disease. This would not only identify women who require closer surveillance, but would also help in selecting those most likely to benefit from any therapeutic measures.

1.5 RESEARCH OBJECTIVES

1.5.1 OBJECTIVE 1

Determine the sensitivity of first and second trimester uterine artery spectral Doppler assessment in predicting pre-eclampsia or FGR

Papageorghiou and co workers postulated that first trimester uterine artery spectral Doppler can identify over half of the women who will develop pre-eclampsia (Papageorghiou *et al.*, 2006 :594). Uterine artery Doppler screening can help in identifying patients at risk for pre-eclampsia and in so doing these patients can be closely monitored for better pregnancy outcomes. The clinical application of uterine artery Doppler spectral analysis is an accurate test which could routinely be used in the future to assess the risk for pre-eclampsia and FGR in order to plan appropriate antenatal care, with the aim of achieving improved patient management and perinatal outcomes.

1.5.2 OBJECTIVE 2 a & b

Statistically analyse data in an attempt to:

a) **Identify associations between normal and abnormal uterine artery Doppler waveforms and pregnancy outcomes.**
b) **Determine the most effective Doppler indices in the first and second trimester as a predictor of PET in the third trimester.**

Once data has been collected the data can be analysed to identify normal and abnormal uterine artery Doppler waveforms in association with pregnancy outcomes. The most effective Doppler Indies can also be correlated with pregnancy outcomes.

Uterine artery Doppler assessment is a non invasive test used to measure blood flow through the uterine circulation (Papageorghiou *et al.*, 2006 :595). Low end diastolic velocities and an early diastolic notch characterize the normal waveforms of uterine artery blood flow in women who are not pregnant or are in their first trimester of pregnancy (Cnossen *et al.*, 2008 : 701).

Uterine artery Doppler screening can help in identifying patients at risk for PET and in so doing these patients can be closely monitored and possibly treated for better pregnancy outcomes.

1.5.3 OBJECTIVE 3

Develop ultrasound management guidelines

Once effective Doppler indices have been established for the population ultrasound management guidelines can be developed.

Accurate prediction of pre-ecalmpsia preferably in the first trimester of pregnancy to allow early intervention is therefore paramount to providing appropriate surveillance and therapy in an effort to improve perinatal outcomes (Mcleod., 2008 : 727).

The use of uterine artery spectral Doppler as a screening tool may help in providing good antenatal care by identifying the majority of pregnancies destined to develop complications of uteroplacental insufficiency and also by identifying a large group of women at particularly low risk of developing such complications (Papageorghiou *et al.*, 2005 : 588).

1.6 DEFINITION OF TERMS

1.6.1 First trimester

Between week 1 and week 13

1.6.2 Second trimester

Between week 14 and week 27

1.6.3 Third trimester

Between week 28 and week 39

1.6.4 Pre-eclampsia

Pre-eclampsia (PET) is a multi-system disease specific to pregnancy and is characterized by high blood pressure, proteinuria, renal, liver and haematological abnormalities.

1.6.5 Eclampsia

The occurrence of generalized convulsions during pregnancy, not due to epilepsy or other convulsive disorders.

1.6.6 Proteinuria

Proteinuria is defined as >300mg total protein in a 24-H urine collection or 1+ proteinuria by dipstick in two consecutive occasions at least four hours apart. Severe proteinuria is defined as >5g of protein per day.

1.6.7 Oedema

Extravascular fluid.

1.6.8 HELLP syndrome

Haemolytic anaemia, Elevated liver enzymes, Low platelet count

1.6.9 Foetal growth restriction

Foetal Growth Restriction (FGR) is defined as birthweight below the 10th per centile or a birthweight less than 2.5kg.

1.6.10 Hypertension

Hypertension is defined as a blood pressure of at least 140mm Hg (systolic) or at least 90 mm Hg (diastolic) on at least two occasions and at least 4-6 hours apart.

Severe hypertension is defined as a rise in blood pressure to at least 160 mm Hg (systolic) or at least 110 mm Hg (diastolic) (Sibai *et al.*, 2005 : 785).

1.6.11 Chronic hypertension

Blood pressure reading of 140/90 mm Hg or greater before pregnancy or before the 20th week of gestation (Wagner *et al.*, 2007: 560).

1.6.12 Gestational hypertension

Hypertension that occurs for the first time during the 2nd half of pregnancy in the absence of proteinuria.

For the purpose of this study "foetus" was spelt in accordance with the South African dictionary

1.7 SUMMARY

Pre-eclampsia remains an important cause of maternal and perinatal morbidity and mortality.

The importance of this disease is strengthened by the fact that always two individuals are affected and have long term alterations.

Uterine artery spectral Doppler screening for PET is the best performing of all the available clinical tests to date and is definitely the most widely studied. It has been argued that this single screening test can be "piggy backed" onto existing ultrasound examinations, does not involve significant extra costs, has a low false positive rate and will identify a cohort of at risk patients who would benefit from increased surveillance, and in so doing meets all the criteria for a worthwhile screening program (Papageorghiou *et al.*, 2007: 104).

Thus determining the most effective Doppler indices in the first and second trimester as a predictor of PET in the third trimester would have an enormous benefit for public health.

CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

Hypertensive disorders of pregnancy (chronic hypertension, proteinuric hypertension/ pre-eclampsia, eclampsia, HELLP syndrome and rupture of the liver) complicate about 10 % of all pregnancies (Wagner *et al.*, 2007: 560).

Pre-eclampsia is a multisystem disorder of unknown cause and is unique to human pregnancy (Sibai *et al.*, 2005: 785).

2.2 CLASSIFICATION OF HYPERTENSION IN PREGNANCY

A) New-onset hypertension and/or proteinuria in pregnancy:

1) Gestational hypertension (without proteinuria)
2) Gestational proteinuria (without hypertension)
3) Pre-eclampsia (hypertension and proteinuria)

B) Chronic hypertension and renal disease:

1) Chronic hypertension without proteinuria
2) Chronic renal disease (proteinuria with or without hypertension)
3) Chronic hypertension with superimposed preeclampsia (i.e. with new onset hypertension in pregnancy)

C) Unclassified:

1) Hypertension and/or proteinuria noted when the first presentation of the disease is after 20 gestational weeks
2) As above, when noted for the first time during pregnancy, labour or puerperium and there is insufficient background data to permit a diagnosis

Women who are hypertensive and pregnant are then subdivided into those with:

• Chronic hypertension

Or

• Pregnancy induced or gestational hypertension

Women with pregnancy induced hypertension are even further subdivided into:

• A majority with non proteinuric pregnancy induced hypertension and

• A minority suffering from pre-eclampsia

(McCarthy *et al.*, 2009: 136)

2.3 CLINICAL PRESENTATION OF PRE-ECLAMPSIA

The clinical presentation of pre-eclampsia may be subtle or sudden. Some women may be asymptomatic at the time they are found to have hypertension and proteinuria, while others may present with symptoms of severe pre-eclampsia (Wagner 2004 : 2319). In clinical terms the disease varies in time of onset, speed of progression, degree to which the mother or foetus or both are endangered and the pattern of maternal organ involvement (Redman *et al.*, 2004 : 566).

Pre-eclampsia can manifest as either a maternal syndrome (hypertension and proteinuria), with or without other multisystem abnormalities or a foetal syndrome (foetal growth restrictions (FGR), reduced amniotic fluid and abnormal oxygenation of the foetus), (Sibai *et al.*, 2005 : 785). Although the diagnosis of the condition relies on the demonstration of hypertension and proteinuria in the mother the clinical outcome depends primarily on the presence of multisystem dysfunction in the mother or impairment of growth and oxygenation in the foetus (Yu *et al.*, 2008 : 310).

The maternal syndrome is probably more than one disease with major differences between near-term pre-eclampsia without demonstrable foetal involvement and pre-eclampsia which is associated with low birthweight and preterm delivery (Sibai *et al.*, 2005 : 785).

2.4 MATERNAL FEATURES OF PRE-ECLAMPSIA

Due to its multisystem nature the maternal syndrome is broadly classified into four main groups depending on the cardiovascular, renal, cerebral and hepatic signs namely:

1. Gestational hypertension : hypertension only
2. Pre-eclampsia-hypertension plus proteinuria
3. Eclampsia : generalised convulsions
4. HELLP Syndrome : hepatic and haematological dysfunction

(Drife *et al.*, 2004:367)

Pre-eclampsia is regarded as serious if severe hypertension is associated with mild proteinuria or if mild hypertension is associated with severe proteinuria (> 5g per day). Pre-eclampsia is also regarded as severe in the presence of multi-organ involvement such as pulmonary oedema, seizures, oliguria (< 500ml per day), thrombocytopenia with a platelet count < 100 000 per µL (Table 1), abnormal liver enzymes associated with persistent epigastric or right upper quadrant pain or persistent and severe CNS symptoms such as altered mental status, headaches, blurred vision or blindness (Sibai *et al.*, 2005 : 786).

According to Sibai and co-workers (2005 : 785) maternal and perinatal outcomes in pre-eclampsia depend on one or more of the following:

1) Gestational age at time of disease onset
2) Severity of the disease
3) Quality of patient management
4) Presence or absence of pre-existing medical disorders such as:
   - Chronic Hypertension
   - Diabetes

Between 4 and 14% of women with pre-eclampsia present with superimposed HELLP syndrome (Wagner 2004 : 2319).

TABLE 2.1: ELEMENTS OF SEVERE PRE-ECLAMPSIA

ELEMENT	DEFINITION
Severe hypertension	Blood pressure > 160 mm Hg Systolic or > 110 mm Hg diastolic
Severe proteinuria	> 5g protein in 24 hrs or > 3+ protein by dipstick analysis
Oliguria	Urine output < 500 ml in 24 hours
Microangiopathic haemolytic anaemia	Schistocytes on blood smear
Renal impairment	Serum creatinine level > 1.2mg/dL
Neurologic signs and symptoms of impending eclampsia	Altered mental status, headache or visual changes or loss
Cardiac decompensation	Pulmonary oedema
Impaired liver function	Right upper quadrant pain (may herald impending hepatic rupture), elevated liver function test results
Thrombocytopenia	Platelet count < 100 X 10 to the power 9 /L
Foetal complications	FGR, intrauterine foetal distress

Table 2.1 outlines the elements and definitions of severe pre-eclampsia.

2.5 FOETAL FEATURES OF PRE-ECLAMPSIA

Ultrasound features of pre-eclampsia demonstrated in the foetus include:

- Foetal growth restriction
- Changes in amniotic fluid volume (reduced amniotic fluid/oligohydramnios)
- Abnormal Doppler waveforms

Severe growth restriction leads to premature delivery, with the related risk of long term respiratory and neurodevelopmental problems. There is an increased perinatal mortality, particularly in very low birth weight infants, and neurodevelopmental sequels are related to birthweight as well as gestation at delivery. Intrauterine hypoxia which can occur in FGR may contribute to the risk for cerebral palsy. If

central redistribution of bloodflow in the foetus occurs, there can be ischeamia of the gut leading to necrotising enterocolitis (Loughna 2006 : 266).

2.6 AETIOLOGY OF PRE-ECLAMPSIA

Pre-eclampsia is characterised by an abnormal vascular response to placentation which is associated with increased systemic vascular resistance, enhanced platelet aggregation, activation of the coagulation system and endothelial cell dysfunction (Sibai *et al.,* 2005 : 785). Pre-eclampsia therefore seems to arise from complex interactions, among placenta-derived products, maternal constitutional factors and exaggerated adaptive mechanisms that normally occur during pregnancy (inflammatory response, hypercoagulable state) (Wagner *et al.*, 2007: 561).

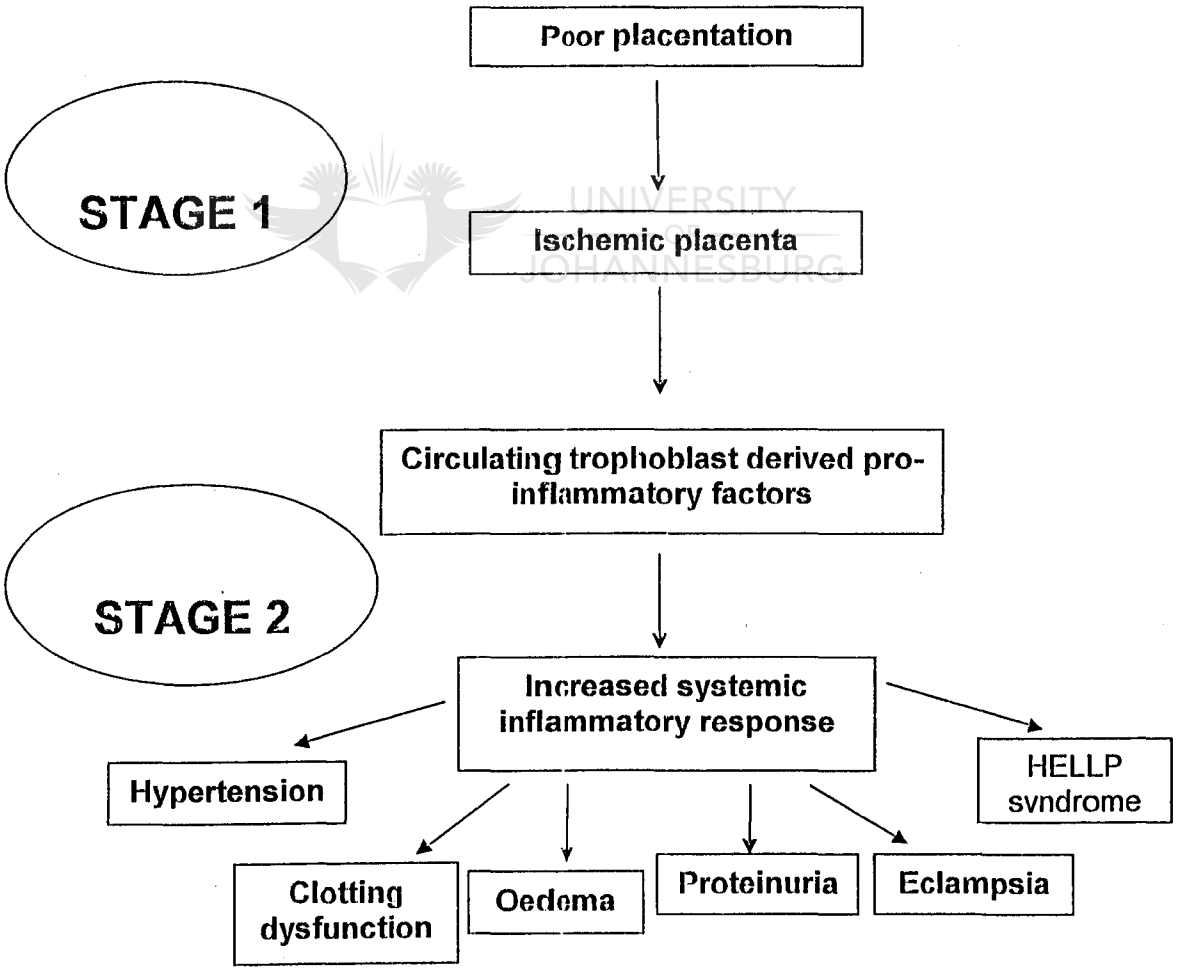


FIGURE 2.1: DEMONSTRATING THE 2 STAGE EVOLUTION OF PREECLAMPSIA (Redman *et al.*,2004 : 569)

These features arise from the total circulatory disturbances caused by systemic maternal endothelial cell dysfunction or activation which represents part of the inflammatory process (Redman et al., 2004 : 566).

Although the exact cause is still unknown inspite of extensive research (Hallack., 2000 :639), it is fair to assume that pre-eclampsia is related to the presence of the human placenta or alternatively to the maternal response to placentation. Sibai and co-workers (2005 : 785) postulate that if poor placentation is not the cause of pre-eclampsia it is undoubtedly a powerful predisposing factor for the disease during pregnancy.

Research suggests that, normal placentation involves successful trophoblastic invasion of maternal decidua, myometrium and blood vessels, in particular the spiral arteries. Extravillous trophoblast invasion of the spiral arteries allow for the adjustment of their endothelial lining and intima media and in so doing cause progressive dilatation of these small blood vessels. Maternal spiral arteries are small-caliber vasoreactive vessels, which are altered into loose distended uteroplacental arteries during pregnancy, creating a low resistance vascular bed with a high blood flow, ensuring a more than 10 fold increase in blood supply to the intervillous space during pregnancy (Ozkaya *et al.,* 2007 : 382). This physiological change thus converts the spiral arteries from small muscular arteries to dilated tortuous uteroplacental vessels able to accommodate the increased blood flow and the linked hemodynamic forces of pregnancy. The diameter of the spiral arteries increases from 150-200 to 300-500mm thus reducing the impedance to flow and optimising foeto-maternal exchange in the intervillous space. Uterine blood flow increases from 100 to 500-800ml/min at term (Swanepoel , 2004 : 4), which is thought to be the consequence of a decrease in downstream resistance through trophoblast invasion of the maternal spiral arteries, a process beginning at conception and continuing until the end of the second trimester (Lees *et al.,* 2001 : 369).

Trophoblast invasion occurs in a stepwise manner starting with plugging of the distal ends of the arteries followed by movement of the trophoblastic cells into its decidual segments and after several weeks delay, finally into the myometrial segments. The first phase of this process takes place between weeks 8-10 of gestation while the second phase takes place between weeks 14-24 (Martin *et al.,* 2001 : 586). Failure

of trophoblastic invasion and consequent underperfusion of the placenta leads to the release of hormonal factors into the maternal circulation. These placental factors cause endothelial dysfunction, which may be the underlying mechanism for the subsequent development of the clinical syndrome of hypertension and proteinuria (Yu *et al.*, 2003 : 238).

2.7 PATHOPHYSIOLOGY OF PRE-ECLAMPSIA

Although the pathophysiology of pre-eclampsia and eclampsia is still inadequately understood, vasospasm has been recognised as one of the main factors giving rise to this syndrome (Mitani *et al.*, 2009 : 882).

Pre-eclampsia is recognised as a syndrome or cluster of features that together define the disorder among which newly diagnosed hypertension and proteinuria give prominence (Redmen *et al.*, 2004 : 566).

One of the most prominent physiological changes is intense systemic vasospasm, which is responsible for decreased perfusion of almost all organ systems. Perfusion is also reduced because of vascular haemoconcentration. Also pre-eclampsia is accompanied by an exaggerated inflammatory response and inappropriate endothelial activation. Activation of the coagulation system and resultant microthrombi formation further reduces blood flow to organs (Wagner *et al.*, 2004 : 2319).

Severe vasospasm and high blood pressure may give rise to the following serious secondary features of the syndrome:

1) **<u>The brain:</u>**

- Severe frontal headache
- Visual disturbances
- Nausea and vomiting
- Occular fundal changes may be seen
- Twitching, which may be the first signs of Eclampsia.

A vision disorder of unpredictable seriousness sometimes with complete blindness may develop as a result of local oedema or ischemia in the occipital cortex.

2) **The liver:**
   - Epigastric pain

Upper abdominal pain occurs in pre-eclamptic complications and HELLP syndrome.

3) **The kidney:**
   - Severe proteinuria
   - Generalised oedema
   - Oliguria

Pre-eclampsia may be associated with significant protein loss in urine, resulting in a lowering of plasma albumin. Protein loss may cause considerable oedema and sometimes also ascites and pulmonary oedema. Oliguria often occurs and has no effect provided serum creatinine levels remain normal.

Ischemia of the kidneys leads to renal damage with increased capillary permeability and subsequent proteinuria. Retention of salt, in turn aggrevates oedema while impaired renal function is responsible for oliguria (McCall Sellers., 2004 : 1162-1163).

4) **The uterus:**

   - Placenta abruption
   - Foetal distress
   - Foetal death

5) **The placenta:**

   - Placental insufficiency

- FGR, leading to
- Foetal hypoxia & foetal distress and possibly
- Intra-uterine foetal death

Due to the vasospasm, there is reduced blood flow through the decidual arteries - causing hypoxia. To overcome the hypoxia, the following occurs:

- Hyperplasia of the syncytial and cytotrophic layers of the chorionic villi, causing more branched villi
- Swelling of the villi occurs
- Thickening of the basement membrane occurs
- As these small villi are fragile and not well attached, there is separation of these villi causing tiny emboli to be released into the mothers general circulation. These emboli are then destroyed with the release of thromboplastin which initiates the process of Disseminated Intravascular Coagulation.

These changes to the placenta result in:

- Placental insufficiency and a small placenta with infarcts and calcifications leading to:

- FGR with progressive acidosis and hypoxia which in turn leads to:
- Foetal distress and possibly
- Foetal death

(McCall Sellers., 2004 : 1166)

The combination of early developmental pathology in the placental bed and villi with subsequent ischemic thrombotic vascular pathology, results in so called placental insufficiency that presents clinically as impaired foetal growth, placental separation (abruption), due to the presence of multiple placental infarcts (Costa *et al.*, 2008 :1034).

It is generally accepted that pre-eclampsia is a two-stage disorder, (figure 2.1) with firstly, an impaired early placentation and secondly, placental release of angiogenic factors leading to endothelial dysfunction. It implies that, although the clinical

appearances of the syndrome appear beyond 20 gestational weeks, the pathogenic substrate has already been recognised in the first half of pregnancy (Herraiz *et al.*, 2009 : 1123). FGR is thus a result of chronic uteroplacental insufficiency (Melchiorre *et al.*, 2009 : 524).

2.8 PERINATAL MORBIDITY AND MORTALITY

Pre-eclampsia and Foetal Growth Restriction (FGR) are major causes of perinatal morbidity and mortality (Papageorghiou *et al.*, 2001 : 441), Pre-eclampsia complicates between 2 and 8 % of all pregnancies and is the second most common cause of maternal deaths in the developing world (Papageorghiou *et al.*, 2006 : 594)

Pre-eclampsia is an extremely unpredictable and inconsistent condition and progression is often rapid and severe when it occurs early in pregnancy (Drife *et al.*, 2004 : 370). It is therefore a leading cause of foetal and maternal morbidity and mortality worldwide particularly in cases with an early onset < 34 weeks (Herraiz *et al.*, 2009 : 1123). In general, maternal and perinatal outcomes are encouraging in women with mild pre-eclampsia developing beyond 36 weeks gestation. Hence maternal and perinatal mortalities and morbidities are increased in women developing the condition before 33 weeks gestation, in those with pre-existing medical disorders and in women from developing countries (Sibai *et al.*, 2005: 785).

In developed countries the perinatal mortality rate among pre-eclamptic pregnancies is five times as great as non pre-eclamptic pregnancies and indicated preterm deliveries for pre-eclampsia account for fifteen (15%) of preterm births (Bodnar *et al.*, 2005:475). Pre-eclampsia is therefore the most common cause for iatrogenic prematurity, and through the association with FGR is a significant contributor to perinatal death.

2.9 MATERNAL COMPLICATIONS

Perinatal outcomes are affected by the severity and length of the condition as well as by preventative and therapeutic management strategies (Mcleod., 2008 : 728). Maternal complications of pre-eclampsia include:

- Placental abruption (1-4%)
- HELLP syndrome (10-20%)
- Pulmonary oedema (2-5%)
- Acute renal failure (1-5%)
- Eclampsia (< 1%)
- Liver failure or haemorrhage (<1%)
- Stroke (rare)
- Death
- Long term cardiovascular morbidity

(Sibai *et al.*, 2005 : 786)

Death associated with pre-eclampsia-eclampsia may be due to cerebrovascular events, renal or hepatic failure, or HELLP syndrome (Wagner 2004 : 2319).

2.10 NEONATAL COMPLICATIONS

Evidence suggests that pre-eclampsia often coexists with FGR (Papageorghiou *et al.*, 2008 : 367). The report on Confidential Enquiry into Stillbirths and Deaths in Infancy cites one in six stillbirths that occur in pregnancies complicated by maternal hypertension (McCarthy *et al.*, 2009 : 136).

According to (Sibai *et al.*, 2005 : 786) foetal complications of preeclampsia include:

- Preterm delivery (15-67%)
- FGR (10-25%)

- Hypoxia-neurologic injury (<1%)
- Perinatal death (1-2%)
- Long term cardiovascular morbidity associated with low birthweight

Newborns affected by FGR are at an increased risk for hypertension, cardiovascular disease and diabetes later in life (Mcleod., 2008 : 727), suggesting that the origins of adult disease lie in a hostile intra-uterine environment (Lees *et al.*, 2001 : 369). According to the Barker Hypothesis, FGR is identified as a major risk factor for premature artherosclerosis (Dornhofer *et al.*, 2008 : 35).

2.11 HYPERTENSIVE DISORDERS OF PREGNANCY IN SOUTH AFRICA

Hypertensive disorders of pregnancy are the most common medical complications in pregnancy, and remain the commonest direct cause of maternal mortality in South Africa (Moodley, 2010 : 717).

In South Africa hypertensive disorders of pregnancy account for 19% of all deaths (Moodley, 2007 : 560). In the same way 18% of all maternal deaths in the USA are reported to be due to hypertensive disorders of pregnancy (Moodley., 2007 : 560).

The latest Saving Mothers report (table 2) indicate that in South Africa there were 622 maternal deaths from hypertensive disorders of pregnancy during the period 2005-2007 (Moodley 2007 : 717).

Table 2.2: Primary obstetric causes of death in the different subcategories of hypertensive disorders of pregnancy.

SUBCATEGORIES	2005-2007		2002-2004	
	N	%	N	%
Chronic hypertension	38	6.1	37	5.9
Proteinuric hypertension	173	27.8	171	27.2

Eclampsia	344	55.3	347	55.3
HELLP syndrome	54	8.7	70	11.1
Rupture of liver	10	1.6	3	0.5
Acute fatty liver	3	0.48	0	0.0
Total	**622**		**628**	

Table 2.2 shows the primary causes of death in South Africa during pregnancy as related to the subcategories of hypertensive disorders. Eclampsia accounted for 55.3% of deaths in the period 2005-2007 and cerebral complications accounted for 45.5% (Moodley 2010 : 717).

Eclampsia is therefore the commonest direct cause of maternal deaths in South Africa which is of concern since it is avoidable if pre-eclampsia is identified early and correctly managed (Moodley, 2010 : 717).

The majority of maternal deaths from hypertensive disorders in South Africa are associated with preventable factors and inadequate antenatal care (Moodley , 2010 : 719).

Recent evidence suggests that pre-eclampsia can be further subdivided into early pre-eclampsia and late pre-eclampsia where early pre-eclampsia is associated with a higher frequency of foetal growth restriction and both short and long term maternal mortality and morbidity (Poon *et al.*, 2009 : 497).

2.12 PREDISPOSING FACTORS FOR PRE-ECLAMPSIA

According to several authors (McCall Sellers, 2004 : 1163, Wagner *et al.*, 2007 : 561, Sibai *et al.*, 2005 : 787) the syndrome is found to occur more commonly in women with the following predisposing conditions.

- Primigravida (especially the older primigravida >35y and the teenage primigravida, particularly under 16 years of age)
- Lower income groups
- Chronic hypertension (either essential or secondary)
- Diabetes Mellitus
- Chronic nephritis
- Obesity
- A history of pregnancy induced hypertension, and/or proteinuria

-In a previous pregnancy

-In the family

- Multiparity
- Multiple gestations
- Thrombophilias
- Autoimmune and connective tissue diseases
- Trophoblastic disease

The incidence of pre-eclampsia in a previous pregnancy carries a recurrence risk that varies from 7% to 13%. Primigravidas are 15 times more likely to develop pre-eclampsia than their parous counterparts, furthermore a strong family history of pre-eclampsia increases the risk of developing the disease eight-fold. Pre existing hypertension or renal disease and foetal conditions (egg: multiple pregnancy, hydatidiform mole and triploidy) can considerably increase the risk for pre-eclampsia (Fayyad *et al.*, 2005 : 866).

2.13 BLOOD SUPPLY OF THE UTERINE ARTERIES

The uterus is supplied by the left and right uterine arteries which ascend along the lateral aspect within the broad ligament and end by anastomosing with the respective ovarian artery. At intervals along their length the vessels give rise to arcuate arteries that pass medially and penetrate the myometrium. The arcuate arteries divide almost instantly into anterior and posterior branches that run circumferentially between the outer and middle thirds of the myometrium and

anastomose freely with their counterparts from the opposite side in the midline. During their course the arcuate arteries give rise to the radial arteries that are directed towards the lumen of the uterus. As they approach the myometrial-endometrial boundary each radial artery gives off lateral branches, the basal arteries that supply the myometrium and the deeper basalis parts of the endometrium and continues as a spiral artery. The spiral arteries are highly coiled within the basalis and the deeper parts of the functionalis, but as they approach the uterine lumen they narrow and divide into several smaller branches. (Burton *et al.*, 2009 : 474).

Normal pregnancy requires that two distinct but inter-related changes in cardiovascular function take place. Firstly the blood supply to the uterus is enhanced and a maternal circulation to the placenta is recognised, efficiently diverting blood away from the lower limbs. Secondly numerous hemodynamic alterations in the mothers circulation occurs. These alterations promote an effective uteroplacental blood supply (Burton *et al.*, 2009 : 473).

Normal pregnancy is characterized by the formation of large arterio-venous shunts that persist in the immediate post-partum period (figure 2-B & C). By contrast pregnancies complicated by severe pre-eclampsia are characterized by minimal arterio-venous shunts, and thus narrower uterine arteries (figure 2-D). Extravillous cytotrophoblast invasion in normal pregnancy extends beyond the decidua into the inner myometrium (figure 2-B) resulting in the formation of funnels at the discharging tips of the spiral arteries.

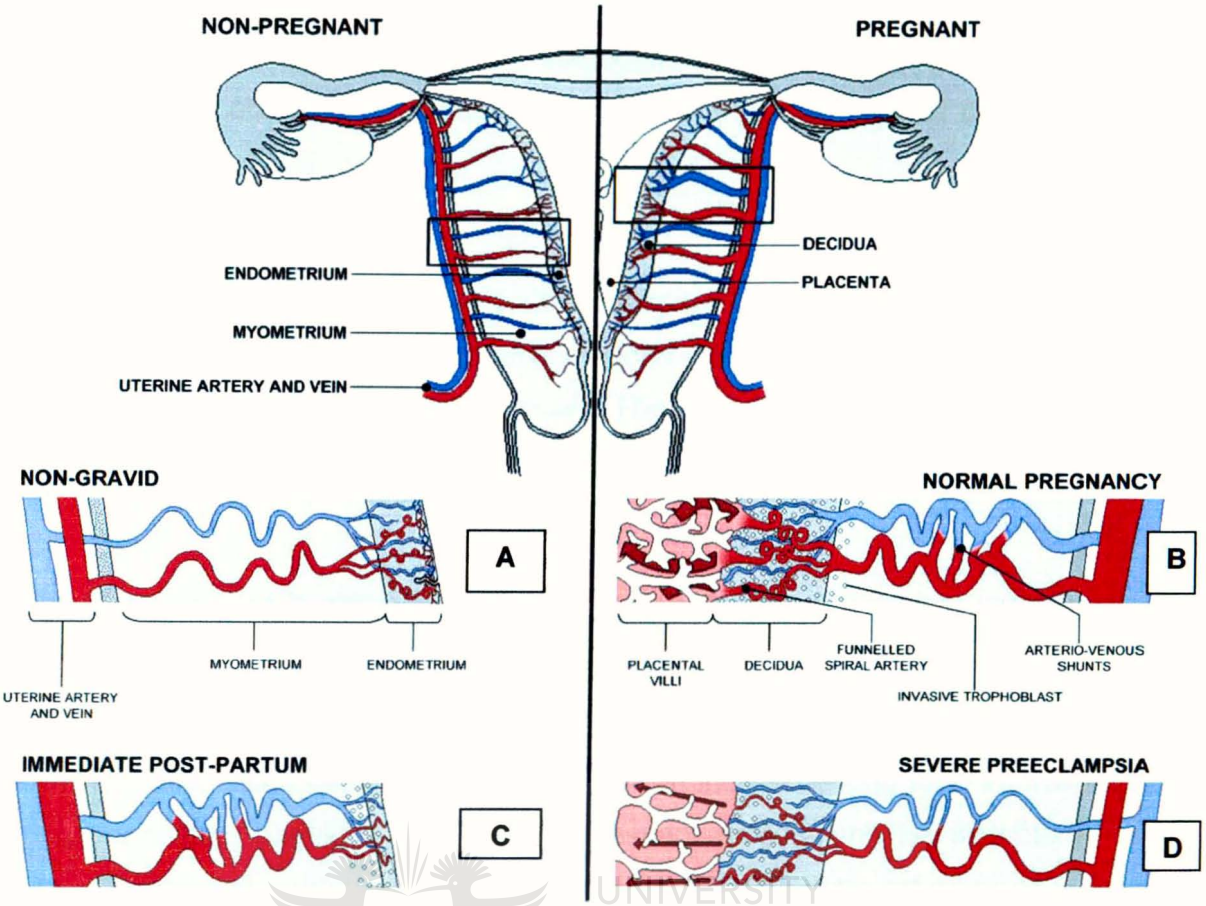


FIGURE 2.2: Diagrammatic representation of uterine and placental vasculature (red arterial; blue venous) in the non-pregnant, pregnant and immediate postpartum state. (Burton *et al.*, 2009 : 475)

2.14 ANTENATAL CARE

The purpose of antenatal care is to maintain both the mother and the foetus in the best positive state of health of the foetus and the mother by screening for actual and potential problems as early as possible so that suitable referral or pregnancy management can be implemented. With this in mind antenatal care is of great importance.

The use of ultrasound has revolutionised prenatal care and a high number of foetal complications as well as abnormalities are now detected before birth (Tegnander *et*

al., 2006 : 252). With the use of diagnostic ultrasound prenatal detection is increased, thus obstetric ultrasonography has become a vital part of prenatal care (Tegnander *et al.*, 2006 :)

At the Rahima Moosa Mother and Child Hospital based in Johannesburg South Africa routine antenatal ultrasound examinations are performed to assess the foetal well being in low and high risk pregnancies. The scan is received by more than 50% of the pregnant population and is mainly performed by trained sonographers.

2.15 UTERINE ARTERY DOPPLER SCREENING FOR ADVERSE PREGNANCY OUTCOMES

To screen for a disease, the condition should have a well understood biology, and early recognition and treatment should lead to an increased long term improvement of the condition, should not create unnecessary anxiety and be suitable to the subjects screened. Although screening for pre-eclampsia does not meet all of these criteria, early recognition of hypertension in pregnancy allows for clinical monitoring and prompt therapeutic intervention for severe pre-eclampsia or eclampsia and experience proposes that early detection and treatment of pre-eclampsia is advantageous to both mother and foetus (Fayyad *et al.*, 2005 : 866).

2.16 SCREENING FOR PLACENTAL INSUFFICIENCY

Placental insufficiency is a major cause of perinatal mortality and morbidity. Pre-eclampsia. FGR, placental abruption and some cases of foetal death during the second half of pregnancy are thought to result from impaired placentation in early gestation (Palma Dias *et al.*, 2008: 462). Most cases of FGR are caused by uteroplacental insufficiency (Loughna., 2006 : 262).

Screening for chromosomal abnormalities has in the last decade changed from the 2nd to the 1st trimester. Keeping this in mind the 11-14 week scan offers an excellent opportunity to screen for pregnancy complications related to uteroplacental

insufficiency at an early stage when intervention might be possible (Pilalis 2007: 538).

Doppler sonography is a non-invasive screening method for disorders of placental function early in pregnancy (Ozkaya *et al.*, 2007:385).

2.16.1 FIRST TRIMESTER SCREENING

According to Pilalis *et al* (2007 : 532), 1st trimester abnormal uterine artery Doppler flow patterns are likely to identify the cases of pre-eclampsia associated with severe growth restriction and have a greater sensitivity in identifying early onset of severe disease. A 1st trimester uterine artery Doppler assessment is thus useful in identifying a subgroup of the population at a considerable risk for early, severe pre-eclampsia or growth restriction (Pilalis *et al* 2007; 532)

In a study done by Pilalis *et al* the results suggest that uterine artery Doppler examinations are helpful in predicting pre-eclampsia from as early as the 1st trimester (Pilalis *et al.*, 2007 : 139).

Melchiorre and co workers (2008 : 135) found that 1st trimester uterine artery Doppler indices and prevalence of bilateral notching in normal pregnancies were considerably different from those in women destined to develop preterm pre-eclampsia but not term pre-eclampsia. The results of a study done by Melchiorre and co workers (2009 : 528) indicated a significant relationship between 1st trimester uterine artery Doppler indices and the consequent development of small for gestational age foetuses.

2.16.2 SECOND TRIMESTER SCREENING

Second trimester uterine artery Doppler screening has proven to be a sensitive and accurate method for predicting pre eclampsia and foetal growth restriction especially the severe forms and early onset of the disease (Pilalis 2007:533)

The finding of an abnormal uterine artery velocimetric profile, defined as either a high pulsatility index or the presence of a diastolic notch in the 2nd trimester, denotes that a strict protocol of monitoring should be considered (Soregaroli 2001; 42).

Doppler screening in the second trimester is more sensitive than in the 1st trimester, in identifying the more severe and therefore clinically most relevant cases of pre-eclampsia and FGR (Papageorghiou *et al.*, 2001: 448).

2.16.3 IDEAL TIME FOR SCREENING

Screening for pre-eclampsia by uterine artery Doppler assessments is possible from at least 11 weeks of gestation. Trophoblastic invasion is maximal in the 1st trimester and pre-eclampsia develops from a relative failure of this event, validates the evaluation of uterine artery Doppler assessment in the 1st trimester (Melchiorrie 2008 : 133), however screening too early leads to false positive rates and lower positive predictive values as what appears to be abnormal uterine artery Doppler waveforms in early second trimester may fully develop and normalise by late second trimester (Swanepoel 2004 : 6).

Screening in the second trimester leads to improvement in the false positive rates and positive predictive values (Swanepoel 2004 : 6).

Cnossen and colleagues (2008 : 703), echo Swanepoel's view that Doppler testing for both pre-eclampsia and FGR is less accurate in the 1st trimester than in the 2nd trimester, while Papageorghiou (2008 : 368) argued that in the 1st trimester the sensitivity for predicting severe or early onset disease is much higher than is for mild or late onset disease. Melchiorrie (2005 : 134) is of the opinion that 1st and early second trimester tests are only likely to be able to predict the development of preterm pre-eclampsia cases that have defective spiral artery changes.

Numerous studies found the potential advantage of earlier screening is that prophylactic intervention, such as maternal ingestion of low dose aspirin may be more effective in the prevention of the subsequent development of pre-eclampsia and FGR (Martin *et al.*, 2001 : 586), (Fratelli *et al.*, 2009).

Aspirin therapy may be of specific benefit if started in the first trimester in women at high risk of developing the disease on the basis of history and abnormal first

trimester uterine artery Doppler waveforms (Papageorghiou 2008 : 369). In a study by Yu and co workers, (2003 : 238) there is particular evidence that the administration of low dose aspirin to women with abnormal flow in the uterine arteries at this early stage may provide effective prophylaxis against pre-eclampsia.

A reason for a move towards first trimester screening is that prevention of pre-eclampsia by starting pharmacological intervention in the second trimester has by and large failed (Papageorghiou 2008 : 369).

2.16.4 IDEAL POPULATION FOR SCREENING

Normal uterine artery Doppler waveforms in the first trimester identify women who are suitable for routine antenatal care hence the importance of uterine artery Doppler assessment between 11-14 weeks gestation especially in high risk pregnancies (Fratelli 2008 : 406).

The results of a study done by Harrington and colleagues confirm the potential of uterine artery Doppler analysis in the screening of high risk populations for uteroplacental complications in the second trimester (Harrington *et al.*, 2004 : 54). According to Swanepoel screening patients with high risk pregnancies yields findings with a high sensitivity because of a high incidence of disease in contrast to screening unselected patients with low risk pregnancies (Swanepoel 2004 : 6).

An early identification of a high risk population for pre-eclampsia and FGR could lead to a more intensive maternal-foetal management (Soregaroli *et al.*, 2001 : 45) and intensive monitoring of this population provides a measure of reassurance to those found to be at a lower risk (El Hamedi., 2005 : 142).

2.16.4.1 UTERINE ARTERY DOPPLER WAVEFORMS IN LOW RISK PATIENTS

Doppler of the uterine artery is a test with high negative predictive values for the development of severe pregnancy complications in low risk populations (Oei., 2005 : 312).

The clinical value of uterine artery Doppler in the prediction of perinatal complications in the low risk population is controversial, however uterine artery

Doppler analysis in the high risk population has been promising (Harrington *et al.*, 2004 : 50).

In a study done by Cnossen and colleagues it was found that an increased PI alone or in combination with notching was most valuable for predicting FGR in low risk women (McLeod 2008 : 721).

2.16.4.2 UTERINE ARTERY DOPPLER WAVEFORMS IN HIGH RISK PATIENTS

Uterine artery Doppler waveform analysis is helpful in the prediction of severe adverse outcomes in high risk pregnancies (El Hamedi *et al.*, 2005 : 142). In a study done by Cnossen and co-workers it was found that an increased resistance to blood flow in the placenta was the best predictor of FGR in high risk women (Mcleod 2008 : 727).

2.17 SCREENING FOR FGR

There is clearly a continuous relationship between uterine artery Doppler indices and severity of FGR (Melchiorre *et al.*, 2009 : 528).

The diagnosis of FGR ideally requires a serial assessment of foetal growth during pregnancy, although the diagnosis can be made on a single assessment of uterine artery blood flow assessments (Loughna, 2006 : 261). FGR is strongly associated with an increased resistance in the uterine arteries (Loughna., 2006 : 262).

When uterine artery Doppler analysis is employed as a screening test at 24 weeks gestation, the presence of bilateral notches is associated with an increased risk of FGR requiring preterm delivery before 34 weeks (Loughna,2006 : 262).

2.18 RELATIONSHIP BETWEEN SCREENING AND PERINATAL OUTCOMES

The finding that the sensitivity of uterine artery Doppler assessment for both pre-eclampsia and FGR was inversely related to the gestational age at delivery demonstrates that Doppler assessment of the uterine arteries is much better at identifying the more severe and therefore clinically most relevant cases of pre-eclampsia (Martin *et al.*, 2001 : 585).

According to a recent Cochrane review (2004), Doppler ultrasound waveform analysis showed moderate predictive accuracy in predicting pre-eclampsia (Dornhofer *et al.*, 2008 : 33).

Abnormal uterine artery waveforms are a better predictor of pre-eclampsia than of FGR (Cnossen *et al.*, 2008 : 701). The majority of women destined to develop serious complications from impaired placentation can be identified with a Doppler assessment. Accurate prediction of those women destined to develop severe pre-eclampsia and or FGR followed by increased surveillance and appropriate intervention may improve outcomes (Papageorghiou *et al.*, 2001 : 448). Implementation of a uterine artery screening program into routine antenatal care would help recognise the intensity of subsequent surveillance because in those with increased mean PI, there is a six fold increase in likelihood of serious complications, whereas in those with a normal PI there is a halving of such likelihood (Papageorghiou *et al.*, 2001 : 448).

The development of Doppler ultrasound in the mid 1960's was a major technological advancement, as previously circulatory changes could only be studied with angiography (Papageorghiou *et al.*, 2005 : 584). Doppler ultrasonographic examination of the arterial velocity waveforms allows the assessment of vascular impedence to flow by comparing systolic and diastolic waveforms (Ghidini *et al.*, 2008 : 258). Assessment of impedence to uterine artery blood flow using Doppler ultrasound was first reported by Campbell *et* al in 1983, (Papageorghiou ., 2008 : 367). Doppler examination of the uterine arteries is a tool that can be used to indirectly examine trophoblast invasion and uteroplacental perfusion thus determining the quality of placental development (Melchiorre *et al.*, 133 : 2008). There is evidence to believe that trophoblast invasion is maximal in the first trimester (Melchiorre *et al.*, 2009 : 524), and that pre-eclampsia deriving from a relative failure of this event, validates Doppler evaluation of the uterine artery in the first trimester of pregnancy (Melchiorre *et al.*, 133 : 2008).

According to Yu & co-workers Doppler ultrasound studies of the uterine arteries have demonstrated that the clinical signs of pre-eclampsia are preceded by evidence of impaired placentation (Yu *et al.*, 2008 : 310).

Research suggests that there is evidence that uterine artery Doppler assessment can be used as a tool for the evaluation of trophoblast invasion in the first trimester, as the proportion of decidual vessels with endovascular trophoblast invasion is considerably higher in pregnancies with low uterine artery resistance when compared with high resistance ones (Fratelli *et al.*, 2008 : 403).

Doppler assessment of the uterine arteries is presently the only method that allows risk stratification in the second trimester of pregnancy (Dornhofer *et al.*, 2008 : 30). In line with this thought, uterine artery Doppler sonography may be performed via the transabdominal or transvaginal route in the first or second trimester. Uterine artery Doppler waveforms are reported to be readily available in more than 95% of patients, is simple to perform, fast, reliable and reproducible (Dornhofer *et al.*, 2008 : 30, Goffinet *et al.*, 2001 : 510), and allows noninvasive evaluation of the uteroplacental and foetal circulations(Hamedi *et al.*, 2005 : 138).

The uterine artery is identified with the use of colour Doppler at the apparent crossover with the external iliac arteries (figure 2.3 &2.4). Pulsed wave Doppler is then used to obtain uterine artery waveforms (Mcleod 2008 : 727). When three similar consecutive waveforms with a clear envelope are obtained the pulsatility index (PI) is calculated. An increased PI has been associated with an increased risk for pre-eclampsia and FGR (Mcleod 2008 : 727).

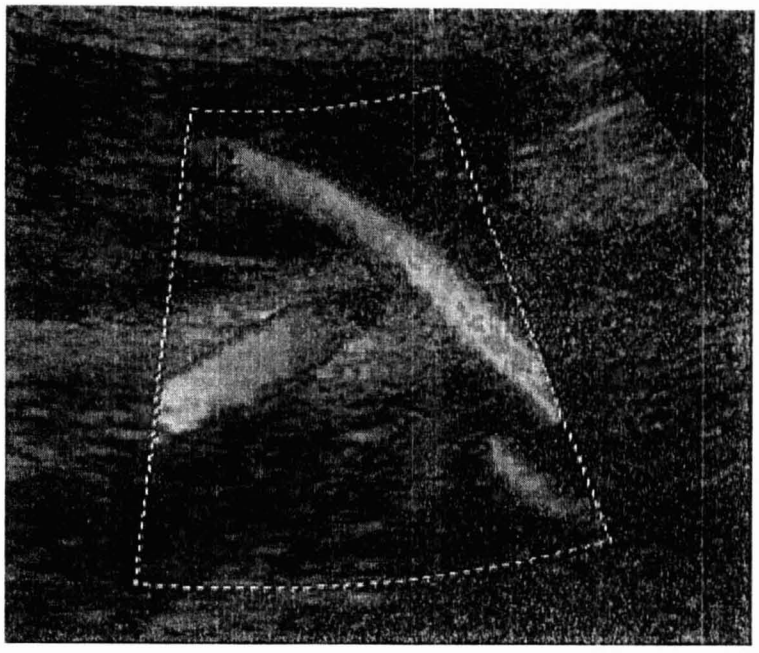


FIGURE 2.3

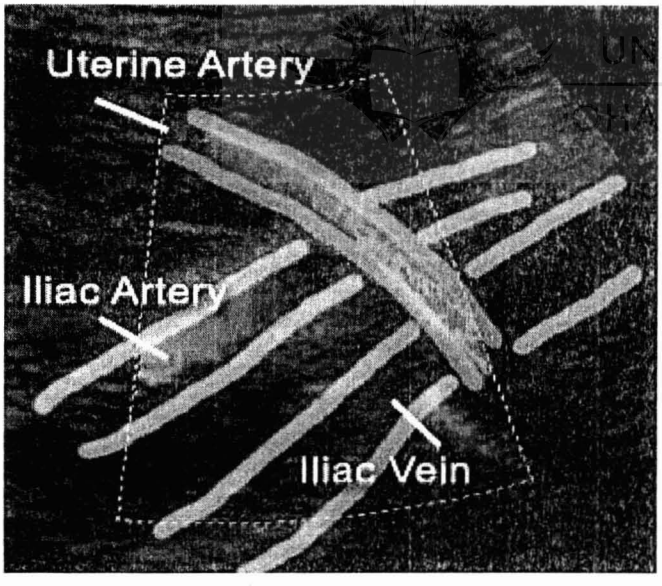


FIGURE 2.4:

FIGURE 2.3 & 2.4: ultrasound images demonstrating the uterine artery at the apparent cross over with the iliac artery and vein.

Examination of the uterine circulation in the first trimester in order to predict pre-eclampsia and FGR has been reported by Papageorghiou and co-workers, (2006 :

594), who postulated that first trimester uterine artery spectral Doppler waveforms can identify over half of the women who will develop pre-eclampsia. In a study by Papageorghiou, (2006 : 595), evidence suggests that impedence to flow in the uterine arteries decreases with gestation in normal pregnancies (figure 2.7). Studies in pregnancies with established pre-eclampsia or FGR showed that impedence to flow in the uterine arteries was increased, and therefore women with normal impedence to flow in the uterine arteries constitute a group that have a low risk of developing obstetric complications related to uteroplacental insufficiency (Papageorghiou *et al.*, 2004 : 393). The consequent increased resistance in the uteroplacental circulation forms the basis of screening for the condition by uterine artery spectral Doppler sonography (Spencer *et al.*, 2006 :658). A disturbed uterine perfusion indicates an elevated utero-placental resistance and might reflect the gap between impaired trophoblast development in the first trimester and the development of the syndrome later in pregnancy (Dornhofer *et al.*, 2008 : 30). It is clear that a failure of the uterine artery to modify by the second half of pregnancy identifies a group of women who are at increased risk of pre-eclampsia and preterm delivery due to FGR (Hamedi *et al.*, 2005 : 139). The normal uterine artery Doppler waveform has an early diastolic notch in the non pregnant state which often persists in pregnancy until 20-26 weeks gestation (Swanepoel., 2004 : 5), (Figure 2.5 &2.6). Persistence of a diastolic notch beyond 26 weeks gestation (figure 2.8) or abnormal flow velocity ratios have been associated with an inadequate trophoblast invasion.

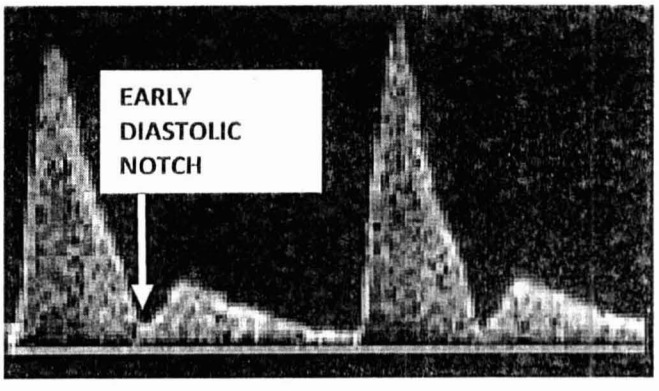


Figure 2.5: (1st trimester)

Image showing normal impedance to flow in the uterine arteries in the 1st trimester

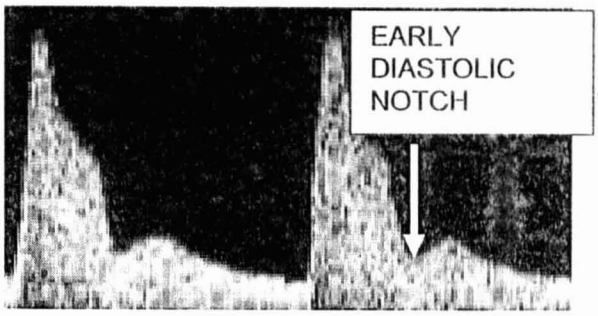


Figure 2.6: (early 2nd trimester)

Image showing normal impedence to flow in the uterine arteries in the early second trimester

Notching can be considered normal at this gestation

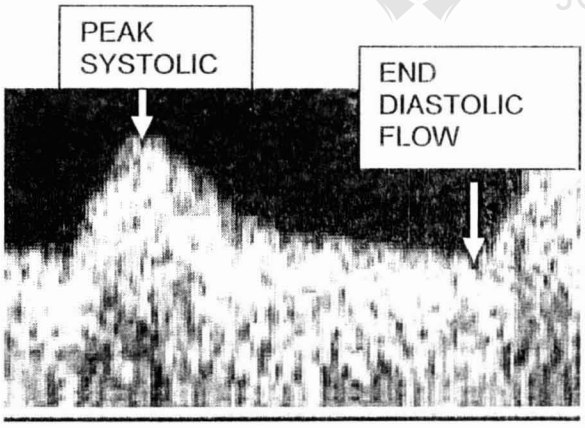


Figure 2.7: (late 2nd trimester and 3rd trimester)

Image showing normal impedence to flow in the late 2nd trimester and early third trimester

No notching seen in this image

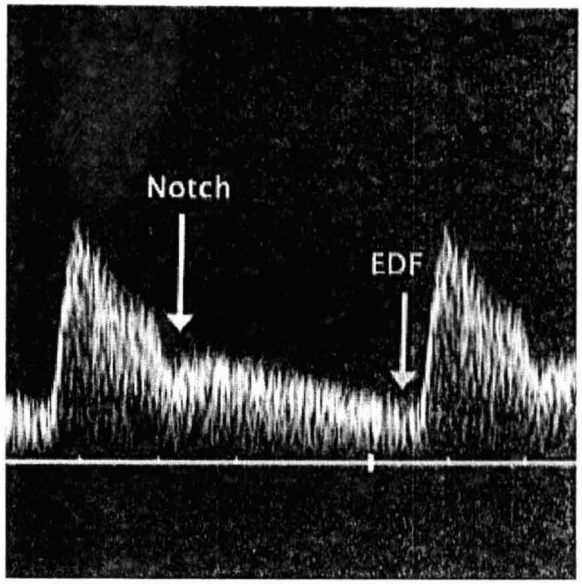


FIGURE 2.8: Image showing flow velocity waveform from the uterine artery at 24 weeks of gestation in a pregnancy with impaired placentation; in early diastole there is a notch and in late diastole there is decreased flow.

Image 3-8 obtained from

www.centrus.com.br/DiplomaFMF/SeriesFMF/doppler/capitulos

2.19 ULTRASOUND SAFETY

Diagnostic ultrasound is generally perceived as a safe technique with no adverse effects. Although no adverse effects arising from ultrasound examinations during pregnancy have been identified in humans, clinical safety is and will always remain a concern.

Regulations governing the output of diagnostic ultrasound have been set by the USA's Food and Drug Administration (FDA). In revising its regulations in 1993, the FDA altered its approach to ultrasound safety. The new regulations have been set out to allow users to employ effective and judicious levels of ultrasound appropriate to the examination undertaken.

The new regulations allow an eight-fold increase in ultrasound intensity to be used in foetal examinations, but place considerably more responsibility on the user to understand the output measurements and to apply them during scanning.

The output display is based on two indices:

- The mechanical index (MI)
- The thermal index (TI)

2.19.1 MECHANICAL INDEX

The mechanical index is an estimate of the maximum amplitude of the pressure pulse in tissue. It gives an indication as to the relative risk of mechanical effects (streaming and cavitation). The FDA regulations allow a mechanical index of up to 1.9 to be used for all applications except ophthalmic (maximum 0.23).

2.19.2 THERMAL INDEX

The thermal index is the ratio of the power used that is required to cause a maximum temperature increase of 1°C. A thermal index of 1 indicates a power causing a temperature increase of 1°C. A thermal index of 2 would be twice that power but would not necessarily indicate a peak temperature rise of 2°C. Because temperature rise is dependent on tissue type and is particularly dependent on the presence of bone, the thermal index is subdivided into three indices:

(1) TIS: thermal index for soft tissue;

(2) TIB: thermal index with bone at/near the focus;

(3) TIC: thermal index with bone at the surface (e.g. cranial examination).

For foetal scanning, the highest temperature increase would be expected to occur at bone and TIB would give the 'worst case' conditions. The mechanical index and thermal index must be displayed if the ultrasound system is capable of exceeding an index of 1.

(www.centrus.com.br/DiplomaFMF/Series FMF/Doppler/capitulos-html)

2.20 A PRACTICAL APPROACH TO SAFE SCANNING

Ultrasound organizations have produced statements on the safe use of ultrasound.

To date no injurious effects have been identified from ultrasound scanning of the foetus. However, changes in power output, increased use of Doppler ultrasound, and a change in regulations governing outputs mean that every possible measure should be taken to maintain and ensure safe practice. The following scanning practice will be adhered to:

The ALARA ("As Low As Reasonably Achievable") principle should be maintained. Power outputs used should be adequate to conduct the examination. If in doubt, use a low power and increase it as necessary

Do not scan for longer than is necessary to obtain the diagnostic information.

(www.centrus.com.br/DiplomaFMF/Series FMF/doppler/capitulos-html)

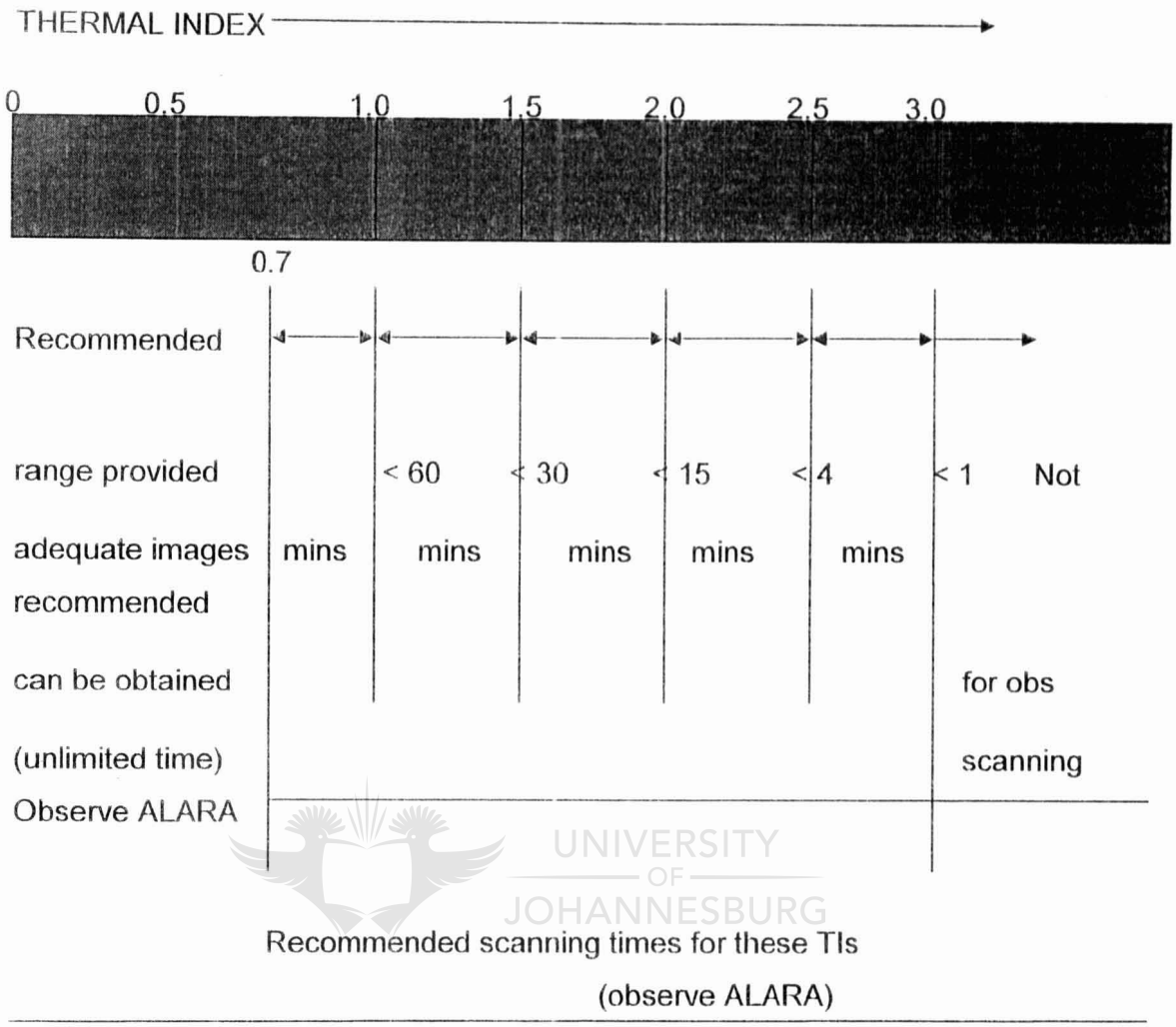
The WFUMB recommends that ultrasound causing a temperature rise of no more than 1.5°C may be used without reservation on thermal grounds.

Thermal indices exceeding 1.5 should not be used routinely and, if required for specific diagnostic information, should be used for the minimum time necessary.

Regulations pertaining to the avoidance of possible harmful heating and mechanical effects will be obeyed through adherence to mechanical (MI) and thermal (TI) indices as prescribed by the FDA.

(www.centrus.com.br/DiplomaFMF/Series FMF/doppler/capitulos-html)

A value of < 0.3 is considered safe for MI and a value of < 0.7 is considered safe for (TI) (figure 2.9) (www.bmus.org)



(www.bmus.org/policies)

FIGURE 2.9: Recommended maximum scanning times for obstetric examinations conducted with different displayed Thermal Indices (TI).

Machine functions for obstetric scanning should bring in each mode at its lowest output so that the operator is required to increase power if the examination demands it.

The examination should begin with B-mode and use colour and spectral Doppler only when necessary.

The operator should be aware of changes to the indices in response to changes in control settings.

Special care should be taken in febrile patients, since ultrasound heating will cause additional heating to the foetus.

2.21 MANAGEMENT OF PRE-ECLAMPSIA

Adequate and proper prenatal care is most important in the management of pre-eclampsia.

Optimal management relies on identification and regular follow up of individuals with hypertension, close monitoring for early signs of pre-eclampsia, prophylaxis for seizures in pre-eclamptic patients, careful use of antihypertensive medications and correct timing of delivery (Wagner 2007 : 566).

Pre-eclampsia generally resolves with the removal of the placenta, thus delivery remains the definitive treatment. The decision to induce labour should be based on gestational age and the severity of the disease (Wagner *et al.*, 2007 : 562), bearing in mind, the main concern of the management of pre-eclampsia is the safety of the mother. Since these women are also at risk for complications from the disease process in the period after delivery, continued frequent observations must be ensured (Moodley 2010 : 717). Although delivery is always appropriate for the mother, it might not be the answer for the premature foetus.

The objective can be achieved by formulating a management plan that considers one or more of the following:

1) Foetal gestational age
2) Maternal and foetal status at time of initial assessment
3) Presence of labour or rupture of foetal membranes

(Sibai *et al.*, 2005 : 794)

Urgent delivery is indicated for severe forms of pre-eclampsia in women at or near term, for eclampsia, HELLP syndrome and severe hypertension not responding to treatment after 24 to 48 hrs and in women who develop symptoms and signs of disease progression (Wagner *et al.*, 2007 : 562).

Clinical guidelines for management of hypertensive disorders of pregnancy and in particular, the management of obstetric emergencies should be made available for all health care personnel. Once the diagnosis of mild pre-eclampsia is made, subsequent therapy will depend on the results of the maternal and foetal evaluation (Figure 2.10).

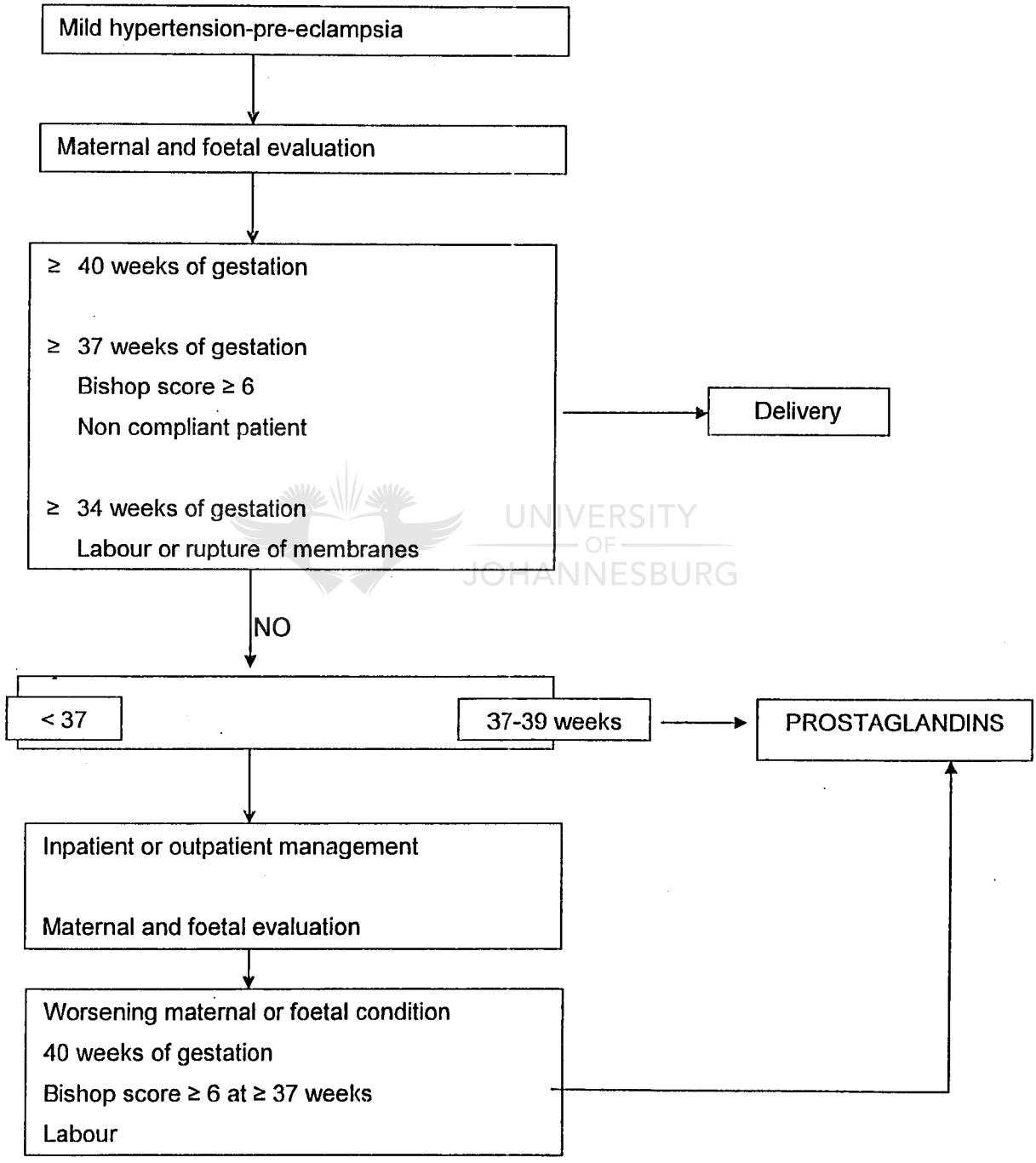


FIGURE 2.10 ALGORITHM SHOWING RECOMMENDED MANAGEMENT OF MILD PRE-ECLAMPSIA (SIBAI, 2003 : 186)

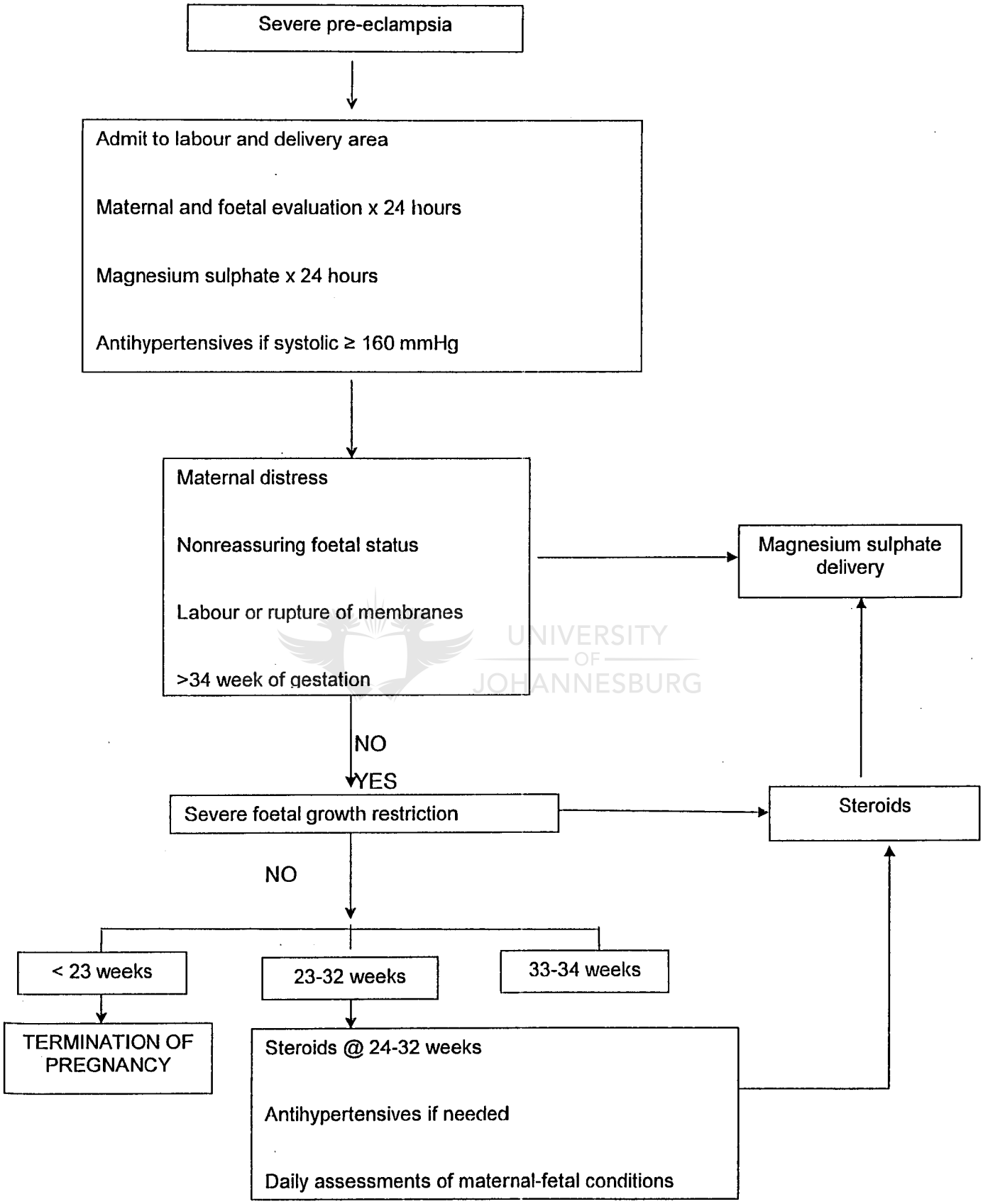


FIGURE 2.11: ALGORITHM SHOWING RECOMMENDED MANAGEMENT OF SEVERE PRE-ECLAMPSIA (Sibai., 2003 :188).

Once severe pre-eclampsia is diagnosed, maternal and foetal conditions are assessed and a decision is made regarding delivery (Figure 2.11). Maternal evaluations include monitoring of blood pressure, urine output, cerebral status and the presence of epigastric pain, tenderness labour or vaginal bleeding. Laboratory evaluations are also carried out. Foetal evaluation includes continuous foetal heart monitoring and an ultrasound for the assessment of foetal growth assessment and amniotic fluid.

2.22 PREVENTION OF PRE-ECLAMPSIA:

There are currently no well-established measures for preventing pre-eclampsia (Wagner 2004 : 2323). Effective prevention relies on recognition of an early latent phase of the disease that can be averted or reverted, as well as the availability of effective methods of intervention (Fayyad *et al.*, 2005 : 866).

Several different approaches have been tried for prevention of pre-eclampsia, including use of low dose aspirin, calcium and magnesium supplements, a low salt diet, diuretics and antioxidants (Wagner *et al.*, 2007 :563).

Although pre-eclampsia is not preventable many deaths from the disorder can be prevented. Women who do not receive prenatal care are seven times more likely to die from complications related to pre-eclampsia-eclampsia than women who receive some level of prenatal care. To decrease pre-eclampsia related mortality, appropriate prenatal care must be available to all women. Early detection, appropriate monitoring and treatment of pre-eclampsia are vital in preventing mortality related to this disorder (Wagner 2004 : 2323).

2.23 SUMMARY

Antenatal care is free of charge in South Africa and antenatal clinics are widely available, however infrequent antenatal attendance remains a challenge. In South Africa most women book for antenatal care at a later stage in pregnancy, usually the 2nd trimester (Moodley, 2010 : 719). Improvement in education may help to overcome this challenge and ultimately better pregnancy outcomes.

CHAPTER 3

METHODOLOGY

3.1 INTRODUCTION

The objectives of this research are to:

- Determine the sensitivity of first and second trimester uterine artery spectral Doppler assessment in predicting pre-eclampsia or FGR.
- Statistically analyse data in an attempt to identify associations between normal and abnormal uterine artery Doppler waveforms and pregnancy outcomes.
- Determine the most effective Doppler indices in the first and second trimester as a predictor of PET in the third trimester.
- Develop ultrasound management guidelines.

3.2 RESEARCH SETTINGS

Rahima Moosa Mother and Child Hospital formerly known as Coronation Hospital, based in Coronationville, Johannesburg South Africa is a large regional referral hospital.

Approximately 11000 babies are delivered per year at Rahima Moosa Mother and Child Hospital. Being a regional hospital, numerous primary health care facilities refer high risk pregnancies and suspected foetal abnormalities to this hospital for further pregnancy management. These primary health care clinics include the following:

1) Westbury
2) Randburg
3) Crosby
4) Mayfair
5) Bosmont
6) Discovery
7) Witkoppen and

8) Claremont clinic

Routinely an antenatal card is issued for each patient attending a primary health care clinic or the antenatal clinic at Rahima Moosa Mother and Child Hospital at the 1st visit (Annexure B)

The following general information is recorded on the antenatal card:

- Personal details: (name, age, address and telephone number)
- Past obstetric history: (complications and outcomes of all previous pregnancies)
- Medical and family history: (conditions affecting or affected by pregnancy, psychological health and a family history of congenital abnormalities, diabetes or twins)
- Clear recording of gestational age and method used to determine it, with an estimated date of delivery
- General physical examination including weight and height
- A problem list: risk factors found or anticipated, with a brief delivery plan

The following information on pregnancy progress is recorded at each visit:

- Blood pressure
- Proteinuria
- Foetal movements
- Foetal lie and presentation
- Symphysis-Fundal height
- A note of any problems to be made

Nulliparous patients are scheduled for three visits where only the blood pressure and urine protein are checked.

ROUTINE INVESTIGATIONS PERFORMED

a) URINE TESTS:

> At all visits the urine is tested for traces of protein and glucose

> A urine pregnancy test for suspected pregnancies when the uterus is not palpable abdominally

b) BLOOD TESTS:

The following tests are performed on all pregnant women:

- Rapid Plasma Reagin (RPR) or equivalent
- Rhesus blood grouping
- Haemoglobin (Hb), at the 1st visit and at 36 weeks
- Human Immuno Virus testing (www.ais.up.ac.za/med/block/9/antenatalcarepolicy.pdf)

Rahima Moosa Mother and Child Hospital serves a large population from different urban areas.

- The hospital serves a wide variety of ethnic groups including African, Asian, coloured and white.
- The hospital also serves a wide variety of immigrants/asylum seekers from the following countries: Somalia, Nigeria, India, Pakistan, Malawi and the Democratic Republic of Congo.
- Being a state facility the majority of the patients attending Rahima Moosa Mother and Child Hospital are from a working class population in a low income bracket.

All patients attending the antenatal clinic at Rahima Moosa Mother and Child Hospital are referred to the ultrasound department after a clinical assessment. Four trained sonographers perform the obstetric and gynaecology ultrasound examinations. Examinations offered include:

1) Dating scans
2) Nuchal translucency scans
3) Amniocentesis-offered to women older than 35 years of age or on women on whom soft markers for aneuploidies were identified during the detailed anatomy scans.

4) Anomaly scans (between 22-24 weeks) gestation
5) Third trimester scans including Doppler assessments are offered to high risk patients which include:
   - Diabetics
   - Hypertensive patients
   - Patients in whom foetal growth restriction (FGR) is suspected.
6) Cervical length measurements if a short cervix is clinically suspected or in patients with recurrent miscarriages in the 1st trimester.
7) Gynaecology scans (transabdominal and transvaginal)
8) General ultrasound examinations are also done.

Approximately 40-50 obstetric scans are done per day culminating to ± 1000 patients per month.

All patients are offered two routine scans, the 1st being a dating scan performed at any gestation less than 18 weeks and the 2nd scan being an anomaly scan performed between 22-24 weeks gestation. If there is a valid clinical indication a third trimester ultrasound scan is also booked.

The dating scan is performed to confirm viability, determine the gestational age, diagnose major foetal defects, measure the nuchal translucency if the gestation is between 11-14 weeks and to determine the chorionicity in multiple pregnancies.

The second scan, the anomaly scan is performed between 22-24 weeks gestation. A transabdominal approach is used to perform a biometric assessment of foetal growth which includes a measurement of the Biparietal diameter (BPD), Head circumference (HC), abdominal circumference (AC) and femur length (FL) and a foetal assessment for any structural abnormalities. Biometric measurements are plotted on a foetal growth chart as per (Annexure E)

The 3rd trimester scan is only offered to high risk patients for monitoring of foetal growth, liquor volume assessment, and an umbilical artery Doppler.

3.3 STUDY POPULATION

All patients attending the Rahima Moosa Mother and Child Hospital antenatal clinic who were referred to the sonar department for a routine dating scan (between 11-14 weeks) were recruited to participate in this study.

3.4 RESEARCH DESIGN

A prospective quantitative experimental study was done in order to test the hypothesis that uterine artery spectral Doppler screening for PET and FGR is able to identify patients at risk for the manifestation of these complications in the third trimester of pregnancy in the Gauteng context.

3.5 SAMPLING

A convenience sampling method was applied by recruiting all patients (between 11 - 14 weeks gestation) attending the antenatal clinic at Rahima Moosa Mother and Child Hospital who were willing to participate in the study. All patients who attend the antenatal clinic are routinely referred to the ultrasound department so that an appropriate anomaly scan booking can be facilitated.

Three hundred patients were suggested for the sample to ensure a statistically significant study population. Due to the lack of referrals only 144 patients were recruited.

3.5.1 INCLUSION CRITERIA

All patients between (11-14 weeks) gestation referred to the ultrasound department who were willing to participate in the study were included

3.5.2 EXCLUSION CRITERIA

Patients with the following conditions were excluded from the study:

- Multiple pregnancies-as these pregnancies are known to have a higher incidence of placental insufficiency
- Foetal abnormalities- as these patients may opt for a pregnancy termination the research on these patients would be incomplete
- Patients on treatment for hypertensive disorders- these patients results would not be a true reflection as they are already on medication

3.6. RELIABILITY & VALIDITY

To ensure result consistency the researcher was the only person performing the scans. The researcher is a qualified competent sonographer experienced in uterine artery Doppler assessment, the interpretation of the Doppler waveform and conversant with safety regulations. Measurements were taken using a 2004 GE vivid 3 ultrasound unit (figure 3.1). The ultrasound unit was serviced and calibrated on a regular basis. The results were obtained by a routine procedure guided by computer software applications.

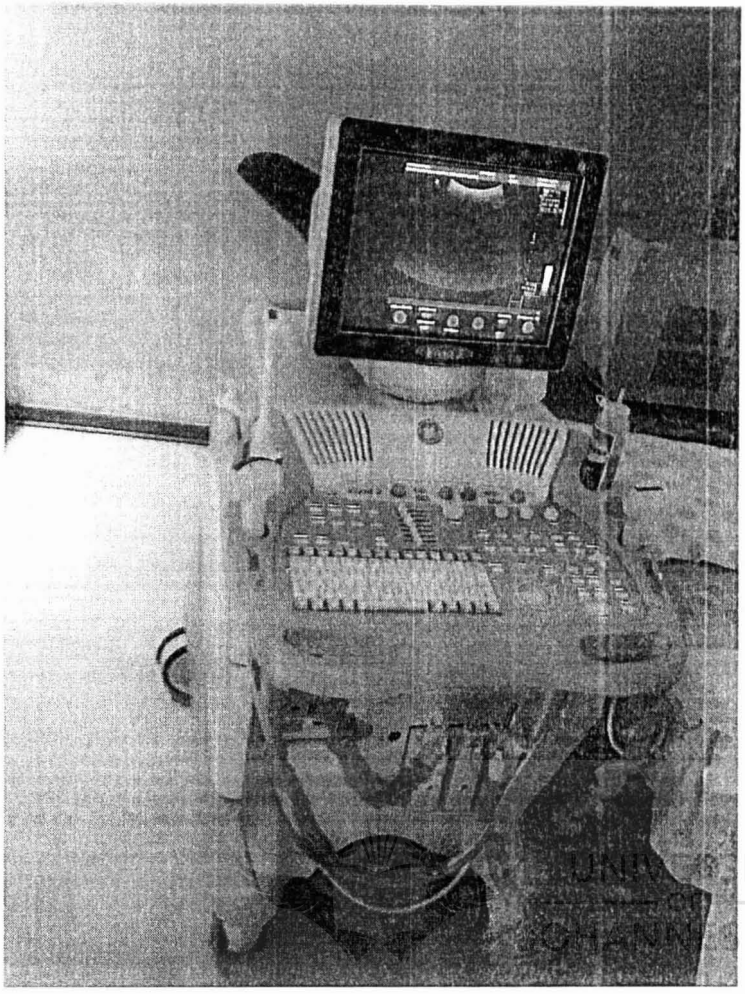


FIGURE 3.1. Image showing ultrasound unit used for the study

A curvilinear transducer was used throughout the research. The transducer has a frequency capability of between 2 and 6 mHz.

Patients recruited to participate in the study were encouraged to attend antenatal clinics as scheduled. Optimal management of every pregnancy was maintained by the antenatal clinic as per Rahima Moosa Mother and Child Hospital protocol at all times.

Table 3.1: Antenatal visits scheduled for a multiparous women

VISIT NUMBER:	GESTATIONAL AGE: (WEEKS)	SPECIFIC OBJECTIVES:
1	6-20	Risk assessment, gestational age and blood

		tests.
2	24-28	Multiple pregnancy, hypertension and risk for preterm labour
3	32-34	Foetal growth and hypertension
4	36-38	Foetal growth, lie, presentation, hypertension and anaemia
5	40-42	Foetal growth, lie, presentation, hypertension and post dates

(www.ais.up.ac.za/med/block/9/antenatalcarepolicy.pdf)

Table 3.2: Antenatal visit scheduled for a primigravid women

VISIT NUMBER:	GESTATIONAL AGE (WEEKS):	SPECIFIC OBJECTIVES:
1	6-20	Risk assessment, gestational age and blood tests
2	24-28	Multiple pregnancy, hypertension and risk for preterm labour
3	28-30	Hypertension
4	32-34	Foetal growth and hypertension
5	34-36	Hypertension
6	36-38	Foetal growth, lie, presentation hypertension and anaemia
7	38-40	Hypertension

8	40-42	Foetal growth, lie, presentation, hypertension and post dates

(www.ais.up.ac.za/med/block/9/antenatalcarepolicy.pdf)

Table 3.1. and 3.2 outlines the antenatal visit schedules for nulliparous and multiparous women.

More frequent visits may be scheduled for high risk women depending on patient needs.

Table 3.3: Demonstrating ultrasound management of low risk patients vs. high risk patients at Rahima Moosa Mother and Child Hospital

LOW RISK PREGNANCIES	HIGH RISK PREGNANCIES
- Dating scans	- Dating scans
- Anomaly scans	- Anomaly scans - Follow up scans

The above table demonstrates the ultrasound management in low and high risk pregnancies at the Rahima Moosa Mother and Child Hospital

3.6.1 1st Trimester dating scan

The transducer was placed in a longitudinal section in the midline just above the symphysis pubis. The lower abdomen was scanned (i.e. uterus and adnexae) and the following was checked/confirmed:

1) Embryonic foetal cardiac activity
2) Confirmation of an intrauterine pregnancy

3) Number of foetus'
4) The maternal adnexae were scanned for any masses.

The biometric assessment included either a Crown Lump (CRL) measurement or a (BPD, AC & FL) measurement. The nuchal translucency was routinely measured on foetuses that were between 11-14 weeks gestation. The estimated date of delivery was calculated.

Patients who met the inclusion criteria were offered the option to participate in the study. Written informed consent was immediately obtained from women who agreed to participate (Annexure A).

The uterine arteries were then sampled. Uterine artery spectral Doppler assessment may be performed via the transvaginal or transabdominal route in the first or second trimester, however in this study the transabdominal approach was used. The uterine artery is located on either side of the uterus and enters the uterus at the level of the internal os but may branch before or at the crossover with the external iliac artery (Lees *et al.*, 2003:59).

The probe was then moved to the right adnexa and the transducer was gently tilted medially until the uterine artery was identified where it crosses over the external iliac artery (image 3.2). The sample gate was then placed over the entire diameter of the artery. Pulsed wave Doppler was then used to obtain uterine artery waveforms and once three consecutive waveforms were obtained, the image was then frozen. The angle of insonation was corrected ensuring that it was less than 60° at all times. The pulsatility index was then measured and the image was documented. The transducer was then moved to the contra lateral side and the procedure was repeated. According to Swanepoel (2004:4) the impedence to blood flow is found to be lower on the side of the placenta.

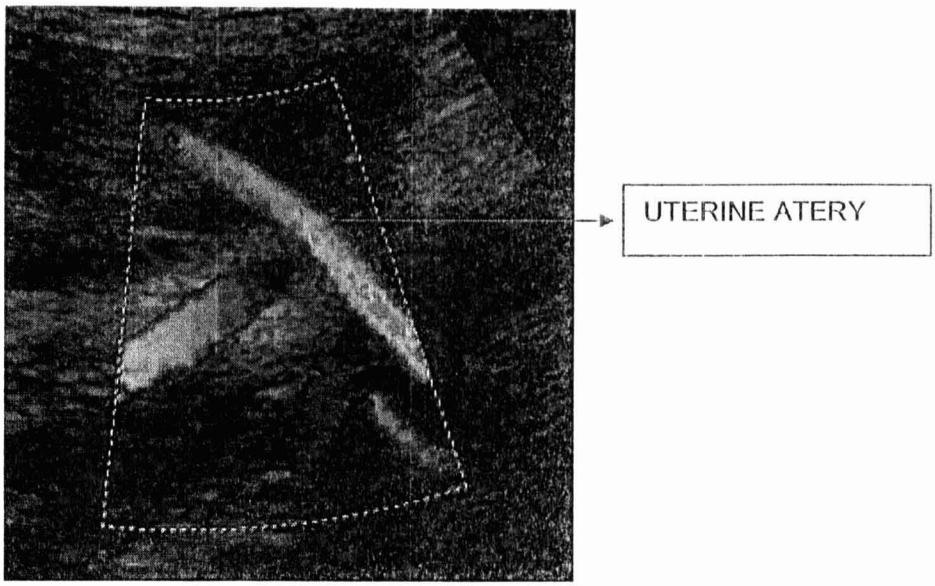


IMAGE 3.2. Demonstrating the uterine artery at the apparent crossover with the external iliac artery. (www.fetalmedicine.com/fmf/Doppler%20in%20Obstetrics.pdf)

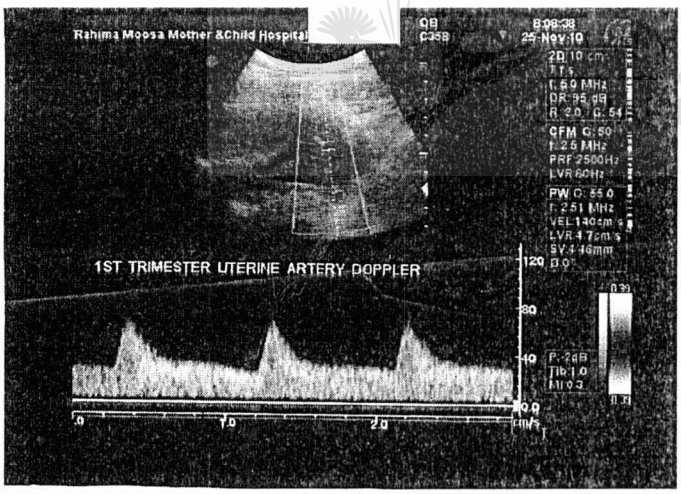


Image 3.3: Demonstrating a normal 1st trimester uterine artery Doppler (Researchers collection)

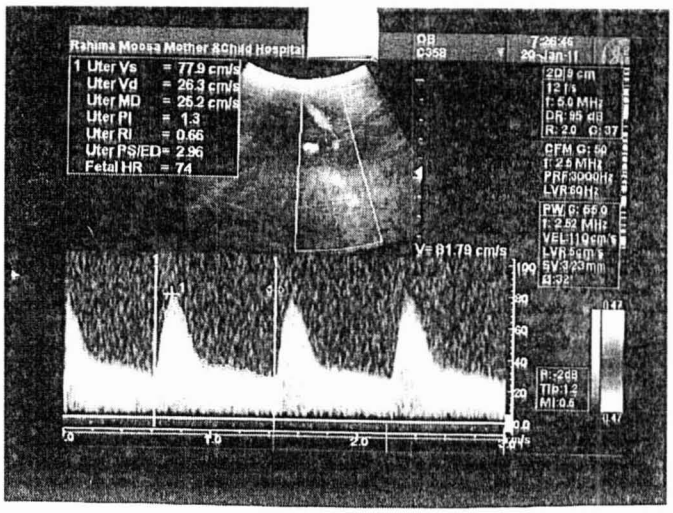


Image 3.4: Demonstrating a normal second trimester uterine artery Doppler (Researchers collection)

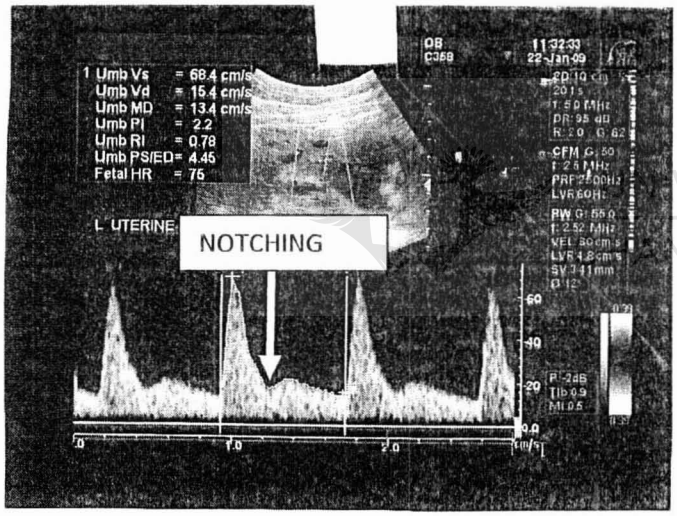


IMAGE 3.5. Demonstrating an abnormal uterine artery Doppler waveform noted with notching and a high PI. (Researchers collection)

The pulsatility index is defined as a measure of the variability of blood velocity in a vessel equal to the difference between the peak systolic and minimum diastolic velocities divided by the mean velocity during the cardiac cycle

(http://medical-dictionary.thefreedictionary.com/PI)

Pulsatility index is an arterial blood-flow velocity waveform index designed to quantify the pulsatility or oscillations of the waveform.

(www.medcyclopaedia.com/library/topics/volume_i/p/pulsatility_index_pi)

PI is calculated with the aid of software installed on the ultrasound machine using the following formula:

Pulsatility index = (Vmax-Vmin)/Vmax mean,

where Vmax is the peak systolic velocity, Vmin is the minimum forward diastolic velocity in unidirectional flow, or the maximum negative velocity in diastolic flow reversal, and Vmax mean is the maximum velocity averaged over (at least) one cardiac cycle.

(www.medcyclopaedia.com/library/topics/volume_i/p/pulsatility_index_pi)

Table 3.4: Normal pulsatility indices with gestation.

Gestational age	**1st trimester (PI)**	**2nd trimester (PI)**	**3rd trimester (PI)**
5th centile	1.1	0.7	0.6
50th centile	1.7	1.0	0.8
95th centile	2.7	1.5	1.2

(Gomez *et al.*,2008)

The above table shows the PI values for the 5th, 50th and 95th centiles for the different gestational ages. Ideally as gestation increases the pulsatility index should decrease

3.6.2. Second trimester anomaly scan

Routinely pregnancies that were dated were followed up at (22–24 weeks gestation) with a detailed anomaly scan, with the aim of detecting foetal malformations. Once again the examinations were performed transabdominally using the GE vivid 3 ultrasound unit. The curvilinear transducer was once again used.

This scan included the measurements of foetal biometry as well as a thorough assessment of the foetal anatomy following a checklist. The following structures are routinely examined:

- Foetal skull and brain(3^{rd} 4^{th} and lateral ventricles, cavum septum pellucidum, midline echo, cerebellum, thalami and cisterna magna)
- The foetal neck
- Face (tangential, profile and palate views)
- Thorax-diaphragm
- Heart (4 chambers and right and left outflow tracts)
- Stomach bubble+abdominal organs
- Spine & kidneys (sagittal, coronal and axial views)
- Foetal bladder
- Cord insertion
- Number of vessels in the cord
- Both upper and lower limbs (including counting of fingers and toes)
- Liqour volume

The estimated foetal weight is documented.

Once no soft markers or foetal anomalies were noted, the uterine arteries were once again examined using the above protocol. The pulsatility index of both uterine arteries were measured and documented.

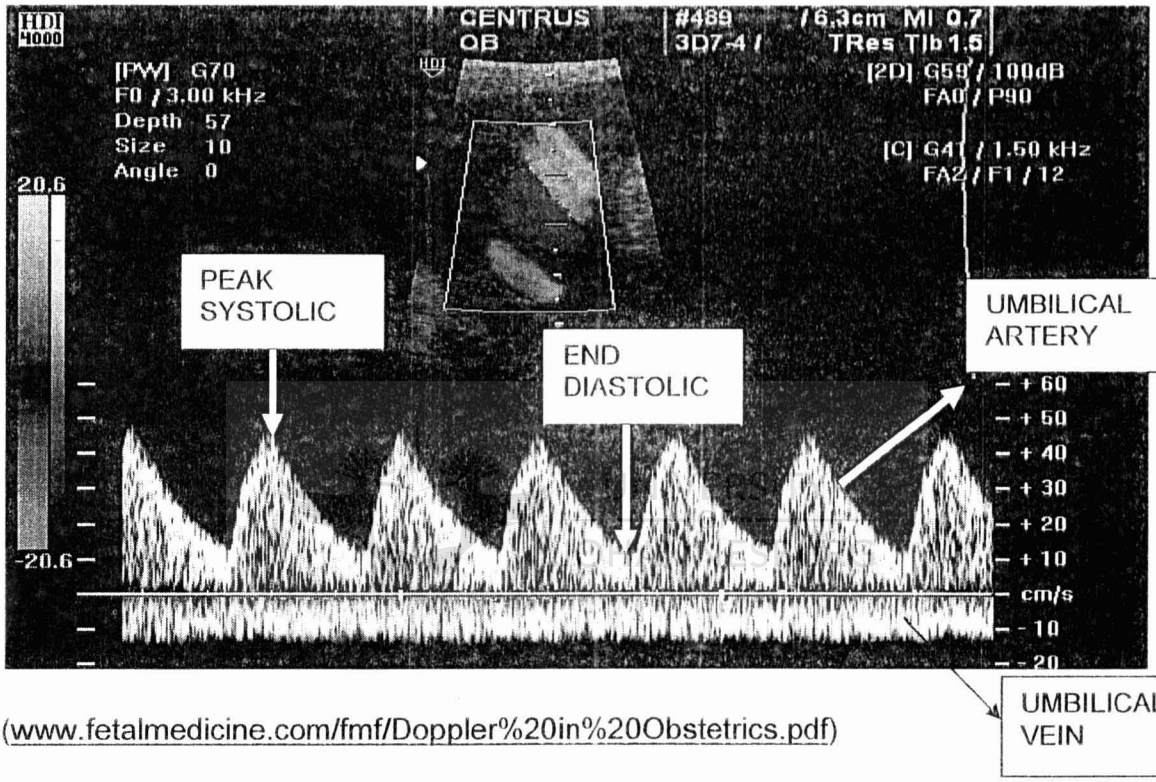
The pulsatility index is re-measured as impedence to flow in the uterine arteries decreases with gestational age in normal pregnancies, the impedence to flow is increased in established pre-eclampsia and FGR (Papageorghiou *et al.*, 2007: 103).

3.6.3. Third trimester scan

A third trimester follow up scan (between 28-32 weeks gestation) was performed on participants to monitor foetal well being and growth and to assess the liquor volume. The foetal biometry was once again measured and an estimation of foetal weight was done. The liquor volume was also assessed and measured. Any discrepancy in growth or liquor volume warranted an umbilical artery Doppler measurement.

Thereafter the uterine arteries were once again examined using the above protocol. The pulsatility index was measured and documented.

To obtain an umbilical artery Doppler a free floating portion of the cord was identified. The Doppler sample volume was placed over an artery and a vein. Pulsed wave Doppler was then switched on and once three consecutive waveforms were obtained the image was frozen and documented (image 3.6)



(www.fetalmedicine.com/fmf/Doppler%20in%20Obstetrics.pdf)

Image 3.6. Demonstrating Normal flow velocity waveforms from the umbilical vein (bottom) and artery (top)

All patients were managed as per the Rahima Moosa Mother and Child Hospital ultrasound scan protocols as per Table 3.3, which includes an umbilical artery Doppler assessment in patients in whom foetal growth discrepancy or a reduced liquor volume is recorded. If any structural foetal abnormality was found the referring clinician was informed immediately for further management.

3.7. VARIABLES STUDIED

Dependent and independent variables are used to distinguish between two types of quantities being considered, separating them into those available at the start of a process and those being created by it, where the latter (dependent variables) are dependent on the former (independent variables). The independent variable (controlled variable) is typically the variable being manipulated or changed and the dependent variable is the observed result of the independent variable being manipulated (**http://en.wikipedia.org/wiki/Dependent_variable**).

3.7.1 Independent variables

- Pre-existing conditions such as hypertension, poor obstetric history and previous FGR
- BMI (incidence of pre-eclampsia higher in women with an increased BMI)
- Maternal age (incidence of pre-eclampsia is higher in the very young and the older women > 35 years of age)
- Parity (the higher the parity the greater the incidence of pre-eclampsia)

3.7.2 Dependent variables

- Uterine artery Mean pulsatility index & notching
- Diagnosed Pre-eclampsia
- Diagnosed FGR

3.8. DATA COLLECTION AND ANALYSIS

The data was captured on the data capturing sheet (Annexure C). A unique research number was issued to each patient willing to participate

After consultation with the statistician it was decided that three hundred patients would provide statistically significant results.

The data was captured into an SPSS data file, and was ready for the preliminary phase of analysis which was the obtaining of frequencies and descriptive statistics. 2 x 2 contingency tables were drawn for cross tabulations and the odds ratios was

calculated in the black population, the outcome variable the development of PET or not and the predictor variables the presence or absence of uterine artery notching. The high risk group, (i.e. the patients who developed preeclampsia) were studied closely. The profile of low birth weight babies was also looked at and again the odds were calculated, this time the outcome variable was birthweight and the predictor variable was once again uterine artery notching. The results were reported in the form of tables and graphs for all the significant tests done.

3.9 ETHICAL CONSIDERATIONS

Ethical approval for this study was obtained from the Ethics Committees of the Faculty of Health Sciences, University of Johannesburg, Mrs. S Jordaan the CEO of Rahima Moosa Mother and Child hospital, Ms S Patel assistant director of the x-ray department at Rahima Moosa Mother and Child Hospital and Dr N Pirani, Head of the Obstetrics and Gynaecology Department at Rahima Moosa Mother and Child Hospital (Annexures D). An information leaflet was given to all participants informing them of the aims, objectives and potential value of the study (Annexure A). Patients who were willing to participate in this study were formally asked to complete and sign a consent form (Annexure A). Each patient was scanned according to the standard protocols of the Rahima Moosa Mother and Child Hospital ensuring that all patients were being treated equally and safe practice was maintained at all times. If any foetal abnormality or abnormal uterine artery Doppler waveforms were detected the referring clinician was informed immediately. Ultrasound scans were only performed by the researcher who is a competent qualified sonographer conversant with ultrasound safety regulations.

To date no injurious effects have been identified from ultrasound scanning of the foetus. However, changes in power output, increased use of Doppler ultrasound, and a change in regulations governing outputs mean that every possible measure was taken by the researcher to maintain and ensure safe practice. The following scanning practices were adhered to:

- The ALARA (as low as reasonably achievable) principle was maintained at all times by limiting scan times and high intensity sound exposures to the foetus.

- Colour and spectral Doppler was only used when necessary.
- The WFUMB recommends that ultrasound causing a temperature rise of no more than 1.5°C may be used without reservation on thermal grounds.
- Regulations pertaining to the avoidance of possible harmful heating and mechanical effects was obeyed through adherence to mechanical (MI) and thermal (TI) indices as prescribed by the FDA. (www.centrus.com.br/DiplomaFMF/doppler/capitulos-html_02.htm)

A value of < 0.3 is considered safe for MI and a value of < 0.7 is considered safe for (TI) (www.bmus.org) and a value exceeding 1.5 for TI should not be used routinely. (www.fetalmedicine.com/fmf/Doppler%20in%20Obstetrics.pdf

3.10 SUMMARY

This prospective study was carried out on all patients referred to the ultrasound department at Rahima Moosa Mother and Child Hospital. The ultrasound scans and uterine artery Doppler assessments were performed by a competent qualified ultrasonographer who is conversant with safety regulations. Ethical considerations were considered before the research was carried out.

CHAPTER 4

RESULTS

4.1 ORGANIZATION OF DATA ANALYSIS

The chapter will commence with a statistical overview of baseline obstetric and demographic data followed by an attempt to meet the study objectives and prove the hypothesis by investigating the use of uterine artery spectral Doppler analysis as a screening tool in order to predict pre-eclampsia and FGR before the clinical onset of the disease.

For the purpose of this study the predictor variable can be defined as the Doppler ultrasound examination while the dependant variables are the uterine artery (UA) Pulsatility Indices (PI), UA notching, as well as the development of PET and/or FGR in the study population. These are influenced by the independent variables defined as:

- Race
- Age
- BMI
- Parity
- Previous history of PET

4.2 RESEARCH AIM

The aim of this study is to assess the sensitivity of uterine artery spectral Doppler screening in the prediction of pregnancies with a high risk of developing pre-eclampsia or FGR before the clinical onset of the disease. This would not only identify women who require closer surveillance, but would also help in selecting those most likely to benefit from any therapeutic interventions.

4.3 OBJECTIVES

4.3.1 OBJECTIVE 1

Determine the sensitivity of first and second trimester uterine artery spectral Doppler assessment in predicting pre-eclampsia or FGR

4.3.2 OBJECTIVE 2 a & b

Identify associations between normal and abnormal uterine artery Doppler waveforms and pregnancy outcomes.

Determine the most effective Doppler indices in the first and second trimester as a predictor of PET in the third trimester.

4.3.3 OBJECTIVE 3

Develop ultrasound management guidelines

4.4 STUDY POPULATION

In this prospective study a total of 144 participants were recruited, however 23 (15.9%) participants had to be excluded from the final analysis due to the following reasons:

1) did not return for follow up scans
2) pregnancy outcomes were not available from hospital records,

Records of 121 participants were available for the final analysis. Three hundred patients were suggested by the statistician for the sample to ensure a statistically significant analysis of data. However due to a lack of referrals this number was not attained in spite of a 12 month extension of the study period. The impact of the small sample size did not allow for regression models to be used and instead cross tabulations were employed.

4.5 BASELINE OBSTETRIC AND DEMOGRAPHIC DATA

Table 4.5.1 Baseline obstetric and demographic data

DATA	N = 121	MEAN	± STANDARD DEVIATION
Race distribution		N/A	N/A
Black	55 (45%)		
Coloured	57 (47%)		
Indian	6 (5%)		
White	3 (3%)		
Age range (years)			
18-29	82 (68%)	27.0	± 5.42
30-34	24 (20%)		
35-39	14 (12%)		
40+	1 (1%)		
Parity			N/A
1st pregnancy	37 (31%)	N/A	
2nd pregnancy	33 (27%)		
3rd pregnancy	23 (19%)		
4th pregnancy	28 (23%)		

As shown in table 4.5.1. it can be seen that 55 (45%) of the population were blacks, 57 (47%) were coloureds, 6(5%) of the patients were Indians and a small proportion of the patients 3(3%) were whites. The majority of participants, 82(68%), were in the age group 18 – 29, while 24(20%) were between 30 and 34 years of age, and 15 (12%) were older than 35 years of age, with the mean age being 27.0 (±SD 5.42). For 37(31%) patients it was their first pregnancy while 33 (27%) were gravida 2, 23 (19%) gravida 3 and 28 (23%) gravida 4.

4.6 UTERINE ARTERY DOPPLER SCREENING

Uterine artery Doppler screening was performed in the 1st, 2nd and 3rd trimester of pregnancy for each patient to assess its sensitivity in predicting PET & FGR as per objective 1.

Table 4.6.1 UTERINE ARTERY DOPPLER PULSATILITY INDICES (CURRENT STUDY)

DEPENDANT VARIABLE	NUMBER	RANGE	±STD DEVIATION
Uterine artery PI (right)			
1st trimester	121	(0.6-2.9)	±0.47
2nd trimester	121	(0.5-2.3)	±0.33
3rd trimester	113	(0.5-1.9)	±0.25
Uterine artery PI (left)			
1st trimester	121	(0.6-2.9)	±0.52
2nd trimester	121	(0.3-2.3)	±0.33
3rd trimester	113	(0.5-2.4)	±0.28
Lost to follow up	8		

The above table demonstrates the mean pulsatility index (PI) for each trimester.

Table 4.6.2 UTERINE ARTERY DOPPLER SPECTRAL WAVEFORM ANALYSIS

DEPENDANT VARIABLE	NUMBER
Notching (1st trimester)	**N=121**
Yes	50 (41%)
No	71 (59%)
Notching (2nd trimester)	**N=121**
Yes	18 (15%)
No	103 (85%)
Notching (3rd trimester)	**N = 113**

Yes	13 (11%)
No	100 (83%)
Lost to follow up	8 (7%)

Participants with notching decreased from 50 in the 1st trimester to 18 in the 2nd trimester and 13 in the 3rd trimester.

The majority of participants (59%-in the 1st trimester), (85%-in the 2nd trimester) and (83%-in the 3rd trimester) had a uterine artery spectral waveform which displayed no notching, in keeping with normal trophoblast invasion of the maternal spiral arteries.

4.7 PREGNANCY OUTCOMES

Pregnancy outcomes were recorded.

TABLE 4.7.1 PREGNANCY OUTCOMES

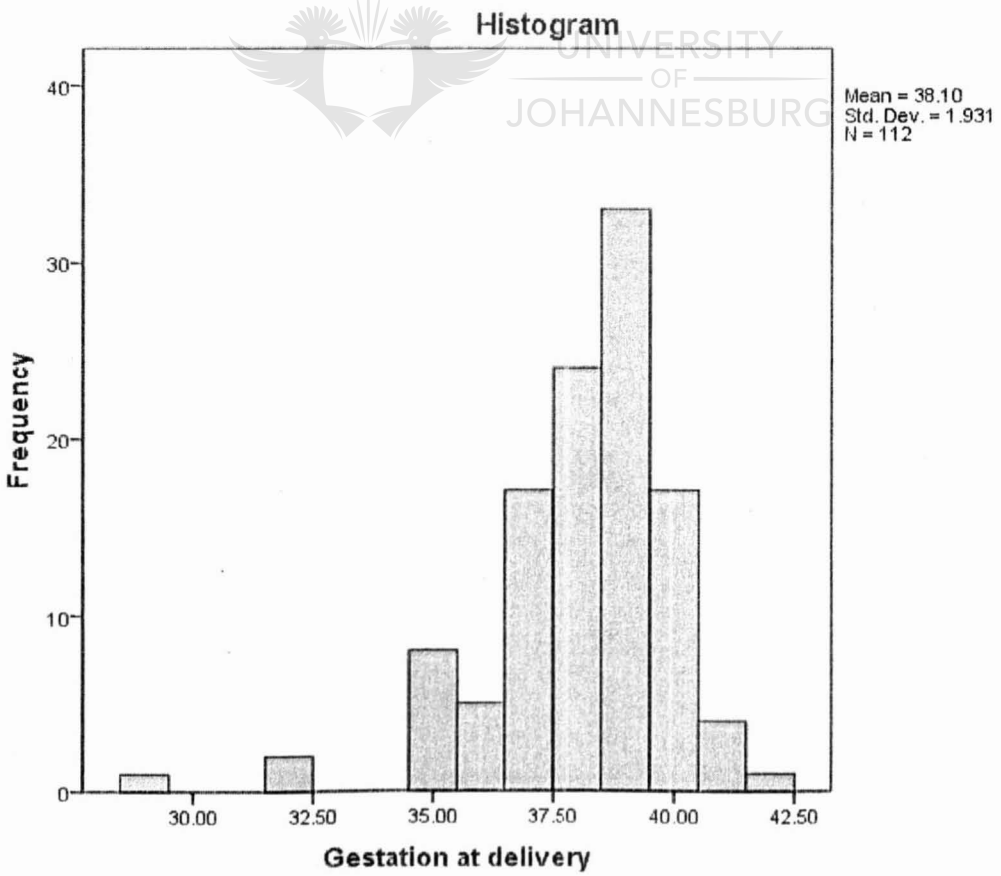
OUTCOME	N =121
Gestational age at delivery	
<37 weeks	16(13%)
37 – 42 weeks	96(80%)
>42 weeks	0
Unavailable	9 (7%)
Birth weight	
<2500g	18 (15%)
>2500g	92 (76%)
Unavailable	11 (9%)
Developed PET	7 (6%)
FGR neonates	18 (15%)
Intrauterine foetal death	1 (<1%)

Babies weighing less than 2500 g at term are considered small for gestational age, whereas foetal growth restriction (FGR) implies that a foetus has not achieved its optimal growth potential.

Pregnancy is considered "at term" when gestation attains 37 completed weeks but is less than 42 weeks. Delivery before the end of 37 weeks is considered preterm and after 42 weeks is considered post-term.

The above table and bar graph below demonstrates that 96 (80%) of the population delivered their babies at term and only 16 (13%) of the population delivered their babies prematurely at less than 37 weeks gestation while 0 exceeded term. Weights were not available for 9(7%) The mean gestational age was 38.1 weeks (±SD 1.91) (graph 1).

It is also evident that only 18 (15%) participants delivered foetuses < 2500g while 92 (76%) delivered foetuses weighing > 2500g. For nine (9) patients gestational ages at the time of delivery were not recorded and eleven (11) foetal weights were unavailable. PET was diagnosed in 7 (6%) of the patients and in a single case intrauterine foetal death occurred.



Graph 1 showing the gestation at delivery.

4.8 PREDISPOSING FACTORS FOR PRE-ECLAMPSIA IN THE PATIENTS WHO DEVELOPED PRE-ECLAMPSIA

TABLE 4.8.1

PREDISPOSING FACTORS FOR PRE-ECLAMSPIA IN PATIENTS WHO DEVELOPED PRE-ECLAMSPIA

DATA	N = 7	MEAN	±STANDARD DEVIATION
Race distribution		N/A	N/A
Black	5 (73%)		
Coloured	1 (14%)		
Indians	1 (14%)		
Age range (years)			
18-29	4 (57%)	28.9	4.8
30-34	2 (29%)		
>35	1 (14%)		
Parity		N/A	N/A
1st preg	2 (29%)		
2nd preg	2 (29%)		
3rd preg	2 (29%)		
4th preg	1 (14%)		
PET in a previous pregnancy		N/A	N/A
Yes	1 (14%)		
No	4 (57%)		
1st preg	2 (29%)		

Table 4.8.1 demonstrates that out of the 7 patients who developed preeclampsia 5 (73%) patients were black, 1 (14%) patient was coloured and 1 (14%) patient was

Indian. The above table shows that 4 (57%) patients were in their teens or twenties while 2 (29%) patients were between the ages of 30 & 34 and 1(14%) was of advanced maternal age (>35).

The above table demonstrates that 1(14%) participant had a previous pregnancy complicated by hypertension, 4 (57%) participants had no previous complications while 2 (29%) participants were primigravidas.

4.9 UTERINE ARTERY DOPPLER PI

The uterine arteries were sampled and the PI values were measured.

TABLE 4.9.1 UTERINE ARTERY DOPPLER PI IN THE PATIENTS WHO DEVELOPED PRE-ECLAMPSIA

DEPENDANT VARIABLE	NUMBER	MEAN PI	RANGE	± SD
UA PI(RIGHT)				
1st trimester	7	1.5	(0.9-2)	0.35
2nd trimester	7	1.3	(0.8-2.2)	0.5
3rd trimester	6	1.0	(0.7-1.4)	0.3
Lost to follow up	1			
UA PI (LEFT)				
1st trimester	7	1.2	(0.9-1.5)	0.18
2nd trimester	7	1.3	(0.7-2.3)	0.6
3rd trimester	6	1.3	(0.7-2.4)	0.6
Lost to follow up	1			

The 1 patient that was lost to follow up was the patient who had an intrauterine foetal death.

Table 4.9.2 UTERINE ARTERY DOPPLER SPECTRAL WAVEFORM ANALYSIS IN THE PATIENTS WHO DEVELOPED PRE-ECLAMPSIA

DEPENDANT VARIABLE	N = 7
UA Notching 1st trimester	
No	4 (57%)
Yes	3 (43%)
UA Notching 2nd trimester	
No	4 (57%)
Yes	3 (43%)
UA Notching 3rd trimester	
No	4 (57%)
Yes	2 (28%)
Not available	1 (14%)

Table 4.9.3 PROFILE OF THE PATIENTS WHO DEVELOPED PREECLAMPSIA

PATIENT NUMBER	PATIENT PROFILE	PREDISPOSING FACTORS	PULSATILITY INDEX			PRESENCE/ ABSENCE OF NOTCHING (UNI, BIL, No notching)			GA @ ONSET (WKS)	GA @ DEL (WKS)	BIRTHWEIGHT (g)
			1st	2nd	3rd	1st	2nd	3rd			
1	26 year old black 2nd pregnancy, IUFD at 28wks	Black	1.75	2.25	MISSING	No	No	MISSING	27	28	MISSING
2	32 year old black, primigravida, BMI 38	Black, BMI > 35 Primigravida	1.45	1.4	1.9	Yes	Yes	Yes	28	29	940
3	27 year old black, 3rd pregnancy	Black, Previous PET	1.5	1.35	0.75	Yes	Yes	Yes	30	32	1380
4	22 year old coloured primigravida, BMI 23	Primigravida	1.25	0.9	1.4	Yes	Yes	No	28	32	1475
5	30 year old black, 3rd pregnancy	Black	1.25	1.2	1.05	No	No	No	35	37	2695
6	28 year old black, 2nd pregnancy	Black	1.3	1.2	1.10	No	No	No	34	40	3270
7	37 year old Indian, 4th pregnancy, BMI 27	Age > 35	0.9	0.8	0.8	No	No	No	36	40	3495

From table 4.9.3 it is evident that notching predicted the disease in the severe cases with poor trophoblast invasion of the maternal spiral arteries already in the 1st trimester in 3 out of 4 cases. Severe cases in this study are defined as patients who developed PET in early 3rd trimester before 32 weeks of gestation. The interpretation of PI values in the cases with PET is difficult since the nomogram employed in this study was not predominantly developed for a South African population. PI values in this study were all below the 95th centile for gestational age.

4.10 PREGNANCY OUTCOMES IN THE PATIENTS WHO DEVELOPED PRE-ECLAMSPIA

TABLE 4.10.1 TABLE DEMONSTRATING THE PREGNANCY OUTCOMES IN THE PATIENTS WHO DEVELOPED PRE-ECLAMSPIA

DATA	N=7
Birthweight	940g 1 (14.3%) 1380g 1 (14.3%) 1475g 1 (14.3%) 2695g 1 (14.3%) 3270g 1 (14.3%) 3495g 1 (14.3%) MISSING 1 (14.3%)
Gestation @ delivery	29 weeks 1 (14.3%) 32 weeks 2 (28.6%) 37 weeks 1 (14.3%) 40 weeks 2 (28.6%) MISSING 1 (14.3%)

The above table demonstrates that in the mothers who developed preeclampsia 3 (42.9%) babies were born at less than 1500g, while 3 (42.9%) babies were born at a weight greater than 2500g. In addition the above table also shows that 3 (42.9%)

babies were born at a gestational age less than 36 weeks, and 3 (42.9%) babies were born at term. The weight record and gestational age of 1 (14.3%) baby was missing

4.11 BASELINE OBSTETRIC AND DEMOGRAPHIC DATA FOR THE PATIENTS WHO DELIVERED LOW BIRTHWEIGHT BABIES

TABLE 4.11.1 BASELINE OBSTETRIC AND DEMOGRAPHIC DATA FOR THE PATIENTS WHO DELIVERED LOW BIRTHWEIGHT BABIES

DATA	N = 18	MEAN	± STANDARD DEVIATIAON
Race distribution		N/A	N/A
Black	6 (33%)		
Coloured	9 (50%)		
Indians	2 (11%)		
Whites	1 (6%)		
Age range (years)		28	5.9
21-29	11 (61%)		
30-35	3 (17%)		
>35	4 (27%)		
Parity		N/A	N/A
1st preg	5 (28%)		
2nd preg	4 (22%)		
3rd preg	4 (22%)		
4+ preg	5 (28%)		

The above table demonstrates that in the group that delivered SGA babies 6 (33%) patients were black, 9 (50%) were coloured, 2 (11%) were Indian and 1 (6%) was white. The age range for patients who delivered low birthweight babies were as follows; Eleven (11) (61%) patients were between the ages of 21 and 29, 3 (17%) patients were between the ages of 30 and 35 years and 4 (27%) patients were older

than 35 years. The parity range for the above group was as follows; 5 (28%) were primigravidas, 4 (22%) patients had 1 previous pregnancy, 4 (22%) patients had 2 previous pregnancies and 5 (28%) had 3 previous pregnancies.

TABLE 4.11.2.

UTERINE ARTERY DOPPLER PULSATILITY INDICES IN LOW BIRTHWEGHT BABIES

DEPENDANT VARIABLE	NUMBER	MEAN PI	RANGE	± SD
UA PI (RIGHT)				
1st trimester	18	1.4	(0.6-2.5)	0.6
2nd trimester	18	1.1	(0.6-2.2)	0.5
3rd trimester	18	0.9	(0.5-1.9)	0.4
UA PI (LEFT)				
1st trimester	18	1.4	(0.7-2.9)	0.7
2nd trimester	18	1.2	(0.6-2.3)	0.6
3rd trimester	18	1.0	(0.6-2.4)	0.5

TABLE 4.11.3. ULTRASOUND DOPPLER WAVEFORM ANALYSIS IN LOW BIRTHWEIGHT BABIES

DEPENDANT VARIABLE	N = 18
UA Notching 1st trimester	
No	10 (55%)
Yes	8 (45%)
UA Notching 2nd trimester	
No	15 (61%)
Yes	7 (39%)

UA Notching 3rd trimester	**N = 18**
No	14 (78%)
Yes	4(22%)

4.12 PREGNANCY OUTCOMES IN LOW BIRTHWEIGHT BABIES

TABLE 4.12.1. PREGNANCY OUTCOMES IN LOW BIRTHWEIGHT BABIES

OUTCOME	N=18
Birthweight	
<1000g	1 (6%)
1100g-1500g	2 (11%)
1600g-2000g	2 (11%)
2070g-2450g	13 (72%)
Gestation @ delivery	
29 weeks	1 (6%)
32 weeks	2 (11%)
35 weeks	6 (33%)
36 weeks	2 (11%)
37 weeks	4 (22%)
38 weeks	2 (11%)
39 weeks	1 (6%)
Evidence of pre-eclampsia	
Yes	3 (17%)
No	15 (83%)

Table 4.12.1 demonstrates the pregnancy outcomes in low birthweight babies. There was a single baby born(6%) at less than 1000g, 4 (22%) babies were born between 1100g and 2000g and 13 (72%) babies were born with a weight between

2070g and 2450g. 1 (6%) baby was born at a 29 weeks gestational age, 8 (44%) babies were born between 32 and 35 weeks gestation and 9 babies were born at >36 weeks gestation. Three (17%) of the low birthweight babies had to be delivered early due to maternal PET. In 15 (83%) pregnancies with SGA foetuses born, no evidence of PET was recorded. There was one outlier who showed signs of asymmetrical FGR however the pregnancy was not complicated by PET.

TABLE 4.12.2 PROFILE OF LOW BIRTHWEIGHT BABIES BORN:

PATIENT NUMBER	PROFILE	UTERINE ARTERY PI			UTERINE ARTERY NOTCHING			Birth WEIGHT (g)	Mean Birth weight	GA @ Delivery	Mean GA	PATHOLOGY
1	Black non smoker	1.45	1.4	1.9	Yes	Yes	Yes	940	1374	29/40	32	FGR + PET
2	Black non smoker	1.5	1.35	0.75	Yes	Yes	Yes	1380		32/40		FGR + PET
3	Coloured smoker	1.25	0.9	1.4	Yes	Yes	No	1475		32/40		FGR + PET
4	Coloured smoker	1.6	1.35	1.45	Yes	Yes	Yes	1700		35/40		FGR
5	Coloured smoker	0.9	0.8	0.85	No	No	No	1940	2238	35/40	36	FGR
6	Black non smoker	2.0	1.25	1.55	Yes	Yes	Yes	2070g		36/40		FGR
7	Coloured smoker	0.7	0.7	0.65	No	No	No	2120		37/40		FGR
8	Indian non smoker	0.8	0.65	0.65	No	No	No	2155		37/40		FGR
9	Coloured smoker	1.05	1.15	0.8	No	No	No	2165		35/40		FGR
10	Black, non smoker	0.9	0.9	0.75	No	No	No	2260		38/40		FGR
11	Coloured smoker	2.1	1.5	1.45	No	No	No	2300		35/40		FGR

12	Coloured smoker	1.15	0.65	0.75	No	No	No	2300		37/40		FGR
13	Black non smoker	1.55	1.9	0.75	No	No	No	2300		37/40		FGR
14	Black non smoker	1.9	0.85	0.8	No	No	No	2300		38/40		FGR
15	Coloured non smoker	1.65	1.95	0.8	Yes	No	No	2300		39/40		FGR
16	Indian non smoker	0.95	0.7	0.7	Yes	Yes	No	2325		36/40		FGR
17	Coloured non smoker	1.0	0.9	0.75	No	No	No	2345		35/40		FGR
18	White smoker	1.6	1.0	0.75	Yes	Yes	No	2450		35/40		FGR

4.13 CROSS TABULATIONS

Cross tabulation is the process of creating a contingency table from the multivariate frequency distribution of statistical variables.

A useful way for using the information in cross tabulations where one dimension of the table is an outcome of interest is to calculate the odds and relative odds (odds ratio). The odds ratio is the ratio of the likelihood of an event occurring in one group to the likelihood of it occurring in another group. It is used as a descriptive statistic.

TABLE 4.13.1 EVIDENCE OF PRE-ECLAMPSIA NOTCHING vs. NO NOTCING IN THE 1st TRIMESTER-(BLACK WOMEN)

As is evident from other previous studies black women have a higher incidence of developing pre-eclampsia than other race groups, which was confirmed in this study with 72% of the patients that developed pre-eclampsia being black patients.

EVIDENCE OF PRE-ECLAMPSIA	NO NOTCHING	NOTCHING	TOTAL
No PRE-ECLAMPSIA	23 60.5%	15 39.5%	38 100%
PRE-ECLAMPSIA	2 50.0%	2 50.0%	4 100%
TOTAL	25 59.5%	17 40.5%	42 100%

The odds of a black person with no notching in the 1st trimester developing pre-eclampsia is calculated 2/23=0.086 to 1.

For mothers with notching the corresponding odds are 2/15=0.13 to 1.

The relative odds of black mothers with notching is 0.13/0.086=1.5 to 1.

This means black women with notching in the 1st trimester are 1.5 times more likely to develop pre-eclampsia, than those without notching.

TABLE 4.13.2 EVIDENCE OF PRE-ECLAMPSIA NOTCHING vs. NO NOTCING IN THE 2nd TRIMESTER-(BLACK WOMEN)

EVIDENCE OF PREECLAMPSIA	NO NOTCHING	NOTCHING	TOTAL
No PRE-ECLAMPSIA	34 89.5%	4 10.5%	38 100%
PRE-ECLAMPSIA	1 25%	3 75%	4 100%
TOTAL	35 83.3%	7 16.7%	42 100%

The odds of a black person with no notching in the 2nd trimester developing pre-eclampsia is calculated as 1/34=0.029 to 1.

To black mothers with notching the corresponding odds are 3/4= 0.75 to 1.

The relative odds of mothers with notching compared to with those without notching is 0.75/0.029=25.86 0r approximately 26 to1. In other words a black women with notching in the 2nd trimester is 26 times more likely to develop pre-eclampsia than those without notching.

TABLE 4.13.3 EVIDENCE OF PRE-ECLAMPSIA NOTCHING vs. NO NOTCING IN THE 3rd TRIMESTER-(BLACK WOMEN)

EVIDENCE OF PRE-ECLAMPSIA	NO NOTCHING	NOTCHING	TOTAL
No PRE-ECLAMPSIA	34 94.4%	2 5.6%	36 100%
PRE-ECLAMPSIA	2 66.7%	1 33.3%	3 100%

TOTAL	36 92.3%	3 7.7%	39 100%

The odds of a black person with no notching in the 3rd trimester developing pre-eclampsia is calculated as 2/34=0.058 to 1.

To mothers with notching the corresponding odds are ½=0.5 to 1.

The relative odds of mothers with notching compared with those without notching is 0.5/0.058=8.6 or 9 to 1.

In other words a black women with notching in the 3rd trimester is 9 times more likely to develop pre-eclampsia than those without notching.

4.13.4. EVIDENCE OF PRE-ECLAMPSIA NOTCHING vs. NO NOTCING IN THE 1st TRIMESTER-(coloured women)

EVIDENCE OF PRE-ECLAMPSIA	NO NOTCHING	NOTCHING	TOTAL
No PRE-ECLAMPSIA	33 58.9%	23	56 100%
PRE-ECLAMPSIA	0 0%	1 100%	1 100%
TOTAL	33	24	57 100%

The odds of a coloured person with no notching in the 1st trimester developing pre-eclampsia is calculated as 0/33=0.

To mothers with notching the corresponding odds are 1/23=0.04 to 1.

Unable to calculate the relative odds.

4.13.5. EVIDENCE OF PRE-ECLAMPSIA NOTCHING vs. NO NOTCING IN THE 2nd TRIMESTER-(coloured women)

EVIDENCE OF PRE-ECLAMPSIA	NO NOTCHING	NOTCHING	TOTAL
No PRE-ECLAMPSIA	49 %	7	56 100%
PRE-ECLAMPSIA	0 0%	1 100%	1 100%
TOTAL	49	8	57 100%

The odds of a coloured person with no notching in the 2nd trimester developing pre-eclampsia is calculated as 0/49=0

To mothers with notching the corresponding odds are 1/7=0.14

Unable to calculate the relative odds.

4.13.6 EVIDENCE OF PRE-ECLAMPSIA NOTCHING vs. NO NOTCING IN THE 3rd TRIMESTER-(coloured women)

EVIDENCE OF PRE-ECLAMPSIA	NO NOTCHING	NOTCHING	TOTAL
No PRE-ECLAMPSIA	48 %	6	54 100%
PRE-ECLAMPSIA	1 0%	0 100%	1 100%
TOTAL	49	6	55 100%

The odds of a coloured person with no notching in the 3rd trimester developing pre-eclampsia is calculated as 1/48=0.02

To mothers with notching the corresponding odds are 0/6=0

Unable to calculate the relative odds.

4.13.7 EVIDENCE OF PRE-ECLAMPSIA NOTCHING vs. NO NOTCING IN THE 1st TRIMESTER-(indian women)

EVIDENCE OF PRE-ECLAMPSIA	NO NOTCHING	NOTCHING	TOTAL
No PRE-ECLAMPSIA	4 %	1	5 100%
PRE-ECLAMPSIA	1 0%	0 100%	1 100%
TOTAL	5	1	6 100%

The odds of an Indian person with no notching in the 1st trimester developing pre-eclampsia is calculated as 1/4=0.25

To mothers with notching the corresponding odds are 0/1=0

Unable to calculate the relative odds.

4.13.8. EVIDENCE OF PRE-ECLAMPSIA NOTCHING vs. NO NOTCING IN THE 2nd TRIMESTER-(indian women)

EVIDENCE OF PRE-ECLAMPSIA	NO NOTCHING	NOTCHING	TOTAL
No PRE-ECLAMPSIA	5 %	0	5 100%
PRE-ECLAMPSIA	1 0%	0 100%	1 100%
TOTAL	6	0	6 100%

The odds of an Indian person with no notching in the 2nd trimester developing pre-eclampsia is calculated as 1/5=0.2

To mothers with notching the corresponding odds are 0/0=0

Unable to calculate the relative odds.

4.13.9. EVIDENCE OF PRE-ECLAMPSIA NOTCHING vs. NO NOTCING IN THE 3rd TRIMESTER-(indian women)

EVIDENCE OF PRE-ECLAMPSIA	NO NOTCHING	NOTCHING	TOTAL
No PRE-ECLAMPSIA	5 %	0	5 100%
PRE-ECLAMPSIA	1 0%	0 100%	1 100%
TOTAL	6	0	6 100%

The odds of an Indian person with no notching in the 2nd trimester developing pre-eclampsia is calculated as 1/5=0.2

To mothers with notching the corresponding odds are 0/0=0

Unable to calculate the relative odds.

No attempt was made to calculate the odds and relative odds for the white population as there were no patients who developed pre-eclampsia in that race group.

4.14 EVIDENCE OF LOW BIRTHWEIGHT BABIES: NOTCHING vs. NO NOTCHING

Table 4.14.1. 1st TRIMESTER

BIRTHWEIGHT	NO NOTCHING	NOTCHING (uni or bil)	TOTAL
ADEQUATE (>2500g)	56 84.8%	38 82.6%	94 83.9%
LOW (< 2500g)	10	8	18

	15.2%	17.4%	16.1%
TOTAL	66 100%	46 100%	112 100 %

The odds of a person with no notching in the 1st trimester having delivered a low birthweight baby is calculated as 10/56=0.178 to 1.

To mothers with notching the corresponding odds are 8/38=0.21 to 1.

The relative odds of mothers with notching compared to those without notching is 0.210/0.178=1.17 or approximately 1.2 to 1. In other words mothers with notching in the 1st trimester is 1.2 times more likely to deliver FGR babies than mothers with no notching.

TABLE 4.14.2. 2nd TRIMESTER

BIRTHWEIGHT	NO NOTCHING	NOTCHING	TOTAL
ADEQUATE (>2500g)	85 88.5%	9 56.3%	94 83.9%
LOW (< 2500g)	11 11.5%	7 43.8%	18 16.1%
TOTAL	96 100%	16 100%	112 100 %

The odds of a person with no notching in the 2nd trimester having delivered a low birthweight baby is calculated as 11/85=0.129 to 1.

To mothers with notching the corresponding odds are 7/9=0.77 to 1.

The relative odds of mothers with notching compared to those without notching is 0.77/0.129= 5.96 or approximately 6 to 1. In other words mothers with notching in the 2nd trimester is 6 times more likely to deliver FGR babies than mothers with no notching.

TABLE 4.14.3. 3rd TRIMESTER

BIRTHWEIGHT	NO NOTCHING	NOTCHING	TOTAL
ADEQUATE (> 2500g)	83	9 69.2%	92 83.6%
LOW (< 2500g)	14 14.4%	4 30.8%	18 16.1%
TOTAL	97 100%	13 100%	110 100 %

Two (2) missing patients are seen in the adequate birthweight column. These patients did not arrive for 3rd trimester scans however the birthweights were available from hospital records.

The odds of a person with no notching in the 3rd trimester having delivered a low birthweight baby is calculated as 14/83=0.168 to 1.

To mothers with notching the corresponding odds are 4/9=0.444 to 1.

The relative odds of mothers with notching compared to those without notching is 0.444/0.168=2.64 or approximately 3 to 1. In other words mothers with notching in the 3rd trimester is 3 times more likely to deliver FGR babies than mothers with no notching.

4.15 SUMMARY

Records of 121 pregnancies were available for analysis.

The coloured population made up the majority of the sample due to the fact that the hospital is based in a predominantly coloured residential area. A large number of the patients were between the ages of 18 and 29 years and majority of the patients were primigravidas.

In terms of pregnancy outcomes a large number of patients delivered at term weeks and majority of the babies born had a birthweight > 2500g. Seven patients developed pre-eclampsia and 18 babies were born with a birthweight < 2500g. There was one (1) intrauterine foetal death that occurred.

In the group of patients who developed pre-eclampsia the majority of the patients were black. A large proportion of the patients were between the ages of 18 and 29 years of age and one (1) patient had a previous pregnancy that was complicated by hypertension.

In the group of patients who delivered low birthweight babies the majority of the patients were coloured and most of the patients were between the ages of 21 and 29 years. Eight (8) low birthweight babies were born to smoking mothers. Five (5) babies were born at a birthweight less than 2000g and 9 babies were born prior to term. Three (3) of these patients were diagnosed with pre-eclampsia.

Cross tabulations were used to determine the odds of a black women with and without uterine artery notching who developed pre-eclampsia, and also of low birthweight babies born in relation to the presence or absence of notching.

CHAPTER 5

DISCUSSION

5.1 INTRODUCTION

The findings of this study will be summarised in this chapter so that conclusions can be drawn on the sensitivity of uterine artery Doppler screening in predicting pre-eclampsia and foetal growth restriction.

Pre-eclampsia is the most common pregnancy complication associated with serious maternal-foetal morbidity and mortality. At present the only effective treatment is delivery of the placenta (Poon *et al.*, 2009 : 501). Uterine artery Doppler waveforms can identify women with obstetric complications related to abnormal placentation (Ghidini ., 2008 : 261), since Doppler ultrasonography is a useful method to assess the velocity of uterine artery blood flow. An abnormal velocity waveform is characterised by a high resistance to flow and or an early diastolic notch (Sibai *et al.*, 2005 : 792). Early screening for pre-eclampsia by uterine artery Doppler has been suggested based on the concept that the pathogenic mechanisms of pre-eclampsia may be modified if prophylactic therapies are initiated early in pregnancy (Herraiz 2009 : 1123).

Abnormal uterine artery Doppler waveforms are also able to identify foetuses at high risk of preterm delivery and low birth weight (Ghidini 2008 : 259). Pregnancies complicated by FGR warrant close surveillance for maternal and foetal complications and interventions in anticipation of a preterm delivery due to an apparent high risk for the development of pre-eclampsia (Mitani *et al.*, 2009 : 886). It is hypothesised that the ability to predict those women at risk for pre-eclampsia early in pregnancy might decrease maternal and foetal morbidity through closer surveillance programmes (Poon *et al.*, 2009 : 501).

The purpose of this study was to assess the sensitivity of uterine artery Doppler screening in predicting pre-eclampsia and FGR before the onset of the disease. The

results of this study could be used to evaluate whether it is worthwhile implementing a routine screening program for pre-eclampsia in Johannesburg, South Africa.

5.2 STUDY POPULATION AND SAMPLE SIZE

Patients from different ethnic backgrounds attended the ultrasound department at Rahima Moosa Mother and Child Hospital over the stated period. Women who did not meet the criteria were excluded from the study. Only 144 patients were included in the study which was not an adequate sample for statistical analysis and logistic regression models could not be used to analyse the data, however due to time constraints the available data was used and analysed.

5.3 OBSTETRIC AND DEMOGRAPHIC DATA

Obstetric and demographic data were recorded for all participants.

5.3.1 PARITY

Pre-eclampsia is twice as common in primigravid women as compared to women for whom it is their second or more pregnancy (McCarthy *et al.*, 2009:138). Women with pre-eclampsia are therefore twice as likely to be nulliparous as women without pre-eclampsia. In Duckitts study (2005:2) nulliparity almost triples the risk for developing pre-eclampsia. In our study, only 2 (29%) patients out of the seven who developed pre-eclampsia were primigravidas, thus indicating that gravidity was not a strong predisposing factor for the disease.

5.3.2 MATERNAL AGE

United States data suggests that the risk of pre-eclampsia increases by 30% for every additional year over the age of 34 (Duckitt 2005 : 2). In the current study the majority (86%) of the patients who developed PET were between the ages of 18 and 34 years. Comparing our data to that of the United States only 1 out of the seven patients who developed pre-eclampsia was over the age of 34 years. . In the group

of patients who developed pre-eclampsia none of the participants were exceptionally young mothers or of advanced maternal age, which both carry a higher risk for PET. In our study age, therefore, did not play a role as a risk factor for PET.

5.3.3 RACE

Assis and co workers reported that the risk of pre-eclampsia in non white pregnant women was 14.085 times that of white pregnant women. Furthermore, a study done in Florida also verified an increased risk of pre-eclampsia in non white patients (Assis *et al.*, 208 : 15). Professor Nicolaou stated in a presentation done at the 2010 SASUOG congress that the likelihood ratio for black patients to develop pre-eclampsia was 1.5 while the likelihood ratio for white patients developing pre-eclampsia was 1.0. The findings of our study support the sensitivity of uterine artery Doppler screening in the second trimester in the black population. Out of the seven patients who developed pre-eclampsia 5 (73%) were black. We therefore concur with other researchers that women of Afro-Caribbean origins are especially at risk of developing PET in pregnancy.

5.4 UTERINE ARTERY DOPPLER WAVEFORM ANALYSIS

Uterine artery Doppler waveforms were performed to assess uteroplacental circulation in the first, second and third trimesters in all participants. A series of screening studies involving assessment of impedence to flow in the uterine arteries, have examined the potential value of Doppler assessment in identifying pregnancies at risk of complications due to impaired placentation (www.centrus.com).

Increased impedance to flow in the uterine arteries in pregnancies attending routine antenatal care identifies about 50% of those patients that subsequently develop pre-eclampsia and it identifies about 30% of those patients that subsequently develop FGR (www.centrus.com). Shear and colleagues (2005:1119) reported a relationship between pre-eclampsia and FGR. Their study showed critical maternal complications more frequently in pre-eclamptic patients with associated FGR.

The current study assessed the sensitivity of PI and end diastole notching as a diagnostic tool to predict pre-eclampsia and FGR. Three out of the seven patients who developed pre-eclampsia had abnormal Doppler waveforms which were evident from as early as the first trimester. The study therefore demonstrated that an abnormal uterine artery waveform with early diastolic notching could predict 43% of cases that developed PET from as early as the 1st trimester. What is however significant is that uterine artery waveform analysis was able to predict PET in the most severe cases in patients who presented with early manifestations of the disease and had the worst pregnancy outcomes.

5.4.1 PI VALUES

A study done by Melchiorre (2008:135) reported that uterine artery Doppler indices were significantly higher in women who developed preterm pre-eclampsia.

In the current study PI values up to the 95th centile of the PI chart was considered as normal. The following table was populated with data obtained from a study done by Gomez and co workers (2008 : 130).

TABLE 5.4.1.1. UTERINE ARTERY DOPPLER INDICES

Gomez *et al*	1st trimester (PI)	2nd trimester (PI)	3rd trimester (PI)
5th centile	1.1	0.7	0.6
50th centile	1.7	1.0	0.8
95th centile	2.7	1.5	1.2

These values represent the 50th centile for each of the trimesters of pregnancy at 12 weeks, 22 weeks and 28 weeks of gestation and are also used as cut off values by the Fetal Medicine Unit at Chris Hani Baragwanath Hospital in Johannesburg (Nicolaou, 2011).

Table 5.4.1.2. UTERINE ARTERY DOPPLER INDICES (50th centile-current study)

Current study	1st trimester (PI)	2nd trimester (PI)	3rd trimester (PI)
50th centile	1.3	0.9	0.8

Comparing the mean values in our study to the mean values in the study done by Gomez and colleagues, a difference in the mean (50th centile) in the 1st trimester is noted. The 2nd and 3rd trimester mean values in this study were similar to the values obtained by Gomez *et al.* In both studies it can be seen that the mean PI values decreased as gestation increased as is to be expected in a normal pregnancy.

In our study the 1st trimester PI values in patients who developed pre-eclampsia was not a strong predictor of PET. None of the values recorded were above the 95th centile when compared to the values by Gomez and co-workers. However, in clinical practice a 1st trimester PI value of >1.5 is deemed as elevated and warrants monitoring (Nicolaou, 2011:Personal communication). In the group that developed PET, 1st trimester PI values ranged between 0.9 and 1.75 respectively. It is thus evident that only in selected cases an increased resistance to flow was recorded in the 1st trimester.

In the 2nd trimester only 1 out of the 7 patients had a PI value above the 95th centile which measured 2.25. In four more PET cases a PI value above the 50th centile was measured, signifying that PI performed better as a predictor of PET in the 2nd trimester.

In the 3rd trimester 2 out of the 7 patients had a PI value above the 95th centile while two additional cases had PI values above the 50th centile.

Comparing the mean PI values in the patients who developed pre-eclampsia to the mean PI values developed by Gomez *et al.*, only one out of the seven recorded values were on the 50th centile in the 1st trimester, while 5 out of 7 2nd trimester values were above the 50th centile and 4 out of 7 Doppler PI 3rd trimester values obtained in this study were above the 50th centile.. It can therefore be concluded that PI values did not perform well in our study as only a few patients had increased PI values of who most were marginally elevated.

5.4.2 UTERINE ARTERY NOTCHING

In the 1st and 2nd trimesters 3 out of the 7 patients who developed preeclampsia had uterine artery notching, in the 3rd trimester 2 out of the 7 patients had notching, while the outcome for one patient who did not return for the 3rd trimester follow-up scan was unavailable.

Swanepoel (2004:6) suggested that the presence of a notch is a significantly better predictor of poor pregnancy outcome than the pulsatility index; however, in other studies the presence of notching in the 2nd trimester in a low risk population has been associated with a high probability for developing FGR and preeclampsia (Hernandez-Andrade *et al.*, 2002 : 440). In high-risk pregnancies the risk increases up to 60% (Hernandez-Andrade *et al.*, 2002 : 441). It has been established that uterine artery notching that persist after 26 weeks of gestation be considered a risk factor for poor pregnancy outcomes (Andrade *et al.*, 2002 : 440). An early diastolic was found to persist in 25-40% of cases after 26 weeks gestation (Swanepoel: 2004:6)

In our study the majority (73%) of the patients who developed pre-eclampsia were black women. Cross tabulations for black women were therefore done using notching as a predictor of pre-eclampsia in the first, second and third trimesters. The presence of notching in the second trimester was the best predictor for the development of pre-eclampsia. Black women with notching in the second trimester were twenty six times more likely to develop pre-eclampsia when compared to black women with no notching. Cross tabulations for black women and notching did not fare as well in the other trimesters with a risk increase of 1.5 in the first and 9 in the third trimesters respectively.

Uterine artery Doppler analysis in the high risk population has shown potential for predicting adverse pregnancy outcomes (Harrington *et al.*, 2004 : 50).

The results of our study confirm the work done by Pilalis (2007 : 533) and Harrington (2004:54) who both found that second trimester uterine artery Doppler screening has proven to be a sensitive and accurate tool for predicting pre-eclampsia and foetal growth restriction in high risk populations.

We found that 1st trimester notching persisted into the 2nd trimester in 43% of patients who developed pre-eclampsia and into the 3rd trimester in 29% of cases. It can be argued that a drop in the percentage can be due to the missing 3rd trimester Doppler analysis in the one(1) patient with PET who delivered an IUFD at 28 weeks gestation. The presence of notching, even with a normal PI index, places the patient at a higher risk for adverse foetal outcomes (www.fetal.com).

The sensitivity for predicting pre-eclampsia in patients requiring delivery before 34 weeks gestation was high (3 of 4 cases) in our study. Three patients with 1st and 2nd trimester notching delivered before 34 week while in two of these cases notching persisted into the 3rd trimester. The above patients all required delivery before 34 weeks of gestation. Unfortunately 3rd trimester data for one patient was lost to follow-up due to the fact that the patient suffered an IUFD at 28 weeks gestation.

The findings of our study thus concur with the findings by Mcleod (2009:728) who states that the presence of an early diastolic notch is associated with adverse pregnancy outcomes. Our study also supports the findings of Kurdi (1998:344) who found that women with notching represent a group with an increased risk of developing complications, in particular those that require early delivery.

5.5 PREGNANCY OUTCOMES IN THE STUDY POPULATION

In the current study 80% of the population delivered at term, and 76% of the population delivered babies weighing more than 2500g. Seven(7) patients developed pre-eclampsia, eighteen(18) delivered babies who were small for gestational age and a single(1) patient who developed pre-eclampsia had an IUFD at twenty eight weeks gestation. Of the 18 neonates who were <2500gm only four (4) were asymmetrically SGA and were therefore classified as growth restricted (FGR).

5.6 SCREENING FOR ADVERSE PREGNANCY OUTCOMES

5.6.1 SCREENING FOR PRE-ECLAMPSIA

Patients who would benefit from screening programs include those patients with pre-existing risk factors. According to McCarthy *et al.*, (2009:138) Duckitt *et al.*, (2005:1) and Wagner (2004:2319), women at high risk would be those who are:

- Of Afro-Caribbean origins Older than 34 years of age
- Primigravidas
- Have a BMI > 35
- Have a history of previous pre-eclampsia
- Have pre-existing medical conditions such as:

1) Diabetes

2) Chronic hypertension

3) Renal disease

4) Autoimmune disease

5) Antiphospholipid syndrome

In our study race was the strongest risk factor for PET as 5 out of the 7 patients who developed pre-eclampsia were black patients while notching in the second trimester was the best predictor of PET in the black population.

5.6.2 SCREENING FOR FGR

The analysis of FGR was based on 18 neonates who had a birthweight below 2500gms.

Three(3) out of eighteen FGR neonates were born to mothers whose pregnancies were complicated by PET. The single (1) outlier who was born to a mother whose pregnancy was not yet complicated by PET had normal umbilical artery Doppler indices without notching, although FGR as well as reduced liquor was noted on ultrasound. The patient was referred for further management and was delivered at 35 weeks gestation when severe foetal distress became evident. It is suspected that the mother would have developed pre-eclampsia if the pregnancy was allowed to continue beyond 36 weeks.

Uterine artery Doppler indices were not increased in the 1st trimester, in the 2nd trimester 3 out of the 18 patients had increased uterine artery Doppler indices and in the 3rd trimester and in the 3rd trimester 5 patients had increased uterine artery Doppler indices. Eight of the 18 patients had notching in the 1st trimester, while 7 patients had notching in the 2nd trimester and only 4 patients had notching in the 3rd trimester. It is evident that the pulsatility indices did not predict the outcome in the first trimester, however, notching played a major role in predicting FGR.

Nine(9) FGR babies were born to coloured mothers and 2 were born to Indian mothers. This study is in keeping with the trend observed by Nicolaou (2011:

Personal communication) that Coloured and Indian mothers tend to deliver smaller babies, a phenomenon unique to the South African population.

Eight (8) FGR babies were born to smoking mothers. Lees and colleagues (2001: 371) state that cigarette smoking doubles the risk of severe adverse pregnancy outcomes for a given mean uterine artery PI and is related to FGR. The effect of smoking appears independent of the development of uteroplacental circulation (Lees *et al.*, 2001:371).

5.6.2.1 CROSS TABULATIONS IN LOW BIRTHWEIGHT BABIES

Cross tabulations were done on low birth weight babies using notching in the first second and third trimesters as predictors for FGR. Notching in the second trimester was once again the best predictor. Mothers with notching in the second trimester are six(6) times more likely to deliver a low birth weight baby than mothers with no notching in the second trimester.

5.7 CONCLUSIONS RELATED TO THE STUDY OBJECTIVES

This study evaluated the sensitivity of uterine artery Doppler screening in predicting pre-eclampsia and FGR. The uterine artery Doppler waveforms were analysed for the presence or absence of notching and the PI values were calculated using standard software on the ultrasound machine.

Doppler investigation of the foetus and placenta has evolved in the past years and there is now a better understanding of the pathophysiology involved in PET. Uterine artery Doppler screening in early pregnancy is performed so that those cases at high risk for placental associated disease can be identified.

It is also important to differentiate between growth restricted foetuses and ones who are constitutionally small for gestational age. Growth restricted foetuses are linked to placental insufficiencies whereas the symmetrically small ones are considered to represent the lower end of the normal sized spectrum in the majority of cases. Growth restricted foetuses are associated with increased perinatal mortality and long term neurological morbidity. These foetuses represent an early onset of severe FGR and about one third of these cases are associated with pre-eclampsia.

Uterine artery Doppler waveforms have been demonstrated to improve a number of perinatal outcomes in high risk pregnancies and can therefore be used as a primary surveillance tool in imaging these foetuses (Martinez *et al.*, 2009 : 845-846)

In our study uterine artery Doppler indices in the 2nd trimester performed well in predicting the most severe of cases of PET. Notching in the 2nd trimester was also a good predictor of FGR.

5.8 SUMMARY

Uterine artery notching in the second trimester was the best predictor of pre-eclampsia and FGR. In the most severe cases of PET (3 out of 4 patients) increased pulsatility indices were recorded. This study has confirmed the work of others by finding a link between uterine artery notching in the second trimester and PET. It also confirms that black women are at higher risk of developing pre-eclampsia than any other race group.

Although the exact cause or pre-eclampsia remains unknown it is important to define the risks at the beginning of pregnancy so that antenatal care can be provided according to the needs of the patient and allows for early intervention.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

6.1 INTRODUCTION

The purpose of this study was to assess the sensitivity of uterine artery Doppler screening in identifying women who are at risk of developing pre-eclampsia and FGR. A further objective was to develop guidelines for a screening program from which patients could benefit without harm and pregnancy outcomes could improve. Guidelines will be formulated using inductive reasoning by combining the researcher's interpretation of the study results with that of current literature.

6.2 LIMITATIONS OF THE STUDY

The following limitations were encountered:

6.2.1 SAMPLE SIZE

A great limitation in this study was the sample size. Only 144 patients were included in this study and patients who did not return for follow up scans further reduced the sample size to 121 patients. However, due to a lack of patients presenting at the antenatal clinics during the first trimester of pregnancy the study was completed on the available data. These small numbers make the interpretation of the results difficult and may hamper generalisation of the results to other populations

6.2.2 RACE

The location of the hospital in a predominantly coloured community was also a limitation. The majority of the participants were coloured which is not a true reflection of the South African population as the coloured population constitutes only 9% of the South African population.

(http://www.statssa.gov.za/publications/P0302/P03022011.pdf)

6.2.3 PI VALUES

Findings can only be compared to similar settings as in this study. Perhaps the PI values that were used as a cut off for the 95th centile were not suitable for the studied population as the nomogram employed in this study was not developed specifically for the South African population.

6.2.4 BMI

Very few participants in our study had their BMI's recorded on the antenatal card. If there were more BMI values available it might have proven as a strong predisposing factor for PET as seen in other studies.

6.3 RECOMMENDATIONS

The following recommendations have been made

6.3.1 IMPLICATIONS FOR RESEARCH

In our study uterine artery Doppler screening performed well in the risk assessment of the most severe cases of pre-eclampsia and FGR. A larger prospective multicenter trial in South Africa is long overdue and therefore a follow-up study to assess Doppler as a screening tool in a high risk population, as per the guidelines in 6.3.2., is recommended. Randomised trials could also be conducted as per the researcher's guidelines whereby the effect of Doppler screening is tested in a control group and a treatment group, with a view of reducing the risk for developing PET in the 3rd trimester of pregnancy.

6.3.2 IMPLICATIONS FOR PRACTICE-ULTRASOUND SCREENING PROGRAM

Uterine artery Doppler screening can be beneficial to patients identified as having a high risk for developing PET so that preventative therapies can be initiated early in pregnancy. As the researcher is not a clinician treatment options have not been mentioned as this is beyond the scope of the researcher. Recent studies suggest that identification of abnormal Doppler waveforms during the first trimester and initialising treatment in early pregnancy may be more beneficial than waiting until the second trimester. DeVore advocates that if uterine artery notching persists during the second trimester the treatment should be continued.

(http://www.fetal.com/NT%20Screening/10%20Uterine%20Artery%20Meas.html)

The findings of this study do not promote routine uterine artery Doppler screening in Gauteng. From the results of our study the researcher has noticed an association between severe PET requiring delivery before 32 weeks gestation and PI values higher than 1.5. In an attempt to identify women at high risk for severe PET early, it is recommended that the following factors be considered as inclusion criteria in a screening program:

1) All patients who book in early at the antenatal clinic
2) All primigravidas
3) Patients with a BMI > 30
4) Patients with a previous history of PET
5) Patients with pre-existing hypertension

While other studies have advocated for the inclusion of biochemistry as well as blood pressure readings in a screening programme, the researcher is not a clinician and will therefore, as a sonographer, only attempt to develop guidelines for a purely ultrasound screening program. However, biochemistry and blood pressure readings can be included in addition to the ultrasound screening criteria to improve the sensitivity of screening for PET and FGR. According to Nicolaou (2011: Personal

communication) the combination of low PAPP A and abnormal uterine artery Doppler waveforms almost invariably predicts adverse pregnancy outcomes.

The following biochemistry tests can be carried out:

1) Placental growth factor (PGF)
2) Alpha-Foeto protein (AFP)
3) Free Beta human chorionic gonadotropin (BHCG)
4) Pregnancy associated plasma protein (PAPP A)

In South Africa biochemistry screening can only be performed in the private sector as these tests are not available in the public sector. Closer monitoring should therefore be offered to patients in state hospitals who screen positive with Doppler in the 1st trimester.

The following guidelines are recommended when screening for PET and FGR.

A. First trimester screening:

1. Determine the gestational age
   - Most accurate parameter for determining gestational age
   - Imperative for follow-up of fetal growth
2. If between 11-14 weeks gestation the nuchal translucency should be measured to screen for chromosomal abnormalities
3. The foetus should be assessed for obvious structural anomalies
4. Perform a uterine artery Doppler assessment. Patients with
   a) PI values above the 95th centile
   b) Uterine notching should be closely monitored
      - Two (2) weekly blood pressure(BP) monitoring

B. Second trimester follow-up

1. All patients should routinely receive a detailed foetal anatomy scan at 22wks
2. Liquor volume assessment for signs of oligohydramnios
3. Foetal growth should be monitored with biometric measurements
4. The uterine arteries should be sampled. Patients without:
   a) Signs of PET and/or

b) Normal BP readings and or
c) PI values below the 95th centile and or
d) Absent uterine artery notching need not return for follow up scans unless clinically indicated
e) Attend antenatal care as scheduled

5. Patients who screen positive for PET, with ultrasound or clinically, should be followed up in the 3rd trimester at 28wks

C. Third trimester follow-up

1. Foetal growth assessment for signs of FGR
2. Liquor volume assessment for signs of oligohydramnios
3. The uterine arteries should be sampled. Patients with:
   a) Clinical signs of PET and or
   b) PI values of >0.8 and or
   c) Uterine artery notching and or
   d) Ultrasound features in keeping with FGR
4. Should be followed up with ultrasound on a four(4) weekly basis-in keeping with the protocol of the foetal medicine unit at Chris Hani Baragwanath Hospital
   a) Foetal growth assessment for signs of FGR
   b) Liquor volume assessment for signs of oligohydramnios
   c) Umbilical artery Doppler assessment for signs of increased placental resistance
   d) Middle cerebral artery Doppler assessment for signs of brain sparing in patients with abnormal umbilical artery Doppler flow
   e) Ductus venosus Doppler assessment for signs of reversed flow in patients with abnormal umbilical artery flow
5. Patients with increase umbilical artery resistance >0.75 should be monitored two (2) weekly with ultrasound as per point 4.0 above
6. Patients with absent or reversed end diastolic flow in the umbilical arteries should monitored every second (2) day with Doppler assessment of the:
   a) Umbilical artery for signs of deterioration

b) Middle cerebral artery for signs of brain sparing

c) Ductus venosus for signs of reversed flow

7. Time of the delivery will be determined by the clinician, based on ultrasound findings as well as the clinical condition of the patient

6.4 SUMMARY

The findings of this study do not support the introduction of routine uterine artery Doppler screening in all patients who attend the antenatal clinic at Rahima Moosa Hospital, Gauteng. Pre-eclampsia(PET) , however, remains the main cause for perinatal morbidity and mortality in South Africa. Since an abnormal Doppler flow pattern and resistance to flow in the uterine arteries are strong predictors of the most severe cases of PET and FGR, it is recommended that patients at high risk for these adverse pregnancy outcomes be offered ultrasound screening. Since biochemical screening is not readily available in the South African public sector, clinicians have to depend on the clinical manifestation of the disease before action is taken. An ultrasound screening programme in a population of pregnant women who are at high risk of developing PET and or FGR would offer clinicians the opportunity to pre-empt the disease before it manifests clinically by initiating treatment as from as early as the first trimester.

A larger prospective multicentre trial in South Africa is long overdue and guidelines based on the outcome of the current study can be used to determine the value of routine uterine artery Doppler screening in Gauteng in a high risk population.

LIST OF REFERENCES

Andrade EH, Brodszki J, Lingman G, Gudmundsson S, Molin J and Marsal K (2002). **Uterine artery score and perinatal outcome.** Ultrasound in Obstetrics and Gynaecology 19:438-442.

Bodnar LM, Ness RB, Markovic N and Roberts JM (2005). **The risk of preeclampsia rises with increasing body mass index.** Ann Epidemiol 15(7):475-482.

Burton GJ, Woods AW, Juaniaux E and Kingdom JCP (2009). Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. Placenta 30:473-482.

Cnossen JS, Morris RK, Ter riet G, Mol BWJ, Van der Post JAM, Coomarasamy A, Zwinderman A, Robson SC, Bindels PJE, Kleijnen J and Khan KS (2008). **Use of uterine artery Doppler ultrasonography to predict preeclampsia and intrauterine growth restriction: a systemic review and bivariable meta-analysis.** Canadian Medical Association Journal 178(6):701-711.

Costa SL, Proctor L, Dodd JM, Toal M, Okun N, Johnson JA and Windrim R (2008). **Screening for placental insufficiency in high risk pregnancies: Is earlier better?** Placenta 29: 1034-1040.

Drife J and Magowan B (2004). **Clinical obstetrics and gynaecology. Section 3:Pregnancy and Puerperium** Elsevier Science

Dornhofer N and Stepan H (2008). **Preeclampsia- more than a pregnancy complication.** Human Ontogenetics 2(1):29-38.

Duckitt K and Harrington D (2005). **Risk factors for preeclampsia at antenatal booking: systemic review of controlled studies.** British Medical Journal 330(7491):565-71. Retrieved 20 May 2011 from the World Wide Web:

http://www.bmj.com/cgi/reprint/330/7491/565

El-Hamedi A, Shillito J, Simpson NAB and Walker JJ (2005). **A prospective analysis of the role of uterine artery Doppler waveform notching in the assessment of at-risk pregnancies.** Hypertension in Pregnancy 24(2):137-145.

Fayyad AM and Harrington KF (2005). **Prediction and prevention of preeclampsia and FGR.** Early Human Development 81:865-876.

Fratelli N, Rampello S, Guala M, Platto C and Frusca T (2008). **Transabdominal uterine artery Doppler between 11 and 14 weeks of gestation for the prediction of outcome in high risk pregnancies.** The Journal of Maternal-Fetal and Neonatal Medicine 21(6):403-406.

Ghidini A and Locatelli A (2008). **Monitoring of fetal well-being: Role of uterine artery Doppler.** Seminars in Perinatology 32:258-262.

Goffinet F, Aboulker D, Paris-Llado J, Bucourt M, Uzan M, Papiernik E and Breart G (2001). **Screening with a uterine artery Doppler in low risk pregnant women followed by low dose aspirin in women with abnormal results: a multicentre randomised controlled trial.** British Journal of Obstetrics and Gynaecology 108: 510-518.

Gomez O, Figueras F, Fernandez S, Bennasar M, Martinez JM, Puerto B and GratacosE (2008). **Reference ranges for uterine artery mean pulsatility index at 11-41 weeks gestation.** Ultrasound in Obstetrics and Gynaecology 32:128-132.

Harrington K, Fayyad A Thakur V and Aquilinah J (2004). **The value of uterine artery Doppler in the prediction of uteroplacental complications in multiparous women.** Ultrasound in Obstetrics and Gynaecology 23: 50-55.

Herraiz I, Arbues J, Camano E, Gomez-Montes E, Graneras A and Galindo A (2009). **Application of a first trimester prediction model for preeclampsia based on uterine arteries and maternal history in high-risk pregnancies.** Prenatal Diagnosis 29:1123-1129.s

Kremkau FW. **Diagnostic ultrasound:principles and instruments (2006).** Saunders Elsevier.

Kurdi W, Campbell S, Aquilina J, England P and Harrington K (1998). **The role of colour Doppler imaging of the uterine arteries at 20 weeks gestation in stratifying antenatal care.** Ultrasound in Obstetrics and Gynaecology 12: 339-345.

Lees C, Parra M, Missfelder-Lobos H, Morgans A, Fletcher O and Nicolaides KH (2001). **Individualised risk assessment for adverse pregnancy outcome by**

uterine artery Doppler at 23 weeks. The American College of Obstetrics and Gynaecology 98(3); 369-373.

Loughna P (2006). **Intrauterine growth restriction: Investigation and management.** Current Obstetrics and Gynaecology 16: 261-266.

Martin AM, Bindra R, Curcio P, Cicero S and Nicolaides KH (2001). **Screening for preeclampsia and fetal growth restriction by uterine artery Doppler at 11-14 weeks of gestation.** Ultrasound in Obstetrics and Gynaecology 18: 583-586.

McCall S (2004). **Midwifery Vol 2. Chapter 7:complications in Pregnancy.** Juta and Co

McCarthy FP and Kenny LC (2009). **Hypertension in pregnancy.** Obstetrics Gynaecology and Reproductive medicine 19(5): 136-141.

Mcleod L (2008). **How useful is uterine artery Doppler ultrasonography in predicting preeclampsia and intrauterine growth restriction.** Canadian Medical Association Journal 178(6): 727-729.

Melchiorre K, Wormald B, Leslie K, Bhide A and Thilaganathan B (2008). **First trimester uterine artery Doppler indices in term and preterm preeclampsia.** Ultrasound in Obstetrics and Gynaecology 32: (133-137).

Melchiorre K, Leslie K, Prefumo F, Bhide A and Thilaganathan B (2009). **First trimester uterine artery Doppler indices in the prediction of small for gestational age pregnancy and intrauterine growth restriction.** Ultrasound in Obstetrics and Gynaecology 33: (524-529).

Mitani M, Matsuda Y, Makino Y Akizawa Y and Ohta H (2009). **Clinical features of fetal growth restriction complicated later by preeclampsia.** Journal of Obstetrics and Gynaecology 35(5): 882-887.

Moodley J (2008). **Maternal deaths due to hypertensive disorders in pregnancy.** Best Practice and Research in Clinical Obstetrics and Gynaecology 22(3): 559-567.

Moodley J (2010). **Maternal deaths associated with eclampsia in South Africa: Lessons to learn from the Confidential Enquiries into Maternal Deaths, 2005-2007.** South African Medical Journal 100(11): 717-719.

Oei SG (2005). **The value of uterine artery Doppler flow velocity in the prediction of uncomplicated pregnancies.** Gynaecology, Obstetrics and Reproductive Medicine in Daily Practice 1279:310-314.

Ozkaya U, Ozkan S,Ozeren S and Corakci A (2007). **Doppler examination of the uteroplacental circulation in early pregnancy: can it predict adverse outcome?** Journal of Clinical Ultrasound35(7): 382-386.

Papageorghiou AT, Yu CKH, Bindra R, Pandis G and Nicolaides (2001). **Multicentre screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation.** Ultrasound in Obstetrics and Gynaecology 18(5):441-449.

Papageorghiou AT, Yu CKH and Nicolaides KH (2004). **The role of uterine artery Doppler in predicting adverse pregnancy outcome.** Best Practice and Research Clinical Obstetrics and Gynaecology 18(3):383-396.

Papageorghiou AT and Roberts N (2005). **Uterine artery Doppler screening for adverse pregnancy outcomes.** Current Opinion in Obstetrics and Gynaecology 17:584-590.

Papageorghiou AT and Campbell S (2006). **First trimester screening for preeclampsia.** Current Opinion in Obstetrics and Gynaecology 18:594-600.

Papageorghiou AT and Leslie K (2007). **Uterine artery Doppler in the prediction of adverse pregnancy outcome.** Current Opinion in Obstetrics and Gynaecology 19:103-109.

Papageorghiou AT (2008). **Predicting and preventing preeclampsia-where to next?** Ultrasound in Obstetrics and Gynaecology 31: 367-370.

Palma-Dias RS, Fonseca MMC, Brietzke E, Fritsch A, Schlatter D, Maurmann CB, Stein NR Magalhaes JAA (2008). **Screening for placental insufficiency by transvaginal uterine artery Doppler at 22-24 weeks of gestation.** Fetal Diagnosis and Therapy 24:462-469.

Pilalis A, Souka AP, Antsaklis P, Daskalakis G, Papantoniou N, Mesogitis S and Antsaklis A (2007). **Screening for preeclampsia and fetal growth restriction by uterine artery Doppler and PAPP-A at 11-14 weeks' gestation.** Ultrasound in Obstetrics and Gynaecology 29:135-140.

Pilalis A, Souka AP, Antsaklis , Basayiannis K, Bernadis P, Haidopoulos D, Papantoniou N, Mesogitis S and Antsaklis A (2007). **Screening for preeclampsia and small for gestational age foetuses at the 11-14 weeks scan by uterine artery Dopplers.** Acta Obstetricia et Gynecologica 86:530-534.

Poon LCY, Karagiannis G, Leal A, Romero XC and Nicolaides KH (2009). **Hypertensive disorders in pregnancy: screening by uterine artery Doppler imaging and blood pressure at 11-13 weeks.** Ultrasound in Obstetrics and Gynaecology 34:497-502.

Redman CWG and Sargent IL (2004). **Preeclampsia and the systemic inflammatory response.** Seminars in Nephrology 24:565-570.

Shear RM, Rinfret D and Leduc L (2005). **Should we offer expectant management in cases of severe preterm preeclampsia with fetal growth restriction?** American Journal in Obstetrics and Gynaecology 192: 1119-1125.

Sibai BM (2003). **Diagnosis and management of gestational hypertension and preeclampsia.** Obstetrics and Gynaecology 102:181-192.

Sibai B, Dekker G and Kupferminc M (2005). **Preeclampsia.** Lancet 365:785-799.

Soregaroli M, Valcamonico A, Scalvi L, Danti L and Frusca T (2000). **Late normalisation of uterine artery velocimetry in high risk pregnancy.** European Journal of Obstetrics and Reproductive Biology 95:42-45.

Spencer K, Yu CKH, Savvidou M, Papageorghiou AT and Nicolaides KH (2006). **Prediction of preeclampsia by uterine artery Doppler ultrasonography and maternal serum pregnancy-associated plasma protein-A, free B-human chorionic gonadotropin and inhibin A at 22 + 0 to 24 + 6 weeks gestation.** Ultrasound in Obstetrics and Gynaecology 27:658-663.

Swanepoel HS (2004). **Uterine artery Doppler.** Obstetrics and Gynaecology forum 14(2):4-9.

Tegnander E and Eik-Nes EH (2006). **The examiners ultrasound experience has a significant impact on the detection rate of congenital heart defects at the second trimester fetal examination.** Ultrasound in Obstetrics and Gynaecology 28(1):8-14.

Wagner SJ, Barac S and Garovic VD (2007). **Hypertensive pregnancy disorders: Current concepts.** The Journal of Clinical Hypertension 9(7):560-566.

Wagner LK (2004). **Diagnosis and management of preeclampsia.** American Family Physician 70:2317-2324.

Yu CKH, Papageorghiou AT, Parra M, Palma Dias R and Nicolaides KH (2003). **Randomised controlled trial using low-dose aspirin in the prevention of preeclampsia in women with abnormal uterine artery Doppler at 23 weeks gestation.** Ultrasound in Obstetrics and Gynaecology 22:233-239.

Yu CKH, Khouri O, Onwudiwe N, Spiliopoulos Y and Nicolaides KH (2008). **Prediction of pre-eclampsia by uterine artery Doppler imaging: relationship to gestational age at delivery and small for gestational age.** Ultrasound in Obstetrics and Gynaecology 31:310-313.

www.centrus.com.br/DiplomaFMF/Series

www.bmus.org

(www.bmus.org/policies)

(www.ais.up.ac.za/med/block/9/antenatalcarepolicy.pdf)

(www.fetalmedicine.com/fmf/Doppler%20in%20Obstetrics.pdf)

(http://medical-dictionary.thefreedictionary.com/PI)

(www.medcyclopaedia.com/library/topics/volume_i/p/pulsatility_index_pi)

(www.fetalmedicine.com/fmf/Doppler%20in%20Obstetrics.pdf)

http://en.wikipedia.org/wiki/Dependent_variable)

(www.centrus.com.br/DiplomaFMF/doppler/capitulos-html_02.htm)

(www.fetal.com).

(http://www.statssa.gov.za/publications/P0302/P03022011.pdf)

(http://www.fetal.com/NT%20Screening/10%20Uterine%20Artery%20Meas.html)

http://www.bmj.com/cgi/reprint/330/7491/565

ANNEXURE A

PATIENT INFORMATION LEAFLET and CONSENT FORM

UNIVERSITY
OF
JOHANNESBURG

ANNEXURE A

PATIENT INFORMATION LEAFLET

Introduction

Hello and welcome to the ultrasound department. My name is Yasmin Casmod and I am a qualified sonographer. I am currently conducting research into the feasibility of uterine artery Doppler screening in the prediction of pregnancy outcome. My research is entitled **"THE SENSITIVITY OF UTERINE ARTERY SPECTRAL DOPPLER SCREENING IN PREDICTING PRE-ECLAMPSIA AND FOETAL GROWTH RESTRICTIONS".**

Procedure

It will be required for the participant to have three ultrasound scans, i.e. a dating scan (between 11-14weeks gestation), an anomaly scan (between 22 & 24 weeks gestation) and a follow up scan (between 28-32 weeks gestation). At each scan a Doppler study will be done which involves measuring the flow of blood in the uterine arteries. This test is non invasive and will only take 5-10 minutes to perform.

Benefits

Participation in this research will help the medical profession to learn more about the use of uterine artery Doppler assessment in predicting pre-eclampsia and foetal growth restriction thereby allowing us to manage our high risk pregnancies more effectively.

Risks

There are no anticipated risks for this trial. To date no adverse side effects have been demonstrated with the judicious use of Doppler ultrasound.

Rights as a participant of this study

Your participation in this study is voluntary and you can refuse or discontinue participation at any time. Your withdrawal from this research will not affect your access to other medical care. All information obtained from this study will be strictly confidential. Each participant will be allocated a research number. Your name will only be used to correlate with the research number but will not be made public.

My contact details

I can be contacted at the Coronation Hospital ultrasound department during office hours at 011 470 9054. My supervisor Mrs. Barbara Van Dyk can be contacted at the University of Johannesburg on 011 559 6242.

Reimbursement

There will be no reimbursement for participation in this study.

CONSENT FORM

I_____ (file no) _____am willing to participate in this research that is currently being carried out.

I clearly understand the implications of participating in this study. I also know that my name will not be used; I will be assigned a research number. I am also aware that I can withdraw from the study at any time.

SIGNATURE: _____ DATE: _____

CONTACT DETAILS:

Home: _____

Cell: _____

I the researcher believe that the aims, procedures and protocols of this study have been fully explained.

RESEARCHER: _____ DATE: _____

Witness 1: _____

Witness 2: _____

ANNEXURE B

ANTENATAL CARD

ANTENATAL CARD

DEPARTMENT OF HEALTH
PROVINCIAL GOVERNMENT

SONAR

TPH 261 A (81/03886)

AME.....

OSPITAL ..... BIRTH
UMBER ..... DATE .....

DDRESS.....

..... TEL (H) ..... (W) .....

LINIC/
OCTOR..... TEL .....

ISTORY PL = Live END = early neonatal death
MIS = miscarriage LND = late neonatal death
IUD = intra-uterine death ID = infant death

Year	Gest wks	Delivery	Sex	Weight	♂	Complications

G.....P.....G.....Cycle...../.....

LMP ...../...../.....sure/unsure

of reception.....Stopped.....

ause family planning

octor .....

EDICAL AND GENERAL HISTORY

ypertension ☐ Renal ☐ Epilepsy ☐ TB ☐
ardiac ☐ Diabetes ☐ Asthma ☐

.....

.....

.....

.....

edication.....

pergic to .....

ergies .....

AMILY HISTORY: Twins ☐ Diabetes ☐ Congenital abnormality ☐

.....

EXAMINATION Date D D M M Y Y Y Y

Height ..... cm Weight ..... kg

Blood pressure ..... Urine .....

General .....

Thyroid ..... Breasts .....

Heart .....

Lungs .....

Abdomen .....

..... fundal height ..... cm

Other .....

VAGINAL EXAMINATION: V + V .....

Cervix .....

Uterus .....

Adnexa .....

Doctor/ Midwife

SPECIAL INVESTIGATIONS date result.....

☐ ☐ ☐ ☐ Hb .....

☐ ☐ Rh..... Antibodies .....

☐ ☐ RPR..... FTA..... Rx 1 ☐ 2 ☐ 3 ☐

☐ ☐ HIV consent ..... Tet. tox. ☐

☐ ☐ Cx. cytology .....

☐ ☐ MSU .....

☐ .....

☐ .....

PLAN: ANC: midwife/doctor			Labour: midwife/doctor		
Normal	Moderate	High risk	Normal	Moderate	High risk

Date				
Best. Gest.				
Presentation				
Placenta				
Liquor				
F. Heart				
F. Mov.				
B.P.D.				
FL				
AC				
Spine				
Stomach				
Kidneys				
Bladder				
Head				
Sonar Gest				
Weight				
UARI				
NAME				

Date	Notes

ANNEXURE C

DATA CAPTURING SHEET

DATA CAPTURING SHEET:

RESEARCH NO: _____

PERSONAL DETAILS:

SURNAME: _____ INITIALS: _____

HOSPITAL NO: _____

DATE OF LMP: ___/___/___

PARITY: ____ GRAVIDITY: ____

AGE: _____

RACE:

INDIAN	
COLOURED	
WHITE	
BLACK	

NATIONALITY:

SOUTH AFRICAN	
NON SOUTH AFRICAN	

ANTENATAL CARE:

HEIGHT: _____ **WEIGHT:** _____

BMI: _____

BOOKING BLOOD PRESSURE:	

MEDICAL & GENERAL HISTORY:

HYPERTENSION	
CARDIAC	
EPILEPSY	
DIABETES	
ASTHMA	
TB	
RENAL COMPLICATIONS	

FAMILY HISTORY:

HYPERTENSION	
DIABETES	
CONGENITAL ABNORMALITIES	
TWINS	

OBSTETRIC HISTORY:

YEAR	GEST: WKS	DELIVERY	SEX	WEIGHT	COMPLICATIONS

PREVIOUS PREGNANCY COMPLICATIONS:

STILLBIRTHS	
C/SECTION	
PREGNANCY INDUCED HYPERTENSION	

HIV STATUS:

POSITIVE	
NEGATIVE	
UNKNOWN	

MEDICATION:

YES	
NO	

IF YES:

_____

_____

OPERATIONS:

YES	
NO	

IF YES:

_____

_____

ALLERGIES:

YES	
NO	

IF YES:

_____

_____

ULTRASOUND REPORT:

FOETAL BIOMETRY:

	1st scan (Dating Scan)	2nd scan (Anomaly Scan)	3rd scan (Follow up)
CRL			
BPD			
HC			
AC			
FL			
Concordant			
Discordant			

FOETAL HEARTBEAT:

	1st scan (Dating Scan)	2nd scan (Anomaly Scan)	3rd scan (Follow up)
Yes			
No			

FOETAL MOVEMENTS:

	1st scan (Dating Scan)	2nd scan (Anomaly Scan)	3rd scan (Follow up)
Yes			
No			

FOETAL LIE:

	1st scan (Dating Scan)	2nd scan (Anomaly Scan)	3rd scan (Follow up)
Cephalic			
Breech			
Transverse			

PLACENTAL POSITION:

	1st scan (Dating Scan)	2nd scan (Anomaly Scan)	3rd scan (Follow up)
Anterior			
Posterior			
Fundal			
High			
Low			

LIQUOR VOLUME:

	1st scan (Dating Scan)	2nd scan (Anomaly Scan)	3rd scan (Follow up)
Normal			
Reduced			
Increased			
AFI			

FOETAL ANATOMY:

	1st scan (Dating Scan)	2nd scan (Anomaly Scan)	3rd scan (Follow up)
Spine			
Stomach			
Kidneys			
Bladder			
Head			

ESTIMATED FOETAL WEIGHT (EFW):

	1st scan (Dating Scan)	2nd scan (Anomaly Scan)	3rd scan (Follow up)
Efw (g)			

ESTIMATED DATE OF DELIVERY (EDD):

____/____/____

UTERINE ARTERY:

	1st scan (Dating Scan)	2nd scan (Anomaly Scan)	3rd scan (Follow up)
Rt PI			
Lt PI			
Rt (notching)			
Lt (notching)			

UMBILICAL ARTERY:

	3rd Scan (Follow up)
Normal	
High	
Absent	
Reversed	

COMMENT:

_____

_____

_____

NAME: _____ **DATE:**_____

PREGNNCY OUTCOME

Birthweight: _____

Gestation @ delivery: _____

Date of delivery: _____

ANNEXURE D:

PERMISSION REQUEST AND GRANTING OF PERMISSION

MRS S JORDAAN (CEO-RAHIMA MOOSA MOTHER AND CHILD HOSPITAL)

DR PIRANI (CLINICAL HEAD-OBSTETRIC AND GYNAECOLOGY DEPARTMENT)

MS S PATEL (ASSISTANT DIRECTOR-X/RAY AND ULTRASOUND DEPARTMENTS)

Yasmin Casmod

16 Statice Street

Extension 3

Lenasia

1827

Chief Executive Officer

Coronation Hospital

Dear Sir/Madam

Permission to use the ultrasound facilities at the Coronation Hospital:

I Yasmin Casmod persal number 21770115 would like to request permission for the use of the ultrasound facilities at Coronation Hospital for the duration of my research.

The study is focused on uterine artery Doppler assessment, as a predictor of pre-eclampsia and fetal growth restriction. My research is entitled **"THE SENSITIVITY OF UTERINE ARTERY DOPPLER SCREENING IN PREDICTING PRE-ECLAMPSIA AND FOETAL GROWTH RESTRICTION".** This research will hopefully allow us to manage our pregnant patients more accurately, thereby allowing us to identify the high risk patients early enough for treatment to be effective in the prevention of PET and FGR.

All patients participating in the trial will be treated equally. All information will be treated with strict confidentiality.

Thanking You

Yours Faithfully

Casmod.

Y.Casmod (Miss)

I _____ CEO of Coronation Hospital hereby grant Yasmin Casmod permission to use the ultrasound facilities and patients at the Coronation Hospital to conduct her study.

_____. 1/8/08 .

DATE

Yasmin Casmod

16 Statice Street

Extension 3

Lenasia

1827

Clinical Head (O & G Department)

Coronation Hospital

Dear Sir/Madam

Permission to use the ultrasound facilities at the Coronation Hospital:

I Yasmin Casmod persal number 21770115 would like to request permission for the use of the ultrasound facilities at Coronation Hospital for the duration of my research.

The study is focused on uterine artery Doppler assessment, as a predictor of pre-eclampsia and fetal growth restriction. My research is entitled **"THE SENSITIVITY OF UTERINE ARTERY SPECTRAL DOPPLER SCREENING IN PREDICTING PRE- ECLAMPSIA AND FOETAL GROWTH RESTRICTION".** This research will hopefully allow us to manage our pregnant patients more accurately, thereby allowing us to identify the high risk patients early enough for treatment to be effective in the prevention of PET and FGR.

All patients participating in the trial will be treated equally. All information will be treated with strict confidentiality.

Thanking You

Yours Faithfully

Y.Casmod (Miss)

I Dr. N. E. PIRANI Clinical Head of the O & G Department at the Coronation Hospital hereby grant Yasmin Casmod permission to use the ultrasound facilities and patients at the Coronation Hospital to conduct her study.

05.08.2008

SIGNATURE DATE

Yasmin Casmod

16 Statice Street

Extension 3

Lenasia

1827

Assistant Director (X-Ray Department)

Coronation Hospital

Dear Sir/Madam

Permission to use the ultrasound facilities at the Coronation Hospital:

I Yasmin Casmod persal number 21770115 would like to request permission for the use of the ultrasound facilities at Coronation Hospital for the duration of my research.

The study is focused on uterine artery Doppler assessment, as a predictor of pre-eclampsia and fetal growth restriction. My research is entitled **"THE SENSITIVITY OF UTERINE ARTERY DOPPLER SCREENING IN PREDICTING PRE-ECLAMPSIA AND FOETAL GROWTH RESTRICTION".** This research will hopefully allow us to manage our pregnant patients more accurately, thereby allowing us to identify the high risk patients early enough for treatment to be effective in the prevention of PET and FGR.

All patients participating in the trial will be treated equally. All information will be treated with strict confidentiality.

Thanking You

Yours Faithfully

Casmod.

Y.Casmod (Miss)

I Selma Patel Assistant Director of the X-Ray department at the Coronation Hospital hereby grant Yasmin Casmod permission to use the ultrasound facilities and patients at the Coronation Hospital to conduct her study.

05/08/08

DATE

ANNEXURE E

FOETAL GROWTH CHART

NAME:.....

HOSP. NO.....

FETAL GROWTH CHART (Hofmeyr et al 1993)

GEST. (Wks / days) ON :

D	M	Y

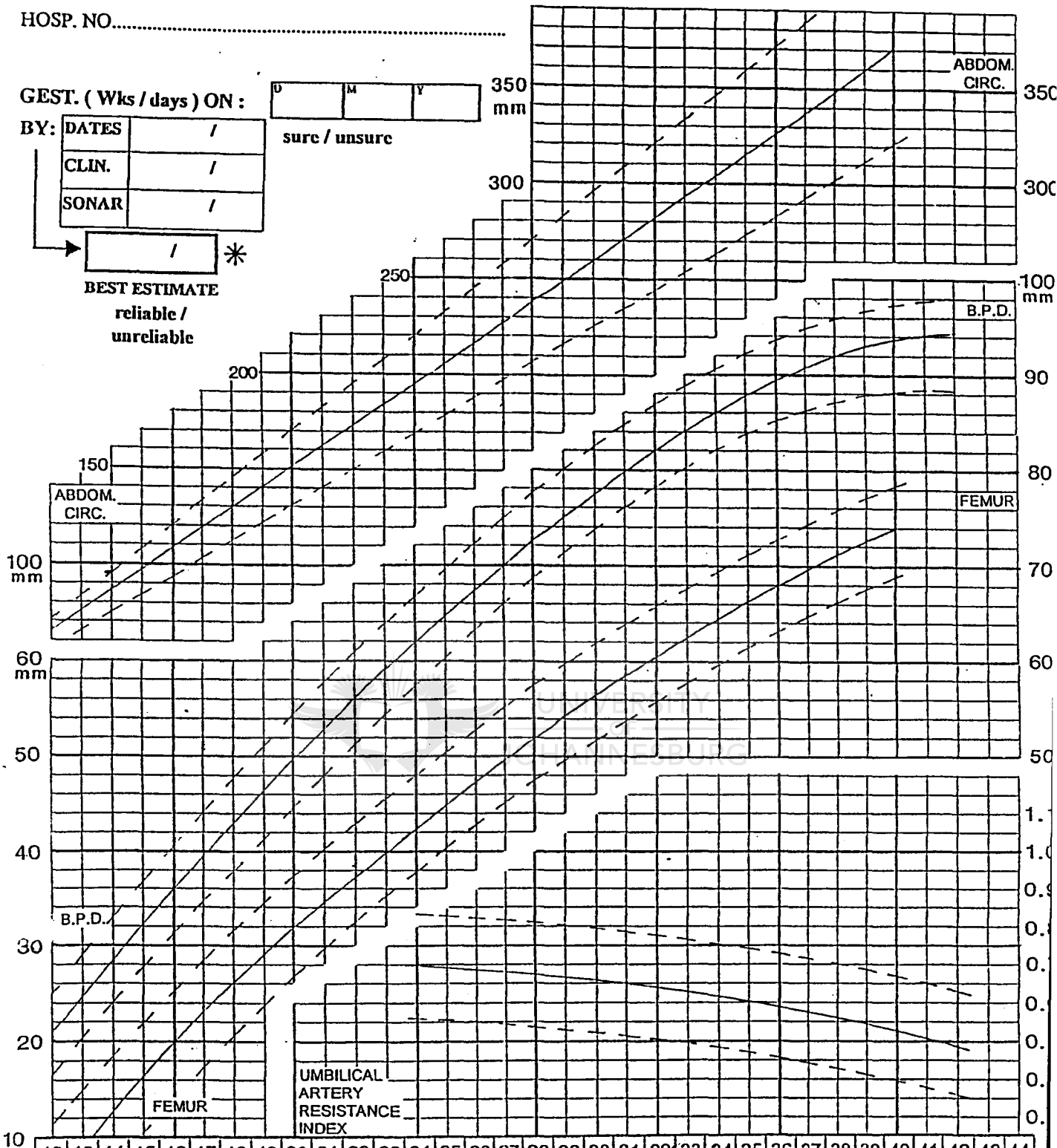
sure / unsure

BY:

DATES	/
CLIN.	/
SONAR	/

/ *

BEST ESTIMATE
reliable / unreliable



SONAR Date	Best estimate Gest. *	Position	Placenta	Liquor	F. Heart	F. Mov.	CRL mm	B.P.D. mm	FL mm	Abd.⊙ mm	Head⊙ mm	Spine	Stomach	Kidneys	Bladder	Head	Sonar Gest. wks / days	Weight g	NAM