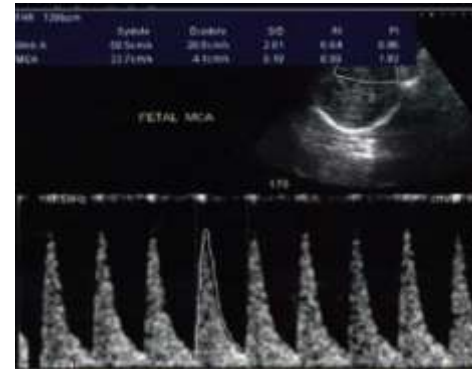


The Cerebro- Placental Ratio as a Prognostic Factor of Fetal Outcome in Patients with Hypertensive States of Pregnancy in Third Trimester at Kenyatta National Hospital



Dissertation to be submitted in Part Fulfillment for the award of the Degree of Masters of Medicine in Diagnostic Imaging of University of Nairobi.

By

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DECLARATION

I, **Dr. Parmar Linal Parshuram**, declare that this dissertation has not been submitted for another degree in this or any other University or Institution of Higher learning and that the views expressed herein are mine unless otherwise stated, and where such has been the case acknowledgement or reference has been quoted.

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LIST OF ABBREVIATIONS

ABO	Blood groups A, B and O system
AFV	Amniotic Fluid Volume
ANC	Antenatal Clinic
BP	Blood Pressure
BPPS	Biophysical Profile Score
CI	Confidence Interval
CPR	Cerebro-Placental ratio
CTG	Cardiotocography
C/U RI	Cerebral/umbilical resistive index
CW	Continuous Wave
EDF	End Diastolic Flow
EDV	End Diastolic Velocity
ERC	Ethics and Research Committee
FANC	Focused Antenatal Care
FHR	Fetal Heart Rate
FKC	Fetal Kick Chart
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
HSP	Hypertensive States of Pregnancy
IQR	InterQuartile Range
IUFD	Intrauterine Fetal Death
IUGR	Intrauterine Growth Restriction
KNH	Kenyatta National Hospital
KNH/UoN-ERC	Kenyatta National Hospital/University of Nairobi-Ethics and Research Committee
MCA	Middle Cerebral Artery
MCA RI	Middle Cerebral Artery Resistive Index
MCA PI	Middle Cerebral Artery Pulsatility Index
MCH	Maternal and Child Health clinic

Mg/dl	Milligrams per deciliter
MHz	Mega Hertz
mmHg	Millimeters of Mercury
NICU	Neonatal Intensive Care Unit
NBU	New Born Unit
NRFS	Non reassuring Fetal Status
NST	Non Stress Test
OR	Odds ratio
PET	Pre-eclamsic Toxaemia
PE	Pre-eclampsia
PI	Pulsatility Index/Gosling index
PSV	Peak Systolic Velocity
PW	Pulsed Wave
RI	Resistive Index/Pourcelot index
SB	Still Birth
S/D	Systolic/ Diastolic Ratio
SD	Standard Deviations
SVD	Spontaneous Vaginal Delivery
UEC	Urea, Electrolytes and Creatinine
UoN	University of Nairobi
UA	Umbilical Artery
UA RI	Umbilical Artery Resistive Index
UA PI	Umbilical Artery Pulsatility Index
U/S	Ultrasound scan or Ultrasonography

ABSTRACT

Introduction

Hypertensive states of pregnancy affect maternal and fetal circulations (1). The pathophysiology can be assessed safely and non-invasively by Doppler ultrasound using arterial Doppler indices of umbilical and middle cerebral arteries thus attaining the cerebro-placental ratio (ratio of the middle cerebral artery resistive index over that of the umbilical artery) (2)

Study Objective

This study aimed at determining the role of the cerebro-placental ratio (CPR) as a prognostic factor of fetal outcome in patients with hypertensive states of pregnancy delivered at or after 32 weeks of gestation by dates.

Study Design and Methodology

A prospective cohort study carried out at the Kenyatta National Hospital (KNH) over a period of nine months. Gravid patients at least 32 weeks gestations by dates were recruited from labor ward after obtaining informed consent. Consecutive sampling method was used. The cerebro-placental ratio was then calculated. Follow up for fetal outcome, the 5 minute APGAR score and birth weight was made. Ethical Approval was sought from and granted by the Kenyatta National Hospital/University of Nairobi-Ethics and Research Committee (KNH/UoN-ERC).

Problem Statement

Fetuses at greater risk of adverse perinatal outcome will have a high resistance umbilical artery waveform and a low resistance waveform of the middle cerebral artery waveform thus a $CPR < 1$

Findings

A total of 160 patients were recruited into the study.

Median age was 28 years. Sixty two percent (62%) were primiparous. Median gestation at admission was 34 weeks while at sonography, the average gestation was 31 weeks

Twenty nine percent (29%) had an abnormal CPR (< 1.0) while seventy eight percent (78%) had a normal CPR (≥ 1.0). Seventy eight percent (78%) were delivered via caesarean section while twenty two percent (22%) were delivered vaginally.

51 out of 160 (32%) had severe PET out of which 39% had $CPR < 1.0$ and 61% had $CPR \geq 1.0$. while 109 out of 160 patients(68%) had mild PET out of which 24% had $CPR < 1.0$ and 76% had $CPR \geq 1.0$.

Still births were 12.5 times more likely in mothers with $CPR < 1.0$ than those with $CPR \geq 1.0$,

An APGAR score < 7 was 66 times more often in mothers with $CPR < 1.0$ than mothers with $CPR \geq 1.0$. Low birth weight was 4.7 times more likely among mothers with $CPR < 1.0$ as compared to those with mothers with $CPR \geq 1.0$ (95% CI 2, 11.1; $p < 0.001$).

An APGAR score < 7 was 66 times more likely among neonates delivered vaginally as compared to those born via caesarean section(95% CI 1.3, 23; $p = 0.02$)

Still births were 14.5 times more often than among neonates born vaginally as compared to those born via caesarean section (95% CI 3, 84; $p < 0.001$).

The prognostic OR for CPR was 12.5 for live births (95% CI 2, 74; p=0.005), 66 for APGAR score <7 (95% CI 13, 340; p< 0.001) and 4.7 for low birth weight (95% CI 2, 11.1; p< 0.001) and 1.1 (95% CI 0.9, 1.4; p=0.327).

The prognostic OR of BPPS for live births was 1.7 (95% CI 1.1, 2.5; p=0.009), 1.3 for APGAR score <7 (95% CI 0.9, 1.9; p=0.07) and 1.1 for low birth weight (95% CI 2, 11.1; p< 0.001) and 1.1 (95% CI 0.9, 1.4; p=0.327).

Conclusion

CPR is significantly predictive of adverse perinatal outcome when used to monitor mothers with hypertensive states of pregnancy than UA RI or BPPS used alone. CPR was predictive of adverse perinatal outcome (live birth, APGAR score and low birth weight). Caesarian section should be the recommended mode of delivery for hypertensive mothers.

BACKGROUND

Introduction

Hypertensive states of pregnancy (HSP) are defined as conditions in which there is development of *new* [arterial hypertension](#) in gravid women after 20 weeks of gestation without the presence of protein in the urine (5). The HSP include pre-eclampsia/eclampsia (PE), chronic hypertension, and chronic hypertension with superimposed pre-eclampsia and gestational hypertension (6).

HSP causes deficient infiltration of spiral arteries by trophoblast, failure of the spiral arteries to convert into utero-placental arteries and therefore the tenfold increase in uterine perfusion occurs and interferes with blood flow in the uterine artery on the maternal side (7).

On the fetal side, HSP cause poor vascularization of terminal villi, villous stromal hemorrhage and hemorrhagic endovasculitis or even obliteration of stem villi (7).

Doppler ultrasound allows safe, non invasive and rapid investigation of the fetoplacental circulation (7) using three arterial indices devised (Pourcelot 1974) (59) to assess quality of flow in vessels.

These indices are Resistive Index (RI)/Pourcelot index, Pulsatility Index (PI)/Gosling index and Systolic/Diastolic ratio (S/D ratio)/Stuart and Drumm (2). The Resistive Index (RI); also known as the Pourcelot index (Pourcelot 1974) is an indicator of resistance of an organ to perfusion. It is the most commonly used index as it is easier to calculate and is reflective of vascular resistance (2). Using Doppler ultrasonography, it is calculated by measuring peak systolic velocity (PSV) and subtracting end diastolic velocity (EDV) from it and then dividing it by peak systolic velocity (2.) Therefore, the Resistive Index is calculated as follows:

$$RI = \frac{\text{Peak Systolic Velocity (PSV)} - \text{End Diastolic Velocity (EDV)}}{\text{Peak Systolic Velocity (PSV)}}$$

The Umbilical Artery Resistive Index (UA RI) reflects downstream placental vascular resistance which has been found to correlate with intrauterine growth restriction (IUGR) and multisystem effects of placental deficiency (8). Abnormalities of the umbilical artery (UA) Doppler waveform are progressive beginning with reduction, loss and finally a reversal of diastolic flow. When the blood flow pattern in the Umbilical Artery (UA) becomes abnormal, the differentiation of fetal status requires Doppler information from systemic vessels (8) and one of

the systemic vessels that can be investigated is the Middle Cerebral Artery (MCA) which is used for assessment of the fetal cerebral circulation. It is easy to identify the MCA as the major branch running antero-laterally from circle of Willis towards lateral edge of orbit (8 and 10). RI of both the Middle Cerebral Artery (MCA) and Umbilical Artery (UA) can be obtained. A comparison giving the cerebro-placental ratio (CPR).

A ratio >1.0 indicates preferential flow to vital structures like brain, heart and adrenal glands and is therefore considered normal while that <1.0 is indicative of high resistance in utero-placental circulation via Umbilical Artery (UA) Doppler waveform and inadequate supply to fetal brain via Middle Cerebral Artery (MCA) Doppler waveform known as centralization and is considered to be predictive of adverse perinatal outcome. (8).

The cerebro-placental resistive index ratio is the ratio of the MCA R.I to the UA R.I. It is calculated as shown in the formula below.

$$CPR = \frac{\text{Resistive index of middle cerebral artery (MCA RI)}}{\text{Resistive index of umbilical artery (UA RI)}}$$

The brain sparing effect is seen when circulatory adaptation occurs with chronic hypoxia in form of cerebral vasodilatation to preserve blood flow to the brain. This is demonstrated by a lower value of MCA RI relative to gestational age and UA RI. Its disappearance is a critical event and precedes fetal death (8). Also studies done have shown the CPR to be predictive of adverse perinatal outcome. Doppler studies of multiple feto-placental vessels can be used to monitor compromised fetus predicting adverse perinatal outcome and assisting in optimal time of delivery (11-15). At the Kenyatta National Hospital (KNH), the biophysical profile score (BPPS) and umbilical artery resistive index (UA RI) are used in management of patients with HSP to determine method and optimal time of delivery. However there had been no study carried out at locally to assess the role of the CPR as a prognostic factor in the prediction of fetal outcome in patients with HSP in the third trimester.

This aim of this study was to determine the role of CPR in antenatal fetal monitoring in patients with HSP so as to assess the fetus at greater risk of adverse perinatal outcome and thereby greatly improve management and reduce neonatal mortality and morbidity.

Literature Review

Hypertensive States in Pregnancy

The incidence of HSP varies between 5-10% in different communities.(15) In our set up, Mati 1975 found an incidence of 7.1% with a range of between 1.5-9% (15) The prevalence of pre-eclampsia in KNH in 1992 was found to be 5.4% (16). HSP are classified into 4 categories, as recommended by the National High Blood Pressure Education Program Working Group (NHEP) on High Blood Pressure in Pregnancy (17) and these are pre-eclampsia/eclampsia, chronic hypertension, chronic hypertension with superimposed pre-eclampsia and gestational hypertension. The predisposing factors to HSP include primigravidas, black race, and maternal age below 20 or above 35 years, low socio-economic status and multiple gestations (57).

Pre-eclampsia is hypertension associated with proteinuria and edema occurring primarily in nulliparas after the 20th gestational week and most frequently near term. Recent data supports the elimination of edema as a diagnostic criterion because it is common in normal pregnancy and pre-eclampsia can occur without edema which is called the dry type (18).Hypertension is defined as blood pressure (BP) equal to or greater than 140/90mmHg. A rise of 30mmHg or more in systolic blood pressure or a rise of 15mmHg or more in diastolic blood pressure in 2 occasions 6 hours apart is considered abnormal. A mean arterial blood pressure of >105mmHg or an increase in mean arterial pressure of 20mmHg is also considered abnormal (1).

Proteinuria is defined as the excretion of 300 mg or more in a 24 hour specimen or 30 mg/dL in a random specimen or >1+ on the dipstick. Heavy proteinuria is defined as the excretion of 2g or more in a 24 hour specimen or >2+ on dipstick (1).The criteria for superimposed pre-eclampsia are worsening hypertension (30mmHg systolic or 15mmHg diastolic above the values before 20 weeks gestation) together with non-dependent edema or proteinuria (1). Gestational hypertension is divided into transient hypertension if pre-eclampsia is present at time of delivery and pressure returns to normal by 12 weeks postpartum or chronic hypertension if the pressure remains elevated beyond 12 weeks postpartum (1). Pre-eclampsia can be mild or severe. Pre-eclampsia can be defined as Blood Pressure(BP) >160/110 mmHg on 2 occasions 6 hours apart and proteinuria exceeding 2 grams in 24 hour period or 2-4+ on dipstick. (1, 18,19). Pre-eclampsia is a disorder of placental dysfunction leading to a syndrome of endothelial dysfunction associated

with vasospasm. The pathology demonstrates evidence of placental insufficiency with associated abnormalities such as diffuse placental thrombosis, an inflammatory placental decidual vasculopathy, and/or abnormal trophoblastic invasion of the endometrium. Thus abnormal placental development or placental damage from diffuse micro thrombosis is thought to be central to the development of this disorder (21). The widespread endothelial dysfunction may manifest as a maternal syndrome, fetal syndrome, or both. On the maternal side, it causes deficient infiltration of the spiral arteries by the trophoblast, failing to convert it into utero-placental arteries. Subsequently, the tenfold increase in uterine perfusion that occurs in normal pregnancy, fails to occur. This interferes with blood flow in the uterine artery (21) and therefore the mother may manifest with dysfunction of multiple organ systems, including the central nervous, hepatic, pulmonary, renal, and hematological systems. The Endothelial damage leads to pathologic capillary leak that can present in the mother as rapid weight gain, non-dependent edema (face or hands), pulmonary edema, haemo-concentration, or a combination thereof (21). On the fetal side, there is poor vascularization of the terminal villi, villous stromal hemorrhage, hemorrhagic endovasculitis or obliteration of the stem villi. This results in a decrease in fetal perfusion which manifests clinically as non-reassuring fetal heart rate testing, low scores on a biophysical profile, oligohydramnios, or as intrauterine growth restriction (IUGR) (22). Thus HSP can cause harm to the gravid patient and also to the fetus (22). It is one of the leading causes of maternal and perinatal morbidity and mortality (23-29). HSP is a major determinant of the timing of admission, timing of delivery and mode of delivery (30-33) It is therefore vital to have reliable maternal and fetal monitoring methods that can be used antenatally so as to reduce maternal and perinatal morbidity and mortality.

Fetal Monitoring

At KNH, focused antenatal care (FANC) system is used. A gravid mother who comes to the Maternal and Child Health clinic (MCH) or ante-natal clinic (ANC) is followed up at four divided visits throughout her pregnancy.

At each ante-natal visit, the following is usually done

- Checking of maternal weight
- Blood pressure(BP) measurement
- Urinalysis(UA)-for proteinuria or leucocytes

- Checking the hemoglobin(Hb) level
- Check the blood group(ABO and Rh status)
- Check the patient's serostatus (HIV status)
- Assessment of fundal height and correlating it with gestation by dates.
- Assessment of fetal presentation and lie.
- Assessment of fetal heart rate using Pinnard fetoscope
- Administration of ferrous and folic acid
- Administration of tetanus toxoid (35)

For patients with high risk pregnancies, ante-natal follow up is then tailored to the individual needs of the patient. The standard work up for patients with pre-eclampsia includes the following:

- Hemoglobin(Hb) and haematocrit level(Hct)
- Serum urea, creatinine and uric acid level.(U/E/C)
- Transaminase, albumin and lactic acid dehydrogenase levels.
- Blood smear
- Coagulation profile

Some of the tests mentioned above rule out haemolysis and hepatic involvement. They are also useful for monitoring progression and specific organ involvement (36). Assessment of fetal well being includes daily monitoring of fetal movements with more specific tests like non stress test(NST), ultrasonographic assessment of fetal movements and amniotic fluid volume (AFV) (36). Patients with mild pre-eclampsia may be followed up as outpatients bi-weekly and admitted if this is not possible. The patient should be warned on the danger signs of pre-eclampsia and eclampsia. Extra rest is advised and no dietary restrictions are necessary (36). When the fetal well being/fetal status are in doubt, closer monitoring is required. There are various methods of doing this.

- Fetal kick chart (FKC) is a chart invented by Sadowsky in 1977 and the mother fills in the chart over a period of 12 hours daily for a period of ten days and in this period, less than 10 fetal kicks are considered abnormal (37).Studies have shown that the fetal kick

chart is not an accurate method of monitoring fetal status as a mother may exaggerate kicks (38).

- Cardiotocography (CTG) is an electronic method of simultaneously recording fetal heart rate, fetal movements and uterine contractions to identify presence of fetal hypoxia (39). Poor standardization in interpretation and disagreement about appropriate interventions has resulted in a lack of reliable and valid data to demonstrate efficacy of CTG monitoring (40).
- Ultrasound scan (U/S) is performed to assess fetal presentation, placental position, and fetal viability, attain fetal heart rate, ultrasonographic gestational age, and perform BPPS and Doppler indices of UA and MCA (37). The BPPS has been found to be reflective of the fetal condition (40, 41) and is better for detection of acute fetal distress as most of its parameters measure acute asphyxia (42). The Umbilical Artery Resistive Index (UA RI) is reflective of utero-placental circulatory status. The Doppler waveform changes have been found to have good correlation with fetal compromise giving an earlier warning of fetal distress than CTG or BPPS (44). It is however not reflective of the circulatory status of fetal brain which requires assessment of Middle Cerebral Artery (MCA).

Doppler Ultrasound

Historical Perspective

The Doppler Shift Principle was discovered by Johann Christian Andreas Doppler in 1842 which was initially used in astronomy and later in the military, in various branches of industry, and more recently in medicine (45). The Doppler Shift Principle or Doppler Effect is based on the perceived change in frequency of an energy waveform as the source and the receiver move toward or away from each other (46). In biology, Doppler ultrasonography was used non-invasively, to measure flow velocity in blood vessels. Flow velocity depends on volume and speed of blood relative to diameter of the vessel. Estimating fetal vascular resistance through study of Doppler flow velocity provides a means of indirectly assessing fetal physiology and pathophysiology (8). Johnson and colleagues in 1965, made the earliest mention in the use of Doppler Effect in obstetrics (47). The use of Doppler ultrasonography to investigate the pattern

of waveforms in UA during pregnancy initially was reported in 1977 by Fitzgerald and Drumm. (48). Subsequently, Wladimiroff and associates reported on Doppler assessment of cerebral blood flow in the human fetus (49). The addition of color mapping has enhanced the utility of the Doppler Shift Principle in sonographic assessment of the fetus. The fetal UA and MCA have evolved as primary targets of fetal Doppler studies. Using Doppler systems in 1983, Campbell published the assessment of the utero-placental circulation which showed that high resistance waveforms were obtained in pre-eclampsia (49,50) With use of color Doppler, in 1987, it was possible to study the MCA in fetuses and compare to UA RI to demonstrate centralization of fetal circulation (51). Centralization is the process whereby there is high resistance in placental circulation and circulatory adaptation in hypoxic states leads to preferential flow of blood to the brain as compared to the peripheries. The use of Doppler velocimetry in pre-eclampsia and intra-uterine growth restriction and its correlation with adverse pregnancy outcome is well established (52). Doppler ultrasound provides a safe, non-invasive and rapid method to assess fetal well being. Doppler velocimetry has an important contribution to the surveillance of fetal circulation. These studies are used complementary to the traditional biophysical profile scores and non stress test (53).

Technical Consideration

Continuous Wave (CW), Pulsed Wave (PW), Color Flow (CF) and Power Doppler instrumentation have all been used for fetal blood flow assessments. The most important for Resistive index is the pulsed Doppler. Pulsed Doppler is defined as a technique in which the transducer emits ultrasound in pulses and it is used to assess flow velocity patterns within the arteries and veins that are simultaneously visualized by gray scale ultrasound. Blood flow velocities in the placental and fetal circulations range between 10-80 cm/sec. (3, 54).

Doppler Wavelength Analysis

Quantitative Analysis

A variety of arterial indices have been developed that use the ratio of systolic (S) and diastolic (D) velocities so that the results are angle dependent. There are three arterial indices commonly used to describe peak blood flow velocity waveforms and these are Systolic/Diastolic ratio (S/D

ratio), Resistive Index (RI), and Pulsatility Index (PI) (3). RI/ Pourcelot index (61) is a measure of resistance of an organ to perfusion. It is measured by subtracting end- diastolic velocity (EDV) from peak systolic velocity (PSV) and dividing that by peak- systolic velocity (3).With vascular compliance, RI is dependent on resistance of the vessel and it therefore increases with increase in vascular resistance. It approaches one when the diastolic velocity reaches zero. It is preferred as it has been used worldwide for several years and is easy to measure (55).

PI/ Gosling index (61) is a measurement of variability of blood velocity in a vessel equal to the difference between PSV and EDV divided by the mean velocity during one cardiac cycle (3).It is a more accurate indicator of vascular resistance as it continues to show change even with no diastolic flow. However, it is difficult to measure and therefore has not gained widespread use (56). S/D ratio (61) is a measurement of the ratio of PSV over EDV (3).It reaches infinity once diastolic velocity reaches zero. It is preferred by some investigators as it is simple and is less prone to inter-observer and intra-observer errors (57). However all indices seem to show 100% specificity and 80% sensitivity for prediction of fetal compromise (57) and as RI is most widely used arterial index and is reflective of vascular resistance, it is used in this study.

Qualitative Analysis

The UA Doppler waveforms can be:

- Normal
- Reduced diastolic flow
- Absent end diastolic flow
- Reversed end diastolic flow.

Figure 1 Typical Waveform of umbilical artery and Calculation of Doppler Indices. (59)

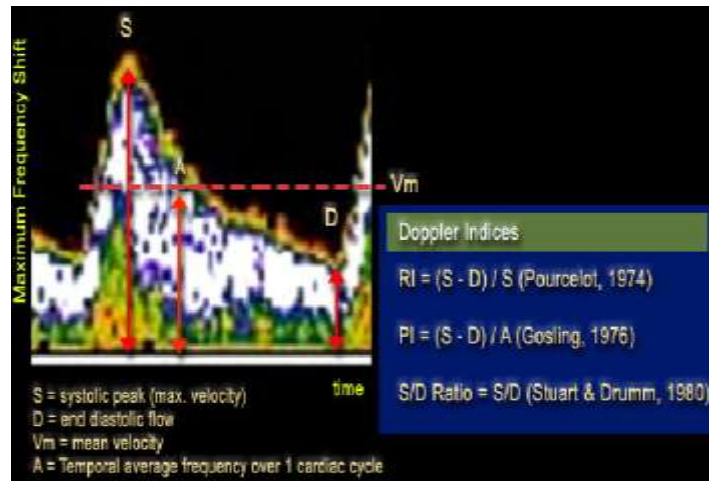


Figure 2 Waveforms of absent end diastolic flow (68)

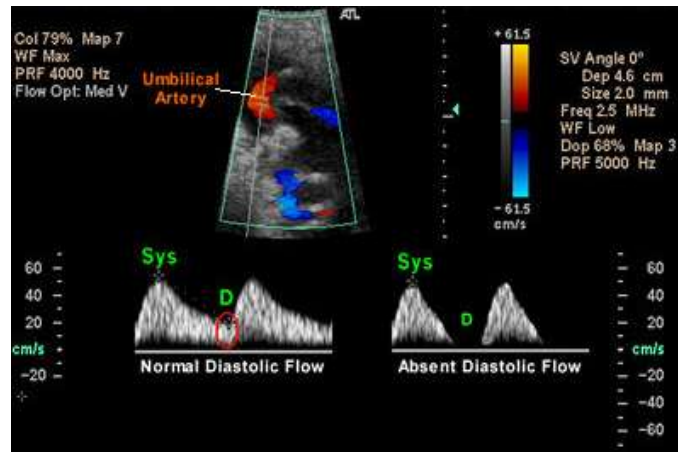
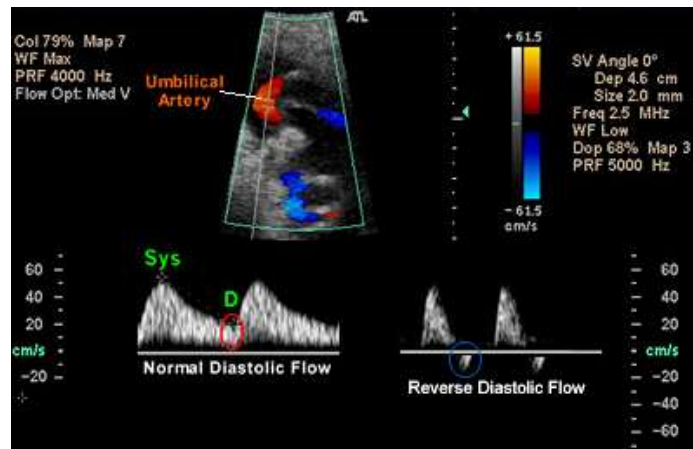


Figure 3 Waveforms of reversed end diastolic flow (68)



Functional Doppler Studies

The Physiology of Placental Blood Flow

Umbilical Artery.

The development of the fetal circulation begins with the coalescence of angioblasts in the mesenchyme of the yolk sac at about day 17(60).The angioblasts begin to coalesce into blood islands in the splanchnopleuric mesoderm of the embryo by day 18. The angioblasts flatten into endothelial cells which join to form networks of endothelial channels that form the primitive circulatory system (60). The endothelial heart tubes fuse to form a single heart tube by the end of the third week and by day 22. The heart begins to beat and the embryo has a functional circulatory system (60). The embryo connects to the developing feto-placental vasculature via the umbilical cord at around 8 to 10 weeks of gestation.The oxygenated blood is delivered to the fetus through the single umbilical vein and deoxygenated blood from the fetus is returned to the placenta for re-oxygenation via two umbilical arteries (61).

Throughout the first trimester, the UA waveform is characterized by absent end diastolic flow. Progressive growth of placental villous tree, together with an increase in fetal cardiac output, increases both systolic and diastolic velocity in the umbilical artery. Therefore RI values progressively fall as pregnancy advances (62). Diastolic velocities are typically present at 14-16 weeks thus absent or reversed end diastolic velocity in the umbilical artery is an abnormal finding by 18-22 weeks. Absent end-diastolic flow in UA is indicative of more severe fetal hypoxia and pathologically is associated with obliteration of capillaries in placental stem villi. Reversed end-diastolic flow carries a very poor prognosis and is an indicator of impending fetal demise (62). The placentas of fetuses that exhibit abnormal Doppler flow velocity have slender capillaries with decreased capillary loops in gas-exchanging terminal villi.

The UA is most commonly assessed fetal vessel and it gives a measure of fetal systemic and placental vascular impedance (53). The abnormal UA Doppler waveforms are indicative of placental insufficiency. Abnormal Doppler waveforms can be reduced end diastolic flow, absent end diastolic flow or reversed end diastolic flow and these are indicative of fetal compromise. The risk of perinatal mortality increases up to 60%, with increasing severity from reduced to reversed end-diastolic flow velocity (63). The time period between identification of an

abnormal UA Doppler waveform and the development of fetal distress and/or death varies widely – from days to weeks. Various studies show that there is a wide variability in the interval between detection of UA absent or reverse end-diastolic flow velocities and the occurrence of heart rate decelerations (64).

Figure 4 Characteristic Saw-tooth Appearance of Umbilical Arterial Flow (59)

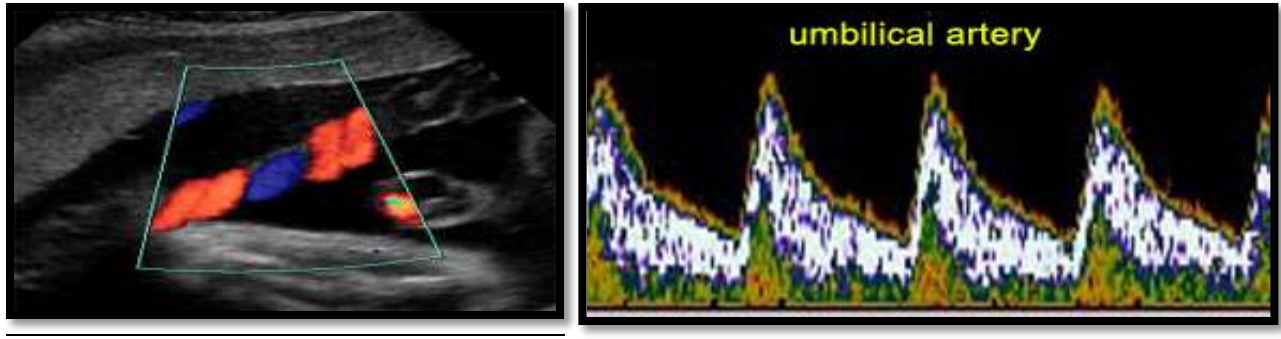
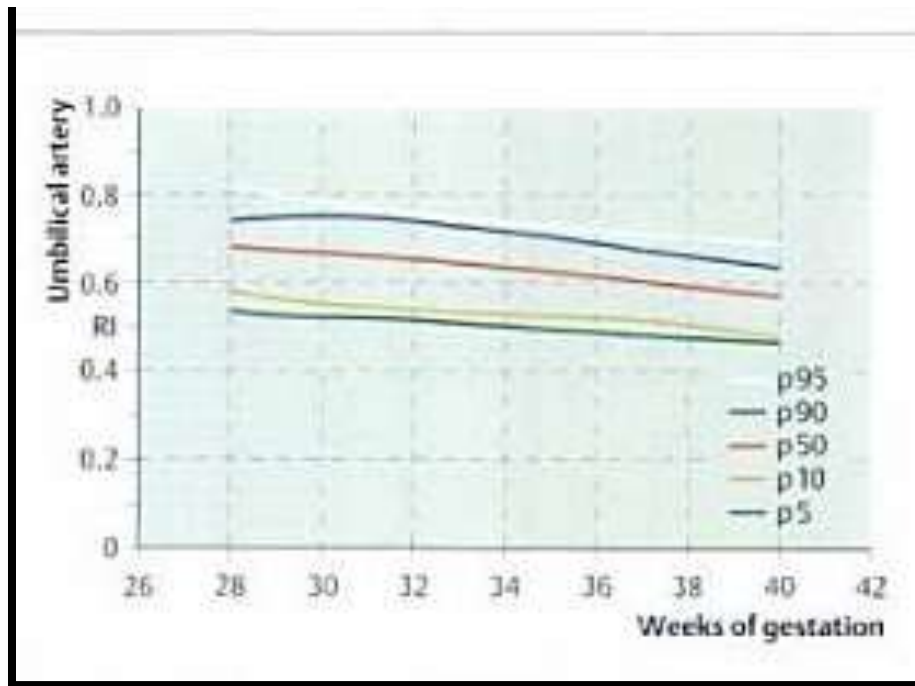


Figure 5 Reference Curves for the UARI (68)



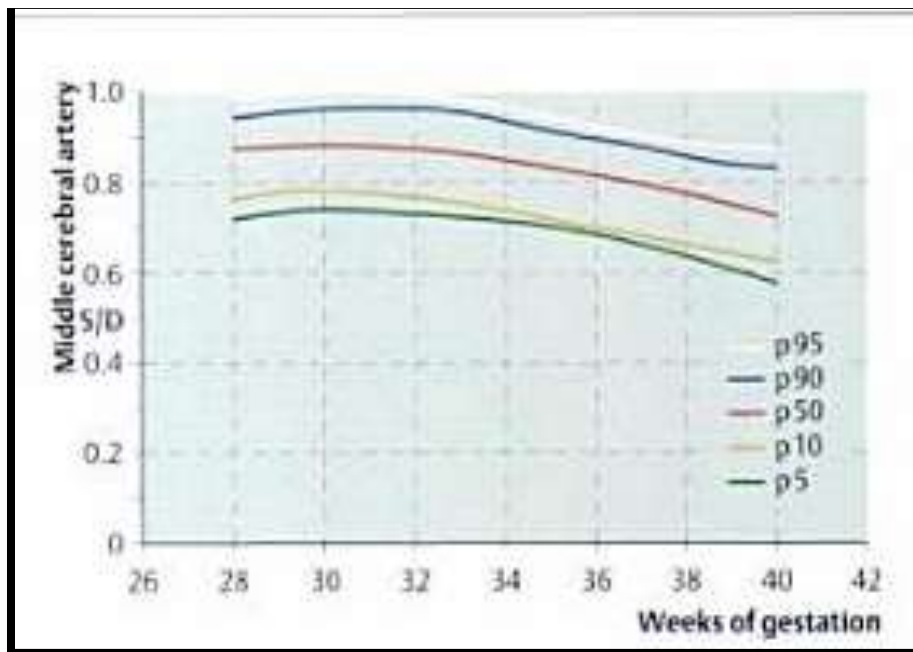
Middle Cerebral Artery

The circle of Willis is easily demonstrated by Color Doppler ultrasound at the base of the skull in the transverse fetal head position. In this orientation, the middle cerebral arteries run in vertical alignment along the edge of the sphenoid bone (3). MCA Doppler indices provide a measure of fetal central nervous system vascular resistance. The measurement of MCA flow velocity can be used in two primary settings which are to detect evidence of redistribution of fetal blood flow to the brain in cases of placental insufficiency, fetal hypoxia, associated fetal growth restriction and to detect increased blood flow to the brain in cases of fetal anemia (8). The typical MCA waveform at 28-32 weeks is characterized by high systolic velocities and minimal diastolic velocities resulting in high RI values greater than 0.80 which decreases with increasing gestational age (3). The cerebral arteries respond quickly to hypoxemia because of the strong dependence of the brain tissue on oxygen. It is speculated that a compensatory decrease in cerebral-vascular impedance, with a redistribution of blood flow toward the fetal brain, reflects a brain-sparing effect that characterizes chronic fetal hypoxia. In situations of low oxygen tension, vascular tone is reduced in the MCA, resulting in increased diastolic velocity and reduced RI values (3). This is known as centralization and its loss is a sign preceding fetal demise (55). Abnormal UA flow velocity precedes impairment of MCA flow velocity. MCA velocimetry does not improve the predictive value of UA velocimetry in normally grown fetuses. However, in growth-restricted fetuses in which UA study results are abnormal, a MCA flow velocity that is abnormal is indicative of an increase in adverse perinatal outcome (12)

Figure 6 Color Doppler View of middle cerebral arteries and Typical Doppler Waveform. (8)



Figure 7 Reference Curves for MCARI (68)



The Cerebro-Placental Ratio

This is a ratio of the MCA RI over the UA RI and its change is an indicator of peripheral fetal flow distribution (4). The main advantages of measuring the cerebral and placental vascular resistance is that account is taken of placental vascular resistance which can be responsible for an alteration of the maternal to fetal exchanges and also the cerebral hemodynamic consequences of these abnormalities (4). In normal pregnancies, the diastolic component of the MCA waveform is lower than in the UA waveform at any gestational age and therefore cerebral vascular resistance remains higher than placental resistance resulting in a CPR more than 1.0 which is considered normal (4).

According to Gramellini et al, the CPR remains constant in the last 10 weeks of pregnancy and thus a single cut-off value of 1.0 is used in the study (63). When the CPR becomes <1.0 it is considered abnormal because it is indicative of vascular redistribution to the brain and is shown to be predictive of adverse perinatal outcome (6).

Various studies have shown the CPR to be predictive of adverse perinatal outcome. With a CPR threshold of less than 1.08, the sensitivity, specificity, and positive and negative predictive values were 72%, 62%, 68%, and 67%, with an odds ratio (95% confidence interval) of 4.2 (1.2–15.3; area under the receiver operating characteristic curve, 0.67). An abnormal CPR is associated with adverse perinatal outcomes in growth-restricted fetuses. The accuracy of using gestational age-specific reference levels was similar to that of using a categorical threshold. (11,12,13,14,15,66)

The authors found that

A longitudinal study of 80 patients with severe preeclampsia (PA $>160/110$, Proteinuria 3+) was performed. Doppler study done by one operator was performed every 72 hours at the beginning and within 7 days before delivery. Resistance index of middle cerebral artery (MCA) and umbilical artery (UA) were used to calculate the CPR. CPR <1 was considered abnormal. Abnormal CPR identifies 60% of newborns with severe neonatal morbidity (11)

CPR had 64.1% sensitivity, 72.7% specificity, 89.2% positive predictive value, and 36.3% negative predictive value for neonatal morbidity. There was a strong correlation between the CPR and neonatal outcome in women with preeclampsia. CPR <1.0 may be helpful in the

identification of newborns at risk of morbidity, irrespective of whether they are small or appropriate for their gestational age (12).

A longitudinal study of 80 patients with severe pre-eclampsia (BP > 160/110, proteinuria 3+) was performed, Doppler study was performed by one operator was performed every 72 hours in the beginning and before 7 days before delivery. Resistance of MCA and UA were used to calculate the CPR. A CPR < 1.0 was considered abnormal. The CPR had 64.1% sensitivity, 72.7% specificity, 89.2% positive predictive value, and 36.3% negative predictive value for neonatal morbidity. There was a strong correlation between the CPR and neonatal outcome in women with preeclampsia. A conclusion made from the results of the study was that an abnormal CPR identifies 60% of newborns with severe neonatal morbidity in pregnancies with severe preeclampsia (13).

Eleven studies involving nearly 7000 women were included in meta-analysis trials. The trials were generally of good quality. Doppler ultrasound in high risk pregnancy (especially those complicated by hypertension or presumed impaired fetal growth) was associated with a reduction in perinatal deaths (odds ratio 0.71, 95% confidence interval 0.50 to 1.01) as compared to no Doppler sonography. The use of Doppler ultrasound was also associated with fewer inductions of labour (odds ratio 0.83, 95% confidence interval 0.74 to 0.93) and fewer admissions to hospital (odds ratio 0.56, 95% 0.43 to 0.72), without reports of adverse effects. No difference was found for fetal distress in labour (odds ratio 0.81, 95% confidence interval 0.59 to 1.13) or caesarean delivery (odds ratio 0.94, 95% 0.82 to 1.06). (14)

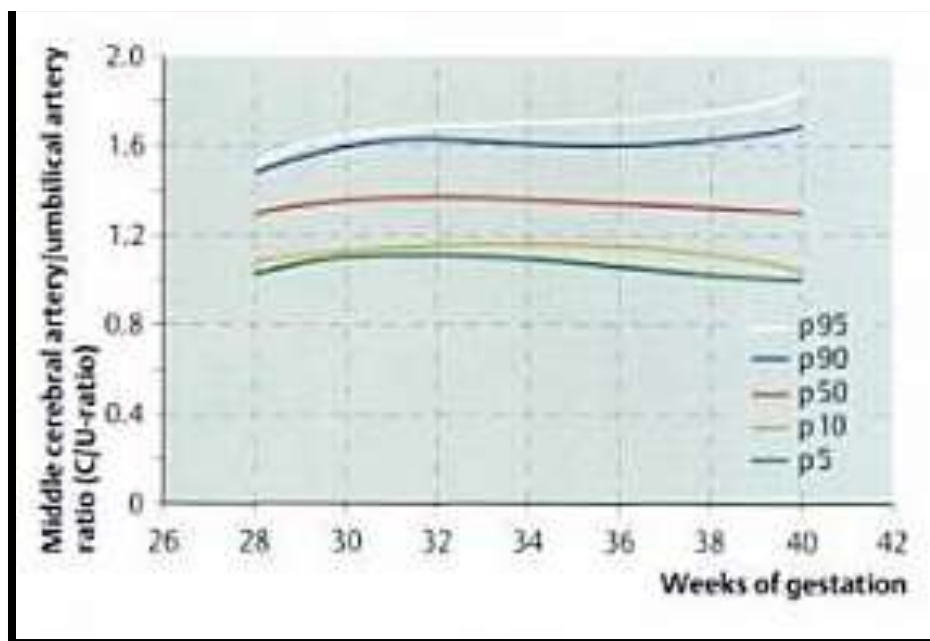
The CPR was 83% sensitive and 75% specific in predicting adverse perinatal outcome. Sensitivity is increased to 91.6 % with multi-vessel Doppler study which include the fetal umbilical artery, fetal ductus venosus, fetal aorta, maternal uterine artery, fetal middle cerebral artery and fetal renal arteries (15).

A meta-analysis of randomized controlled trials suggests that incorporation of umbilical artery Doppler waveform analysis into management protocols for high risk pregnancies significantly decreases perinatal mortality. Compared to no Doppler ultrasound, Doppler ultrasound in high risk pregnancy (especially those complicated by hypertension or presumed impaired fetal

growth) was associated with a trend to a reduction in perinatal deaths (odds ratio 0.71, 95% confidence interval 0.50 to 1.01) (16).

An abnormal CPR is associated with adverse perinatal outcomes in growth restricted fetuses. The accuracy of using gestational age specific reference levels was similar to that of using a categorical threshold. The CPR has been shown to be a good predictor of the fetal oxygenation status at birth and can be used to identify pregnancies that are at risk for adverse outcomes. (66).

Figure 8 Reference Curves for the Cerebro-Placental Ratio (68)



STUDY DESIGN

Problem statement

The incidence of hypertensive disorders of pregnancy is 7.1% in Kenya (19) and a major cause of maternal and perinatal morbidity and mortality. Currently, fetal monitoring in patients with HSP at KNH is done via Pinnard fetoscope and CTG. An ultrasound scan is usually done between 32-38 weeks of gestation including biometric profile, and an UA RI). Currently in KNH, Management on time of delivery and mode of delivery is determined by BPPS and the UA RI (34)

It has been shown that the BPPS is similar to CTG in fetal monitoring and does not add any benefit to fetal monitoring (64). Whereas UA RI is a good indicator of fetal compromise, it is not adequate as it is only reflective of placental circulation and is not indicative of the state of fetal central nervous system circulation. Therefore it does not help in determining which fetus is at greatest risk of adverse perinatal outcome (8). Assessment of MCA Doppler waveform and calculation of CPR allows identification of fetuses at greater risk of adverse perinatal outcome when abnormal UA waveforms are present. This study assesses the CPR in third trimester gestation so as correlate with thee perinatal outcome. It forms a useful resource in development of management protocols or standards for patients with hypertensive states of pregnancy.

Study Objective

Broad Objective

To assess the role of the CPR as a prognostic factor in predicting fetal outcome in patients with hypertensive disorders of pregnancy in the third trimester(at or more than 32 weeks).

Specific Objectives

- To determine the socio-demographic characteristics of patients with hypertensive disorders of pregnancy at Kenyatta National Hospital.
- To classify the severity of hypertensive states of pregnancy using blood pressure and urinalysis at admission or prior to entry into study.
- To attain ultrasonographic fetal heart rate to assess for Non-Reassuring Fetal Status (NRFS).

- To evaluate the CPR for all patients with hypertensive states of pregnancy in the third trimester(at or more than 32 weeks)
- To correlate the CPR with fetal outcome in terms of live or still birth, the 5 minute Apgar score and the birth weight of the live births.

Study Justification

At KNH, the practice is to use the BPPS and UA RI in the management of patients with hypertensive states in pregnancy as concerns mode and time of delivery (34). Investigators suggest that the time period between identification of an abnormal umbilical artery Doppler waveform and the development of fetal distress and/or death varies widely(48) Studies show that there is a wide variability in the interval between detection of umbilical absent or reverse end-diastolic flow velocities and occurrence of heart rate decelerations(48). Abnormal umbilical artery Doppler waveforms (reduced diastolic flow, absent end diastolic flow and reversed end diastolic flow) alone do not determine fetal status. However they are an indicator of impending fetal distress (53) Assessing the Doppler waveform of the MCA and obtaining the cerebroplacental ratio gives us an indication of fetuses that are at greatest risk of adverse outcome(53). This study assessed the Doppler waveform of the middle cerebral artery and umbilical artery and thereby obtaining the CPR. No such study had been published in this region and therefore it was important to assess the role of the CPR in the prediction of fetal outcome in mothers with hypertensive states of pregnancy locally. A positive correlation would greatly enhance antenatal monitoring of the fetus and also improve on the management of these patients.

Research Question

What is the prognostic value of the CPR as a predictor of adverse fetal outcome in patients with hypertensive disorders of pregnancy?

Hypothesis

The CPR is an accurate predictor of adverse fetal outcome in patients with hypertensive states of pregnancy.

Design and Methodology

This is a prospective cohort study conducted at Kenyatta National Hospital over a period of nine months (November 2010 to August 2011) following approval by the KNH/UON- Ethics and research Committee.

Sampling

A cohort of women with hypertensive disorders of pregnancy with or without concomitant IUGR was recruited over the 9 month period after obtaining informed consent. Informed consent was taken from the patient herself or next of kin in patients who were not able to give consent (eclamptics or underage patients). Recruitment took place from the labor ward over a period of 24 hours a day by the principal investigator or research assistant.

Inclusion criteria include

- Consent giving patients
- Singleton pregnancy.
- Gestational age at the time of study entry should be at least 32 completed weeks as this is the time most patients with hypertensive states of pregnancy are admitted to labor ward for closer monitoring/delivery.
- Normal fetal anatomic survey.
- Absence of maternal metabolic disease or any other vascular disease.

Exclusion criteria include

- Non consent giving patients.
- Multiple pregnancies as they have additional risk factors that can bias the study results.
- Patients presenting for the ultrasound scan with IUFD or fetal anomalies.
- Known maternal metabolic disease or other vascular diseases.

There was no discrimination based on race, religion, age, political background or socio-economic status in this study.

Method

After obtaining informed consent from the patient or next of kin, a structured questionnaire was filled out by the principal investigator or research assistant. Blood pressure recording and urinalysis report was recorded to classify severity and type of hypertension. An obstetric

ultrasound scan was carried out on request by the clinician and coded for fetal presentation, placental position, fetal heart rate, approximate ultrasonographic age, BPPS, UA RI and MCA RI. The ultrasound machines used were real time machines, the Phillips HD11 and GE Logic 7. The transducer frequency was 3.5 – 5.0 MHz, the Doppler sample volume was 2 mm and the wall filter was 50–100 Hz. The examination was performed with the mother in a semi-recumbent position during relative fetal inactivity and apnea. This is because the end diastolic flow (EDF) decreases with decreasing fetal heart rate and fetal breathing movements increase variability in the Doppler measurements.

The UA was sampled at the middle of a free loop of umbilical cord. This is because the EDF is higher near the umbilical cord insertion into the fetal abdomen than near the placental insertion and vice versa at the placental end. It could also be assessed at the level of the fetal bladder. For MCA, a transverse image of the fetal head was obtained at the level of the sphenoid bones. Color Flow imaging was used to display the circle of Willis. The MCA in the near field was isonated about 1 cm distal to its origin from the internal carotid artery. By using the optimal spectral trace from each artery, the Resistive Index was calculated from the mean of a minimum of five consecutive waveforms on a frozen image. A series of three readings were taken for each artery to avoid errors. The cerebral/placental ratio was calculated from the MCA RI and UA RI. Patients were divided into groups of two depending on the CPR. A CPR of > 1.0 was considered normal and a CPR of < 1.0 abnormal.

U/S fetal heart rate, biometric measurements, BPPS and MCA/UA Doppler results were used to determine management. Follow up was made for fetal outcome whether it was a live birth or still birth. The 5 minute Apgar score and birth weight were recorded.

Sample size consideration

The study population included pregnant women with hypertensive disorders. The study arms were defined as

Group 0: Mothers with hypertensive disorders and with a Doppler ultrasound indicative of an abnormal cerebral/placental ratio (CPR<1.0).

Group 1: Mothers with hypertensive disorders with a Doppler ultrasound indicative of a normal cerebral/placental ratio (CPR>1.0).

The study outcome variables were

1. Neonate condition (Live birth or still birth)
2. The 5 minute APGAR score-5 min (< 7 or ≥ 7)
3. Birth weight – (<10th percentile of the expected weight for gestation)

For each of the outcome variable, let **p** be the smallest of the proportions of negative or positive cases in the population and **k** be the number of predictor variables (either clinically or statistically significant), then the minimum number of subjects to be enrolled is given by

$$N = \frac{10k}{p}, \text{ Peduzzi et al. (1996) (65)}$$

The maximum number of predictor variables that were included in the model was three while the smallest proportion of outcome was p=0.2. This yields a total sample size of **150** patients but the sample size achieved was **160** patients.

Data management and statistical analysis

A structured questionnaire was used to collect data. The data was entered manually into a database (Ms Access 2007) via user-defined forms. The data entry forms had quality control checks in order to ensure accuracy of the data. The data base security features ensured confidentiality and access to the participants' data. All data was cleaned and exported for statistical analysis. Statistical Package for Social Sciences (SPSS 17.0) was used for the analysis. Descriptive statistics-mean (95% CI), standard deviation, median (IQR) and frequencies were used to characterize the study population. Dummy tables are used to present the study findings. Mann-Whitney U, chi-square and Fisher exact tests was used for comparative analysis. Logistic

regression was used to estimate the odds of each outcome variable associated with every predictor variable, that is:

$$\text{logit}(p) = b_0 + \sum_{i=1}^k x_i$$

Where p is the probability of presence of the characteristic of interest.

$$\text{odds} = \frac{p}{1-p} = \frac{\text{prob}(\text{presence of a characteristic})}{\text{prob}(\text{absence of a characteristic})}$$

Unadjusted odds ratio of each outcome variable associated with CPR was determined; all clinically and statistically significant variables were adjusted for in the multivariate analysis. A 5% level of significance was used to determine if a variable contribute significantly to the prediction of the outcome variable.

Ethical Considerations

This study employed the use of ultrasound which is a sound waveform unlike other methods that use ionizing radiation and has been confirmed to have no biological effect on patients or the fetus at intensities typical of present diagnostic instruments. Permission to carry out the research was sought from and granted by KNH/UON-ERC. Permission was sought from director of clinical services, KNH. Authorities from Department of Diagnostic Imaging and Radiation Medicine and Department of Obstetrics and Gynecology, KNH were consulted and informed.

The following ethical guidelines were used in line with the Helsinki Declaration (World Medical Association – June 1964).

- Patients name, religion and racial backgrounds were not documented in this study. Patients were identified by Hospital numbers to safeguard confidentiality. Information obtained from the study was treated with total confidentiality and results used for academic and clinical improvement purposes only.
- No additional imaging examination was done other than the one requested by the referring clinician.
- The patient did not incur any additional cost.
- No blood sample was collected as it was not indicated in this study

- All patients were managed at the optimal standards depending on clinical state.
- No victimization or preferential treatment was offered to patients as a result of participating or refusing to participate in the study.
- A copy of the research findings would be given to the KNH/UON-Ethics and Research Committee for future references and to facilitate any possible improvement in patient management.
- Informed written consent was obtained from all the participants.
- The results of the ultrasound scan were availed to the clinician immediately to allow for timely and appropriate management

STUDY RESULTS

ULTRASOUND SCANS

FIGURE 9 AND FIGURE 10-ULTRASOUND SCANS OF PATIENT WITH MCA RI OF 0.683 AND UA RI OF 0.967 GIVING A CPR OF 0.71 WHICH IS LESS THAN ONE PREDICTIVE OF ADVERSE PERINATAL OUTCOME.

Figure 9 Ultra-sound scan showing MCA RI of 0.683



Figure 10 Ultra-sound scan showing UA RI of 0.967 and absent end diastolic flow



FIGURE 11 AND 12- ULTRASOUND SCANS OF PATIENT WITH MCA RI OF 0.782 AND UA RI OF 0.596 GIVING A CPR OF 1.31 WHICH IS NORMAL .

Figure 11 Ultra-sound scan showing MCA RI of 0.782



Figure 12 Ultra-sound scan showing UA RI of 0.596



Half of the mothers enrolled into the study were age below 28 (IQR: 24, 33) years with the majority, 141 (88.1%) being married

Table 1 Demographic Characteristics of the study population

Characteristics	n (%) or median (IQR)	Characteristics	n (%) or median (IQR)
Maternal Age	28 (24, 33)	Occupation	
		• Self-employed	27 (17%)
Marital status		• Employed	42 (26%)
• Married	141 (88.1%)	• Not-employed (Housewife)	91 (57%)
• Single	18 (11.3%)		
• Divorced/Separated	1 (0.6%)	Parity	1 (0, 2)
• Widowed	-		
		Gestation age	34 (33, 37)

Seventeen percent were self-employed, 42 (26%) were in formal employment while 91 (57%) were not employed. Half of them had at least one (IQR: 0, 2) child and presented for care at 34 (IQR: 33, 37) weeks gestation.

Table 2 Clinical Observations

Characteristics	n (%) median (IQR)	Characteristics	n (%) median (IQR)
Clinical findings			
Blood pressure-		Fetal heart rate	138 (132, 140)
• Systolic	154 (143, 170)	Urinalysis	2 (2, 3)
• Diastolic	104 (95, 113)		
PET		Biophysical profile score	8 (6, 8)
• Severe	51 (32%)	Approximate ultrasound age	31 (33, 35)
• Mild	109 (68%)		
Ultra-sound findings		Umbilical Artery resistive index (UARI)	0.64 (0.548, 0.72)
Fetal presentation		Middle Cerebral Artery resistive index	0.74 (0.646, 0.817)
• Cephalic	143 (89%)		
• Breech	17 (11%)	Cerebral/Placental Doppler Ratio	
Placenta		< 1.0	47 (29%)
1. Fundo-anterior	86 (54%)	≥ 1.0	113 (71%)
2. Fundo-posterior	74 (46%)		
3. Low-lying	-		

The median Biophysical Profile score was 8 (IQR: 6, 8); the median umbilical artery resistive index was 0.64 (IQR: 0.548, 0.72) while the middle cerebral artery resistive index was 0.74 (IQR: 0.646, 0.817). The CPR < 1.0 was observed in 47 (29%) of the study population.

Table 3 Clinical Management and Fetal Outcome

Characteristics	n (%) median (IQR)	Characteristics	n (%) median (IQR)
Steroid administered		Mode of delivery	
• Yes	99 (62%)	• Caesarian Section	125 (78%)
• No	61 (38%)	• SVD	35 (22%)
Fetal Outcome		APGAR Score (5 minutes)	9 (8, 10)
4. Alive	144 (90%)	• < 7	30 (19%)
5. Still birth	16 (10%)	• ≥ 7	130 (81%)
Infant weight (at birth)	2,100 (1,700, 2638)	Infant admitted in NBU	
• Low	27 (17%)	• Yes	42 (26)
• Normal	133 (83%)	• No	118 (74)

Steroid was administered to 99 (62%) of the mothers. Caesarian section was performed on 125 (78%) of the mothers compared to 35 (22%) who had normal delivery. 10% of the deliveries were still births, 27 (17%) of the infants weighed less than 1,500 grams with median weight 2,100 (IQR: 1,700, 2,638). The median APGAR score (at 5 minutes) was 9 (IQR: 8, 10); 30 (19%) has an APGAR score of less than 7. Forty two percent neonates were admitted in the newborn unit.

Table 4 Correlates of Fetal Outcome among hypertensive pregnant mothers

Characteristics	Fetal Outcome		p-value
	Still birth n (%) or Median (IQR)	Live birth n (%) or Median (IQR)	
Cerebral/Placental Ratio			
• < 1.0	14 (87.5)	33 (23)	< 0.001
• ≥ 1.0	2 (12.5)	111 (77)	
Maternal age	31 (26, 34)	28 (24, 32)	0.2 ^m
Marital Status			
• Married	13 (81)	128 (89)	0.4*
• Not married	3 (19)	16 (11)	
Occupation			
• With Employed	6 (37.5)	63 (44)	0.6
• Not employed	10 (62.5)	81 (56)	
Presentation			
• Cephalic	14 (87.5)	129 (89.6)	0.7*
• Breech	2 (12.5)	15 (10.4)	
Biophysical score	4 (4, 6)	8 (6, 8)	< 0.001 ^m
Parity			
• 1 or none	10 (62.5)	105 (73)	0.4*
• ≥ 1	6 (37.5)	39 (27)	
Mode of delivery			
• SVD	11 (69)	24 (17)	< 0.001*
• Caesarian Section	5 (31)	120 (83)	
	16 (100%)	144 (100%)	
Estimated conditional probabilities for fetal outcome prognosis			
Estimated 95% Confidence Interval for sensitivity and specificity computed using Wilson Score Method			
* Fisher Exact Tests used			
m –Mann Whitney test used			

There was evidence of association between the Cerebral/Placental Ratio (p<0.001), mode of delivery (p<0.001), Biophysical Profile score (p<0.001) and fetal outcome among mothers in the study population. The CPR (C/U RI ratio) had 87.5% (95% CI 64%, 96.5%) sensitivity, 77%

(70%, 83.2%) specificity, 30% positive predictive value, and 98.2% negative predictive value for neonatal mortality. However, there was no significant difference in maternal age ($p=0.2$), marital status ($p=0.4$), occupation ($p=0.6$), fetal presentation-Cephalic vs. Breach ($p = 0.7$) and parity ($p = 0.4$) on fetal outcome.

Table 5: Logistic regression for the correlates of Fetal Outcome among hypertensive pregnant mothers

Characteristics	Fetal Outcome		Prognostic Odds Ratio			
	No. still birth/n	Odds (95% CI)	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Cerebral/Placental Ratio						
• < 1.0	14/47 (29.8%)	0.42 (0.23, 0.78)	23 (5, 108)	< 0.001	12.5 (2, 74)	0.005
• ≥ 1.0	2/113 (1.8%)	0.018 (0.005, 0.07)	Ref		ref	
Biophysical score			2.01 (1.5, 2.8)	< 0.001	1.7 (1.1, 2.5)	0.009
Mode of delivery						
• SVD	11/35 (31.4%)	0.458 (0.23, 0.92)	11 (3.5, 34.5)	< 0.001	14.5 (3, 84)	< 0.001
• Caesarian Section	5/125 (4%)	0.042 (0.02, 0.1)	Ref		ref	

In the univariate analysis, among hypertensive mothers with CPR < 1.0, still births were 0.42 (95% CI 0.23, 0.78) times more likely than live births and 23 (OR 23; 95% CI 5, 108) times more often relative to hypertensive mothers with CPR ≥ 1.0 . For every unit increase in the biophysical score, we expect the odds of a live birth to increase by 2.01 (95% CI 1.5, 2.8). Among SVD neonates, a still birth was 11 (95% CI 3.5, 34.5) times more likely than among CS newborns.

In multivariate analysis, adjusting for biophysical score and mode of delivery, still births among hypertensive mothers with CPR < 1.0 were 12.5 (OR 12.5; 95% CI 2, 74; $p=0.005$) times more often than mothers with CPR ≥ 1.0 . On adjusting for CPR and mode of delivery, for a unit increase in biophysical score, we expect about 70% increase in the odds of a live birth. On adjusting for biophysical score and CPR, still births among SVD neonates were 14.5 (OR 14.5; 95% CI 3, 84; $p<0.001$) times more often than Caesarian section neonates.

Table 6

Correlates of Infant's APGAR (5 minutes) Score of mothers with hypertensive disorder during the index pregnancy

Characteristics	Infant's APGAR score		p-value
	< 7 n (%) or Median (IQR)	≥7 n (%) or Median (IQR)	
Cerebral/Placental Ratio			
• < 1.0	28 (93.3)	19 (14.6)	< 0.001
• ≥ 1.0	2 (6.7)	111 (85.4)	
Maternal age	29 (24, 33)	28 (24, 33)	0.8 ^m
Marital Status			
• Married	24 (80)	117 (90)	0.2*
• Not married	6 (20)	13 (10)	
Occupation			
• With Employed	9 (30)	60 (46)	0.1
• Not employed	21 (70)	70 (54)	
Presentation			
• Cephalic	27 (90)	116 (89)	0.9*
• Breech	3 (10)	14 (10)	
Biophysical score	4 (4, 8)	8 (6,8)	< 0.001 ^m
Parity			
• 1 or none	21 (70)	94 (72.4)	0.8
• ≥ 1	9 (30)	36 (27.7)	
Mode of delivery			
• Caesarian Section	17 (57)	108 (83)	0.002
• SVD	13 (43)	22 (17)	
	30 (100%)	130 (100%)	
Estimated conditional probabilities for fetal outcome prognosis			
Estimated 95% Confidence Interval for sensitivity and specificity computed using Wilson Score Method			
* Fisher Exact Tests used			
m –Mann Whitney test used			

There was evidence of association between the Cerebral/Placental Ratio ($p < 0.001$), Biophysical score ($p < 0.001$) mode of delivery ($p = 0.002$) and APGAR (5 minutes) score in the study population. The CPR (C/U RI ratio) had 93.3% (95% CI 79%, 98%) sensitivity, 85.4% (95% CI 78.3%, 90.4%) specificity, 60% positive predictive value, and 98.2% negative predictive value for 5 minute APGAR score. However, there was no significant difference in marital status ($p = 0.8$), occupation ($p = 0.1$), fetal presentation-Cephalic vs. Breech ($p = 0.9$) or parity ($p = 0.8$) on neonate's APGAR score.

Table 7 Logistic regression for the correlates of Infant's APGAR (5 minutes) Score among mothers with hypertensive disorder during the index pregnancy

Characteristics	Infant's APGAR score		Prognostic Odds Ratio			
	APGAR score (< 7)/n	Odds (95% CI)	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Cerebral/Placental Ratio						
• < 1.0	28/47 (59.6%)	1.47 (0.8, 2.6)	82 (18, 372)	< 0.001	66 (13, 340)	< 0.001
• ≥ 1.0	2/113 (1.8%)	0.018 (0.005, 0.07)	Ref		ref	
Biophysical score			1.8 (1.4, 2.3)	< 0.001	1.3 (0.9, 1.9)	0.07
Mode of delivery						
• SVD	13/35 (37.1%)	0.6 (0.3, 1.16)	3.75 (1.6, 8.83)	0.002	6 (1.3, 23)	0.02
• Caesarian Section	17/125 (13.6%)	0.16 (0.09, 0.3)	Ref			

In the univariate analysis, among infants of mothers with hypertensive disorder during pregnancy with CPR < 1.0, an APGAR score < 7 was 1.47 (95% CI 0.8, 2.6; p<0.001) times more likely than a score ≥ 7 and 82 (OR 82; 95% CI 18, 372; p<0.001) times more likely relative to hypertensive mothers with CPR ≥ 1.0). For every unit increase in the biophysical score, we expect the odds of an APGAR score ≥ 7 to increase by 80%. Among SVD neonates, an APGAR score < 7 was 3.75 (95% CI 1.6, 8.83; p=0.002) times more likely than in CS newborns.

In multivariate analysis, adjusting for mode of delivery and biophysical score, an APGAR score < 7 among infants of hypertensive mothers with CPR < 1.0 was 66 (OR 66; 95% CI 13, 340; p< 0.001) times more often than among infants of mothers with CPR ≥ 1.0. On adjusting for CPR and mode of delivery, for every unit increase in biophysical score, we expect about 1.3 (95% CI 0.9, 1.9; p=0.07) increase in the odds of an APGAR score ≥ 7. However, the increase is not statistically significant. On adjusting for CPR and biophysical score, an APGAR score < 7 among SVD neonates was 6 (OR 6; 95% CI 1.3, 23; p=0.02) times more often than Caesarian section neonates.

Table 8 Correlates of Infant's birth weight among mothers with hypertensive disorder during the index pregnancy

Characteristics	Infant birth weight		p-value
	Low [†] n (%) or Median (IQR)	Normal n (%) or Median (IQR)	
Cerebral/Placental Ratio			
• < 1.0	37 (45.1)	10 (12.8)	< 0.001
• ≥ 1.0	45 (54.9)	68 (87.2)	
Maternal age	29 (24, 33)	27 (23, 33)	0.5 ^m
Marital Status			
• Married	74 (90.2)	67 (85.9)	0.4
• Not married	8 (9.8)	11 (14.1)	
Occupation			
• With Employed	32 (39)	37 (47.4)	0.3
• Not employed	50 (61)	41 (52.6)	
Presentation			
• Cephalic	73 (89)	70 (89.7)	0.8
• Breech	9 (11)	8 (10.3)	
Biophysical score	6 (4, 8)	8 (6, 8)	0.003 ^m
Parity			
• 1 or none	62 (75.6)	53 (67.9)	0.3
• ≥ 1	20 (24.4)	25 (32.1)	
Mode of delivery			
• Caesarian Section	68 (82.9)	57 (73.1)	0.2
• SVD	14 (17.1)	21 (26.9)	
	30 (100%)	130 (100%)	
Estimated conditional probabilities for fetal outcome prognosis Estimated 95% Confidence Interval for sensitivity and specificity computed using Wilson Score Method [†] Low Birth weight <10 th percentile of the expected weight for gestation * Fisher Exact Tests used m –Mann Whitney test used			

There was evidence of association between the Cerebral/Placental Ratio ($p < 0.001$), biophysical score ($p=0.003$) and infant birth weight among the study population. The CPR (C/U RI ratio) had 45.1% (95% CI 35%, 56%) sensitivity, 87.2% (95% CI 78%, 93%) specificity, 79% positive predictive value, and 60.2% negative predictive value for infant's birth weight. However, there was no significant difference in maternal age ($p=0.5$), marital status ($p=0.4$), occupation ($p=0.3$), fetal presentation-Cephalic vs. Breach ($p=0.8$) parity (0.3) or mode of delivery ($p=0.2$).

Table 9

Logistic regression for the correlates of Infant's birth weight among mothers with hypertensive disorder during the index pregnancy

Characteristics	Infant's birth weight		Prognostic Odds Ratio			
	% Low birth weight	Odds (95% CI)	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Cerebral/Placental Ratio						
• < 1.0	37/47 (78.7%)	3.7 (1.9, 7.3)	5.6 (2.5, 12.4)	< 0.001	4.7 (2, 11.1)	< 0.001
• ≥ 1.0	45/113 (39.8%)	0.66 (0.45, 0.96)	Ref		ref	
Biophysical score			1.3 (1.1, 1.6)	0.006	1.1 (0.9, 1.4)	0.327

In the univariate analysis, among infants of mothers with hypertensive disorder during pregnancy with CPR < 1.0, low birth weight (<10th percentile of expected weight at gestation week) was 3.7 (95% CI 1.9, 7.3) times more likely than normal weight and 5.6 (OR 5.6; 95% CI 2.5, 12.4; p<0.001) times more likely relative to infants of hypertensive mothers with CPR ≥ 1.0. The odds of a low birth weight among infants of mothers with hypertensive disorder during pregnancy with CPR ≥ 1 was 0.66 (95% CI 0.45, 0.96). For every unit increase in the biophysical score, we expect the odds of normal birth weight to increase by 30% (95% CI 10%, 60%).

In the multivariate analysis, adjusting for biophysical score, infants of hypertensive mothers with CPR < 1.0 were 4.7 (OR 4.7; 95% CI 2, 11.1; p< 0.001) times more likely to have low birth weight than among infants of mothers with CPR ≥ 1.0. On adjusting for CPR, for every unit increase in biophysical score, we expect about 1.1 (95% CI 0.9, 1.4; p=0.327) increase in the odds of normal birth weight. However, the increase is not statistically significant.

Table 10 Comparison of Prognostic Odds of neonate APGAR Score using CPR Vs UA RI**Table : Logistic regression for the correlates of Infant's APGAR (5 minutes) Score among mothers with hypertensive disorder during the index pregnancy**

Characteristics	Infant's APGAR score		Prognostic Odds Ratio			
	APGAR score (< 7)/n	Odds (95% CI)	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Cerebral/Placental Ratio						
• < 1.0	28/47 (59.6%)	1.47 (0.8, 2.6)	82 (18, 372)	< 0.001	66 (13, 340)	< 0.001
• ≥ 1.0	2/113 (1.8%)	0.018 (0.005, 0.07)	Ref		ref	
UARI						
• ≤ median (0.64)	24/73 (32.9%)	0.5 (0.3, 0.8)	6.6 (2.5, 17.3)	< 0.001		
• > median (0.64)	6/87 (6.9)	0.07 (0.03, 0.2)	Ref			

Table 11 Patients According To Severity of PET and CPR

Characteristic	Number and percentage of patients(160)	
	Total number	Percentage (%)
Severe PET	51/160	32%
• CPR < 1.0	20/51	39%
• CPR ≥ 1.0	31/51	61%
Mild PET	109/160	68%
• CPR ≤ 1.0	27/109	24%
• CPR ≥ 1.0	82/109	76%

DISCUSSION

In this study comprising of 160 patients with hypertensive states in pregnancy, the aim was to determine the CPR as a prognostic factor of fetal outcome. The CPR incorporates data of both the placental status using the umbilical artery and the fetal response using the middle cerebral artery as the brain is a vital structure in the prediction of adverse outcomes. In this study, gestational age-specific thresholds were compared with categorical thresholds of the CPR $</\geq 1$. All the 160 patients were referred by clinicians from labor ward, antenatal clinics and casualty departments, Kenyatta National Hospital.

The study population had a mean age of 28 (95% CI 27, 29). This is in keeping with Odibo Anthony et al where the mean age was 28 years (66). It is also in keeping with Lakhkar B N et al where the mean age was 27 years (13). It is however in contrast with Zavala-Coca Carlos et al where the mean age was 35 years (11). This could mean that the reproductive age in our study population is younger or that PET affects a younger age group in our study population. The marital status showed that majority 141 (88.1%) were married, 18 (11.3%) were single and 1(0.6%) separated or divorced. These have not been documented in other comparative studies. The occupation showed 27(17%) to be self employed, 42(26%) to be employed and majority of 91(57%) to be not employed (housewives). They however did attend all antenatal clinics and received proper management despite low socioeconomic status.

I found 62% of study population to be primigravida which is in keeping with Lakhkar B N et al showing that 60% were primigravidas (13). The median gestation was 34 weeks which is a gestation where the fetus has achieved a good fetal weight. This is a younger gestation than that Odibo A et al where mean gestation was 35 weeks (66) and that of Lakhkar BN et al where gestation was also 35 weeks meaning either patients show up for care earlier or that intervention is carried out earlier.

Thirty two percent (32%) of the patients were found to have severe PET as evidenced by blood pressure on admission and proteinuria on urinalysis. Out of these 39% were found to have a CPR < 1.0 and 61% had CPR ≥ 1.0 . This is much higher than the population studied by Lakhkar BN et al showing 11% to have severe PET thus we have a higher population presenting with severe

PET. This was not explained by any of the etiological causes of PET though it would be worth carrying out other studies to find out why our patients have severe PET. The number of patients with severe PET that had an abnormal CPR was not studied in other studies and is important as it is significant number with sever PET that have an abnormal CPR. Sixty eight percent had mild PET out of which 24% had an abnormal CPR (<1.0) while 76% had a normal CPR (≥ 1.0).this is also significant as even a significant number of patients with mild PET had an abnormal CPR (<1.0) so they also require close monitoring.

Eighty nine percent (89%) had fetuses in cephalic presentation while and eleven percent (11%) had fetuses in breech presentation which can bring additional complications.

Twenty nine percent (29%) had a CPR <1.0 which was abnormal and seventy one percent (71%) had a CPR ≥ 1.0 which was normal. This was not documented in the comparative studies. This is an important finding as it shows that a third of the sample size presented with an abnormal CPR which would imply that we have patients with severe PET. It also demonstrates the high number of patients with abnormal CPR which results in higher neonatal morbidity and mortality therefore proper and timely management is necessary.

The ultrasonographic fetal heart rate was found to be 138 beats per minute which is within normal range (120-160).

86 patients (54%) had a placenta in fundo anterior location while 74 patients (46%) in fundo posterior location. None of the patients had a low lying placenta which comes with its own additional complications.

The median umbilical artery resistive index was 0.64 and middle cerebral artery resistive index was 0.74 as expected according to the normogram.

About 47 patients (29%) had an abnormal CPR <1 while 113 (71%) had a normal CPR (≥ 1). 125 (78%) had delivery via caesarean section which is much higher than the 62% demonstrated by Lakhkar BN et al. (35). 22% delivered SVD which is also higher than Lakhkar BN et al who showed 5% delivering vaginally. This could be due to the smaller sample size which was 58 in Lakhkar BN et al study as opposed to 160 patients in this study. It could also mean that we have

more patients with hypertensive states in pregnancy as compared to other comparative studies. Most caesarean sections were carried out on these patients due to failed induction of labor.

The neonates delivered via cesarean section had better outcome as compared to those delivered vaginally. This was not a study variable in the other two comparative studies. Therefore, delivery via caesarean section is best as it improves on perinatal outcome.

The CPR ≤ 1 had a 93.3% (95% CI 79%, 98%) sensitivity, 85.4% (95% CI 78.3%, 90.4%) specificity, 60% positive predictive value, and 98.2% negative predictive value for adverse perinatal outcome. This contrasts to Lakhkar BN et al who had a CPR sensitivity of 47.2%, specificity of 86.3%, PPV of 85% and NPV of 50% (13) which could be due to a smaller sample size of 58 in the Lakhkar BN study as contrasts to this study which had a sample size of 160 while that of Odibo A et al showed the CPR to have a sensitivity of 67%, specificity of 66%, PPV of 69% and NPV of 64%(66). Among neonates of mothers with hypertensive disorder during pregnancy with UARI \leq median (0.64), an APGAR score < 7 was 0.5 (95% CI 0.3, 0.8; $p < 0.001$) times more likely than a score > 7 and 6.6 (OR 6.6; 95% CI 2.5, 17.3; $p < 0.001$) times more likely relative to hypertensive mothers with UARI $>$ median (0.64). **Combining UA RI and MCA RI improves the prognostic odds ratio from 6.6 to 82. (Table 10.)** This implies that the CPR is a better predictor than UA RI alone for APGAR score < 7 . This refutes Lakhkar BN et al findings that the UA PI is more sensitive than CPR in predicting adverse perinatal outcome (13) but it is in keeping with findings of Gramellini et al (63).

The CPR is predictive of adverse perinatal outcome and therefore very good in antenatal monitoring of mothers with hypertensive states of pregnancy. This should be used in antenatal and perinatal centres for antenatal monitoring of patients with HSP.

CPR is better than BPPS in predicting adverse perinatal outcome. This was a new finding in this study as it was not looked at in the other comparative studies.

This is important as obtaining biophysical profile score only shows the acute hypoxic status of the fetus. Obtaining the CPR would be vital to see chronic hypoxic status and decide on proper timing and method of management so as to reduce on perinatal morbidity and mortality.

The percentage of low birth weight infants in this study was 17% which is much higher than BN Lakhkar BN et al which had a percentage of 6.8%. This could be due to patients being delivered at an earlier gestation (at 32-34 weeks) as compared to 36 weeks in Lakhkar BN et al study or more patients with severe PET causing low birth weight in these fetuses. Further studies should be carried out to determine why our sample population has a severe PET.

CONCLUSION

The following conclusions were drawn from this study:

1. The CPR is predictive of adverse perinatal outcome and therefore very good in antenatal monitoring of mothers with hypertensive states of pregnancy.
2. Algorithm for management of hypertensive mothers should recommend caesarean section as the mode of delivery as it improves perinatal outcomes among mothers with $CPR < 1$.
3. **Combining the UA RI and MCA RI improves the prognostic odds ratio of APGAR score from 6.6 to 82(Table 10).** This implies that the CPR is a better predictor than UA RI alone to improve on neonatal condition.
4. The biophysical profile is shown to predict acute fetal distress but the CPR is predictive of chronic fetal distress and it is predictive of adverse fetal outcome. Therefore CPR should be used for antenatal monitoring of patients with hypertensive states and not biophysical profile score.

RECOMMENDATIONS

1. The CPR should be used by antenatal/ perinatal centres for antenatal monitoring in mothers with hypertensive states of pregnancy to reduce perinatal morbidity and mortality.
2. Clinical decisions on time of delivery should be based on CPR and clinical state of patient.
3. Mothers with hypertensive states of pregnancy should be delivered at appropriate time via caesarean section as it improves on perinatal outcome.
4. Further studies should be carried out to assess factors causing severe PET in our population and also assess the neonatal umbilical artery pH in fetuses born from mothers with hypertensive states of pregnancy so as to correlate with hypoxic status.

APPENDIX A

Research Consent Form

My name is Dr. Parmar Linal Parshuram, a postgraduate student in the department of Diagnostic Imaging and Radiation Medicine at the University of Nairobi.

I am conducting a study on the effect of high blood pressure on the unborn child. This study involves answering some questions and performing an ultrasound scan with a special study of the blood vessels of the unborn child. This will help to check on the well being of the unborn child while in the uterus. This does not pose any danger to you or the unborn child. Follow up will be made to assess the new born baby.

Your name will not be included in the report. Only ultrasound and file numbers will be used. Your information shall be kept confidential.

I would like to recruit you in this study. You are not forced to participate and your failure to consent will not deny you any treatment.

Patient ultrasound number _____

Signature _____

Date _____

I certify that the patient has understood and consented participation in the study.

Dr. Parmar Linal Parshuram

Signature _____

Contact - 0722-888991

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KNH/UON-Ethics and Research Committee

KNH/UON-ERC

P.O Box 20723, Nairobi

Telephone – 020-726300-9

APPENDIX B

Questionnaire

Patient ID:
Date of the Interview

Research Asst ID

Social demographic characteristics

1. Mother's age (years)
2. Marital status
 - a. Married
 - b. Single
 - c. Divorce/separated
 - d. Widowed
3. What is your occupation?
 - a. Self-employed
 - b. Employed
 - c. Not employed (Housewife)
4. Parity
5. LMP
6. Estimated date of delivery (E.D.D)
7. Gestation age (weeks)

Clinical findings

8. Blood pressure (at admission) /
9. Urinalysis
10. Fetal heart rate

Ultra-sound findings

11. Presentation
 - a. Cephalic
 - b. Breech
12. Placenta
 - a. Fundoanterior
 - b. Fundoposterior
 - c. Low lying
13. Fetal heart rate reading
14. Biophysical profile

Biophysical profile	Score
a. Movement of the baby	
b. Tone	
c. Aminotic fluid index (AFI)	
d. Breathing	

15. Approximate ultrasound age
a. BPD
b. Head circumference
c. AC
d. Femur length

16. UARI -Umbilical artery resistance index ▪
17. MCARI-Middle cerebral artery resistance index ▪

Clinical management and fetal outcomes

18. Has steroid been administered? Yes No
19. Mode of delivery
a. Caesarian section
b. SVD
20. Fetal outcome
a. Alive
b. Still birth
21. Infant weight at birth (grams)
22. APGAR Score (5 minutes)
23. Has the infant been admitted to NBU? Yes No

APPENDIX C

Budget

<i>Item</i>	<i>Estimated Amount (KHz)</i>
Stationary	6,000
Secretarial services	15,000
Printing	12,000
Ethics fee	1,000
Data collection and analysis	20,000
Selected imaging	8,000
Compiling report	20,000
Total	82,000

APPENDIX D

Study Database

dbparmar1 : Database (Access 2002 - 2003 file format) - Microsoft Access non-commercial use

Home Create External Data Database Tools

View Paste Cut Copy Format Painter Views Clipboard Rich Text Refresh All Save Delete More Records New Totals Filter Selection Advanced Find Replace Go To Select

All Access Objects << Main Switchboard frmBPunborn

Tables
BPunborn
Switchboard Items

Queries
datacleaning

Forms
frmBPunborn
Switchboard

"Cerebral/Placental Resistive Index Ratio as a determinant of Fetal Outcome In Hypertensive Disorders of Pregnancy"

CaseID: 001 Research Asst ID: 1000
X-ray Number: 82071/10 Interview Date: 07-Dec-2010

Page 1 Page 2

Social Demographic Characteristics

1. Mother's age: 34

2. Marital status:
a. Married
b. Single
c. Divorced/Seperated
d. Widowed

3. What is your occupation?
a. Self-employed
b. Employed
c. Not-employed (Housewife)

4. Parity: 5 + 1

5. Last Menstrual Period: 29-Mar-2010

6. Estimated date of delivery: 05-Jan-2011

7. Gestational Age by dates: 36 (weeks)

Clinical Findings

8. Blood Pressure (at Admission): 130 / 80

9. Urinalysis:
a. 1+
b. 2+
c. 3+
d. 4+

10. Fetal heart rate: 140

Record: 1 of 160 No Filter Search

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