الآية

قال تعالى:

((وَلَقَدْخَلَقْنَا الإِنْسَانَ مِن سُلاَلَةٍ مِّن طِينٍ {12} ثُمَّ جَعَلْنَاهُ نُطْفَةً فِي قَرَارٍمَّكِينٍ {13}ثُمّ خَلَقْنَا النُّطْفَةَعَلَقَةً فَخَلَقْنَاالْعَلَقَةَ مُضْغَةً فَخَلَقْنَا الْمُضْغَةَ عِظَامًا فَكَسَوْنَاالْعِظَامَ لَحْمًا ثم أَنشَأْنَاهُ خَلْقًا آخَرَفَتَبَارَكَ اللَّه أَحْسَن الْخَالِقِينَ{14})).

صدق الله العظيم

سورة المؤمنون

Dedication

To my father

My mother

My Wife

My brothers

My sisters

And

My friends

Acknowledgement

I would like to express my sincere appreciation to my **supervisor Dr. Ahmed Mostafa Abukonna** for his support, encouragement and care, and also my thanks extend to Dr. Mohammed Ibrahim Yassin, Dr. Haitham Abdallah and Dr. Walla Eddin Osman (obstetricians and gynecologists for their support). The staff of ultrasound department of Elobeid hospital, National Insurance Fund especially Mr. Boraai Mohammed Awadallah and to my friend Abdurrahman Mohammed Ali at Eithar Ultrasound clinic.

Abstract

Pre-eclampsia and fetal growth restriction (FGR) remains important causes of maternal and perinatal mortality and morbidity. Pre-eclampsia complicates between 2 and 8% of all pregnancies and is the second most common cause of maternal death in the developing world

The aim of this research was to predict Preeclampsia using uterine artery spectral Doppler. The study was conducted in the Sudan (North Kordofan State) from July to November 2018.51 patients attending the antenatal clinic who were referred to the Ultrasound department for a routine dating scan (between *11-14wks)* were recruited to participate in this study. Uterine artery spectral Doppler assessment was performed via transabdominal route in the second and third trimester.

The result of this study showed that the Mean right uterine artery resistive index (RI) in second and third trimester were (0.51 and 0.68) respectively in preeclampsia which were significantly different from normal pregnancy. Furthermore, the mean right uterine artery pulsatility index (PI) in third trimester was (1.62) which was significantly different from normal pregnancy. There was no significant difference observed in left uterine artery (PI and RI) in both second and third trimester.

Abnormal uterine artery waveforms are a better predictor of pre-eclampsia than of intrauterine growth restriction. A pulsatility index, resistive index or combined with notching, were the most predictive Doppler index. These indices should be used in clinical practice. Future research should also concentrate on combining uterine artery Doppler ultrasonography with other tests.

المستخلص

يعتبر مقدم الارتعاج وضمورالجنين عاملين اساسيين في إعياءووفاة كثيرمن الحوامل والأجنة .مقدم الارتعاج يتميزبإستجابةغيرطبيعية لتكوين المشيمة ,وتؤثرفي عدةأنظمةفي جسم الحامل والجنين, وليس له سبب معروف . ويصيب الحوامل بمعدل 2 إلي 8% من جميع الحوامل ويأتي في المركزالثاني من حيث التسبب في وفاةالحوامل في البلدان النامية.

والهدف من هذه الدراسةهودراسةإمكانيةالتنبؤ وإستكشاف هذاالمرض باستخدام الشريان الرحمي عن طريق الموجات فوق الصوتية الملونة (الدوبلر). وهذه الدراسة قد أجريت في السودان بولاية شمال كردفان في الفترة من يوليو حتي نوفمبر 2018, علي 51 مريض بعيادة رعاية الامومة وقسم الموجات فوق الصوتية لاجراء الفحص الدوري,واستهدفت الدراسة الحوامل في الفترة من الاسبوع (11-14) .

وتم تقييم الشريان الرحمي بواسطة موجات الدوبلر عن طريق الفحص خلال البطن في المرحلة الجنينية الثانية والثالثة.وأوضحت نتائج هذه الدراسة بأن متوسط مقاومة الشريان الرحمي اليمين في الفترة الجنينية الثانية والثالثة (0.51 و0.68) علي التوالي في مرضي مقدم الارتعاج التي اختلفت عن قياسات الحمل الطبيعي.علاوة علي ذلك متوسط موشر النبضية للشريان الرحمي اليمين في الفترة الجنينية الثالثة كان (1.62) وهو مايختلف بشكل ملحوظ عن الحمل الطبيعي, واوضحت الدراسة انة لايوجد إختلاف في مؤشري النبضية والمقاومة في الشريان الرحمي الأيسر خلال الفترات الجنينية الثانية والثالثة.الشكل الموجي للشريان الرحمي غير الطبيعي يعتبر مؤشر لحالات مقدم الارتعاج أكثر من ضمور الجنين.مؤشر النبضية ومؤشر المقاومة المصاحب يعتبران مؤشرين حقيقين وبالتالي يمكن إستخدامهم في الممارسة السريرية.البحوث المستقبلية يجب أن تركز علي دمج موجات الدوبلر للشريان الرحمي مع الفحوصات الأخري.

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List of Abbreviations

AFP	Alpha- Feto protein
B-HCG	Beta-human chorionic gonadotropin
BMI	Body mass index
BP	Blood pressure
CNS	Central nervous system
FGR	Fetal growth restriction
HELLP	Hemolytic anemia –elevation liver enzyme-low platelets
MCA	Middle cerebral artery
PAPP	Pregnancy associated plasma protein
PGF	Placenta growth factor
PE	Pre-eclampsia
PI	Pulsatility index
RI	Resistive index
UA	Uterine artery
LUA	Left uterine artery
RUA	Right uterine artery

Chapter One

Introduction

1.1 Introduction

Monitoring the growth and wellbeing of the fetus 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 prenatal morbidity and mortality (Brosens et al., 2018).

Preeclampsia (PE) remains important causes of maternal and prenatal mortality and morbidity. Preeclampsia is a multisystem disorder of unknown cause specific to pregnancy which affects the health of both mother and fetus. Preeclampsia is associated with the highest maternal and fetal mortality and morbidity of all pregnancy complications with the highest incidence of serious adverse outcomes occurring in developing countries (Chan et al., 2018). Maternal complications include the HELLP syndrome, eclampsia, coagulopathy, cerebrovascular accident and death. The introduction of diagnostic ultrasound has been one of the great medical advances in recent decades. The use of diagnostic ultrasound to assess fetal 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 fetal development (Ezeigwe et al., 2018).

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 .Preeclampsia is a heterogeneous disorder with variable maternal and fetal manifestation. Preeclampsia occurs in about 3% of pregnancies with a recurrence risk ranging from 7.5 % to 65 % (Chen et al., 2018).

Direct assessment of trophoblastic invasion in human pregnancy is not possible; however the use of Doppler ultrasound permits noninvasive evaluation of the uteroplacental circulation (Farzaneh et al., 2018).

Due to the high risk preeclampsia carries it may be beneficial to ascertain the predictive value of uterine artery spectral Doppler analysis for preeclampsia. Uterine artery Doppler waveform screening may enable caregivers to identify and target patients at higher risk for close monitoring and intervention with prophylactic therapy. The aim of this study was to predict preeclampsia using uterine artery spectral Doppler by screening the maternal of high risk of developing preeclampsia 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.

1.2 Problem of the study:

In the developing world, hypertensive disorders represent the second most common cause of maternal death as well as prenatal fetal mortality and morbidity. 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 preeclampsia before the clinical onset of the disease.

1.3 Objectives of the study:

1.3.1 General Objective:

The general objective of this study was to predict preeclampsia using uterine artery spectral Doppler

1.3.2 Specific Objectives

- 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 (PE) in the third trimester.

- To correlate Doppler Indices to pregnancy outcomes.

1.4 Thesis layout:

This study consisted of five chapters, with chapter one is an introduction which includes; problem of the study, question study objective and significance of the study. Chapter two represents comprehensive literature review about different measurement studies, while chapter three is a methodology which include material used to collect the data and method of data acquisition and analysis. Chapter four includes presentation of the result using tables and figures, finally chapter five included discussion, conclusion and recommendation.

Chapter two

Literature Review

2.1 Diagnostic Criteria

One of the pitfalls in pre-eclampsia research over the years has been differences in diagnostic criteria used worldwide. A number of different terms and systems are used; some are more detailed than others, some are more inclusive than others, and in some cases the same term has been used to describe different disorders by different authors. To combat this, a working group of the International Society for the Study of Hypertension in Pregnancy (ISSHP) published a Consensus statement in 2000, which is now the most commonly used set of criteria in the literature(Moghaddas Sani et al., 2018).

In brief, in the consensus statement hypertension in pregnancy is split into 4 main categories; gestational hypertension, pre-eclampsia, chronic hypertension (essential or secondary) and pre-eclampsia superimposed on chronic hypertension. Gestational hypertension is defined as de novo arterial hypertension (systolic BP ≥ 140 mmHg and / or diastolic BP ≥ 90 mmHg on 2 occasions > 6 hours apart) occurring after gestational week 20, which returns to normal post-partum. Pre-eclampsia is defined as gestational hypertension plus proteinuria, in turn defined as ≥300 mg/24 hours, protein: creatinine ratio ≥ 30 mg/mmol or if neither are available dipstick analysis of (which “is often but not always associated with 300 mg/24 hrs”)(Moghaddas Sani et al., 2018).

Chronic hypertension is hypertension diagnosed before the 20th gestational week or de novo hypertension which fails to settle post-partum. Pre-eclampsia superimposed on chronic hypertension is defined as the appearance of de novo proteinuria starting after gestational week 20. A sudden increase in blood pressure or proteinuria, or the appearance of thrombocytopenia or deranged transaminases are said to be suggestive but not diagnostic of superimposed pre-eclampsia. Despite this general agreement, many questions remain about how

the disease should be classified(Nascimento et al., 2018). Some classifications define pre-eclampsia as pregnancy-induced hypertension in association with evidence of multi-organ dysfunction; proteinuria, or other complications such as renal insufficiency, liver disease, neurological problems, haematological disturbance, or intra-uterine growth restriction (Patabendige et al., 2018).

Further definitions separate proteinuric from non-proteinuricpre-eclampsia; proteinuric pre-eclampsia is reported to carry a worse prognosis than non-proteinuric pre-eclampsia, which is in turn reported to carry a worse prognosis than gestational hypertension alone (Maric et al., 2018). Further questions remain over whether "early onset" (usually defined as that occurring before 34 weeks' gestation) and "late onset" variants of pre-eclampsia are the same disease, or whether they have completely different pathological mechanisms. How to define "severe" and "mild" pre-eclampsia is another matter for debate. A further complicating factor is that the association of pre-eclampsia with preterm delivery, small for gestational age (SGA) babies, or both, appears to have different consequences, particularly for the mother's future cardiovascular health (Mahmoud et al., 2018).

2.2 Pathogenesis of pre-eclampsia:

Although the cause of pre-eclampsia remains largely unknown, the pathogenesis is thought to occur in two main phases. The first phase begins in the placenta, while the second stage is characterized by an abnormal maternal endothelial response, resulting in the hypertension, proteinuria and edema that characterize the condition(Grum et al, 2018).

2.2.1 Placental phase

The placenta is well recognized as having a key role in the development of pre-eclampsia. This is known to be the case since pre-eclampsia occurs only during pregnancy, it resolves after delivery of the placenta, and it can occur in the absence of a viable fetus, for example in molar pregnancies. Blood supply to

the placenta is via the spiral arteries, branches of the uterine arteries; placental development is a closely regulated process which is essential for normal fetal development(Pergialiotis et al., 2017).

The spiral arteries are remodeled in pregnancy in several stages, beginning at around the time of implantation. Remodeling transforms the arteries from low-flow, highly resistant vessels into the high-flow, low resistance vessels which are vital for normal placental development. Impaired remodeling of the spiral arteries is considered to be a key factor in the pathogenesis of pre-eclampsia. In pre-eclampsia, disturbance of spiral artery remodeling may occur as early as the time of implantation, offering a potential explanation for the fact that women with a history of sub-fertility or early miscarriage are at increased risk of the condition (Nilsen et al., 2018).

Intervillous flow, characterized by the appearance of connecting channels between the spiral arteries and the blastocyst, begins at 7-8 weeks' gestation. Following this, the cytotrophoblast cells of the developing placenta invade the decidual segments of the spiral arteries at around 10-12 weeks' gestation, and then the myometrial segments, at around 15-16 weeks' gestation. The trophoblastic then invades both the endothelium and the highly muscular tunica media of the maternal spiral arteries. In pre-eclampsia the cytotrophoblast invades the decidual portion of the spiral arteries, but invasion of the myometrial segments is impaired; the spiral arteries remain narrow, and blood supply to the fetus is restricted. The effects of this on the fetus become more significant as pregnancy progresses, since the uterine vasculature is unable to keep up with the increased amount of blood and nutrients necessary for fetal development(Mahmoud et al., 2018).

What causes the impaired development of the uteroplacental circulation in pre-eclampsia remains unknown, and is a subject of much debate. Vascular, environmental and genetic factors all appear to play a role. Maternal natural killer (NK) cells are now thought to have an important role in these early stages

of disease development. NK cells are the main maternal immune cells in the endometrial prior to implantation, and are having their main role in regulation of placental development. Interaction between maternal NK cells and fetal major histocompatibility complex (MHC) antigens may represent an initial step. Particular combinations of maternal NK cells and fetal MHC-C genotypes are linked to impaired placental development, and are reported to be associated with an increased risk of miscarriage and pre-eclampsia. Ongoing studies examining the interaction between NK cells and fetal gene expression may help to improve understanding of the vital initial stages in pre-eclampsia development(Figueras, 2018).

Reduced perfusion of the placenta from the abnormal remodeling of the spiral arteries appears to be related to impaired placental development. In keeping with this theory, conditions associated with vascular insufficiency, including hypertension, diabetes, systemic lupus erythematosis (SLE) and renal disease all increase the risk of abnormal placentation and pre-eclampsia(Pergialiotis et al., 2017).

Hypoperfusion of the developing placenta results in placental ischemia; placental pathological findings indicative of ischemia include atherosis, fibrinoid necrosis, thrombosis and placental infarction. The typical placental pathological appearances are not seen in all women with pre-eclampsia, but their presence does appear to correlate with disease severity. The interface between the placental and maternal components of pre-eclampsia development is thought to occur when the under-perfuse, ischemic placenta releases a variety of factors into the maternal circulation (Figueras, 2018).

2.2.2 Maternal response

The second phase of pre-eclampsia development is characterized by exaggerated maternal endothelial activation and a pro-inflammatory state compared to normal pregnancy. Placental hypoxia leads to oxidative stress, destruction of syncytial architecture, and release of components from the

intervillous space into the maternal circulation. The trophoblastic debris in the maternal circulation includes syncytiotrophoblastic membrane microparticles, and factors arising from the syncytiotrophoblastic including soluble endoglin (sENG), and the soluble form of the vascular endothelial growth factor (VEGF) receptor, (sFLT1) (Mansilla et al., 2018).

These and other as yet unknown factors lead to production of inflammatory cytokines in the maternal circulation, endothelial dysfunction and increased vascular reactivity. Loss of integrity of the maternal endothelium contributes to reversal of the physiological vascular changes in pregnancy, and subsequent hypertension, proteinuria and edema(Hutabarat et al., 2018).

2.3 Maternal Risk Factors

Although accurate prediction of pre-eclampsia remains difficult, there are a number of maternal risk factors which can be easily assessed in early pregnancy that are known to be associated with an increased risk of developing pre-eclampsia.

2.3.1 Nulliparity

The most common risk factor of the pre-eclampsia is nulliparity, defined as never having previously given birth to a viable fetus; nulliparity has been shown to almost triple the risk of pre-eclampsia. The protective effect of having had a previous birth is lost, however, when a subsequent pregnancy is conceived with a new partner, or when there is a long interval between pregnancies. This had led to the theory that prior exposure to paternal antigens has a protective role against pre-eclampsia. This theory was supported by a study of Nulliparous women, whereby women with previous termination of pregnancy with the same partner as the index pregnancy were nearly half as likely to develop preeclampsia as women who had a previous termination with a different partner. Reduced exposure to paternal antigen, by limited exposure to their sperm is also a risk factor for pre-eclampsia. Women who conceive after a short period of

sexual relations, or by alternative techniques such as non-partner donor insemination or intracytoplasmic sperm injection (ICSI) are also at increased risk of disease (Sibai et al., 1995).

2.3.2 Obesity

Obesity is another important risk factor for pre-eclampsia; increased body mass index or increased abdominal circumference before pregnancy or in early pregnancy are well established risk factors for the condition. The maternal risk of pre-eclampsia increases with increasing degree of obesity, which persists after accounting for other potential confounding factors. This is likely to be related to the altered metabolic state associated with marked obesity rather than the obesity itself. Maternal obesity results in alteration of the plasma lipid profile with higher serum triglyceride and VLDL cholesterol, and lower HDL cholesterol concentrations than those observed in lean pregnant women. This pattern of dyslipidaemia is similar to that of the “metabolic syndrome” described in the non-pregnant population. Obesity is also associated with chronic low-grade inflammation, a feature common tomany of the other risk factors for the condition (Agarwal et al., 2017).

2.3.3 Diabetes

The association of pre-gestational diabetes and pre-eclampsia is well recognized, and women with a history of diabetes have an up to 4-fold increased risk of development of pre-eclampsia compared to the general population. Recent data from both the UK and the USA suggest that 0.5 - 0.75% of pregnant women have pre-existing type 1 or type 2 diabetes. In keeping with the general population, rates of gestational, type 1 and type 2diabetes in pregnant women rose significantly between 1994 and 2004 in all agegroups. The increase in rates of type 2 diabetes in pregnant women has beenthe most striking, and is likely to be related to increased rates of obesity(Lisonkova and Joseph, 2013).

Diabetes in pregnancy increases the risk of poor maternal and neonatal outcomes. As well as the increased risk of pre-eclampsia, the condition is also associated with elevated risk of pregnancy loss, maternal infection, polyhydramnios, premature labour and failure to progress in the first or second stage of labour. Fetal and neonatal complications associated with diabetes include congenital malformation, macrosomia, respiratory distress syndrome, hypoglycemia and jaundice. Further, the babies born to diabetic mothers have been shown in long-term follow up studies to be at increased risk of future obesity and type 2 diabetes themselves (Middleton et al., 2010).

Improving glycaemic control in early pregnancy is associated with a reduced risk of miscarriage and congenital malformations, but ithas been less clear whether rates of pre-eclampsia are similarly affected. In astudy of 290 pregnant women with type 1 diabetes, Temple et al. reported that HbA1c, an indicator of long-term glycaemic control, at week 12 and week 24was strongly associated with pre-eclampsia on univariate analysis. In this study, however, pre-pregnancy care to target pre-conceptual glucose control, and improved glucose levels in very early pregnancy was not associated with a difference in rates of pre-eclampsia. Gestational diabetes, the onset or first recognition of glucose intolerance in pregnancy, is also dramatically increasing in incidence in the Western world. Until recently there has been a lack of consensus on how the condition should be diagnosed or treated, and in particular it has not been clear how aggressively blood glucose should be monitored or lowered. A recent study designed to investigate the use of metformin and / or insulin in gestational diabetes examined the influence of baseline oral glucose tolerance test (OGTT) results, HbA1cand both fasting and post-prandial capillary glucose levels on a variety of maternal outcomes (Lisonkova and Joseph, 2013).

Diagnostic OGTT results (from the time of diagnosis of gestational diabetes, at mean gestation 30 weeks) did not predict outcomes, but the key finding was that capillary glucose levels were strongly and independently

related to the primary outcome composite of neonatal outcomes, pre-eclampsia and frequency of large for gestational age (LGA) babies. Pre-eclampsia itself was most strongly associated with elevated post-prandial glucose levels, and since fluctuating glucose levels are thought to contribute to endothelial dysfunction in non-pregnant patients with diabetes, this is perhaps not surprising(Middleton et al., 2010).

2.3.4 Ethnicity

Pre-eclampsia rates vary significantly around the world; whether this is related to different diagnostic criteria, or whether there are truly differences between different ethnic population remains uncertain. Further, whether both maternal and paternal ethnicity plays a role in determining pre-eclampsia risk is also unclear. A retrospective American cohort study of 127,000 low-risks pregnant women reported that rates of pre-eclampsia were higher among African-American women (5.2%, OR 1.41, 95% CI 1.25-1.62), and lower amongst Latina (4.0%, OR 0.9, 95% CI 0.84-0.97) and Asian women (3.5%, OR 0.79, 95% CI 0.72-0.88) compared to white women (31). Paternal ethnicity followed a similar pattern, with highest rates in African-American fathers, and lowest rates in Asian fathers. When maternal and paternal ethnic discordance were examined, the overall rate of pre-eclampsia was higher among mothers whose ethnicity differed from the father (Crombag et al., 2017).

2.3.5 Relative risk of individual risk factors

Established risk factors associated with pre-eclampsia, along with relative risk and 95% confidence intervals are shown in table below.

In addition to these well-established risk factors,others have more recently been reported to be associated with pre-eclampsia. Asthma, another condition characterized by chronic inflammation, has been implicated; in a study of 650 asthmatic and 1000 non-asthmatic pregnant women, women with moderate to severe asthma symptoms had an increased risk of developing pre-eclampsia, regardless of treatment, compared to those without symptoms (Rezende et al., 2017).

Table 2-1 maternal risk factors for pre-eclampsia. Adapted from (Duckitt and Harrington, 2005)

Risk Factor	Relative Risk (95% CI)
Nulliparity	2.91 (1.28 to 6.61)
Previous pre-eclampsia	7.19 (5.85 to 8.83)
Age > 40 yrs	1.96 (1.34 to 2.87)
BMI ≥ 35 kg/m²	1.55 (1.28 to 1.88)
Twin pregnancy	2.93 (2.04 to 4.21)
Diastolic BP > 80 at booking	1.38 (1.01 to 1.87)
Pre-existing diabetes	3.56 (2.54 to 4.99)
Family history (mother or sister)	2.90 (1.70 to 4.93)
Antiphospholipid antibody	9.72 (4.34 to 21.75)

In addition, a history of coronary heart disease in the pregnant woman's father has been recently reported as conferring an almost 2-fold increased risk of pre-eclampsia .The problem with using these factors to stratify pre-eclampsia risk is that many of them are extremely common in the pregnant population. Further, the majority of these risk factors are non-modifiable. The relationship between different risk factors is also uncertain; for example it is not known whether a multiparous woman with high BMI remains at increased risk of pre-eclampsia if her previous pregnancies were uncomplicated(Crombag et al., 2017).

As women in modern Western society begin to have children at a later stage in life, and as the population as a whole becomes more obese, these risk factors will become less useful in risk stratification. There is now therefore more of a clinical need than ever to identify clinical or biochemical parameters that will help to inform clinicians which women are at increased risk of developing pre-eclampsia(Rocha et al., 2017).

2.4 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 anatomizes 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 endometrial and continues as a spiral artery(Yu et al., 2017).

The spiral arteries are highly coiled within the basalis and the deeper parts of the functionalize, but as they approach the uterine lumen they narrow and divide into several smaller branches. 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 recognized, efficiently diverting blood away from the lower limbs. Secondly numerous homodynamic alterations in the mothers' circulation occur. These alterations promote an effective uteroplacental blood supply (Boutin et al., 2018).

Normal pregnancy is characterized by the formation of large arterio-venous shunts that persist in the immediate post-partum period. By contrast pregnancies complicated by severe pre-eclampsia are characterized by minimal arterio-venous shunts, and thus narrower uterine arteries. Extra villous cytotrophoblast invasion in normal pregnancy extends beyond the deciduas into the inner myometrium resulting in the formation of funnels at the discharging tips of the spiral arteries (Baekgaard Thorsen et al., 2018).

2.5 Antenatal care

The purpose of antenatal care is to maintain both the mother and the fetus in the best positive state of health of the fetus 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 revolutionized perinatal care and a high number of fetal complications as well as abnormalities are now detected

before birth. With the use of diagnostic ultrasound perinatal detection is increased, thus obstetric sonography has become a vital part of perinatal care (Sharma et al., 2018).

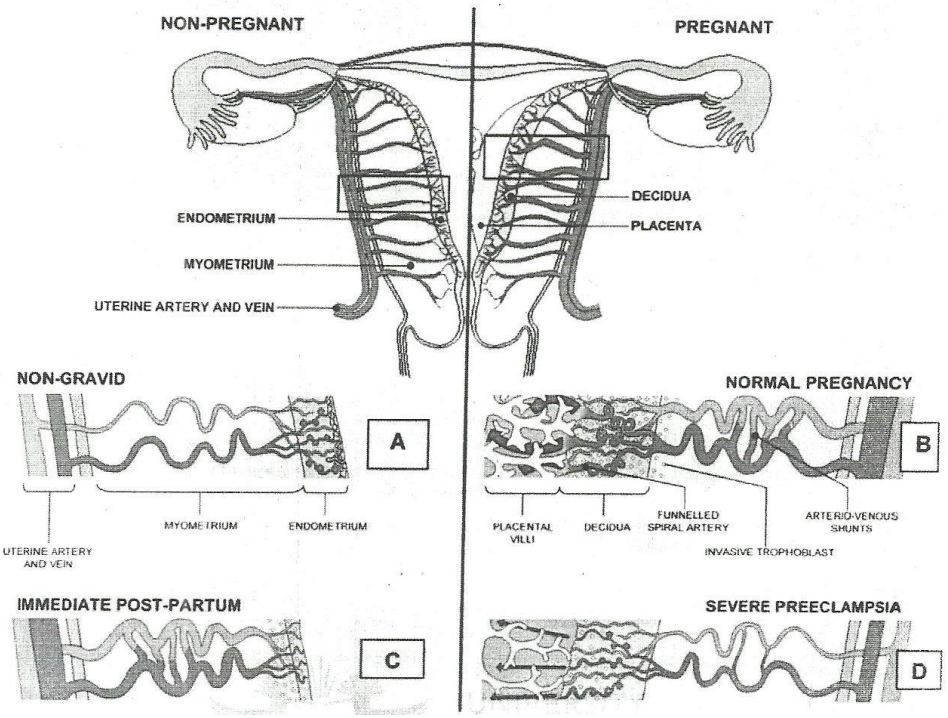

Figure 2.1: Diagrammatic representation of uterine and placental vasculature (lower arterial: above venous) in the non-pregnant, pregnant and immediate postpartum state (Sharma et al., 2018)

2.6 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 propose that early detection and treatment of pre-eclampsia is advantageous to both mother and fetus (Zhang et al., 2017).

2.7 Screening for Placental Insufficiency

Placental insufficiency is a major cause of perinatal mortality and morbidity; Pre-eclampsia, FGR, placental abruption and some case of fetal death during the second half of pregnancy are thought to result from impaired placentation in early gestation. Most cases of FGR are caused by uteroplacental insufficiency. 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. Doppler sonography is a non-invasive screening method for disorders of placental function early in pregnancy (Ramos-Orosco et al., 2018).

2.8 First Trimester Screening

According to(Barati et al., 2014)first 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 first trimester uterine artery Doppler assessment is thus useful in identifying a subgroup of the population at a considerable risk for early, severe preeclampsia or growth restriction. In a study done by Pilalis the results suggest that uterine artery Doppler examinations are helpful in predicting pre-eclampsia from as early as the first trimester. Melchiorre and coworkers (2008) found that first trimester uterine artery Doppler indices and prevalence of bilateral notching in normal pregnancies were considerably different from those in women destined to develop preterm preeclampsia but not term pre-eclampsia. The results of a study done by Melchiorre and coworkers (2009) indicated a significant relationship between first trimester uterine artery Doppler indices and the consequent development of small for gestational age fetuses(Myatt et al., 2012).

2.9 Second Trimester Screening

Second trimester uterine artery Doppler screening has proven to be accurate method for predicting pre eclampsia especially the severe forms and early onset of the disease. 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 2 trimester, denotes that a strict protocol of monitoring should be considered. 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 preeclampsia and FGR (Abdel Razik et al., 2018).

2.10 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 an d pre-eclampsia develops from a relative failure of this event, validates the evaluation of uterine artery Doppler assessment in the 1st trimester 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 normalize by late second trimester (Carbillon, 2018).

Screening in the second trimester leads to improvement in the false positive rates and positive predictive values. 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) 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. 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. In a study by Yu and coworkers (2003) 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 preeclampsia by starting pharmacological intervention in the second trimester has by and large failed (Demers et al., 2018).

2.11 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. The results of a study done by Harrington and colleagues confirm the potential of uterine artery Doppler analyze in the screening of high risk populations for uteroplacental complications in the second trimester 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 (Carbillon, 2018).

2.12 Uterine artery Doppler studies

The advent of ultrasound has revolutionized the practice of obstetrics in the last 50 years, by offering a window to the womb through which the anatomic structures of the fetus can be evaluated. The morerecent addition of Doppler flow studies of the maternal and fetal vessels have provided further useful information, allowing assessment of the physiology of the feto-maternal unit. Doppler studies are non-invasive, acceptable to patients, and can be carried out at the same time as a detailed anomaly scan, and assuch have been studied

extensively for their role in screening for adverse fetal and maternal outcomes(Salem and Ammar, 2018).

2.13 Doppler studies in normal pregnancy

In the non-pregnant state there is a rapid rise andfall in uterine artery flow velocity during systole and a “notch” in the descending waveform in early diastole. Remodeling of the spiral arteries in early pregnancy is an important step in regulating and maintaining placental perfusion. The reduction in resistance of the spiral arteries as a result of remodeling in pregnancy can be reflected in uterine artery Doppler studies, by a high diastolic velocity with continuous flow throughout diastole, and the loss of the diastolic “notch” at 20 to 24 weeks’ gestation. These changes can be quantified by demonstrating changes in the resistance index (RI, maximum – minimum velocity / maximum velocity) and the pulsatility index (PI, maximum – minimum velocity / mean velocity) of the uterine vessels which begin to decrease in normal pregnancy from between 8 and 18 weeks’ gestation(Owen et al., 2003).

2.14 Doppler studies in pre-eclampsia

In pre-eclampsia the remodeling of the spiral arteries is impaired; the spiral arteries maintain their muscular elastic coating, and impedance to blood flow persists. This pathological resistance to placental flow can be detected by Doppler studies of the maternal uterine vessels, offering the potential to detect women at risk not only of pre-eclampsia, but also of intra-uterine growth restriction. The majority of research has focused either on an elevation in RI or PI using percentile cut-off values, or by persistence of the diastolic “notch.”

Abnormal Doppler studies in both the first and second trimesters have been reported to be associated with pre-eclampsia. Abnormalities are detectable as early as 12 weeks’ gestation; for women with abnormal first trimester testing the likelihood ratio (LR) for development of pre-eclampsia is approximately 5, while normal Doppler studies carry an LR of 0.5 (75). Although this

relationship persists into the second trimester, the optimal timing for performing these studies remains uncertain(Anshul et al., 2010).

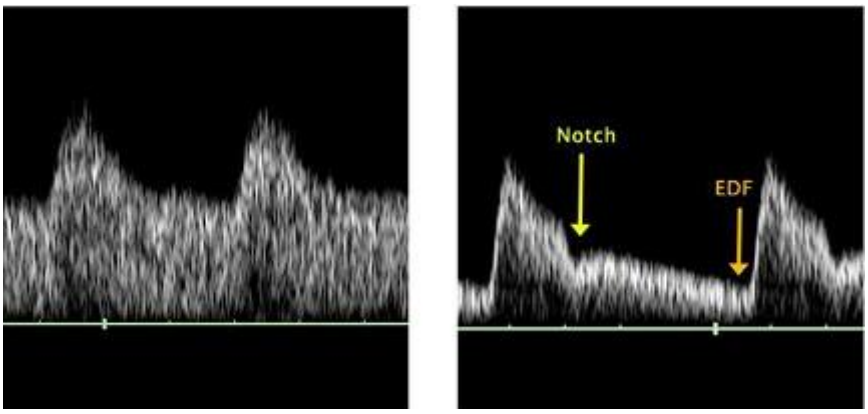

Figure 2.2: Uterine artery Doppler studies at week 28 in a woman with a normal pregnancy (left) and in women with pre-eclampsia

The use of uterine artery Doppler was perhaps best summarized in a recent comprehensive meta-analysis. Cnossen et al reviewed 74 uterine artery Doppler studies including nearly 80,000 pregnant women, of whom 2,500 developed pre-eclampsia. The majority of Doppler indices had poor predictive characteristics, but this varied with patient groupstudied and severity of disease. For all women the overall risk of pre-eclampsia was best predicted by an elevated second trimester PI accompanied by persistent bilateral uterine artery notching. For women deemed on the basis of risk factors to be at low-risk, positive likelihood ratio (+LR) was 7.5, and negative likelihood ratio (-LR) was 0.59. For women at high risk of developing pre-eclampsia, +LR was 21, and LR was 0.82(Cnossen et al., 2008).

As a result of these findings the authors concludedthat Doppler studies were more accurate for prediction of future pre-eclampsia when performed in the second trimester rather than the first trimester. Since the false positive rate was relatively high, they felt that the increased anxiety and expense associated with abnormal results could not justify their use for screening in low-risk women. The majority of studies using uterine artery Doppler studies to predict pre-

eclampsia have been performed in large centers withsignificant experience and expertise in their use. It remains to be seen whether these findings are applicable in smaller centers, or in the developingworld where they would be more likely to be clinically useful. The tests are also relatively time-consuming, taking around 20 minutes to perform, which maypreclude their use in the general pregnant population. The combination of these studies with maternal risk factors, or with analysis of serum markers such as anti-angiogenic factors may ultimately be more clinically useful(Cnossen et al., 2008).

2.15 Blood pressure measurement

Although blood pressure measurement is clearly essential for the detection of hypertensive disorders of pregnancy, it remains to be seen whether measurement of blood pressure in the first or second trimesters can predict which women will develop problems later on. Increased diastolic blood pressure is associated with an increased risk of pre-eclampsia, but studies using assessment of blood pressure in the first or secondtrimester for prediction of pre-eclampsia have reported false-positive rates ranging from 7 - 52% and detection rates ranging from 8 – 93%. It is likely that these differences relate to differences in the populations studied, different techniques used to measure blood pressure, and different definitions of pre-eclampsia. A meta-analysis of 34 studies evaluated the role of systolic pressure (SBP), diastolic pressure (DBP), mean arterial pressure (MAP) and increase in blood pressure during the first or second trimester to predict pre-eclampsia in low and high-risk women. MAP was shown to be superior to SBP, DBP and increase in blood pressure between the first and second trimester in predicting pre-eclampsia; second trimester MAP of ≥90 mmHg was associated with a positive likelihood ratio of 3.5 for pre-eclampsia and a negative likelihood ratio of 0.46(Cnossen et al., 2008b).

Ambulatory blood pressure monitoring (ABPM) allows multiple readings to be taken using automated blood pressure devices, in a non-clinic environment.

As such this may provide a better estimate of true blood pressure, since it is not confounded by the “white-coat” effect. Few studies have examined ABPM in the context of pre-eclampsia prediction, and the majority of these are suboptimal. One study which examined over 1100women who had 24 hour ABPM between 18 and 24 weeks’ gestation did not find ABPM to be a useful predictor of hypertension later on in pregnancy, since absolute differences in ABPM measurements were small, and overlap between hypertensive and normotensive women was high(Poon et al., 2008).

2.16 Previous studies:

(Christina et al., 2005) conducted study to develop a predictive model for preeclampsia.It was a prospective screening study for preeclampsia using uterine arteryDoppler ultrasound in unselected low-risk singleton pregnancies at community hospitals in the UK (n = 32,157). Logistic regression models were developed and their predictive ability assessed using the area under the receiver operator curve (AROC).

Six hundred twelve (2.0%) women developed preeclampsia, and 144 (0.5%) required early delivery (<34 weeks). A model using both maternal and ultrasound factors had an AROC of 0.798, which was higher than ultrasound alone (0.729, ***P***< .0001) or maternal factors alone (0.712, ***P***< .0001). In early onset disease, the ROC of ultrasound alone (0.922) was not significantly improved by adding maternal predictors (0.945, ***P*** = .27). In contrast, late onset disease was better predicted by the combined model (AROC 0.798) than ultrasound alone (AROC 0.729, ***P***< .0001) or maternal factors alone (AROC 0.712, ***P***< .0001).The combination of uterine artery Doppler ultrasound and maternal factors provided the best estimate of risk(Christina et al., 2005).

Another study conducted by (Myatt et al., 2012)to identify clinical characteristics and biochemical markers in first-trimester samples that would possibly predict the subsequent development of preeclampsia. They conducted a multicenter observational study in 2,434 low-risk nulliparous women to identify

biomarkers that possibly predict preeclampsia. Clinical history, complete blood count, and biochemical markers were assessed in the first trimester. The trophoblastic and angiogenesis markers ADAM-12 (a disinterring and metalloprotease 12), pregnancy-associated plasma protein-A (PAPP-A), PP13, placental growth factor (PlGF), soluble fms-like tyrosine kinase-1, and endoglin were measured in a case-control subset of 174 women with preeclampsia and 509 controls. Univariable analysis revealed maternal age, race, and maritalstatus; years of education, source of medical payment, prenatal caregiver, body mass index (BMI), and systolic blood pressure at enrollment were significantly associated with preeclampsia. Mean platelet volume was greater at enrollment in women who later developed preeclampsia (median 9.4 vs. 9.0fl, p=0.02). First-trimester concentrations (multiples of the median) of ADAM-12 (1.14 vs. 1.04, p=0.003), PAPP-A (0.94 vs. 0.98, p=0.04), and PlGF (0.83 vs. 1.04, p<0.001) were significantly different in women who developed preeclampsia compared with controls. The optimal multivariable model included African American race, systolic blood pressure, BMI, education level, ADAM-12, PAPP-A and PlGF, and yielded an area under the curve of 0.73 (95% CI 0.69–0.77) and a sensitivity of 46.1% (95% CI 38.3–54.0) for 80% specificity.

A multivariable analysis of clinical data and biochemical markers in the first trimester did not identify a model that had clinical utility for predicting preeclampsia in a low-risk Nulliparous population(Myatt et al., 2012).

Chapter three

Materials and Method

3.1 Subjects:

All patients attending the antenatal clinic who were referred to the Ultrasound department for a routine dating scan (between *11-14wks)* were recruited to participate in this study.

3.2 Sampling

A convenience sampling method was applied by recruiting all patients (between 11-14 weeks gestation) attending the antenatal clinic. 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 51 patients were recruited.

3.3 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 preeclampsia
- Patients on treatment for hypertensive disorders- these patients results would not be a true reflection as they are already on medication

3.4 Study variables

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.
- Uterine artery (RI,PI and notching).

3.5 Machine Used:

Image shows US Machine that was used in this theses, Mindary DC-N6 with 2 probes (convex and linear 5-10 MHz).

3.6 Technique Used:

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; embryonic or fetal cardiac activity, confirmation of an intrauterine pregnancy, number of fetuses and 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 estimated date of delivery was calculated. The uterine arteries were then sampled. Uterine artery spectral Doppler assessment may be performed via transabdominal route in the second and third trimester; however in this study the transabdominal approach was used. The uterine artery is located on either side of the uterus serviced and calibrated - on a regular basis. The results were obtained by a routine procedure guided by computer software applications and enter the uterus at the level of the internal oss but may branch before or at the crossover with the external iliac artery.

The probe was then moved to the right adnexae and the transducer was gently tilted medially until the uterine artery was identified where it crosses over the external iliac artery. 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. 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.

3.7 Data collection and analysis:

The data was captured on the data collecting sheet a unique research number was issued to each patient willing to participate. 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, The outcome variable the development of PE or not and the predictor variables the presence or absence of uterine artery notching.

3.8 Ethical considerations:

An information leaflet given to all participants informing them of the aims, objectives and potential value of the study. Patients who were willing to participate in this study were formally asked to complete and sign a consent form. Each patient was scanned according to the standard. Subjects were treated equally and safe practice was maintained at all times.

Chapter four

Results

Table 4.1 Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Age	51	18	40	28.20	6.13
BMI	51	15.40	34.40	26.19	4.13

Table 4.2 Age group

Age range	N	Percent
18-25	18	(35%)
26-33	20	(39%)
34-40	13	(26%)

Table 4.3 LUA Notch

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	45	88.2	88.2	88.2
	Yes	6	11.8	11.8	100.0
	Total	51	100.0	100.0	

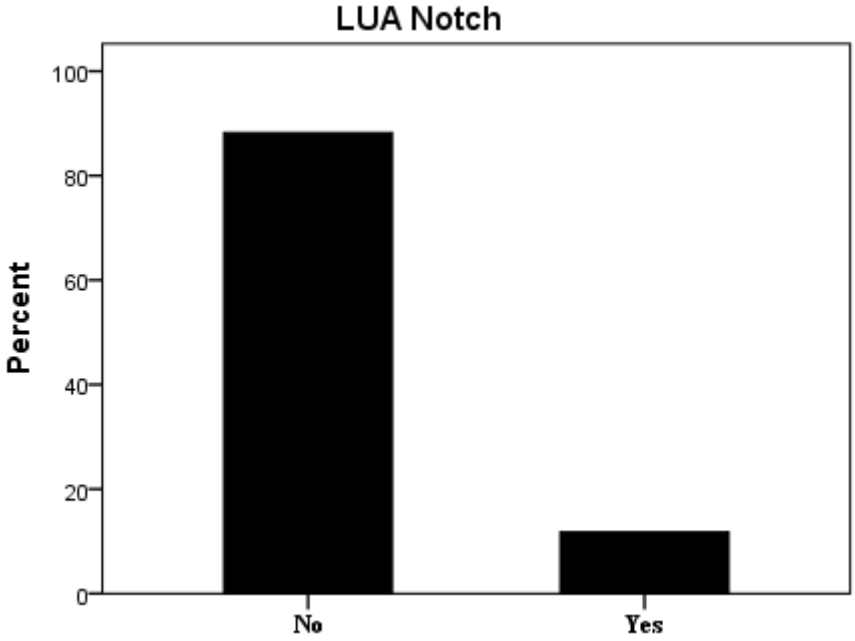

Figure 4.1 presence of LUA notch

Table 4.4 Group Statistics					
	LUA Notch	N	Mean	Std. Deviation	Std. Error Mean
RUA RI Second Trimester	No	46	0.62	0.19	.027
	Yes	5	0.51*	0.08	.034
LUA RI Second Trimester	No	46	0.58	0.18	.026
	Yes	5	0.50	0.06	.029
RUA PI Second Trimester	No	46	1.15	0.45	.066
	Yes	5	1.14	0.61	.275
LUA PI Second Trimester	No	46	2.96	12.97	1.91
	Yes	5	1.38	0.65	0.29

* Significant difference (*P<0.05)*

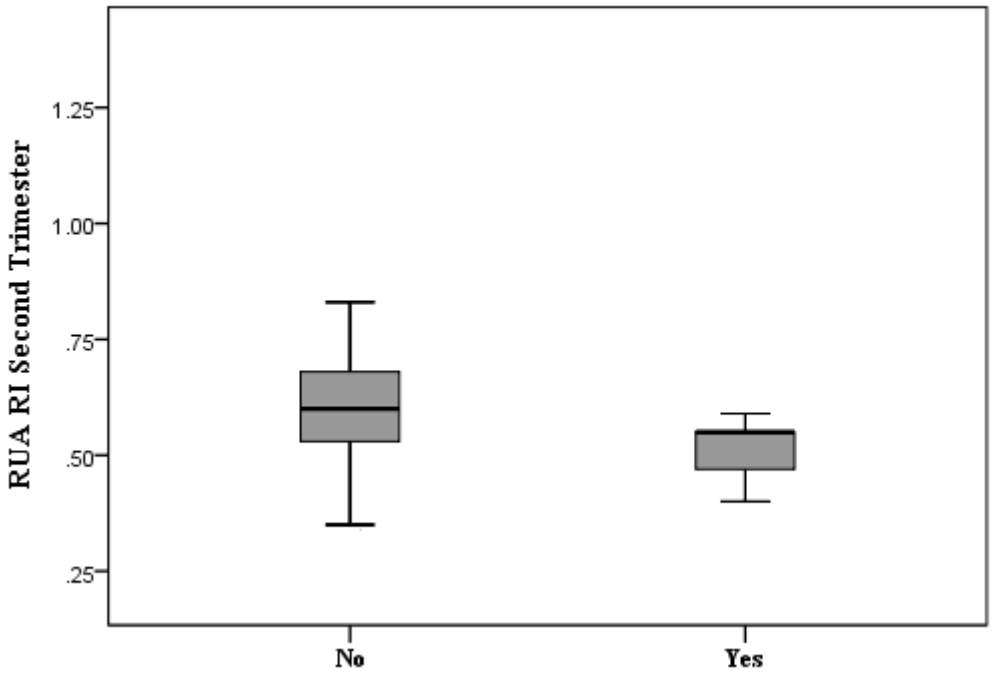

Figure 4.2 Mean RI in the presence and absent of Notching in second trimester

Table 4.5 Group Statistics					
	LUA Notch	N	Mean	Std. Deviation	Std. Error Mean
RUA RI Third Trimester	No	45	0.45	0.14	0.02
	Yes	6	0.68*	0.21	0.09
LUA RI Third Trimester	No	45	0.44	0.10	0.01
	Yes	6	0.66	0.21	0.09
RUA PI Third Trimester	No	45	0.76	0.33	0.05
	Yes	6	1.62*	0.82	0.33
LUA PI Third Trimester	No	45	0.78	0.23	0.03
	Yes	6	1.54	0.83	0.34

* Significant difference (*P<0.05)*

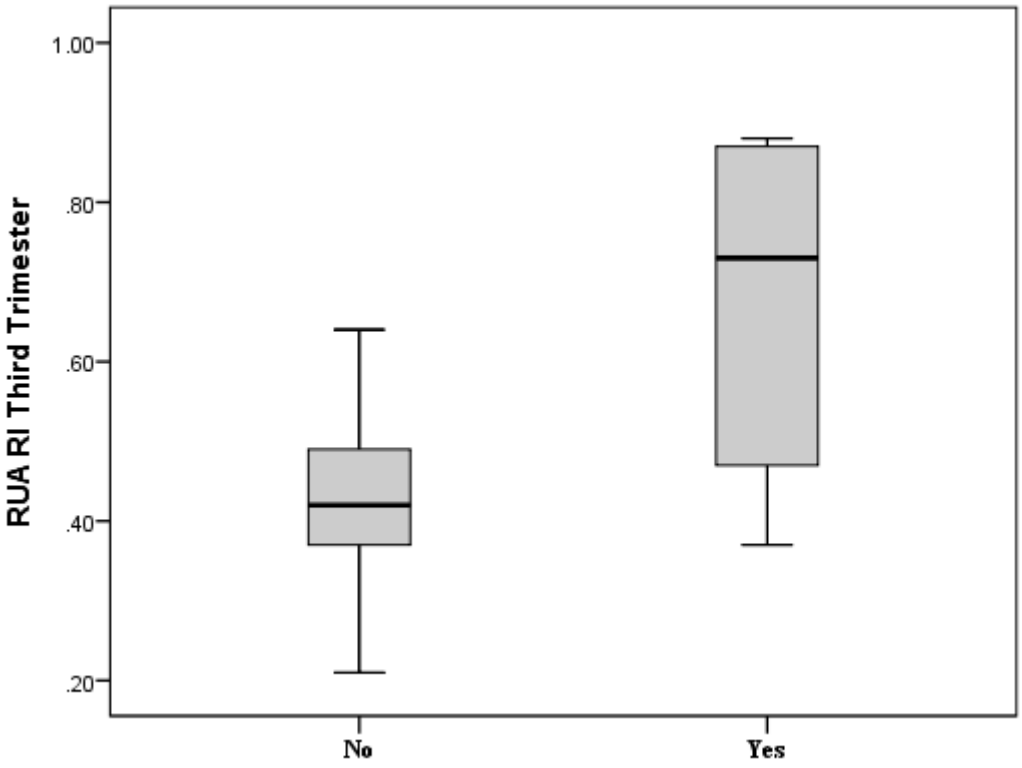

Figure 4.3 Mean RI in the presence and absent of Notching in third trimester

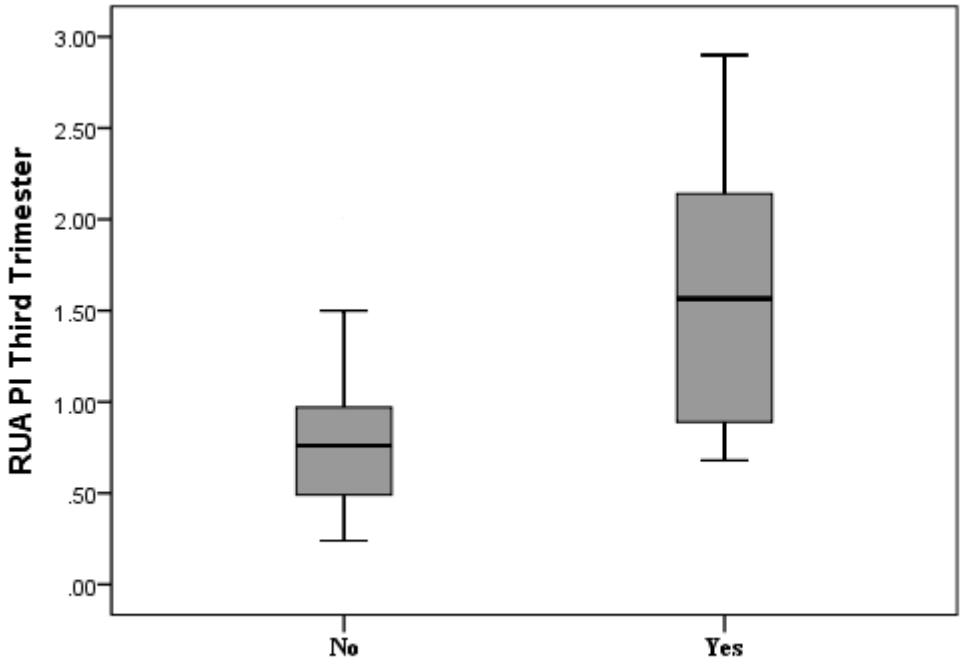

Figure 4.4 Mean PI in the presence and absent of Notching in third trimester

Chapter Five

Discussion, conclusion and recommendations

5.1 Discussion:

Pre-eclampsia is the most common pregnancy complication associated with serious maternal- fetal morbidity and mortality. At present the only effective treatment is delivery of the placenta (Poon et al, 2009). Abnormal uterine artery Doppler waveforms may synchronized with the hypothesis that the ability to predict those women at risk for pre-eclampsia early in pregnancy might decrease maternal and fetal morbidity through

The majority of participants, 20(39%), were in the age group 26 — 33, while 18(35%) were between 18 and 23 years of age, and 13 (26%) were older than 35 years of age, with the mean age being 28.20 (±SD 6.13). For 13(25.5%) patients it was their first pregnancy while 13 (25.5%) were gravid 2, 12 (23.5%) gravid 3 and 13 (25.5%) gravid 4 and more.

The results of this study could be used to evaluate whether it is worthwhile implementing a routine screening program for pre-eclampsia. 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 P1 values decreased as gestation increased as is to be expected in a normal pregnancy. In our study the 1st trimester P1 values in patients who developed pre-eclampsia was not a strong predictor of PE. None of the values recorded were above the 95th centile when compared to the values by Gomez and co-workers(Gómez et al., 2008).

Regarding presence of notching, the result of the study showed that The percent of Notch in 2nd and 3rd trimester displayed 45(88.20%) as NO notching in waveform, and 6(11.80%) as Yes which remain good indicator for Predictive

value for Preeclampsia. In the 1st and2nd trimesters all6 patients who developed preeclampsia had uterine artery notching, in the 3rd trimester5 out of the 6 patients had notching, 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 preeclampsia. It has been established that uterine artery notching that persist after 26 weeks of gestation be considered a risk factor for poor pregnancy outcomes. An early diastolic was found to persist in 25-40% of cases after 26 weeks gestation (McLeod, 2008).

5.2 Conclusion:

Uterine artery Doppler waveforms were analyzed for the presence or absence of notching and the P1; RI values were calculated using standard software on the ultrasound machine. Doppler investigation of the fetus and placenta has evolved in the past years and there is now a better understanding of the pathophysiology involved in PE. Uterine artery Doppler screening in early pregnancy is performed so that those cases at high risk for placental associated disease can be identified.

Uterine artery notching in the second trimester was the best predictor of preeclampsia. In the most severe cases of PE increased pulsatility indices and resistive index were recorded. This study has confirmed the work of others by finding a link between uterine artery notching in the second trimester and PE.Although the exact cause of pre-eclampsia remains unknown it is important to define the risk at the beginning of pregnancy so that antenatal care can be provided according to the needs of the patient and allows for early intervention.

A large number of the maternal were between the ages of 18 and 40 years and majority of the patients were multiparous.

Six patients developed pre-eclampsia. In terms of high risk most of predicting PE were controlled (3) by aspirin, one was sectioned in (26) weeks due to high severity of PE. Other two maternal were sectioned in 3rd trimester after 33wks of GA.

5.3Recommendations:

- Uterine artery Doppler screening for maternal with history of PE showed be assessed routinely.
- Assessment of uterine artery in 2ndtrimester in PE patient can reduce the complication of PE in 3rdtrimester of pregnancy.
- Future research should also concentrate on combining uterine artery Doppler ultrasonography with other tests.

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