Impact of Severe Preeclampsia on Maternal and Fetal Outcomes in Preterm Deliveries

Dr Thabane Poonyane

Dissertation for MMed (Obstetrics and Gynaecology) and FCOG Part II

Supervisor: Dr K A Frank

Declaration

I, Dr Thabane Poonyane declare that this dissertation is my own work and it is being submitted to the CMSA, for the Fellowship of the College of Obstetricians and Gynaecologists of South Africa Part 2. This work has not been submitted nor presented for any degree or examination purposes at this institution or any other institution.

Acknowledgements

The idea behind this research was conceived by my Supervisor, my mentor and teacher. My gratitude goes to Dr KA Frank, who assisted me in choosing the research topic, patiently stood by me through all my struggles, always believed in me, supported me, being a mentor and source of inspiration.

To Professor EJ Buchmann for analysing the data, this work would not be a success without your assistance.

Table of Contents

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ACE-I	Angiotensin converting enzyme inhibitor
AGA	Appropriate for gestational age
AKI	Acute kidney injury
ALT	Alanine transaminase
AMA	Advanced maternal age
AMD	Alpha methyldopa
ANC	Ante-natal clinic
ARDS	Acute respiratory distress syndrome
ARF	Acute renal failure
ART	Anti-retroviral therapy
AST	Aspartate transaminase
BMI	Body mass index
BP	Blood pressure
BPP	Biophysical profile
Cd4	Cluster of differentiation four
CI	Confidence interval
Cr	Creatinine
CVA	Cerebro-vascular accident
DBP	Diastolic blood pressure
DIC	Disseminated intravascular coagulation
ENND	Early neonatal death

FBC	Full blood count
FD	Fetal distress
HELLP	Haemolysis elevated liver enzymes, low platelets
HIV	Human immunodeficiency virus
ICU	Intensive care unit
IE	Imminent eclampsia
IQR	Inter quartile range
IUGR	Intra-uterine growth restriction
IVH	Intra ventricular haemorrhage
NEC	Necrotizing enterocolitis
NICE	National institute of Clinical Excellence
NICU	Neonatal Intensive Care Unit
NVD	Normal vaginal delivery
OR	Odds ratio
RDS	Respiratory distress syndrome
Rh	Rhesus factor
RPR	Rapid Plasma Reagent
RR	Relative Risk
SGA	Small for gestational age
SOMANZ	Society of Obstetric Medicine of Australia and New Zealand
VLBW	Very low birth weight

Abstract

Background

Hypertensive disorders in pregnancy are common and their incidence appears to be on the increase. Preeclampsia is a multi-organ, heterogeneous disorder of pregnancy associated with significant maternal, fetal and neonatal morbidity and mortality. Because preeclampsia is a progressive disorder, invariably delivery remote from term is often necessary to halt disease progression to benefit the mother and fetus.

Objectives

- To determine the maternal outcomes in women with severe preeclampsia
- To determine fetal and neonatal outcomes of infants born preterm

Methods

This was a prospective, descriptive study performed in three academic hospitals affiliated to the University of the Witwatersrand in Johannesburg. Data was collected from women with severe preeclampsia, who delivered between gestational ages of 26 weeks and 33 weeks, with a minimum neonatal weight of 500g as determined by sonography.

Results

In the sample of 92 patients enrolled, there were two maternal deaths as a result of severe preeclampsia. Eclampsia and HELLP syndrome were the most frequently observed maternal complications at 34% and 49% respectively. Caesarean section was the most frequent method used to expedite delivery in 84% of women. Of the 97 babies delivered, 20% were confirmed intra-uterine fetal deaths, 7% demised during the early neonatal period and a there was a 40% very low birth weight rate.

Conclusion

Despite interventions to reduce maternal and neonatal morbidity and mortality in our setting, our outcomes are similar to those observed in other parts of the world.

1. Introduction

1.1 Background

Despite advances in research into preeclampsia, a clear understanding of the processes preceding the development of this common and serious vascular complication of pregnancy has not yet been achieved. It is now well accepted that the proteinuria and hypertension of preeclampsia occur as a result of extensive endothelial dysfunction [1].

Hypertensive disorders of pregnancy are among the most common medical problems in pregnancy with an incidence of between 5-10% [2]. The incidence varies amongst different hospitals, regions and countries. Hypertensive disorders in pregnancy are a major cause of maternal and perinatal morbidity and mortality worldwide [3].

The clinical findings of preeclampsia can manifest as either a maternal syndrome (hypertension and proteinuria with or without other multi-organ involvement) or fetal syndrome (fetal growth restriction, oligohydramnios, abnormal umbilical artery Doppler findings and reduced placental growth with infarctions). Despite advances in perinatal care, the incidence of gestational hypertension-preeclampsia has not changed [4].

1.2 Epidemiology

Up to 10% of women have elevated blood pressures during their pregnancies [5]. Three to eight percent of these women in developed countries develop preeclampsia [6, 7] and up to 0.56 /1000 births are complicated by eclampsia [8]. Due to absence of epidemiological information in many low and middle income countries; lack of effort and capacity for data collection and reporting of vital statistics, the exact prevalence of preeclampsia and associated morbidity and mortality from low and middle income countries is unknown. However the World Health Organisation (WHO) estimates approximately 16% of maternal deaths in LMIC are due to hypertensive disorders pregnancy, of which eclampsia is the primary contributor [9]. The Saving Mothers 2008-2010: Fifth report into Maternal Deaths in South Africa [10], reports that 14% of all maternal deaths in South Africa were due to hypertensive complications of pregnancy (chronic hypertension, preeclampsia, HELLP syndrome and rupture of the liver).Eclampsia was the major cause of death and accounted for 51.1% of the hypertensive deaths. There were 29.3% deaths from preeclampsia, 5% associated with chronic hypertension, 12.7% were due to HELLP syndrome and 1.3% related to rupture of the liver, while pulmonary oedema accounted for 27% of cases. Cerebral causes were the final cause of death in 51.1% of maternal deaths.

1.3 Risk Factors

Several risk factors have been identified with an increased risk of preeclampsia.

1.3.1 Familial Factors

A familial history of preeclampsia increases the risk of preeclampsia substantially and women whose mothers had preeclampsia are more than likely to have preeclampsia [11]. Males who fathered a pregnancy complicated preeclampsia are more likely to father another pregnancy complicated by preeclampsia in another woman [12].

1.3.2 Sperm Exposure

Preeclampsia often affects young and nulliparous women, whereas older women are at greater risk for chronic hypertension with super imposed preeclampsia. Nulliparous women have a three-fold increased risk of developing preeclampsia as compared with multiparous women [13]. The primiparternity hypothesis suggests that the risks of preeclampsia are increased among women who have limited exposure to their partner's sperm [14]. Data in support of this hypothesis includes lower risks of preeclampsia among multiparous women, among women who have had a previous pregnancy loss and following a prolonged pre-pregnancy conception and those who change partners. A prolonged birthing interval is the alternative explanation offered for the latter phenomenon [15], though the evidence for this observation has been disputed [16].

1.3.3 Obesity

Obesity is a definite risk factor for preeclampsia and the risk increases with a greater body mass index. Obesity has a strong link with insulin resistance, which is a risk factor for preeclampsia however; the exact mechanisms by which obesity and insulin resistance is associated with preeclampsia are poorly understood [17]. Possible explanations are increased shear vascular stress, associated with a hyper dynamic circulation; dyslipidaemia or enhanced cytokine mediated oxidative stress; amplified sympathetic activity and increased tubular sodium resorption; and direct interference of insulin resistance and thus a hyperinsulinaemic state with placentation.

1.3.4 Co-morbid Conditions

Women with gestational diabetes, insulin-dependent or non-insulin dependent diabetes and chronic hypertension are at higher risk of preeclampsia [23]. Studies have also shown that women with anti-phospholipid syndrome [18], thrombophilia, autoimmune disease, renal disease, and infertility [19] are at significantly higher risk of developing preeclampsia.

1.3.5 Smoking

Numerous studies have shown that smoking reduces preeclampsia occurrence by approximately 50% in a dose-dependent manner [20]. This observation however has not been validated with snuff use. Women who are chronic smokers, those who smoke in early pregnancy and stop, do not have a reduced risk, whereas those who start smoking in late pregnancy and those who smoke throughout pregnancy are protected [21], however smoking is associated with unfavourable fetal outcomes in pregnancies complicated by preeclampsia. This data suggest that, although generally harmful in terms of pregnancy outcomes, the combustion products of tobacco have a protective effect in late pregnancy.

1.3.6 Previous Preeclampsia

Preeclampsia in a previous pregnancy is a strong predictor of preeclampsia in a subsequent pregnancy. The risk of recurrence is about 14% [24]. Odegard et al reported an even higher risk, with a 20 fold increase in preeclampsia risk compared with parous women with no previous preeclampsia [22]. In a large review of risk factors for preeclampsia, Duckitt and Harrington [23] reported a seven fold increased risk in women with previous preeclampsia compared with women without previous preeclampsia. Interestingly the recurrence was inversely related to the gestational age at the initial confinement according to Mostello et al [24].

1.3.7 Heterogeneous Factors

Extremes of age, multiple pregnancy and periodontal infections [25] have also been shown to increase the risk of preeclampsia. Chronic oral infections have been implicated as causative agents in variety of systemic illnesses including atherosclerotic cardiovascular disease and cerebrovascular ischaemia. Periodontal disease, a chronic gram negative infection has been associated with atherosclerosis, thromboembolic events and hypercholesterolemia [26-28]. Oral pathogens have been detected in atherosclerotic plaques, where they can play a role in the development and progression of atherosclerosis leading to coronary vascular disease [29]. Periodontal disease may provide a chronic burden of endotoxin and inflammatory cytokines, which serve to initiate and exacerbate atherogenesis and thrombogenesis. It is possible that the placenta may be similarly burdened in pregnant women who develop preeclampsia.

In a matched case control study of 41 preeclamptic women and 41 normotensive healthy pregnant women, Canakci and colleagues found and an association between periodontal disease and risk of developing preeclampsia [30].

1.4 Definition of Hypertension in Pregnancy

Normal pregnancy is characterised by a fall in blood pressure, detectable in the first trimester usually reaching a nadir in the second trimester. Blood pressure rises towards pre- conception levels towards the end of the third trimester. Hypertension in pregnancy is defined as a systolic blood pressure greater than or equal to (≥) 140 mmHg and a diastolic blood pressure greater or equal to (≥) 90 mmHg [31]. These readings should be confirmed by repeated readings over several hours.

The classification of hypertensive disorders in pregnancy reflects the pathophysiology of the constituent conditions as well as the risks and potential outcomes for both mother and baby. Several classification systems have been suggested over many years. The International Society for the Study of Hypertension in Pregnancy (ISSHP) has adopted the classifications proposed by the Australasian Society for the Study of Hypertension in Pregnancy (ASSHP) and the National High Blood Pressure Education Programme (NHBPEP) in the USA [31].

The classification is as follows:

- Preeclampsia-eclampsia
- Gestational hypertension
- Chronic hypertension (Essential or Chronic)
- Preeclampsia superimposed on chronic hypertension

1.4.1 Diagnosis of Preeclampsia

For purposes of this study we shall use the classification adopted by the ISSHP [31], the definitions of which are based on original work done by Davey and MacGillivray.

Preeclampsia

It is High Blood Pressure of 140/90mmHg or more on two separate occasions measured at least four hours apart, arising de novo after 20 weeks gestation in a woman with previously normal blood pressure accompanied by proteinuria, defined as urinary excretion of ≥300mg/24hrs. If 24-hour urine collection is not available, then proteinuria is defined as a concentration of at least 30mg/dl or at least 1+ on urinary dipstick [3].

Severe Preeclampsia is accompanied by one of the following:

- With the patient at rest, a blood pressure reading of at least 160 mmHg systolic or 110 mmHg diastolic, on two occasions at least four to six hours apart
- Renal insufficiency as evidenced by a plasma creatinine of 90μmol/l and oliguria i.e. 400ml/24hrs
- Liver disease (elevated transaminases, severe right upper quadrant pain or epigastric pain with or without sub-capsular haematoma)
- Neurological disturbances: severe headaches, persistent visual disturbances, hyper-reflexia with clonus and convulsion (eclampsia)
- Haematological disturbances: thrombocytopenia, haemolysis and disseminated intravascular coagulation
- Intra-uterine growth restriction.

Oedema is not included in the diagnostic criteria of preeclampsia. It is a common feature of normal pregnancy and severe preeclampsia may be present in the absence of any oedema. Nevertheless rapid development of generalised oedema should alert the clinician to screen for preeclampsia. Rarer disorders may present with some features of preeclampsia. Disorders such as acute fatty liver of pregnancy, haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura may need to be excluded. Rarely preeclampsia presents before 20 weeks gestation, usually in the presence of a predisposing factors such as hydatidiform mole; multiple pregnancy, fetal triploidy and severe renal disease.

1.4.2 Measuring Blood Pressure

It is generally known that measurement of blood pressure is fraught with error. Mercury sphygmomanometry remains the gold standard; however this has largely been replaced by aneroid and automated machines. These machines, although easy to use, have inherent problems pertaining to validation. For example aneroid machines require calibration every 6 -12 months and their accuracy may deteriorate with time.

According to the Working Group, the diastolic blood pressure is that at which the sound disappears (Korotkoff 5). In order to minimise inaccurate readings, an appropriate size cuff should be used (length 1.5 times upper arm circumference or a cuff with bladder encircling 80% or more of the arm) [31].

The pregnant patient should be seated, with feet supported for 2-3 minutes. Systolic blood pressure should be palpated at the brachial artery and cuff inflated to 20 mmHg above this level. The blood pressure cuff should be deflated slowly, at approximately

2mmHg per second. The systolic blood pressure is accepted as the first sound heard (K1) and diastolic as (K5).

1.4.3 Proteinuria

New onset proteinuria in pregnancy complicated by hypertension has formed the basis of the clinical diagnosis of preeclampsia for many years, and is included in all international guidelines; however the SOMANZ group does not define the necessity to have proteinuria to make the clinical diagnosis of preeclampsia. In non-gravid women, abnormal total protein is defined as protein excretion greater than 150mg/day. In normal pregnancy, urinary protein excretion increases substantially, secondary to increased glomerular filtration rate and increased permeability of the glomerular basement membrane. Hence a total protein excretion in excess of 300mg/day is considered abnormal in pregnancy.

In most settings a dipstick is used to assess proteinuria, although inexpensive and commonly used, it has a significantly high false positive and false negative rate. Inaccuracies have also been identified with the 24 hour urine collection method, prompting use of alternative methods of measuring proteinuria in hypertensive pregnancies. The spot urine protein-creatinine ratio has been endorsed by both ISSHP [26] and NICE [32] as an acceptable method for assessment of proteinuria in pregnancy. A spot PCR cut off level of 30mg/mmol equates to a 24hr urine protein of > 300mg/day and has therefore been defined as significant in diagnosing preeclampsia. Current evidence suggests that the severity of proteinuria is not indicative of the severity of preeclampsia and thus should not be used to guide management. Although part of diagnostic criteria of preeclampsia, proteinuria may be absent. Data has shown that

10% of women with clinical manifestations of preeclampsia have no proteinuria and 20% of eclamptic women do not have significant proteinuria prior to their eclamptic fit [33-41].

1.5 Prediction of Preeclampsia

Despite an intensive research effort to elucidate the origins of preeclampsia, there is currently no well validated effective method of identifying women at risk. There are certain at-risk groups of patients such as those with chronic hypertension, pre-gestational diabetes, multi-fetal gestations and previous pre-eclampsia. These patients account for the majority of cases of preeclampsia in multiparous women, yet only account for 14% of preeclampsia in nulliparous women. Thus, the majority of cases of preeclampsia arise from nulliparous women without medical complications.

Prediction of risk will ideally identify patients for more careful monitoring but may also identify a population that is highly suited for research into aetiology of preeclampsia and for potential treatment and prevention. Many tests have been assessed for their relation to placental perfusion, vascular resistance, placental products, endothelial dysfunction, oxidative stress and fetal derived products. Of 27 tests reviewed by Meads and colleagues [42], only a few reached specifications above 90%. These were BMI of 34kg/m² or higher, α-fetoprotein and bilateral uterine artery Doppler notching. Sensitivity of higher than 60% was achieved only by uterine artery Doppler resistance index and combination of indices [43]

Logistic regression analysis combining information on uterine artery pulsatility index, mean arterial pressures, serum PPAP-A, serum free PGF, BMI and presence of nulliparity or previous preeclampsia showed promising high sensitivity and specificity in prediction of early preeclampsia [44].

1.6 Prevention of preeclampsia

Many therapeutic interventions have been trialled with a pattern of outcomes being similar, with initial small trials showing promising results followed by disappointing outcomes in larger studies.

Prevention of a disease can either be primary, secondary or tertiary. Primary prevention implies avoiding the emergence of disease, secondary prevention entails halting the disease process prior to emergence of clinically recognisable disease and tertiary prevention means prevention of complications caused by the disease.

1.6.1 Primary Prevention

It has proved to be a monumental task to prevent emergence of preeclampsia. We now know that poor endovascular cytotrophoblast invasion of the spiral arteries; an exaggerated inflammatory response and inappropriate endothelial cell activation are instrumental in the pathogenesis of preeclampsia [45]. Therefore contraception is currently the most effective and reliable method of preventing preeclampsia in high risk patients. However numerous risk factors have been recognized, consequently manipulation of some of them may allow primary prevention. Obesity is a definite and a modifiable risk factor for developing preeclampsia and gestational hypertension. In a cohort study of 878 680 pregnancies, Conde-Agudelo and Belizan found that the frequency of preeclampsia for lean women (BMI<19.8) was 2.6% versus 10.1% in obese women (BMI>29.0) [46]. Although the exact mechanisms by which obesity is associated with an increase in preeclampsia are poorly understood, possible explanations are: increased shear stress due to hyper dynamic circulation associated

with obesity, dyslipidaemia or increased cytokine- mediated oxidative stress and direct haemodynamic effects of hyperinsulinaemia (increased tubular sodium resorption and increased sympathetic activity). Global increase in obesity is most likely causes a rise in the incidence of preeclampsia, thus prevention or effective treatment of obesity could result in a substantial decline in the frequency of preeclampsia.

Cigarette smoking is associated with an approximate 30-40% decline in the risk of preeclampsia. Nevertheless, this benefit is negated by the adverse effects of smoking on the growing fetus, risk of an abruption and cardiovascular risks. An understanding of how smoking prevents preeclampsia could help unravel crucial aspects of its pathophysiology.

1.6.2 Secondary Prevention

Current strategies focus largely on pharmacological therapy, dietary interventions and lifestyle modification.

I. Aspirin

Inflammation plays an important role in the pathogenesis of preeclampsia; investigators have studied the role of aspirin in prevention and treatment of preeclampsia using this model. Alterations in the balance of thromboxane A2 and prostacyclin, along with platelet activation and endothelial dysfunction, provide the rational for aspirin use as a preventative modality. Duley et al. performed a meta-analysis of 59 randomised controlled trials, which included 37,560 women and reported on the effectiveness of anti-platelet agents in preventing preeclampsia [47]. It showed that anti-platelet agents reduced the risk of preeclampsia by 17% (RR 0.83; 95% CI 0.77-0.89), with 72 women

needing treatment to benefit one woman. While there was no statistical difference in relative risk (RR) based on maternal risks, there was a considerable increase in absolute risk reduction of preeclampsia for high risk compared to low risk women. In addition anti-platelet agents were associated with an 8% reduction in risk of preterm birth (29 trials, 31 151 women, RR 0.92, 95% CI 0.88 - 0.97); NNT 72. A further 14% reduction in fetal and neonatal death was noted from 40 trials, involving 33 098 women, RR 0.86, (95% CI 0.76 to 0.98); NNT 243. In addition, Duley and co-workers observed a 10% reduction in small for gestational age babies in 36 trials, involving 23 638 women, RR 0.90, (95% CI 0.83 to 0.98).

Commencing aspirin early in pregnancy was associated with a greater reduction in the incidence of preeclampsia than treatment beginning in later in pregnancy. The RR for preventing preeclampsia was 0.47 (95% CI 0.34 - 0.65) for aspirin started before 16 weeks, and 0.81 (95% CI 0.63 - 1.03) started after 16 weeks of gestation [48]. Analysis of optimal dosage of the drug by the National Institute of Health and Clinical Excellence Guideline showed that 75mg of aspirin is the optimal dosage for prevention of preeclampsia - the increase in benefit was not observed for higher doses [32]. Current NICE Guidelines recommend high risk women take 75mg of aspirin daily from 12 weeks of gestation until birth of the baby.

Other agents like nitric oxide donors, LMWH, progesterone, diuretics and anti-hypertensive for mild and moderate hypertension have been considered however there is insufficient evidence to recommend their routine clinical use for prevention of preeclampsia.

II. Calcium

Women with high intake of calcium have been observed to have a low incidence of hypertensive disorders of pregnancy [49]. This has led to the hypothesis that an increase in calcium intake might actually reduce the incidence of preeclampsia, especially in women with sub-optimal calcium intake. Calcium acts by reducing smooth muscle contractility and therefore vasoconstriction by its effect on the parathyroid gland and intracellular calcium. It might also have an indirect effect on smooth muscle function by increasing magnesium levels. Carroli et al have recently shown that calcium affects uteroplacental blood flow by reducing resistance in the uterine and umbilical vasculature [50].

Hofmeyr et al. carried out a systematic review of 13 RCTs (15 730 women) and assessed the effectiveness of calcium supplementation in preventing preeclampsia [51]. Approximately two thirds of women had a low dietary calcium intake (10 678 women) and 587 women were at high risk of developing hypertensive disorders of pregnancy, i.e. teenagers, women with previous preeclampsia, women with increased sensitivity to angiotensin two and women with pre-existing hypertension. Calcium was effective in preventing preeclampsia (RR 0.45; 95% CI 0.31 - 0.65). The beneficial effects were largely observed in the high risk group (RR 0.21; 95% CI 0.12 - 0.42) and in the group with low nutritional calcium intake (RR 0.36; 95% CI 0.20 - 0.65). The subgroup analysis of women with optimal dietary calcium intake showed no significant effect on the incidence of preeclampsia. A recommended daily dose of 1.5 to 2g of calcium reduces the incidence of preeclampsia in high risk women and women with low dietary calcium intake.

III. Anti-oxidants

Data has shown that placental development in preeclampsia leads to reduced placental perfusion, and mediates a state of oxidative stress. Two naturally occurring anti-oxidants (Vitamin C and E) may reduce such oxidation, thus protecting proteins and enzymes from destruction by free radicals.

A systemic review by Rumbold et al. which included nine trials (5 446 women), evaluated the effectiveness of anti-oxidants for prevention of preeclampsia. No evidence was found to suggest that anti-oxidants prevent preeclampsia [52]

IV. Marine oil

Fish oils are a rich source of omega 3 fatty acids i.e. eicosapentaenoic acid and docosahexaenoic acid. These fatty acids are precursors of 3 series prostaglandins and have been shown to modulate inflammatory and vascular effects preeclampsia. Since preeclampsia and gestational hypertension are associated with vasoconstriction and endothelial damage, it is likely that marine oil fatty acids, especially eicosapentaenoic acid, can regulate these responses through direct competition with thromboxane A2 precursor, arachidonic acid.

Other agents such as evening primrose oil contain gamma linoleic acid which is a precursor of 1 series prostaglandins. These prostaglandins have the same mode of action as those derived from omega 3 fatty acids.

In a meta-analysis by Makrides et al, six trials involving 2783 were reviewed. Of the six randomised controlled trials, four (1683 women) comparing marine oil or evening primrose oil with placebo, did not show a reduction in preeclampsia [53]. The authors

concluded that evidence is lacking to support routine use of marine oil or evening primrose oil supplements during pregnancy to reduce the risk of preeclampsia.

V. Lifestyle modification

Preconception counselling in high risk women may offer the opportunity to optimise health. Women with diabetes and one factor of maternal vascular disease (diabetic retinopathy; diabetic nephropathy and pre-existing hypertension) have a 25% risk of developing preeclampsia and intra-uterine growth restriction (IUGR). Howarth et al reports that good glycaemic control modifies this risk [54]. Obesity is known to be a risk factor for both gestational hypertension and preeclampsia; in comparison with women of BMI 20-29.4; morbidly obese women (BMI>35) faced the highest risk of preeclampsia {Odds ratio (OR) 7.2} [55]. Weight loss in overweight and obese women before pregnancy may modify these risk factors including associated adverse outcomes.

There is currently no evidence to demonstrate that lifestyle interventions, such as rest, exercise and dietary salt restriction prevent preeclampsia.

1.6.3 Tertiary prevention

By far the most important part of tertiary prevention is without a doubt, proper antenatal care programmes. The aim of treating a pregnant woman is the prevention of complications. There is a consensus that drug treatment of severe hypertension is necessary and beneficial. The more concerning issues are the roles of pharmacological treatment for conservative management in severe preeclampsia aimed at prolongation of pregnancy, the ability of treatment to modify the course of the disease and the effect on fetal and maternal outcome [56]. The tertiary prevention of pre-eclampsia shall be addressed in the section on the management of the condition.

1.7 Management of severe preeclampsia

Maternal and neonatal morbidity and mortality associated with hypertensive crises may have significant consequences. An important consideration is early involvement of senior obstetric and anaesthetic staff and experienced midwives in the assessment and management of women with severe preeclampsia. Up to 70% of all severely preeclamptic patients admitted to a critical care unit develop multi-organ dysfunction. Maternal complications associated with preeclampsia include eclampsia (<1%), HELLP syndrome (10-25%), acute kidney injury (AKI) (1-5%), pulmonary oedema (2-5%) and placental abruption (1-4%). The fetus may be small for gestational age with decreased fetal movements and decreased amniotic fluid volume. Severe preeclampsia is a significant risk factor for intrauterine fetal demise, with an estimated stillbirth rate of 21/1000 [57]. Further, preterm delivery increases risks of neonatal death and serious morbidity from prematurity.

The basic management objectives of pregnancy complicated by preeclampsia are:

- Termination of pregnancy with the least possible trauma to the mother and fetus
- Birth of an infant who subsequently thrives
- Complete restoration of health to the mother

1.7.1. Antepartum management

Initial assessment is aimed at classifying the severity of disease, the gestational age of the fetus and whether or not the patient is a candidate for expectant management. Once the diagnosis is made, the definitive treatment is delivery to prevent maternal or fetal complications from disease progression. The decision to deliver is based on gestational age, severity of the disease and maternal and fetal conditions. Evidence of severe maternal end-organ dysfunction or non-reassuring tests of fetal wellbeing are indications for prompt delivery irrespective of gestational age.

Patients who are beyond 37 weeks gestation are delivered after stabilisation, however prior to term, the risks of adverse outcomes from disease progression need to be balanced against the risks of preterm birth. Alternatively, when the mother and fetus are stable and without complications, a conservative approach with close surveillance for evidence of disease progression is reasonable in order to gain fetal growth and lung maturity.

On admission evaluation should include a full blood count (FBC), liver transaminases (AST and ALT), renal function (urea and creatinine), 24 hour urine collection or a spot protein creatinine ratio (PCR). Additional tests, where indicated, may include lactate dehydrogenase (LDH) level and a peripheral smear to exclude microangiopathic haemolysis and platelet destruction.

1.7.1.1. Blood pressure control

Women with preeclampsia should be stabilised prior to delivery. It is important to take the blood pressure with a cuff of appropriate size. Korotkoff phase 5 is the appropriate measurement of diastolic blood pressure and manual aneroid sphygmomanometer is preferable.

Targeting a systolic blood pressure (SBP) of <140-150mmHg and diastolic blood pressure (DBP) of 80-90mmHg minimises the risk of haemorrhagic stroke, as auto-regulation is impaired when the mean arterial pressure (MAP) exceeds 145mmHg. Rapid reduction of SBP should be avoided; it may result in acute hypoperfusion and ischaemia of vital organs. Blood pressure should be checked every 15 minutes until the patient is stabilised. Most women can be managed with oral therapy alone, common therapeutic agents being labetalol, nifedipine, hydralazine and methyldopa.

I. Labetalol

Labetalol is an alpha and beta adrenoceptor blocker with greater sensitivity for β receptors. It reduces blood pressure almost immediately, primarily by vasodilatation and reduction of heart rate at high doses. Unlike conventional vasodilators, it is not associated with maternal tachycardia and can be given orally or intravenously as an infusion. Compared to hydralazine, labetalol is as good as or more effective in reducing blood pressure [58] and does not affect uterine function. Labetalol should be avoided, if possible, in women with known asthma. Labetalol is an ideal drug when hypertension is associated with tachycardia or myocardial ischaemia.

II. Nifedipine

Nifedipine is a commonly used second-line antihypertensive agent and is a calcium channel blocker that results in vascular smooth muscle relaxation and vasodilatation. Only slow release preparations should be used. In particular, sublingual nifedipine may cause a precipitous drop in maternal blood pressure and thus should be avoided. Slow release nifedipine is used orally and blood pressure usually falls within 30 minutes of oral administration.

III. Methyldopa

This drug is a centrally acting oral antihypertensive. Due to its good safety profile, it is often used as a first line antihypertensive agent. However studies have suggested superior benefits of labetalol over methyldopa. Occasionally, methyldopa is associated maternal transaminitis or a positive Coomb's test.

IV. Hydralazine

Hydralazine acts directly on vascular smooth muscle to cause vasodilatation. Although evidence is not strong enough to preclude its use, it has largely been superseded by labetalol. Magee and colleagues conducted a meta-analysis of 21 trials (893); eight compared hydralazine with nifedipine, and five compared hydralazine with labetalol [59]. Hydralazine was associated with significantly higher maternal side effects and worse maternal and perinatal outcomes than either labetalol or nifedipine.

V. Angiotensin converting enzyme inhibitors

ACE-1, when used in the second and third trimester, has been associated with renal dysfunction in the fetus, leading to oligohydramnios and anuria. ACE-I have also been associated with pulmonary hypoplasia, fetal growth restriction and hypoplasia of the fetal skull. Therefore this class of antihypertensive medication is absolutely contraindicated in pregnancy due to its teratogenic effects on the developing fetus.

1.7.1.2 Fluid management

Pulmonary oedema is a common cause of maternal death, often being associated with inappropriate fluid management. Therefore accurate assessment of fluid balance is important to avoid iatrogenic pulmonary oedema. A systematic review by Duley et al. published in 2000; discourages fluid expansion and demonstrates that this confers good maternal outcomes [60]. Total fluids should be limited to 80ml/hr or 1ml/kg/hr. Urine output should be measured as part of input/output assessment and fluid restriction should be maintained until there is post-partum diuresis, at least 05ml-1ml/kg/hr.

1.7.1.3 Thromboprophylaxis

Preeclampsia is a significant risk factor for thrombosis, particularly in the presence of additional risk factors such as obesity, age above 35 years, previous thrombotic event, and family history of thrombosis, nephrotic range proteinuria and immobility in the ward. Antenatally, in labour and postnatally, all patients should have thromboprophylaxis in the form of graduated compression stockings, with or without low molecular weight heparin until they regain mobility. Heparin administration is not a contraindication to the insertion of an epidural catheter. However low molecular weight heparin should not be given until two hours after epidural anaesthesia and an epidural catheter should not be removed until 10 hours after the last dose, because of the risk of an epidural haematoma.

1.7.1.4 Fetal assessment

After initial clinical assessment, fetal condition should include a non-stress test, umbilical artery Doppler waveform estimation, measurement of fetal growth and amniotic fluid volume index should be carried out. If immediate delivery is not imminent, and it is anticipated that there will be time for fetal benefit, antenatal corticosteroid should be administered regardless of a plan for expectant management. Randomised controlled trials involving pregnancies complicated by severe preeclampsia have found ante natal corticosteroid treatment to result in less respiratory distress syndrome (RR 0.50; 95% CI 0.35-0.72), intra-ventricular haemorrhage (RR 0.38; CI 0.17-0.87) and neonatal death (RR 0.50; CI 0.29-0.87) [61].

1.7.1.5. Timing of delivery

The clinical course of severe preeclampsia is almost invariably a progressive deterioration in both maternal and fetal condition. Historically, a diagnosis of preeclampsia resulted in immediate delivery, either by induction of labour or caesarean section, to prevent further maternal morbidity and mortality.

Table 1 Maternal indication for expeditious delivery in severely preeclamptic women

Uncontrolled severe hypertension (BP ≥ 160mmHg systolic or ≥ 110mmHg diastolic) despite maximum doses of at least two antihypertensive agents
Eclampsia
Pulmonary Edema
Abruption placentae
Oliguria (<0.5ml/kg/hr) that does not respond to fluid intake
Imminent eclampsia
HELLP syndrome with platelets < 100 000/µl
Deteriorating renal function (serum creatinine ≥ 100µmol/l

Currently, in women with preterm severe preeclampsia the decision-making process has become slightly more complex and delivery may be delayed following assessment of maternal and fetal well-being, gestational age, and available supportive services for both mother and neonate.

The only intervention known to date that can halt further progression of preeclampsia is delivery of both fetus and the placenta, as a result, delivery will always benefit the mother and rarely benefit the fetus. Most authorities agree that in the extremes of prematurity (24-30 weeks), if at all possible, delivery should be deferred at least long enough to administer corticosteroid therapy.

Table 2 Fetal indications for expeditious delivery in severe preeclamptic women

Repetitive late decelerations
Severe variable decelerations
Decreased short term variability (<3 bpm)
Biophysical profile ≤ 4on two occasions at least four hours apart
Severe oligohydramnios

Thus expectant management of severe preeclampsia may be considered in preterm pregnancies where the maternal condition is stable and fetal status is reassuring. However delivery is recommended in the presence of multi- organ dysfunction, fetal compromise or once a gestation of 32-34 weeks has been reached.

1.7.1.6. Role of Doppler Velocimetry

The use of has been studied extensively in the IUGR fetus and patients with underlying medical diseases, in particular hypertensive disease of pregnancy. It is considered a primary tool for assessment of feto-maternal vascular status and management of pregnancy at risk of IUGR. Most of the work has been done in preterm pregnancies, with a focus on umbilical and middle cerebral arteries and the venous system. Absent or reverse flow in the umbilical artery is associated with approximately 60%-70% obliteration of placental arteries, rates of 50%-80% of intra-uterine hypoxemia, and an 80-fold increased risk of perinatal mortality [62, 63, 64, 65, 66].

Several meta-analyses have demonstrated that use of umbilical Doppler Velocimetry in conjunction with standard antenatal testing reduces the rate of fetal demise [67, 68, 69]. Through studies, such as those by Rizzo et al [70] and Hecher et al [71], it has become apparent that reverse venous flow in the ductus venosus and inferior vena cava during atrial contraction is most reflective of fetal metabolic acidosis. Several studies that have investigated venous Doppler changes and biophysical testing in severely growth restricted foetuses found that venous Doppler changes, especially ductus venosus, precede biophysical profile and fetal heart rate abnormalities. Thus it has been proposed that abnormal venous Doppler findings should be used to prompt delivery of the growth restricted fetus [72, 73, 74]. Doppler triggers for delivery, need to be reconciled with the gestational age, because gestational age is the strongest predictor of survival at least until 29 weeks' gestation [73, 75]. Unfortunately, data regarding Doppler blood flow in pregnancies beyond 34 weeks gestation are limited for two reasons: (1) the overwhelming majority of fetal vascular Doppler studies have been

done on fetuses less than 34 weeks of gestation, and (2) umbilical artery Doppler is less reliable after 34 weeks.

1.7.2 Intrapartum Management

A diagnosis of preeclampsia should initiate two important management goals:

1. Control blood pressure and
2. Prevention of eclampsia.

It is well established that treatment of severe hypertension will prevent cerebrovascular accidents and cardiovascular complications [2, 3]. Continuous maternal and fetal monitoring is indicated to identify worsening hypertension, deteriorating maternal hepatic, renal, cardiopulmonary, and neurological or haematological function as well as non-reassuring fetal heart traces.

1.7.3 Prevention of convulsions

Different therapies to prevent eclamptic convulsions in the setting of severe preeclampsia have been well studied. However, magnesium sulphate remains the drug of choice for seizure prophylaxis and for controlling seizures in eclampsia. The MAGPIE Trial in 2002 was a randomised, placebo-controlled trial that compared intravenous magnesium sulphate with placebo [76]. The study enrolled 10 141 women with preeclampsia from 33 countries and found that magnesium sulphate given as a 4g intravenous loading dose and 1g/hr maintenance dose significantly reduced the risk of eclampsia by half, thus reducing the risk of maternal death. Another study by Belfort et al. conducted in 2003 on 1650 women, which compared magnesium sulphate with nimodipine for seizure prophylaxis in women with severe preeclampsia, concluded that

magnesium sulphate was more effective than nimodipine (2.6% versus 0.8%, p=0.01) for seizure prophylaxis [77].

A randomised controlled trial in 1995 of 2138 women compared phenytoin and magnesium sulphate for prevention of eclamptic convulsions in pregnant women with hypertension [78]. The results noted that 10 of 1098 women randomly assigned to phenytoin had eclamptic convulsions compared to none of the 1049 women assigned to magnesium sulphate. The study concluded that magnesium sulphate was superior to phenytoin when given prophylactically for eclamptic seizure for women with peripartum hypertension. A meta-analysis by Duley in 2010 reviewed 15 trials comparing magnesium sulphate and other anticonvulsants for women with preeclampsia. The meta-analysis concluded that magnesium sulphate was superior to placebo, phenytoin and nimodipine; in addition it more than halved the risk of eclampsia [79].

1.7.4 Anaesthetic considerations

Whenever possible an anaesthetist should be informed about a woman with severe preeclampsia prior to labour or operative delivery, because appropriate anaesthetic management is associated with a reduction in both fetal and maternal morbidity and mortality [80].

Relevant issues to be addressed include risk assessment, blood pressure control, fluid management, eclampsia prophylaxis and planning of a choice analgesia or anaesthesia [81, 82, 83]

1.8 Postpartum management

During the immediate postpartum period, women with preeclampsia should receive close monitoring of blood pressure, symptoms consistent with severe disease and accurate measurements of fluid intake and output. Any laboratory test abnormalities or physical finding that has not returned to normal before post-delivery discharge should be reassessed at postpartum follow-up.

The expectation is that hypertension and other signs or symptoms of organ dysfunction associated with preeclampsia will have remitted by the 6-week postpartum examination; if abnormalities persist, however, the patient should be re-examined again six weeks later, when any persisting pathological conditions will probably be chronic and appropriate referral should be made.

1.8.1 Counselling regarding future pregnancies

Women who experience pregnancies affected with hypertensive disorders have an increased risk of recurrence in subsequent pregnancies. The estimate of this risk was recently defined using the current definitions in a study from Finland of 895 women [84]. Depending on the diagnosis in the initial pregnancy, there is 58% to 94%recurrence risk of some type of hypertensive disorder in the second pregnancy. There is a higher risk of recurrence of hypertensive disorder in the next pregnancy if the diagnosis was made before 34-weeks of pregnancy, the patient is overweight or a significant weight gain between pregnancies. This will direct future counselling and impetus for a healthy lifestyle after pregnancy.

Thus it is advisable to counsel women at their 6-week postpartum visit about these future risks, to begin discussing the plan for maintaining a healthier diet and exercise habits as they had during pregnancy, and helping transition to a primary care provider who can further guide their interpregnancy health habits. Such patients should be advised to seek out a preconception consultation as well. To facilitate such consultations, the intra uterine devise is a great form of contraception as it requires a clinician visit for removal to become pregnant.

2. Problem Statement

Preeclampsia, a human-specific disease is defined as the occurrence of hypertension and or proteinuria in a previously normal woman on or after 20th week of gestation; associated with significant maternal, fetal and neonatal morbidity and mortality. It is the most common medical complication of pregnancy whose incidence continues to increase both in South Africa and worldwide.

Because preeclampsia is a progressive disorder, in some circumstances, delivery is a necessity to halt disease progression to benefit the mother and the fetus. However the need for premature delivery has adverse effects on important neonatal outcomes not limited to the most premature infants.

The obstetrics protocol used in the Department of Obstetrics and Gynaecology of the University of the Witwatersrand is for management only. Outcomes have not previously been described for severe preeclampsia at gestations less than 34 weeks (remote from term), hence the need for this study.

2.1. Objectives

I. To determine outcomes of infants born preterm (26 weeks gestation to 34 weeks gestation) to mothers with severe preeclampsia

II. To determine maternal morbidity and mortality in women with severe preeclampsia

2.2 Methods

2.2. 1 Setting

The study took place at the three central referral hospitals affiliated to the University of the Witwatersrand namely: Charlotte Maxeke Johannesburg Academic Hospital, Chris Hani Baragwanath Academic Hospital and Rahima Moosa Mother and Child Hospital.

2.2.2 Study Population

The study recruited all women with severe preeclampsia between the 26 and 34 weeks of gestation or with a fetus weighing 500g or more on ultrasound assessment. Definitions, classifications and complications used were those adopted by the University of the Witwatersrand Department of Obstetrics and Gynaecology.

2.2.3 Study Design and Data Collection

This was a prospective, descriptive study of severely preeclamptic women presenting at 3 three academic hospitals with pregnancies remote from term. The study also followed up their babies for a period of three days during admission. All women were counselled prior to data collection and were invited to participate in the research. A consent form and an assent form in case of a minor were provided before data could be collected. Where maternal information was not readily available, it was obtained on admission and neonatal information was gathered from the neonatal ward and maternal registry book.

2.2.4 Sample Size

All patients who met the criteria of severe preeclampsia and consented to participate were recruited into the study conducted over one calendar year: 01 June 2012 to 30 June 2013. During this time period 92 women were recruited. The sample size could potentially have been larger, however, some patients were missed as the data was not collected on consecutive days, Often patients declined to participate in the study and the most limiting factor was missing data which from maternity registry booklets.

2.2.5 Inclusion criteria

This study included women, who were diagnosed with severe preeclampsia, between 26 weeks and 34 weeks of gestation at delivery.

2.2.6 Data management

An antenatal card provided the patient's demographics, booking weight and height, blood pressure measurement, urine analysis, booking haemoglobin, rhesus status, syphilis and an HIV test result. At the clinics rapid test kits are generally used to test for syphilis and HIV. Blood pressure measurements at the three referral centres were obtained using an automated blood pressure machine. Blood pressure readings were routinely taken with patients in a supine position and urine protein estimation done using urinary dipstick. All bloods obtained for investigation were sent to the National Health Laboratory Service at the respective hospitals, where reference ranges for respective bloods have been standardised for the general population and pregnancy.

Laboratory variables

Test	Reference Range
Haemoglobin	12.1-16.3 g/dl
Platelets	150-400*10^9/l
Urea	2.1-7.1 mmol/l
Creatinine	49-90 µmol.l
AST	13-35 U/l
ALT	7-35 U/l

Data was entered into a Microsoft Excel spread sheet and then exported to the STATA 11 statistical software package. Descriptive data were expressed as means with standard deviations, and medians with ranges.

2.2.7 Ethics

Ethics approval was granted by the University of the Witwatersrand ethics committee (HREC) and permission to access patients was granted by the CEOs of the three respective hospitals, consent forms attached in appendix section.

2.2.8 Funding

The study was funded by the researcher.

2.3. Definitions used in the study (Adapted from Williams Obstetrics 23ed, 2011

- **Imminent eclampsia** defined as acute hypertensive crisis, characterised by sudden rise in blood pressure, severe frontal headaches, visual disturbance and epigastric pain.

- **HELLP** syndrome is characterised by haemolysis, elevated liver enzymes, low platelets and haemolysis. In addition AST≥70IU/L, platelet count less than 100,000cells/ µl and characteristic schistocytes, also called helmet cells on a peripheral blood smear.
- **Proteinuria** is defined as ≥ 0.3g of protein in a 24 hour urine specimen or a persistent 1+ (20mg/l) on dipstick or a random protein: creatinine ratio >0.3. **Eclampsia** defined as new onset of convulsions in women with either gestational hypertension or preeclampsia.
- **Placental abruption** defined as premature separation of a normally situated placenta. It can either be concealed or revealed.
- **Disseminated intravascular coagulation** defined as a pathological process produced by stimulation of coagulation activity, leading to consumption of clotting factors and platelets, leading to defective clotting.
- **Acute renal failure** defines as an abrupt decrease in glomerular filtration rate, with serum creatinine of 100µmol/l, urea ≥ 5mmol/l and urine output less than 400ml/24hours.
- **Stillbirth** defined as a baby born dead after 28 weeks of intra- uterine life or with a mass of 1000g or more.
- **Neonatal death** has 2 definitions: early neonatal death which occurs within six days of life and late neonatal death occurring from the seventh day of life up to twenty eight days from birth.
- **Birth asphyxia** is a syndrome characterised by disturbed neurologic function in the earliest hours to days of life, manifested by:

- Apgar score of less than five at five minutes and at ten minutes;
- Fetal umbilical artery academia: fetal umbilical pH<7.0 or a base deficit ≥12mmol/l and often
- Accompanied by difficulty initiating and maintaining respiration, and by depression of tone and reflexes.

3. Results

3.1 Demographic data

Ninety-two women diagnosed with severe preeclampsia from 01 June 2012 to 31 May 2013, having matched the inclusion criteria were recruited to the study and their records analysed. Table 3 indicates age ranges of women with severe preeclampsia. The mean age for women was 29.5 ± 6.6 years. Sixty five women (70%) were below the age of 35, while twenty seven (30%) were of advanced maternal age. Eighty-five (92%) women were Black, four (4%) were Coloured and three (3%) were of Indian descent.

Table 3: Age ranges of women with severe preeclampsia (N=92)

Range	Number (N)	Percentage (%)
15 -24	25	27%
25 – 34	40	43 %
>35	27	30 %

3.1 Maternal risk factors

Table 4 outlines maternal risk factors related to preeclampsia. Over-all seventy five (81%) of women were booked either at local clinic or at the tertiary institutions. Five (5%) women were known smokers, four (4%) reported occasional consumption of alcohol in the current pregnancy; however the volume consumed was not quantified. The mean gravidity of the women in the study was 2.4, with the highest gravidity being seven (1%). A mean parity of 2.3 was observed. Sixteen (17%) women were known chronic hypertensive patients on chronic anti-hypertensive medication, eighteen (19%) had a previous history of gestational hypertension and twenty five (27%) had preeclampsia in their previous pregnancies.

Three (3%) were taking hypoglycaemic agents and five (5%) of the 92 women had twin pregnancies. Forty five patients (48.9%) had a family history of first degree relative with hypertension and of the 70 women who have previously been pregnant, fifty three (76%) were involved with same partner. for all

Table 4: Table of pregnancy-related risk factors on history

Variable	Number (N)	Percentage (%)
Booking Status	75	81%
Smoker	5	5%
Alcohol	4	4%
Twins	5	5%
Chronic Hypertension	16	17%
Gestational Hypertension	18	19%
Previous Preeclampsia	25	27%
Diabetes	3	3%
***Partner**	53	76%%%
Family History	45	49%

*Partner – is it the same partner for all pregnancies.

3.2 Gestational age of patients at diagnosis and delivery.

Table 5.1 and 5.2 gives the gestational ages of patients at diagnosis and delivery. Of the 92 patients, 17 (18%) patients were un-booked; the mean booking gestational age was 19.8±6.54 weeks. The mean gestation at diagnosis was 29±2.67 weeks and the mean gestational age at delivery was 30±2.48 weeks. One patient was diagnosed with severe preeclampsia at 24 weeks and delivered at 30 weeks, while two patients were diagnosed 25 weeks delivered at 28 and 31 weeks respectively.

Table 5.1 Gestational at Diagnosis in weeks (N=92)

Range	Frequency	Percentage (%)
20 – 24	1	1 %
25 -29	43	47 %
30 -34	48	52 %

Table 5.2 Gestational Age at Delivery in weeks (N=92)

Range	Frequency	Percentage %
25 -29	36	39 %
30 -34	56	61 %

3.3 Antenatal booking blood results

Of the 92 patients, 88 (95.6%) had booking haemoglobin results available. The booking Hb ranged from 6.0g/dl-16g/dl, with the mean Hb of 12±2.2g/dl. Not all patients consented to HIV testing in pregnancy, sixty one (66%) were HIV negative; twenty three (25%) were HIV positive and eight (9%) had an unknown while twenty two (96%) of the twenty three HIV positive patients were on anti-retroviral therapy. Table 6 gives the CD4 count ranges of all HIV positive patients; the median CD4 count for the patients was 382 cell/mm^3 (IQR 184-549 cells/mm^3). Six of the patients had CD4 counts less than 350 cells/mm^3 and seven patients had no record of their CD4 count.

Table 6 CD4 counts of HIV positive women in the study (N=16)

Range	Number (N)	Percentage (%)
100 -299	6	38 %
300 – 499	5	31 %
500 -699	3	19 %
700 -899	2	12 %

3.4 Body mass index distribution

Table 7 gives the BMI of patients in the study. Of the 92 women in the study, 90 had their body weight and height recorded either at antenatal visit or on admission at the hospital. The mean body mass index was 30±6.2kg. Of note forty seven (52%) of the women in the study were obese as per the BMI.

Table 7 Body mass index (N=90)

BMI Ranges	Number(N)	Percentage (%)
Underweight <18.5 kg/m²	1	1 %
Normal 18.5 - 24.9 kg/m²	15	17 %
Overweight 25 – 29.9 kg/m²	27	30 %
Obese > 30kg/m²	47	52 %

3.5 Blood pressure measurements

On admission the patients' blood pressures were recorded using automated machines. The mean SBP was 181±28 mmHg while the mean DBP was 112±16 mmHg.

3.6 Biochemical findings

Bloods taken on admission included haemoglobin (Hb); platelets; urea; creatinine; alanine transaminase (ALT) and aspartate transaminase (AST). The mean Hb was 12±2 g/dl, the mean platelet count was 131±72; lowest platelet count was 31 and the highest count was 308.

The mean urea was 5.7±3.7, 25% of patients had abnormal urea readings. Ninety-one patients had their creatinine levels recorded. The median creatinine was 71µmol/L (IQR 71-96µmol/L)

The ALT was recorded for 75 patients; the median ALT was 52U/L (IQR 23-111U/L) with AST available in 79 patients. The median AST was 61U/L (IQR 33-147U/L)

All patients had proteinuria on urine dipsticks analysis; 74 (80%) patients received steroids for fetal lung maturity.

Table 8 Platelet count range (N=92)

Platelet count	Number (N)	Percentage (%)
< 50 000/µl	13	14%
50 000 – 100 000/µl	20	21%
100 000 – 150 000/µl	27	29%
150 000 – 200 000/µl	15	17%
250 000 – 300 000/µl	14	15%
>300 000/µl	3	3%

3.7 Medication administered

Figure 1 below depicts the antihypertensive medication administered; 83 (90%) patients received MgSO4 as prophylaxis and treatment, while 66 (72%) of patients received alpha methyldopa (AMD); 79 (86%) received nifedipine either as first line or as add on agent and 4 (4%) of patients needed labetalol for blood pressure control.

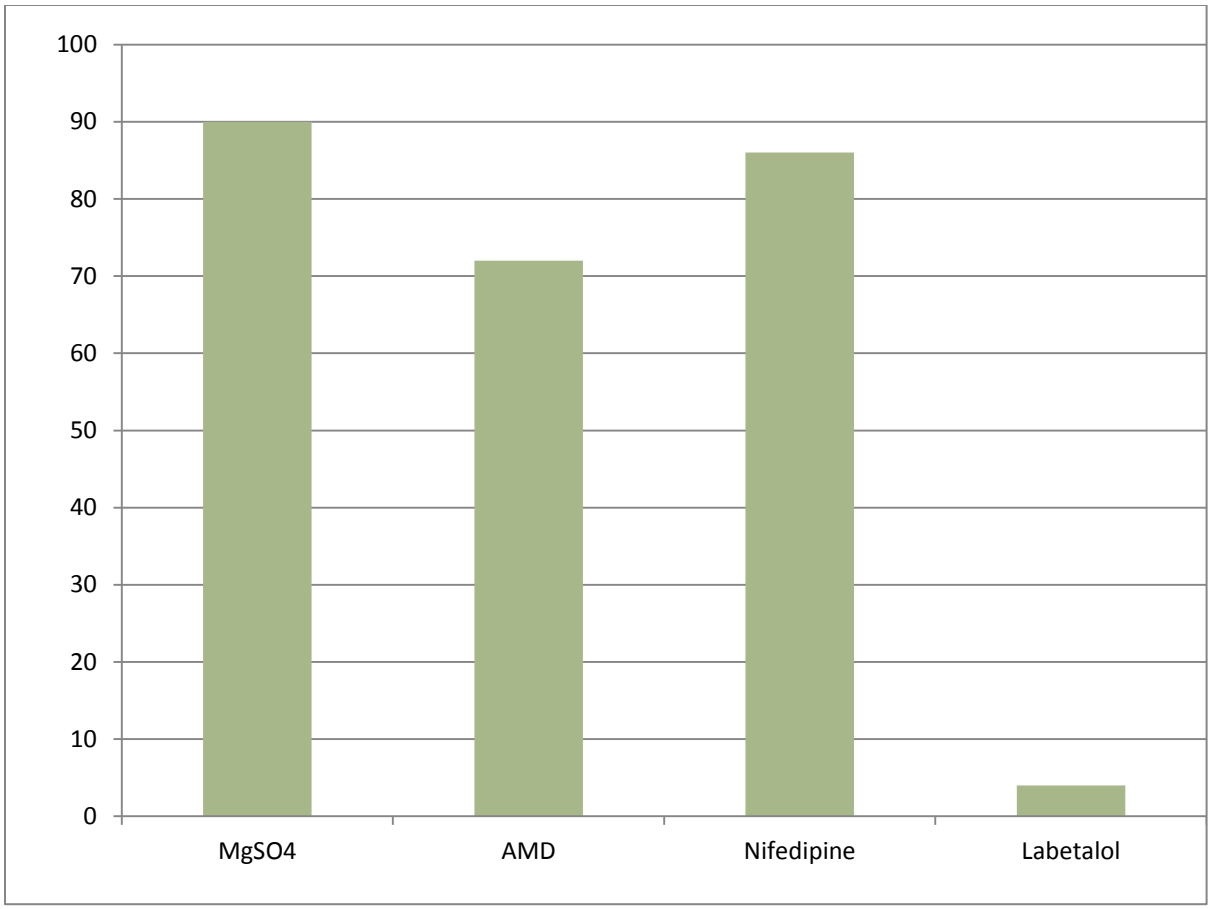

Figure 1 Antihypertensive drugs administered to women in the study (Y-axis = % of drugs given, X-axis = type of drug)

3.8 Decision to deliver

Table 9 shows the indications for delivery in our study population. Fetal distress was the most frequently observed indication for delivery (40) 43%; HELLP syndrome accounted for (16) 18% followed by eclampsia (16) 17%. Placental insufficiency including IUGR accounted for (5) 5% of all indications for delivery and those who were imminently eclamptic accounted for 5% of deliveries. For patients who were diagnosed as imminently eclamptic, they were first stabilised, by means of blood pressure control, administration of magnesium sulphate at the same time corticosteroids were administered to improve fetal lung maturity. Once stabilised patients were delivered either for maternal reasons, that is worsening of symptoms and deterioration in fetal condition.

Table 9 Frequencies of Indications for Delivery (N=92)

Indication	Patients (N)	PERCENTAGE (%)
Abruption	9	10 %
ATN	1	2 %
Eclampsia	16	17 %
FD	40	43 %
HELLP	16	18 %
IE	5	5 %
IUGR	5	5 %

ATN, acute tubular necrosis; FD, fetal distress; HELLP, haemolysis elevated liver enzymes and low platelets; IE, imminent eclampsia, IUGR, intra uterine grown restriction.

3.9 Mode of delivery

Of the 92 pregnancies; one patient with a placental abruption went into spontaneous labour, 77 (84%) were delivered by caesarean section and 14 (15%) had successful inductions of labour.

3.10 Maternal outcomes

Maternal outcomes are illustrated in Table 10. Two women 2 (2%) demised in the study and the maternal mortality ratio was 2:100 000 for this study. One had a massive intra-cerebral bleed and the second patient demised from disseminated intravascular coagulation and renal failure. Most women in the study had more than one outcome, 45 (49%) had HELLP syndrome; 31 (34%) had eclamptic seizures; 22 (24%) had acute kidney injury and 17 (18%) had placental abruptions. There were 3 (3%) ICU admissions two of which accounted for the mortalities observed, 3 (3%) had DIC, one which was mortality.

Table 10 Frequencies of Maternal Outcomes (N=92)

Outcome	Frequency (N)	Percentage (%)
Abruption	17	18 %
ARF	22	24 %
CVA	1	1 %
Death	2	2 %
DIC	3	3 %
Eclampsia	31	34 %
HELLP	45	49 %
ICU admission	3	3 %
MMR	2:100 000	

ARF, acute renal failure; CVA, cerebrovascular accident; DIC, disseminated intravascular coagulation; MMR, maternal mortality rate

3.11 Neonatal outcomes

Neonatal outcomes are shown in table 11.1 and table 11.2 respectively. Ninety two patients were analysed, of these 5 were twin pregnancies. Seventy one (73%) babies had five minute Apgar scores of ≥6. There were 17 (19%) admissions to neonatal ICU and 49 (53%) were admitted to the neonatal unit. Fifteen (16%) patients had intrauterine fetal deaths; 6 (7%) had early neonatal deaths; 11 (12%) neonates had birth asphyxia; 18 (20%) neonates had respiratory distress syndrome and 16 (17%) had intrauterine growth restriction. The median birth weight observed in the study was 1380 kg (IQR 999-1800).

Table 11.1 Frequencies of Neonatal outcomes (N=97)

Outcome	Number (N)	Percentage %
Admission	66	72 %
Asphyxia	11	12 %
ENND	6	7 %
IUFD	15	16 %
IUGR	16	17 %
Hypoglycaemia	1	1 %
Jaundice	3	3 %
RDS	18	20 %
NNMR	73/1000	
PNMR	216/1000	

ENND, early neonatal death; IUFD, intra-uterine fetal death, IUGR, intrauterine growth restriction, RDS, respiratory distress syndrome.

Neonatal birth weights are shown in table 11.2 (n=97). Eighty two (85%) of babies delivered weighed below two kilograms, while (15) 15% were above two kilograms. There were nine intra-uterine fetal deaths in the category less than a 1000g, three in the 1000-1499 category and 3 between 1500-2499.

Table 11.2 Frequencies of birth weights born to women in the study

Birth weight range	Number (N)	Percentage %
500 – 999	24	25%
1000 – 1499	33	34%
1500 – 1999	25	26%
2000 – 2499	14	14%
>2500	1	1%

4. Discussion

Severe preeclampsia that develops remote from term is associated with relatively higher rates of maternal morbidity and mortality as well as high perinatal morbidity and mortality. This study focused on a small cohort of women who developed severe preeclampsia before reaching term.

4.1 Demographic Data

In this study most women with severe preeclampsia were between the age ranges of 15-34 years (70%), mean age of 26.5±6.6 years, thus demonstrating that in this study, younger women were more affected by severe preeclampsia. This is in keeping with the studies by Jantasing and Tanawattanacharoen [61], where in their study the mean maternal age was 30.7±6.3 years and that of Moodley and Koranteng where their average age was 29±6.4 years [86].

Although we could not get a fair racial distribution, 85 (92%) of the patients were black; 4 (4%) white and 3 (3%) were of Indian descent. Therefore we could not conclude that in our study there were racial disparities that could have influenced the outcomes. However Bryant et al. in their study found that blacks were more than likely to be diagnosed with preeclampsia (78 vs.53%, p=0.04) and more likely to have had systolic blood pressures more than 160 mmHg (43 vs. 17%, p=0.01) [87]. Among nulliparous women, black women have a risk of preeclampsia that is twice as high as that of white women. Similar results were also reported by Dempsey et al. who also found the risk in African-American women to be higher than in the Hispanic women [88].

The HIV prevalence in this study was 23%, which is slightly lower than the 29.5% rate which was reported by the National Antenatal Sentinel HIV Prevalence Survey of 2011, conducted among women attending state ante natal clinics [89]. Although the primary objective of this study was not to assess association of HIV with preeclampsia, a retrospective study in Soweto, by Frank et al, failed to show any association between HIV seropositivity and the risk of developing preeclampsia [90].

4.2 Maternal risk factors

Although preeclampsia is regarded as a disease of first pregnancy, the risk of preeclampsia increases in those with limited sperm exposure with the same partner prior to conception and a previous pregnancy with same partner is associated with reduced risk of preeclampsia, however this protective risk is lost with a change of partner. In this study more than two thirds of the patients were multiparous and more than half had a different partner in the index pregnancy. These findings however differed with those by Conde-Agudelo and Belizan, in which they found that nulliparity, was associated with an increased risk of preeclampsia [41].

Previous history of hypertensive disease is a known risk factor for developing preeclampsia in pregnancy. Twenty seven percent of patients had a previous history of preeclampsia in this study; 20% had previous gestational hypertension and 17% were chronic hypertensive patients. Moodley et al. reported that a past history of hypertensive disease was present in 46% of their patients and that these patients had a greater fetal loss rate than those without a history of previous hypertensive disorder [86]. This study did not look at associations and therefore cannot confirm an increased risk. Although

maternal diabetes mellitus was only observed in 3% of patients, overwhelmingly, data proves that its presence substantially increases the risk of preeclampsia.

Obesity and overweight are significant risk factors worldwide, contributing to an increased risk of cardiovascular disease, type 2 diabetes and reduced life expectancy. Basu et al. reported a prevalence of BMI of 28±5.9 in a South African pregnant adolescent population. Compared to their study, the incidence of obesity in our study was higher [91]. Of note we did not restrict our study to an adolescent population. Notably in our study, women who were overweight or obese were more likely to be diagnosed with preeclampsia.

High maternal haemoglobin levels are generally associated with favourable maternal and perinatal outcomes. Although in this study it was not our objective to assess the association of haemoglobin level at booking with risk of preeclampsia, we had an average booking haemoglobin of 12±5.0. Murphy et al. showed that high levels of haemoglobin in the first and second trimester were related to adverse outcomes such as preeclampsia [92], while Dekker et al. suggested that serial measurements of haemoglobin and haematocrit could be used to monitor pregnancies at high risk of uteroplacental insufficiency [93]. Aghamohammadi A et al. in 2011 analysed 1008 women from Iran, who booked before their 14^{th} week of gestation, their study showed that the risk of developing pregnancy Induced hypertension was 2.46 times higher in women with Hb ≥ 13.2g/dl than in those with lower haemoglobin concentrations (11g/dl≤ Hb<13.2g/dl)(OR=2.46, 95% CI : 1.0-6.1) [94].

4.3 Medication administered

All women received antihypertensive medication as per institutional protocol. This study was a descriptive study, so no inferences could be made. about the effects of antihypertensive on the observed outcomes as all women in the study were delivered on emergency basis.

Magnesium sulphate is the drug of choice to prevent convulsions in women with severe preeclampsia. In this study a significant number of women received MgSO4, 72% received MgSO4 as treatment for 24 hours post-delivery or as treatment of eclampsia while 17% received only a 4g loading dose of MgSO4 as prophylaxis. A study by Lee W et al. in 2004 on maternal and perinatal outcomes of eclampsia reported that 97% of their patients received magnesium sulphate. This practice is in keeping with current management of preeclamptic patients [95].

4.4 Maternal Outcomes

The Report on Confidential Enquiries into Maternal Deaths in South Africa consistently reports preeclampsia as one of the leading five causes of maternal morbidity and mortality, while there was a 13.7% reduction in deaths due to complications of hypertension from the 2005-2007 report. The details relating maternal urinary, biochemical and haematological indices were recorded from the obstetric case records. Two deaths were recorded in this study, one from cerebrovascular accident and the other from disseminated intravascular coagulation.

All patients recruited in this study had at least one major morbidity, more than the 30% reported by Moodley et al. in 1993 [86]. The most frequent complications were HELLP syndrome at 48% followed by eclampsia at 34%. The 18% incidence rate of abruption placentae was much higher than 4.3% incidence reported by Sibai [96] and the 9% incidence reported by Vigil-De Gracia [97] and similar to the 20% reported by Hall et al [98]. Interestingly in the very large series of expectant management of severe preeclampsia reported by Hall et al [98], the incidence of eclampsia was 1.2%, much lower than the 34% observed in our study.

4.5 Fetal and neonatal outcomes

The increased incidence of perinatal morbidity and mortality seen in pregnancies complicated by preeclampsia, although complex and multifactorial, is due to the need for premature delivery and uteroplacental insufficiency resulting in compromised blood supply to the fetus. In 1989 Derham et al, demonstrated that the most important factor in survival of a healthy neonate was gestational age, which was strongly related to birth weight at delivery [99]; in addition, in 1987 Odendaal et al. showed an increased perinatal survival as birth weight increased [100] and later Moodley et al. demonstrated in their study increased survival rates with increasing gestational age [86].

In this study the majority of intrauterine fetal deaths were due to maternal abruption, and although most patients received steroid therapy, the outcomes observed are purely related to prematurity.

5. Limitations

The study was not without limitations. Due to the distances between the three hospitals data collection was not consistent and thus a larger sample could have been obtained for the time period undertaken.

Although most patients came in as emergencies, some patients were being managed conservatively thus when computing the data, that was not taken into account and may have led to a sampling bias, in addition the sample size was not large enough for this frequent and serious complication of pregnancy.

The neonatal outcomes were strictly limited to the time the mom was hospitalised, thus data is lacking about long term outcomes of these infants.

Another weakness of the study is that of limited information on the general population of Johannesburg - overwhelmingly most patients were black Africans, with limited contribution from other racial groups.

6. Conclusion

This study thus confirms the manifestations of preeclampsia as a cause of both significant maternal and perinatal morbidity and mortality. We also found that a large number of the women had severe morbidity associated with severe preeclampsia and premature delivery is still the leading cause of perinatal morbidity and mortality. The differences with other studies may be attributed to the small number of patients recruited, racial differences, socioeconomic status and some certain demographic parameters such as parity and age. In addition some may be attributable to the fact that our hospitals serve as referral obstetric centres for extended number of primary care facilities of the surrounding semi urban areas.

APPENDIX A

Patient Demographics

Age	__years				
Race	B (1)	C (2)	I (3)	W (4)	O(5)
Habits					
1. Smoker	Y (1)		N (0)		
Alcoholic	Y (1)		N (0)		

Obstetric History			
Parity			
Gravidity			
Chronic Hypertension	Y (1)/N(0)		
Gestational Hypertension	Y(1)/N(0)		
Severe Preeclampsia	Y(1)/N(0)		
Diabetes	GDM(1)	IDDM(2)	NONE(0)
Consort	Same(1)		Different(0)
Family History(First Degree Relative)	Y(1)		N(0)

Gestational Age	
At Booking	__/40
At Diagnosis	__/40
At Delivery	__/40

Booking Parameters		
Hb	__ g/dl	
RH	+(1) / -(0)	Unknown(2)
RPR	+ (1) / - (0)	Unknown(2)
HIV	+(1) / -(0)	Unknown(2)
CD4 Count		
ART	Y(1) N(0)	
Weight	__kg	
Height	__m	
BMI	__kg/m2	

Laboratory Data

Full Blood Count	HB		PLTS		
Urea & Creatinine only	U	Cr			
Uric Acid					
ALT / AST	ALT		AST		
INR /PTT	INR		PTT		
Protein	Dipstick		PCR	24HR Urine	

Treatment Options

Alpha Methyldopa	Y (1) N(0)
Nifedipine	Y(1) N(0)
Labetalol	Y(1) N(0)
Magnesium Sulphate	Load (1) Load and maintain(2) None(0)
Steroids	Single(1) Double(2) None(0)

Decision to Deliver

Fetal Distress	1
Placental Insufficiency (Doppler's)	2
Eclampsia	3
HELLP Syndrome	4
Renal Insufficiency	5
Abruption	6
Severe Oligohydramnios	7
Imminent Eclampsia	8

Mode of Delivery

Induction of Labour	1
Assisted Vaginal Delivery	2
Caesarean Section	3
Spontaneous Labour	4

Outcomes

Maternal Y(1) N(0)	
Eclampsia	
Abruption	
HELLP Syndrome	
Acute Renal Failure	
DIC	
Intensive Care Unit Admission	
Cerebrovascular Accident	
Death	
Sub capsular Haematoma	
Imminent Eclampsia	
Neonatal /Fetal : Y(1) N(0)	
Intra Uterine Death	Jaundice
IUGR	IVH
Birth Weight _____kg	ENND
5 minute APGARS____	
Birth Asphyxia	
Admission | NNU (1) NICU (2)	
RDS	
Necrotising Enterocolitis	
Hypoglycaemia	

APPENDIX B

Patient Information and Consent Form

Hello. My name is Dr Thabane Poonyane. I am a doctor in this hospital (Baragwanath Hospital/ Rahima Moosa Hospital/ Charlotte Maxeke Johannesburg Academic Hospital). My main focus is helping women who might have specific problems relating to their pregnancies. I am trying to find out if we are doing enough for all pregnant women with severe blood pressure problems and what are the effects for both mother and the newborn.

By taking part in this study you will be helping us to find better ways to help women with blood pressure conditions like yours and making sure their new-borns have the best care available. You will not be benefitting directly from this study, but what we find out about you may help others.

To take part in this study all that you have to do is allow me to ask you a few questions and have access to your file and the baby's information. Your identity is going to be concealed and only I will have access to it, all the information given to me will be protected at all times and nobody will have access to it. If you do not wish to have any part in the study your treatment here will not be affected in any way. You will still be appropriately treated for your hypertension, and so will your baby if he/she is not well. If you have decided to take part and then change your mind and withdraw from my study for any reason, there will be no ill-effects. You will still receive the care you are entitled to.

In taking part in this study you will not have to experience any uncomfortable or painful procedures. All I am interested in is what is documented in your file and what you have to say. If you decide to participate in this study the standard of care you will receive will be the same as all the patients in the ward and you will not be given anything in return e.g. food or money for your participation in the study.

You can contact me at any time in connection with the study. My name is Dr Thabane Poonyane and my cell number is: 0826861340.If you are willing to be a participant in this study, kindly sign that you have understood all that has been explained to you and that you are a willing to take part in this study.

Patient name: _____

Patient signature: _____Date: 201__/__/___

Parental Information and Assent Form

Hello. My name is Dr Thabane Poonyane. I am a doctor in this hospital (Baragwanath Hospital/ Rahima Moosa Hospital/ Charlotte Maxeke Johannesburg Academic Hospital). My main focus is in helping women who might have specific problems relating to their pregnancies. I am trying to find out if we are doing enough for all pregnant women with severe blood pressure problems and what are the effects for both mother and the newborn. Your daughter has this condition. Because she is younger than 18 years we require your permission.

By allowing her to take part in this study you will be helping us to find better ways to help women with blood pressure conditions like hers and making sure their newborn have the best care available. She will not be benefitting directly from this study, but what we find out about her may help others.

To take part in this study, all that you have to do is allow me to ask you and your daughter a few questions and have access to her file and the baby's information. Her identity is going to be concealed and only I will have access to it. All the information given to me will be protected at all times and nobody will have access to it. If you do not wish to have any part in the study your daughter's treatment here will not be affected in any way. She will still be appropriately treated even if she decides not to take part and then changes her mind for any reason, there will be no ill-effects. She will still receive the care she is entitled to. In taking part in this study she will not have to experience any uncomfortable or painful procedures. All I am interested in is what is documented in her file and what she has to say.

If you decide to allow her to participate in this study the standard of care she will receive will be the same as all the patients in the ward and she will not be given anything in return e.g. food or money for her participation in the study. You can contact me at any time in connection with the study. My name is Dr Thabane Poonyane and my cell number is: 0826861340.

If you are willing to be a participant in this study, kindly sign that you have understood all that has been explained to you and that you are a willing to allow your daughter to take part in this study.

Patient name: _____

Parent's name: _____

Parent's signature: _____

Date: 201__/___/___

APPENDIX C

Faculty of Health Sciences
Medical School, 7 York Road, Parktown, 2193
Fax: (011) 717-2119
Tel: (011) 717-2076

Reference: Ms Salamina Segole
E-mail: salamina.segole@wits.ac.za
09 November 2012
Person No: 9713850P
PAG

Dr T Poonyane
1546 Zone 6 Ext 3
Residensia
1980
South Africa

Dear Dr Poonyane

Master of Medicine in the specialty of Obstetrics and Gynaecology: Approval of Title

We have pleasure in advising that your proposal entitled "*Impact of severe preeclampsia on fetal and maternal outcomes in preterm deliveries*" has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

APPENDIX D

health and social development
Department: Health and Social Development
GAUTENG PROVINCE

RAHIMA MOOSA MOTHER AND CHILD HOSPITAL

RAHIMA MOOSA MOTHER AND CHILD HOSPITAL
Enquiries: Mrs. S. Jordaan
Tel: (011) 470 – 9030/4
Fax: (011) 477 4117

29 Graham Street (SE 2)
Van der Bijl Park
1911

Re: "Impact of Severe Pre-eclampsia on Maternal - fetal outcomes in Pre-term deliveries"

Dear Dr. Thabane Pooyane

Permission is granted for you to conduct the above survey as indicated in your request:

1. **The Rahima Moosa hospital will not in anyway incur or inherit costs as a result of the said study.**
2. **Your study shall not disrupt services at the study site.**
3. **Strict confidentiality shall be observed at all times.**
4. **Informed consent shall be solicited from patients participating in your study.**
5. **NO file should leave the records department and/or the hospital premises.**

Arrangement will be made with recordkeeping clerks so that you could occupy space in their department.

Kindly forward this office with the results of your research on completion of it.

I, DR T. POONYANE **accept the terms and conditions set-in this document**

sign _____ **date** 2012/03/28

Yours sincerely,

Jordaan

CHIEF EXECUTIVE OFFICER
SJ/cj. 2012-03-28

ADDRESS: cnr. FUEL & OUDSTHOORN STREET CORONATIONVILLE 2093/PRIVATE BAG X20 NEWCLARE 2112

Request to Perform Research in this Institution

Dear Prof F. Guidozzi,

I would hereby like to request the permission of the hospital authorities to perform the following study:

Title of research: **Impact of Severe Preeclampsia on Maternal and Neonatal Outcome in Preterm Deliveries.**

Researcher: Dr Thabane Poonyane

Supervisor: Dr Karlyn A. Frank

Department: University of the Witwatersrand Department of Obstetrics and Gynaecology

Objectives and study design:

Prospective and descriptive cohort aimed at determining maternal and foetal outcomes in patients who are diagnosed to be severely preeclamptic. The hospital will not incur any investigative expense other than routine bloods that are generally pulled from patients with severe preeclampsia, unless otherwise complications arise which might necessitate further diagnostic tests.

Hundred patients will be enrolled onto the study, they will be followed up to three days post delivery and same will apply for their babies.

Starting date: 2011/11/01

Ending date: 2012/11/30

Funding: Self Funded

Cost to the hospital: No additional costs

Involvement of other divisions: Will depend on patient condition

Ethics approval: Pending this approval

I hope you find the above information satisfactory and that it answers all the relevant questions.

Contact details: Cell: 0826861340 email: thabanepoonyane@gmail.com

Signature:

Date: 2012/03/04

Approved
04/03/12

F. Guidozzi

APPENDIX E

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Thabane Pooyane

CLEARANCE CERTIFICATE	M111043
PROJECT	Impact of Severe Preeclampsia on Materal Foetal Outcomes in Preter Deliveries
INVESTIGATORS	Dr Thabane Pooyane.
DEPARTMENT	Obtetrics & Gynaecology
DATE CONSIDERED	28/10/2011
M1110430DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 28/10/2011 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Karlyn Frank

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

References

1. Poston L. Endothelial dysfunction in pre-eclampsia. Pharmacol Rep 2006; 56 Supp: 69-74

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

3. Sibai BM: Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol. 2003; 102(1):181-192.

4. Sibai BM, Dekker G, Kupferminc M. Pre-eclampsia. Lancet 2005; 365:785-799.

5. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol 2009; 33:130-137.

6. Carty DM, Delles C, Dominiczak AF. Preeclampsia and future maternal health. J Hypertens 2010; 1349-1355.

7. Khalil AA, Cooper DJ, Harrington KF. Pulse wave analysis: a preliminary study of a novel technique for prediction of pre-eclampsia. BJOG 2009; 116 (2):268-276.

8. Saftlas AF, Olson DR, Franks AL, Atrash HK, Pokras R. Epidemiology of preeclampsia and eclampsia in the United States, 1979-1986. Am J Obstet Gynecol 1990; 163:460-465.

9. Khan KS, Wojdyla D, Say L et al. WHO analysis of cause of maternal death: a systemic review. Lancet 2006; 367:1066-1074.

10. Saving Mothers Report 2008-2010: Fifth report on the Confidential Enquiries into Maternal Deaths in South Africa. http://www.health.gov.za/docs/Reports_on_Confidential_Enquiries_into_Maternal_Deaths_in_South_Africa.pdf

11. Mogren I, Hogberg U, Winkvist A, Stenlund H. Familial occurrence of pre-eclampsia. Epidemiology 1999; 10(5):518-522.

12. Lie RT, Rasmussen S, Brumborg H, et al. Fetal and maternal contribution to risk of pre-eclampsia: population based study. BMJ 1998; 316:1343-1457.

13. Hartikainen AL, Aliharmi RH and Rantakillo PT. A cohort study of epidemiologic associations and outcomes of pregnancies with hypertensive disorders. Hypertens Pregnancy 1998; 17:31-41.

14. Robillard PY, Hulsey TZ, Alexander GR, et al. Paternity patterns and the risk of pre-eclampsia last pregnancy in multipara. J Reprod Immunol 2003; 59:245-251.

15. Skjaerven R, Wilcox AJ, Lie RT. The interval between pregnancies and risks of preeclampsia. N Engl J Med 2002; 346:33-38.

16. Dekker G, Robillard PY. The birth interval hypothesis-does it really indicate the end of the primiparternity hypothesis? J Reprod Immunol 2003; 59:245-251.

17. O 'Brien TE, Raj JG, Chan WS. Maternal body mass index and the risk of preeclampsia: a systematic overview. Epidemiology 2003; 14:368-374.

18. Yasuda M, Takakuwa K, Tokunaga A, et al. Prospective studies of the association between anticardiolipin antibody and outcome of pregnancy. Obstet Gynecol 1995; 86:555-559.

19. Sibai B, Dekker G and Kupferminc M. Pre-eclampsia. Lancet 2005; 365:785-799.

20. England L and Zhang J. Smoking and risk of pre-eclampsia: a systematic review. Front Biosci 2007; 12:2471-2483.

21. Wikstrom AK, Stephansson O and Cnuttingius S. Tobacco use during pregnancy and pre-eclampsia risk: effects of cigarette smoking and snuff. Hypertension 2010; 55:1254-1259.

22. Odegard R, Vatten LJ, Nilsen ST, et al. Risk factors and clinical manifestation of preeclampsia. BJOGN 2000; 107:1410-1416.

23. Duckitt K and Harrington D. Risk factors for pre-eclampsia at antenatal booking: Systematic review of controlled studies. BMJ 2005; 330:565.

24. Mostello D, Kallogjeri D, Tungsiripat R, Leet T. Recurrence of pre-eclampsia: effects of gestational age at delivery of the first pregnancy, body mass index, paternity and interval between births. Am J Obstet Gynecol 2008; 199: 55.e 1-55.e7.

25. Boggess KA, Lieff S, Murtha AP, et al. Maternal periodontal disease is associated with an increased risk for pre-eclampsia. Obstet Gynecol 2003; 101: 227-231.

26. Beck JD, Pankow J, Tyroler HA, Offenbacher S. Dental infections and atherosclerosis. Am Heart J 1999; 138: 528-533.

27. Beck JD, Offenbacher S, Williams R, Gibbs P, Garcia R. Periodontitis: A risk factor for coronary heart disease? Ann Periodontol 1998; 3: 127-141.

28. Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S. Periodontal disease and cardiovascular disease. J Periodontol 1996; 67: 1123-1137.

29. Haraszthy VI, Zambon JJ, Trevisa M, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. J Periodontol 2000; 71: 1554-1560.

30. Canakci V, Canakci CF, Canakci H, Canakci E, et al. Periodontal disease as a risk factor for preeclampsia: A case control study. Aust NZ J Obstet Gynaecol 2004; 44: 568-573.

31. Brown MA, Lindheimer MD, de Swiet M, van Assche A, Moutquin JM. The classification and diagnosis of hypertensive disorders of pregnancy: a statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 2001; 20(1):9-14.

32. National Institute for Health and Clinical Excellence. Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. Clinical guidance 107 August 2010. http://www.nice.org.uk/guidance/cg107.

33. Higby K, Suiter CR, Phelps JY, Siler-Khodr T, Langer O. Normal values of urinary albumin and total protein excretion during pregnancy. Am J Obstet Gynecol 1994; 171(4):984-989.

34. Waugh JJ, Clark TJ, Divakaran TG, Khan KS, Kilby MD. Accuracy of urinalysis dipstick techniques in predicting significant proteinuria in pregnancy. Obstet Gynecol 2004; 103(4):769.

35. Cote AM, Firoz T, Mattman A, et al. The 24hour urine collection: gold standard or historical practice? Am J Obstet Gynecol 2008; 199:625.e1-625.e6.

36. Cote AM, Brown MA, Lam E, et al. Diagnostic accuracy of urinary spot protein in hypertensive pregnant women: systematic review. BMJ 2008; 336:1003-1006.

37. Lindheimer MD, Kanters D. Interpreting abnormal proteinuria in pregnancy: The need for a more pathophysiological approach. Obstet Gynecol 2010; 115:365-375.

38. von Dadelszen P, Payne B, Li J, et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of full PIERS model. Lancet 2011; 377:219-227.

39. Payne B, Magee LA, Cote AM, et al. PIERS proteinuria: relationship with adverse maternal and perinatal outcome. J Obstet Gynecol Can 2011; 33(6):588-597.

40. Thornton CE, Makris A, Ogle RF, Tosher JM, Hennessy A. Role of proteinuria in defining pre-eclampsia: clinical outcomes for women and babies. Clin Exp Pharmacol Physiol 2010; 37:466-470.

41. Sibai BM. Eclampsia: VI. Maternal-perinatal outcome in 254 consecutive cases. Am J Obstet Gynecol 1990; 163(3):1049-1054.

42. Meads CA, Cnossen JS, Meher S, et al. Methods of prediction and prevention of pre-eclampsia: systematic review of accuracy and effectiveness of literature with economic modelling. Health Technol Assess 2008; 12:3-4; 1-210.

43. Conde-Agudelo A, Romero R, Lindheimer MD. Tests to predict pre-eclampsia. In: Lindheimer MD, Roberts JM, Cunningham FG, eds. Chesley's hypertensive disorders in pregnancy. Amsterdam: Academic Press, Elsevier, 2009:189-211.

44. Poon LCY, Kametas NA, Maiz N, Akolekar R, Nicolaides KH. First trimester prediction of hypertensive disorders in pregnancy. Hypertension 2009; 53:812-818.

45. Dekker GA, Sibai BM. Aetiology and pathogenesis of pre-eclampsia: Current concepts. Am J Obstet Gynecol 1998; 179:1359-1375.

46. Conde-Agudelo A, Belizan JM. Risk factors for pre-eclampsia in healthy nulliparous women: a prospective multicentre study. Am J Obstet Gynecol 2000; 107:75-83.

47. Duley L, Henderson-Smart DJ, Knight M, King J, et al. Antiplatelet agent for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev 2007; 2.CD006490.

48. Bujold E, Roberge S, Lacasse Y, et al. Prevention of pre-eclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. Obstet Gynecol 2010; 116:402-414.

49. Belizan JM, Villar J, Gonzalez L, et al. Calcium supplementation to prevent hypertensive disorders of pregnancy. N Engl J Med 1991; 325:1399-1405.

50. Carroli G, Merialdi M, Wojdyla D, et al. Effects of calcium supplementation on uteroplacental and fetoplacental blood flow in low calcium intake mothers: a randomised controlled trial. Am J Obstet Gynecol 2010; 202:45.e1-45.e9.

51. Hofmeyr GJ, Lawrie TA, Atallah AN, et al. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev 2010; 8. CD001059.

52. Rumbold A, Duley L, Crowther C, et al. Antioxidants for preventing pre-eclampsia. Cochrane Database Syst Rev 2005; 4. CD004227.

53. Makrides M, Duley L and Olson SF. Marine oil and other prostaglandin precursors, supplementation for pregnancy uncomplicated by pre-eclampsia or intrauterine growth restriction. Cochrane Database Syst Rev 2006; 3. CD003402.

54. Howarth C, Gazis A and James D. Association of type 1 diabetes, maternal vascular disease and complications of pregnancy. Diabet Med 2007; 24:1229-1234.

55. Bhattacharya S, Campbell D and Liston W. Effect of body mass index on pregnancy outcomes in nulliparous women delivering singleton babies. BMC Public Health 2007; 7:168.

56. Khedun SM, Moodley J, Naicker T, Maharaj B. Drug management of hypertensive disorders of pregnancy. Pharmacol Ther 1997; 74:221-228.

57. Lewis G. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving Mothers Lives: reviewing maternal deaths to make motherhood safer – 2003-2005. The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. London: CEMACH; 2007.

58. Ashe RG, Moodley J, Richards AM, et al. Comparison of labetalol and dehydrate in hypertensive emergencies of pregnancy. S Afr Med J 1987; 71:354-356.

59. Magee LA, Cham C, Waterman EJ, et al. Hydralazine for treatment of severe in pregnancy: Meta-analysis. Br Med J 2003; 327:955-960.

60. Duley L, Williams J, Henderson-Smart DJ. Plasma volume expansion for treatment of mom with pre-eclampsia. Cochrane Database Syst Rev 2000; 2. CD001805.

61. Roberts D, Dalziel SR. Antenatal corticosteroid for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006; 3. CD004454. Level 1

62. Pardi G, Cettin I, Marconi AM. Diagnostic value of blood sampling in foetuses with growth restriction. N Engl. J. Med 1993; 328:692-696.

63. Kingdom JC, Burrell SJ, Kaufmann P. Pathology and clinical implications of abnormal umbilical artery Doppler waveforms. Ultrasound Obstet Gynecol 1997; 9:271-286

64. Morrow RJ, Adamson SL, Bull SB. Effect of placental embolization on the umbilical arterial velocity waveform in fetal sheep. Am J Obstet Gynecol 1989; 161:1055-1060.

65. Nicolaides KH, Bilardo CM, Soothill PW. Absence of end diastolic frequencies in umbilical artery: A sign of fetal hypoxia and acidosis. BMJ 1988; 297:1026-1027.

66. Bilardo CM, Nicolaides KH, Campbell S. Doppler measurements of fetal and uteroplacental circulations: Relationship with umbilical venous blood gases measured at cordocentesis. Am J Obstet Gynecol 1990; 162:115-120.

67. Divon MY. Randomised controlled trials of umbilical artery Doppler Velocimetry: How many are too many? Ultrasound Obstet Gynecol 1995; 6:377-279.

68. Giles W, Bisits A. Clinical use of Doppler ultrasound in pregnancy: Information from six randomised trials. Fetal Diag Ther 1993; 8:247-255.

69. Alfirevic Z, Neilson JP. Doppler ultrasonography in high-risk pregnancies: Systemic review with meta-analysis. Am J Obstet Gynecol 1995; 172:1379-1387.

70. Rizzio G, Capponi A, Arduini D, Romanini C. The value of fetal arterial, cardiac and venous flows in predicting pH and blood gases measured in umbilical blood at cordocentesis in growth retarded fetuses. Br J Obstet Gynaecol 1995; 102:963-969.

71. Hecher K, Snijders R, Campbell S, Nicolaides KH. Fetal venous, intracardiac and arterial blood flow measurements in intrauterine growth retardation: Relationship with fetal blood gases. Am J Obstet Gynecol 1995; 173:10-15.

72. Baschat AA, Gembruch U, Harman CR: The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. Ultrasound Obstet Gynecol 2001; 18:571-577.

73. Hecher K, Bilardo CM, Stigter RH, et al: Monitoring of fetuses with intrauterine growth restriction: A longitudinal study. Ultrasound Obstet Gynecol 2001; 18:564-570.

74. Ferrazzi E, Bozzo M, Rigano S, et al: Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. Ultrasound Obstet Gynecol 2002; 19:140-146.

75. Baschat AA, Cosmi E, Bilardo CM, et al: Predictors of neonatal outcome in early-onset placental dysfunction. Obstet Gynecol 2007; 109:253-261.

76. Altman D, Carroli G, Duley L et al. MAGPIE Trial Collaboration Group. Do women with preeclampsia and their babies benefit from magnesium sulphate? The Magpie trial: a randomised placebo-controlled trial. Lancet 2002; 359:1887-1890.

77. Belfort MA, Anthony J, Saude GR, Allen JC. A comparison of magnesium sulphate and nimodipine for the prevention of eclampsia. N Engl J Med 2000; 348:304-311.

78. Lucas MJ, Leveno KJ, Cunningham FG. A comparison of magnesium sulphate with phenytoin for prevention of eclampsia. N Engl J Med 1995; 333:201-205.

79. Duley L, Gulmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with preeclampsia. Cochrane Database Syst Rev 2010; (11): CD000025.

80. Gatt S, Clinical management of established preeclampsia/gestational hypertension – perspectives of the midwife, neonatologist and anaesthetist. In Bailliere's Clinical Obstetrics and Gynaecology, Pregnancy and Hypertension Edition (Ed: Brown M), Bailliere's Best Practice and Research, Bailliere Tindall, London: 13:1:95-105, 1999.

81. Morti MG, Schneider MC. Key issues in assessing, managing and treating patients presenting with severe preeclampsia. Int J Obstet Anesth 2000; 9:39-44.

82. Dyer RA, Piercy JL, Reed AR. The role of anaesthetist in the management of the preeclamptic patient. Curr Opin Anaesthesiol 2007; 20:168-174.

83. Engelhardt T, MacLennan FM. Fluid management in preeclampsia. Int J Obstet Anesth 1999; 8:253-259.

84. Hjartardottir S, Leifsson B, Geirsson R. Recurrence of hypertensive disorder in second pregnancy. Am J Obstet Gynecol 2006; 194:916-920.

85. Jantasing S, Tanawattanacharoen S. Perinatal outcomes in severe preeclamptic women between 24-33^{6} weeks' gestation. J Med Assoc Thai 2008; 91:25-29.

86. Moodley J, Koranteng S, Rout C. Expectant management of early onset severe preeclampsia in Durban. SAMJ 1993; 83:584-587.

87. Bryant AS, Seely EW, Cohen A, Lieberman E. Patterns of pregnancy-related hypertension in black and white women. Hypertens Pregnancy 2005; 24(3):281-290.

88. Dempsey JC, William MA, Luthy DA. Weight at birth and subsequent risk of preeclampsia in an adult. Am J Obstet Gynecol 2003; 189:494-500.

89. The 2011 National Antenatal Sentinel HIV and Syphilis Prevalence Survey. http://www.health-e.org.za/2012/12/11-national-antenatal-hiv-syphyllis-prevalence-survey-released/.

90. Frank KA, Buchmann EJ, Schakis RC. Does human immunodeficiency virus infection protect against preeclampsia-eclampsia? Obstet Gynecol 2004: 104(2): 238-242.

91. Basu JK, Basu D. Obesity and its outcomes among South African pregnant adolescents. South Afr J Epidemiol Infect 2012; 27(1):36-38.

92. Murphy JF, O'Riordan J, Newcombe J, Coles EC, Pearson JF. Relation of haemoglobin levels in first and second trimesters to pregnancy outcomes. Lancet 1986; 1:992-995.

93. Dekker G, Sibai B. Primary, Secondary and Tertiary prevention of preeclampsia. Lancet 2001; 357:209-215.

94. Azar A, Zafari M, Tofighi M. High maternal haemoglobin concentration in first trimester as risk factor for pregnancy induced hypertension. Casp J Intern Med 2011; 2(1):194-197.

95. Lee W, O'Connell CM, Basket TF. Maternal and perinatal outcomes of eclampsia: Nova Scotia, 1981-2000. J Obstet Gynecol Can 2004; 26(2):119-123.

96. Sibai BM, Mercer BM, Schiff E, Friedman SA. Aggressive versus expectant management of severe preeclampsia at 28 to 32 weeks' gestation: A randomised controlled trial. Am J Obstet Gynecol 1994; 171:818-822.

97. Vigil-De Gracia P, Montufar-Rueda C, Ruiz J. Expectant management of severe preeclampsia and preeclampsia superimposed on chronic hypertension between 24 and 34 weeks' gestation. Eur J Obstet Gynecol Reprod Biol 2003; 107:24-27.

98. Hall DR, Odendaal HJ, Steyn DW, Grove D. Expectant management of early onset, severe preeclampsia: maternal outcome. BJOG 2000; 107:1252-1257.

99. Derham RJ, Hawkins DF, De Vries LS, Aber VR, Elder MG. Outcome of pregnancies complicated by severe hypertension and delivered before 34 weeks; stepwise logistic regression analysis of prognostic factors. Br J Obstet Gynaecol 1989; 96:1173-1181.

100. Odendaal HJ, Pattinson RC, Du Toit R. Fetal and neonatal outcome in patients with severe preeclampsia before 34 weeks. S Afr Med J 1987; 71:555-558.