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Perinatal Outcomes in fetuses with early-onset fetal growth restriction at Chris Hani Baragwanath Academic Hospital (CHBAH) and accuracy of Doppler findings in predicting outcomes

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Perinatal Outcomes in fetuses with early-onset fetal growth restriction at Chris Hani Baragwanath Academic Hospital (CHBAH) and accuracy of Doppler findings in predicting outcomes.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of the Master of Medicine in Obstetrics and Gynaecology.

MMed (O&G)

Johannesburg, December 2016

Table of Contents:

Declaration page 5

Dedication page 6

Acknowledgements page 7

List of Abbreviations page 8

Abstract page 11

1. INTRODUCTION page 13
2. LITERATURE REVIEW page 14

2.1 Screening for IUGR page 14

2.1.1 History-taking page 14

2.1.1.1 Identifying the fetus at risk and its significance page 14

2.1.1.2 Chronic conditions page 14

2.1.1.3 Fetal factors page 15

2.1.1.4 Infections page 15

2.1.1.5 Toxins page 16

2.1.2 Symphisis-fundal height page 16

2.2Diagnosis of IUGR page 16

2.2.1 The definition of an IUGR fetus page 16

2.2.2 Accurate gestational dating page 17

2.2.2.1 Clinical methods page 17

2.2.2.2 Ultrasound methods page 18

a) First trimester dating page 18

b) Ultrasound dating after the first trimester page 18

c) Transcerebellar diameter page 19

2.3 The Pathophysiology of IUGR page 20

2.4 Fetal Surveillance page 21

2.4.1 The non-stress test page 21

2.4.2 The biophysical profile page 22

2.4.3 Doppler studies page 22

a) The umbilical artery page 22
b) The middle cerebral artery page 23
c) Ductus venosus page 23
2.4.3.1 The significance of Dopplers in IUGR page 24
2.4.3.2 The progression of Doppler changes page 25
2.5 Management of IUGR page 26
2.6 Perinatal Morbidity and Mortality page 28
3. PROBLEM STATEMENT page 31
4. OBJECTIVES FOR THE STUDY page 32
5. METHODOLOGY page 33
5.1 Setting page 33
5.2 Study Design page 33
5.3 Sample Size page 33
5.4 Study Population page 33
5.5 Tools page 34
5.6 Enrolment page 34
5.7 Data Collection page 36
5.8 Surveillance and Definitive Management page 36
5.9 Perinatal Follow up page 38
5.11 Permission to Conduct Research and Ethics Clearance page 40
6. RESULTS page 41
6.1 Maternal Demographics page 41
6.2 Ultrasound Findings page 42
6.3 Delivery Information page 44
6.4 Neonatal Admission Details page 46
6.5 Perinatal Morbidity and Mortality page 47
6.5.1 Intrauterine fetal death page 50
6.5.2 Medical termination of pregnancy page 52
6.5.3 Fresh stillbirth page 53
6.5.4 Early neonatal death page 53
6.5.5 Late neonatal death page 55
6.5.6 Infant death page 56

6.5.7 Discharged home page 56
7. DISCUSSION page 59
7.1 Maternal Demographics page 59
7.2 Ultrasound Findings page 59
7.3 Delivery Information page 60
7.4 Neonatal Admission page 60
7.5 Perinatal Morbidity and Mortality page 61
7.6 Limitations page 63
7.6.1 Registration page 63
7.6.2 Ultrasound findings page 64
7.6.3 Perinatal follow up page 65
7.7 Areas identified for further study page 65
8. CONCLUSION page 66
References page 67
Appendix A: Data collection sheet page 70
Appendix B: The Estimated fetal weight growth curve page 73

Declaration

I, Natalie Odell, declare that the research reported in this work is completely my own.

It is submitted to the Faculty of Health Sciences for the degree of Masters of Medicine in Obstetrics and Gynaecology, at the University of Witwatersrand, Johannesburg.

It has not been submitted before for any other degree or examination at this, or any other university.

Signature: Date:

Dedication

This work is dedicated to my husband, for his patience and understanding while I spent many hours completing this research and to my parents and siblings for their continued support.

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List of Abbreviations:

AC: Abdominal circumference

ACOG: American College of Obstetrics and Gynaecology

APLS: Antiphospholipid syndrome

BPP: Biophysical profile

BPD: Biparietal diameter

BPD: Bronchpulmonary dysplasia

CHBAH: Chris Hani Baragwaneth Academic Hospital

CHPT: Chronic hypertension

CPAP: Continuous positive airway pressure ventilation

CPR: Cerebral-placental ratio

DV: Ductus Venosus

EDD: Expected date of delivery

ELBW: Extremely low birth weight

END: Early neonatal death

EFW: Estimated fetal weight

FAS: Fetal Anomaly scan

FL: Femur length

GHPT: Gestational hypertension

GRIT: Growth Restriction Intervention Trial

GS: Gestational sac

HC: Head circumference

HELLP: Haemolysis, elevated liver enzymes, low platelets

HIV: Human Immunodeficiency Virus

HREC: Human Research Ethics Committee

ID: Infant death

IE: Imminent eclampsia

IUFD: Intrauterine fetal death

IUGR: Intrauterine growth restriction

IVH: Intraventricular haemorrhage

LND: Late neonatal death

LNMP: Last normal menstrual period

MAIN: Morbidity Assessment Index for Newborn

MCA: Middle cerebral artery

Mm: Millimetre

NEC: Necrotizing enterocolitis

NICU: Neonatal intensive care unit

NST: Non-stress test

NVD: Normal vaginal delivery

PET: Preeclampsia

PI: Pulsatility index

PORTO: Prospective Observational Trial to Optimise Paediatric Health in IUGR

RCOG: Royal College of Obstetricians and Gynaecologists

RDS: Respiratory distress syndrome

REDF: Reversed end diastolic flow

RPR: Rapid Plasma Reagin

SFH: Symphysis-fundal height

SFM: Society of Fetal Medicine

TCD: Transcerabellar diameter

TICU: Transitional intensive care unit

TOP: Termination of pregnancy

TRUFFLE: Trial of Randomised Umbilical and Fetal Flow in Europe

UA: Umbilical artery

YS: Yolk sac

ABSTRACT

Background:

Intrauterine growth restriction (IUGR) is a pregnancy-related complication that is diagnosed more frequently due to improved antenatal surveillance with greater access to ultrasound equipment and training in ultrasound and it affects 3-5% of all pregnancies. The addition of Doppler surveillance in high risk pregnancies has been found to decrease morbidity and mortality by 29%.

Methods:

This was a prospective cross-sectional descriptive study that took place at Chris Hani Baragwaneth Academic Hospital (CHBAH), a tertiary hospital in Soweto, Johannesburg, which conducts an average of 23,000 deliveries a year. Study participants were collected over a 15 month period and early-onset IUGR was defined as an abdominal circumference of less than the 5th percentile for a given gestation and diagnosed between 26+0 and 32+0 weeks of gestation. Multivessel Doppler surveillance was performed to monitor these fetuses and optimally time delivery. Pregnancy and neonatal outcomes were followed up.

Results:

A total of 60 women were included in the study. Detailed data on outcomes was available for 47 study participants. Nineteen babies (40.6%) were discharged home after an average hospital stay of 62.6 days and 52.6% of these babies fulfilled the criteria for major morbidity. Twenty eight babies (59.4%) were mortalities, with 9 intrauterine fetal deaths, 2 medical terminations of pregnancy for maternal indications, 3 fresh still births, 9 early neonatal deaths, 3 late neonatal deaths and 2 infant deaths. The average birth weight of babies that survived was 969g and the gestation was 29 weeks and 2 days, while in the group that demised, the average birth weight was 775.8g and the mean gestation was 28weeks and 4 days.

All study participants had abnormalities on Doppler studies, with 38 of the 48 study participants having abnormalities in more than one vessel. Abnormalities in the Ductus Venosus, as well as a low birth weight, were shown to be independent risk factors for perinatal mortality.

Conclusion

Babies born with IUGR at CHBAH tend to have severe, early onset IUGR at the time of diagnosis, with many compounding factors affecting their outcomes, the most important of which is their birth weight and the presence of an abnormal Ductus Venosus Doppler.

Perinatal Outcomes in fetuses with early-onset fetal growth restriction at Chris Hani Baragwanath Academic Hospital (CHBAH) and accuracy of Doppler findings in predicting outcomes.

1. INTRODUCTION

Intrauterine growth restriction (IUGR) is a pregnancy-related complication that is associated with increased risk to the fetus and the risks are increased with a decrease in the fetal weight percentile (1). The purpose of antenatal care is to offer the clinician the opportunity to intervene and improve outcomes in pregnancies where abnormalities or problems are found. Intrauterine growth restriction is one such complication that is diagnosed more and more frequently due to improved antenatal surveillance with greater access to ultrasound equipment and training in ultrasound and affects 3-5% of all pregnancies(2). It is important to identify the growth restricted fetus as interventions may be instituted to minimise morbidity and mortality in those fetuses, as well as preventing iatrogenic complications such as unnecessary preterm delivery or operative delivery (1). Lindqvist and Molin found a 7 fold increase risk of death in IUGR fetuses and determined that the identification of the condition prenatally could offer a 4 fold lowered risk of a poor outcome (3). Queenon et al reported that risk of morbidity and mortality is increased to twenty fold when the fetal weight is less than the 3rd percentile for expected fetal weight (1). The Barker Hypothesis states that IUGR is also associated with a greater risk of chronic conditions, such as Diabetes and hypertension, in adulthood (4).

2. LITERATURE REVIEW

2.1 SCREENING FOR IUGR:

2.1.1 History-taking

2.1.1.1 Identifying the fetus at risk and its significance:

It is pivotal that the attending obstetrician identifies the fetus at risk of developing intrauterine growth restriction in order to implement adequate monitoring. Lindqvist et al reviewed 26968 pregnancies with IUGR, where 54% of these fetuses were identified antenatally, while the rest were not diagnosed until after delivery. The study reported that IUGR babies not diagnosed antenatally had a 4-fold increased risk of serious perinatal morbidity, such as intracranial haemorrhage and cerebral palsy, when compared to the group that were diagnosed antenatally (3). Risk factors for IUGR should be sought when taking a detailed history from the mother. A previous pregnancy complicated by IUGR is a significant risk factor as recurrence occurs in 20% of subsequent pregnancies (5). The cause for the growth restriction may be maternal, fetal or placental and should be identified where possible. Extrinsic causes, such as conditions resulting in utero-placental insufficiency, may carry a better prognosis as intervention may alter outcome or severity of disease progression, versus intrinsic causes, such as aneuploidy, where intervention cannot alter prognosis in that fetus and where the IUGR often develops very early in the pregnancy and is often more severe.

2.1.1.2 Chronic Conditions:

Maternal chronic conditions that affect the development of the placenta, such a preeclampsia (8-15.5% risk of developing IUGR) and Systemic Lupus Erythematosus (28.5% risk of IUGR in active disease) have been proven by a multitude of studies to cause IUGR secondary to placenta insufficiency (5). The maternal comorbidity most strongly associated with poorer perinatal outcomes is hypertension. Hypertensive conditions are associated with earlier onset of IUGR, earlier delivery, lower birth weights and higher rates of perinatal complications. Besides congenitally and structurally abnormal infants, hypertension is the

most common cause of asymmetrical growth restriction, which in itself is associated with poor perinatal outcomes in 14% of pregnancies (versus 5% in appropriate-for-gestation infants) (6). Antiphospholipid Syndrome (APLS) is a common cause of pregnancy complications due to areas of placental thrombosis and the rate of IUGR approaches 30% (7). Pre-gestational diabetes is also a common condition amongst mothers attending antenatal care and the risk of IUGR needs to be recognised, either as a results of the vascular disease at placental level, or due to the congenital abnormalities that may develop in a fetus where the mother has poor glycaemic control (8). Haeri et al found that the risk of IUGR increases proportionally with increasing end organ damage, specifically with worsening nephropathy and proliferative retinopathy (9). Patients that are seen in antenatal clinic with chronic conditions such as these need to be referred from the first trimester if possible for ultrasound assessment and to establish baseline parameters to further assess growth serially through the pregnancy.

2.1.1.3 Fetal Factors:

Intrinsic fetal factors, such as aneuploidy and structural abnormalities, are strongly associated with IUGR and can be found in 10% to 40% of cases with congenital anomalies. Karyotyping should be considered and offered, especially if IUGR is diagnosed early at less than 24 weeks gestation or if it is severe, with the estimated fetal weight being less than the 5^{th} percentile for gestational age. (10) IUGR is especially common in chromosomal aneuploidies with Trisomy 21 generally only causing a mild IUGR, but Trisomy 18 is associated with severe IUGR, especially depending on the severity of the abnormalities found (9).

2.1.1.4 Infections:

Congenital infections may be screened for and ultrasound features may be suggestive of certain congenital infections. Cytomegalovirus has been found to cause cell destruction in the developing fetus, while Rubella causes vascular insufficiency. Syphilis may also lead to IUGR. These infections may be screened for in any pregnancy complicated by IUGR with

ultrasound evidence of infection or with the finding of normal Doppler studies which would exclude utero-placental insufficiency as a cause (8).

2.1.1.5 Toxins:

Mothers that smoke have been shown on average to have babies with birth weights of 458g less than the average birth weight for a given gestation (6). Anticonvulsants and antineoplastic drugs, as well as illicit drugs, such as cocaine, are associated with growth-restricted fetuses (9).

2.1.2 Symphysis-fundal height:

Examination of the symphysis-fundal height (SFH) can be used to screen for IUGR after taking a good history. Measurement of the SFH was the first examination technique described as a screening tool and is measured from the superior edge of the pubis to the top of the fundus but can be inconsistent due to imprecise and varied measurements between health care providers (8). Confounding factors, such as increased maternal adiposity, polyhydramnios and uterine fibroids must be considered when the SFH is not in keeping with the estimated gestational age (11). It is however an easy and inexpensive technique that, when done correctly, can at least identify the fetus that requires further investigation to confirm or exclude IUGR.

2.2 DIAGNOSIS OF IUGR:

Ultrasound is considered the gold-standard for the diagnosis of IUGR. It must be stressed that growth restriction when the gestation is unknown, can only be identified by serial ultrasounds (11). The American College of Obstetricians and Gynaecologists suggests that if on ultrasound, the abdominal circumference is in keeping with the estimated gestational age, then the diagnosis of IUGR is highly unlikely (12).

2.2.1 The Definition of an IUGR Fetus:

A growth restricted fetus is defined as a fetus that is failing to achieve its full genetic growth potential. IUGR is most commonly diagnosed as an estimated fetal weight below the 10th centile for gestational age, although other definitions have been suggested (such as an estimated fetal weight below the 5th and 3rd percentile and an abdominal circumference below the 5th and 3rd percentile) (12) . The abdominal circumference has been found be the first parameter that lags in fetal growth restriction due to decreased glucose storage in the liver secondary to decreased hepatic blood flow, while the transcerebellar diameter is unchanged, even in severe cases of IUGR (1). Many definitions have blurred the lines between the small for gestation fetus, (or commonly called constitutionally small), and the fetus that is small for gestation due to a pathological process. A constitutionally small fetus is not necessarily at risk for a poorer outcome and as many as 70% of fetuses below the 10th centile fall into this group (6). The fetuses often have parents that are smaller in stature or may be from a population group that typically is more petite in build. For this reason, population- specific growth charts may be used to assess growth in the developing fetus (3). Buck et al suggests that a fetus with a normal growth trajectory over serial ultrasounds and who has normal Dopplers and amniotic fluid index, is more likely to be a constitutionally small fetus than a growth restricted fetus due to an underlying pathology (13).

2.2.2 Accurate Gestational Dating:

Accurate dating of a pregnancy is thus very important in identifying the growth restricted fetus, as an accurate gestational age is needed to identify an abnormal growth trajectory. Various clinical and ultrasound methods are used to attempt to accurately date a pregnancy.

2.2.2.1 Clinical Methods:

The first and most commonly used clinical method is taking a history and determining the date of the last normal menstrual period (LNMP). Naegele's Rule, which involves using the date of the last menstrual period, subtracting three months and then adding seven days, is used to determine the expected date of delivery (EDD) the following year. This method is

compromised if a woman does not have a regular 28 day cycle and may be limited by the variation in the fertile window period, as well as in the woman who is unsure of her last menstrual period. Clinical examination of the size of the uterus can also be used as the uterus becomes palpable above the pelvic brim from 12 weeks of gestation but is not very accurate. (14)

2.2.2.2 Ultrasound Methods:

Ideally, dating by ultrasound should be done as early in the pregnancy as possible and in conjunction with the last menstrual period if the woman is sure of her dates. Nielson et al reviewed 34249 pregnancies dated with LNMP and then LNMP with early ultrasound and found that a large majority of women delivered within 7 days of the EDD given by early ultrasound versus using the LNMP in isolation (15).

a) First trimester dating:

Different parameters on ultrasound have been suggested to use in dating a pregnancy, depending on the trimester of the pregnancy. The following can be used in the first trimester:

The gestational sac (GS) is the first sign of pregnancy visualised within the uterus from four and a half to five weeks of gestation. The mean sac diameter is most commonly used as a dating tool and has been found to have a small margin of error up to only five days. Studies have shown that it is only accurate up to a GS diameter of 14 mm and once the fetus is visible, a crown-rump length should be used instead. (16)

The yolk sac (YS) is the first structure visualised within the gestational sac but is not an accurate method to use (16).

The crown-rump length is best done before 14 weeks of gestation and has a margin of error of about 3-5 days (1). It is measured as a straight line from the cephalic pole to the rump of the fetus. Papageorghiou et al found it to be accurate up to a measurement of 84mm, after which other biometric parameters should be used. (17)

b) Ultrasound dating after the first trimester:

Fetal biometry is used after the first trimester, using namely the fetal biparietal diameter (BPD), the head circumference (HC), the abdominal circumference (AC) and the femur length (FL). The measurements are combined using the Hadlock Formula to derive a gestational age that has an accuracy of 7 to 10 days from 14-20 weeks. After the 26th week of gestation, biometry may lead to a margin of error of up to four and a half weeks. (18)

The BPD is considered a highly reproducible measurement and is most commonly measured from the outer edge of the one side of the skull to the inner edge of the opposite side of the skull at either the trans-cerebellar or trans-thalamic planes in an axial view. Oligohydramnios may result in dolicocephaly which affects the accuracy of the BPD measurement. (19)

The abdominal circumference is measured at the level of the union of the right and left portal veins, in a plane where the stomach bubble and lower ribs are also visualised. The abdominal circumference is altered by oligohydramnios and changes in fetal movement. It has been found to have a margin of error of up to four weeks gestation if measured in the third trimester. (19)

Femur length is often used in later gestations to date a pregnancy as it has the smallest margin of error of two weeks in the third trimester and the actual measurement is largely uncompromised by surrounding factors such as liquor volume. Abnormal lengths are found in skeletal dysplasia and early-onset IUGR. (19)

c) Transcerebellar Diameter:

The transcerebellar diameter (TCD) had been recommended to be used as one of the definitive ultrasound measures of dating a pregnancy later in gestation and is largely unchanged in even severe cases of IUGR (1). It is located in the posterior fossa of the fetal skull and is measured as the maximum diameter across the cerebellum in an axial plane

where both the cisterna magna and the septum pellucidum can be seen. The posterior fossa is relatively protected to external pressures and the cerebellum is not affected by alterations in fetal growth. (20) The TCD has been found to correlate in millimetres (mm) with the equivalent gestational age in mm up to 22mm (19).

When analysing 50 singleton pregnancies affected by IUGR, Bhimarao compared the ratios of TCD:AC to HC:AC and found that all other parameters had a margin of error in terms of dating the pregnancies of greater than three weeks, where the TCD was much more accurate. The TCD correlated by three days in 97.5% of second trimester pregnancies and in 93.3% in third trimester pregnancies (20).

2.3 THE PATHOPHYSIOLOGY OF IUGR:

It is essential to understand the pathophysiology of IUGR and the adaptions in the fetus, in order to understand the changes that can be seen on ultrasound. As mentioned, IUGR is most commonly diagnosed on ultrasound when the abdominal circumference or the estimated fetal weight is less than the 10^{th} percentile for gestational age (12). The fetus experiences higher pressures at the materno-placental interface and hypoxemia then stimulates peripheral arterial chemoreceptors in the fetus. The fetus adapts to this environment by increasing blood flow to essential organs, namely the brain, heart and adrenals, while sacrificing blood flow to other organs, such as the kidneys and liver (11). The biometry (biparietal diameter, abdominal circumference and femur length) will all be less than what is expected for a given gestational age. Decreased flow to the liver results in decreased glycogen storage in the fetal liver, often resulting in an abdominal circumference that is more obviously lagging than the other measurements (1).

Another result of this adaption may be oligohydramnios, which is defined as a single deepest pool of amniotic fluid measuring less than or equal to 2cm or an amniotic fluid index measuring less than or equal to 8cm (21). Oligohydramnios results from decreased renal

blood flow secondary to shunting of oxygenated blood to other vital organs and hence decreased urine production, but also from a central activation of vasopressin in the fetal brain as a result of the stress response, leading to decreased urine output (11). The current literature is unclear on how important the finding of oligohydramnios is. A study done by Chauhan et al found that only 10% of IUGR pregnancies are complicated by oligohydramnios, but that these pregnancies have a greater perinatal mortality rate, which increases the smaller the smallest pocket of amniotic fluid. The study also showed that pregnancies complicated by oligohydramnios are twice as more likely to need an emergency caesarean section for a non-reassuring heart pattern during labour on fetal heart monitoring (22). The American College of Obstetrics and Gynaecology states that the amniotic fluid index is of great prognostic value in IUGR, whereas the Green-top guidelines published by the Royal College of Obstetricians and Gynaecologists states that it is of minimal value in IUGR (12, 23).

2.4 FETAL SURVEILLANCE:

Once IUGR has been diagnosed, there are recommended methods to monitor these fetuses and optimally time delivery. Protocols for monitoring will depend on institutes but may include two of three methods, namely the Biophysical profile, non-stress test (NST) and multi-vessel Doppler surveillance. In addition, basic fetal monitoring by the mother by fetal kick movements can also help detect a fetus at risk, as a hypoxic fetus with move less to conserve energy (11).

2.4.1 The Non-Stress Test:

The non-stress test (NST) is an investigation that monitors the fetal heart pattern over a period of time. It is used in practice both antenatally and during labour. The NICE criteria, published in 2014, have become the gold standard for interpreting a NST. A reassuring trace is defined as a fetal heart baseline rate between 100 and 160 beats/minute, with baseline variability of at least 5 beats/ minute and no decelerations in the fetal heart rate. Abnormal traces are defined as a baseline fetal heart rate above 180 beats/minute or less than 100

beats/minute, a drop in baseline by more than 60 beats/minute for greater than 60 seconds, late decelerations for more than 30 minutes, despite instituting intra-partum resuscitation, or a single prolonged deceleration for greater than 3 minutes. (24) In IUGR, a decrease in baseline variability has been linked to acidemia in the compromised fetus, whereas decelerations are considered a late sign of serious decompensation in the fetus (11).

2.4.2 The Biophysical Profile:

The biophysical profile (BPP) is a non-invasive test done to monitor the well-being of a fetus at risk. It has 5 components, 4 of which are ultrasound components (namely looking at distinct fetal movements, fetal tone, fetal breathing and the amniotic fluid volume) and the last is a non-stress test (NST) component (25). The assessment is scored as 0 or 2 for each component and a total score out of 10 is given. A score of 8 is considered normal. It is assumed that with a normal BPP, the regulatory centres in the brain of the fetus are intact (26). It is important to note that there are factors that may alter the BPP and must be kept in mind when interpreting the results. Fetal sleep may lead to an abnormal BPP but no more than two parameters will be abnormal and if repeated after thirty minutes, those parameters should be normal again. The administration of antenatal steroids leads to an abnormal BPP, as well as decreased variability in fetal heart rate on NST. These changes return to normal within 4 days of administration of the drug. (27)

2.4.3 Doppler Studies:

Doppler studies of the arterial and venous system of the fetus have been used in the screening, diagnosis and monitoring of the IUGR fetus. Doppler studies may offer information to predict deterioration in fetal condition, and therefore, an opportunity to intervene. It can also prevent unnecessary admissions for the mother, as well as prevent unnecessary and early delivery of an IUGR fetus (1). If during routine ultrasounds to assess growth in high risk pregnancies, low resistance waveforms are seen, it is a good predictor that there has been adequate trophoblastic invasion into the spiral arterioles during the development of the placenta and thus a lower risk of placental insufficiency (11).

a) The Umbilical Artery

The umbilical artery (UA) Doppler is often the first to be measured. In a normal pregnancy, the fetus receives blood flow through the umbilical artery throughout the fetal cardiac cycle, namely during both the systolic and diastolic phases, but with advancing placental insufficiency and rising resistance in the umbilical artery, the flow may become absent or reversed during the diastolic phase of the cardiac cycle. Once there is established reversed end diastolic flow (REDF), it means that greater than 70% of the placental bed is not functional and during diastole, due to very high pressures in the placenta, backflow from the fetus is observed. The Society for Maternal-Fetal Medicine recommends measuring the UA Doppler near the abdominal wall insertion point when the fetus is not breathing and when there is a uniform waveform for accurate measurements, avoiding measuring near the placental insertion point at there is higher flow and higher pressures at that point. Studies have shown that both absent and reversed diastolic flow are more common in fetuses with IUGR with an estimated fetal weight of less than the 3rd percentile and where oligohydramnios is diagnosed. (21)

b) The Middle Cerebral Artery

The middle cerebral artery (MCA) is measured in a transverse plane of the fetal head, at the proximal end of the vessel near the Circle of Willis. Vasodilation and increased flow in the cerebral arteries is an indicator of 'brain-sparing', which is part of the fetal adaption to counteract a hypoxic environment (21). Various other studies have used the cerebro-placental ratio (CPR), which is the pulsatility index of the MCA divided by the pulsatility index of the UA, to prove brain-sparing in a compromised fetus (21). Flood et al studied 881 fetuses with IUGR and showed that a CPR of less than one is associated with poorer neonatal outcomes in IUGR (28). De Vore et al found the CPR a more valuable predictor of morbidity than a biophysical profile (29).

c) The Ductus Venosus

The Ductus venosus (DV) is the first and commonly, the only venous Doppler performed. It is best measured in a sagittal or transverse section of the abdomen, at the level of the diaphragm (21). The DV have been said to be indicative of the cardiac effects of placental dysfunction (30). It has a triphasic waveform. The first peak correlates with ventricular systole, the second with passive filling of the ventricle. The nadir between the two peaks, called the á-wave, represents atrial contraction during late diastole. It is changes in this a-wave which are most indicative of problems in a compromised fetus. A hypoxic environment leads to compensatory changes in the fetus by venous shunting across the ductus to try increase the blood volume returned to the heart, bypassing the liver and thus compensating by increasing the right ventricular afterload, and in turn maintaining left ventricular output as blood shunted across the foramen ovale is increased (21). With worsening hypoxia, the accumulation of lactic acid leads to myocardial dysfunction and failure of this compensatory mechanism, which is evidenced by changes in the a-wave, namely becoming decreased, absent or eventually reversed (31).

2.4.3.1 The significance of Dopplers in IUGR:

In high risk pregnancies, the addition of Doppler surveillance has been found to decrease morbidity and mortality by 29% (32). Crimmins et al retrospectively compared Doppler findings between live and stillborn growth-restricted fetuses, as well as changes in the biophysical profile in relation to fetal deterioration or death. There were a total of 47 stillbirths and 39 perinatal deaths of the 987 fetuses classified as IUGR. Majority of the stillbirths (79%) occurred before 34 weeks of gestation and all of these fetuses had severe IUGR, classified as an EFW below the 1st percentile for gestational age, which may indicate a greater degree of placenta dysfunction in early-onset IUGR. When analysing the biophysical profile, the 5 criteria were assessed and a score was given. In the stillbirths that occurred before 34 weeks of gestation, a parallel escalation in the umbilical artery and ductus venosus Doppler values was seen which preceded a deterioration in the biophysical profile, which could then be used to anticipate a stillbirth in this group. Absent end diastolic flow (AEDF) in

the Umbilical Artery had the shortest interval between detection and stillbirth and was seen as an indicator for severe compromise. (33)

A staging system for IUGR is described in the literature, based on the Doppler abnormality found. Fetuses classified as Stage I have an abnormal pulsatility index in either the UA or the MCA. Stage II will have an abnormal peak systolic velocity in the MCA, a raised PI in the DV, absent or reversed flow in the UA or pulsations in the umbilical vein. Stage III is the most severe and is diagnosed when there is reversed flow in the Ductus Venosus, reversed flow in the umbilical vein or tricuspid regurgitation in the fetus. A study conducted by Mari et al retrospectively studied 74 IUGR fetuses delivered at or below 32 weeks of gestation and analysed their outcomes according the Doppler findings and staging as described above. The study found that babies classified as Stage I tended to have a later gestational age at delivery and that there was a progressive decline in birth weights with an increase in severity of Doppler findings and hence staging. Poorer outcomes also increased with advancing staging. (34)

2.4.3.2 The Progression of Doppler Changes:

Bashat has published multiple works on the progression of Doppler findings in the IUGR fetus. Many studies have suggested and it has been accepted that there is often a typical or predictable progression of Doppler findings reflecting compensatory changes in the fetus that allows easier monitoring and understanding of the degree of compromise in each IUGR fetus. The first change is a decrease in flow in the umbilical vein, which the fetus detects and then responds to by decreasing blood flow to non-vital organs. The resistance then increases in the umbilical artery when an average of 30% of the placental bed in non-functional, reflected by an increase in the pulsatility index (PI) of the umbilical artery. As the fetus tries to maintain blood perfusion in the brain, vasodilation of the middle cerebral artery is seen by a decrease in the pulsatility index of the MCA. Flow in the umbilical artery becomes further compromised and absent or reversed end diastolic flow is seen on Doppler study of the UA. The fetus becomes more and more hypoxic and cardiac decompensation is then reflected by

an absent or reversed a-wave in the ductus venosus. The deterioration in the BPP and NST will then follow. (31, 35, 36)

Turan et al performed a prospective observational study that was published in 2008 including 104 patients and one aspect that was analysed was the time to progress between each Doppler change and then the duration of each abnormal Doppler finding until delivery. This study was important as it challenged a preconceived notion that the progression of Dopplers tends to be predictable. The study showed that where IUGR is complicated by Doppler changes only after 30 weeks of gestation and if there is no progression from an increased pulsatility index in the umbilical artery within the first 14 days, then there is unlikely to be significant Doppler changes or progression. Only 67% of the pregnancies studied did follow the typical progression described above. (30)

2.5 MANAGEMENT OF IUGR:

One of the most difficult dilemmas faced in managing a pregnancy with IUGR is the optimal time to deliver the fetus. The difficult balance between intervening before severe compromise and death occurs, and preventing iatrogenic complications of prematurity, must be considered. The GRIT Study (Growth Restriction Intervention Trial) is one of the few randomized controlled trials on IUGR and analysed the ideal time to deliver the compromised fetus with IUGR and the perinatal outcomes associated in 587 fetuses. Delivery was the intervention and was either immediate (within 48 hours of diagnosis or completing steroids if less than 34 weeks gestation) or delayed until the clinician found a firm indication to deliver the fetus. The umbilical artery Doppler was the indices studied and was recorded as increased, absent or reversed. The study concluded that delaying delivery of a compromised fetus with IUGR may increase the number of stillbirths (9 vs 2), but immediate delivery increases the complications of preterm delivery such as mechanical ventilation and neonatal deaths (23 vs 12). The average time to delivery in the delayed group was 4.9 days. (37) A follow-up paper was then published detailing long-term outcomes of the GRIT Study, which

showed that at two years of age, children showed no significant difference in cognition, language, motor performance and behaviour between the two groups (38).

The findings of the GRIT Study were not supported by the DIGITAT randomized control trial. Induction of labour in pregnancies complicated by IUGR beyond 36 weeks gestation was compared to expectant management. The admissions to Intensive Care was similar in both groups, but the admissions to intermediate care were higher in the induction group. The neonatal outcomes were analysed using a MAIN (morbidity assessment index for new-borns) Score, which analyses multiple clinical and laboratory findings (such as cord pH, urine output, respiratory rate, thrombocytopenia, development of seizures to name a few, both in the first 24 hours of life and in the seven days after birth), to determine morbidity in the first week of a neonate's life (39). The increase in admissions to intermediate care was found to be insignificant. The significant difference between the two studies is the average gestational age of the fetuses studied and the GRIT study is most relevant to this study as it too focuses on early-onset IUGR. (40)

A prospective study published by the American College of Obstetricians and Gynaecologists (ACOG) assessed 145 IUGR pregnancies and monitoring of fetal well-being using NST, BPP and Dopplers. The study showed that most commonly delivery was indicated when the BPP score was less than or equal to 4 or when there were significant abnormalities on NST. One very significant finding in this study was that fetuses with an abnormal ductus venosus only had changes on NST and BPP on average within 7 days, indicating a possible window to delay delivery and every week in utero can decrease morbidity by 50% (41). Turan et al published a study on the duration of abnormal ductus venosus and found that an abnormal ductus cannot be prolonged for greater than one week, as long as the NST remains reactive in that time. Of 177 IUGR fetuses, 18 were stillbirths and 34 suffered major morbidity. The average birth weight of the fetuses with major morbidity was 635g, adding severe prematurity as a compounding factor in the poor outcomes of these fetuses. Intrauterine fetal death developed within 6 days on average and an absent or reversed a-wave was far more common in the stillbirth group (versus just a raised PI). (42)

In terms of management guidelines, there are various important bodies to consult. The Society for Maternal-Fetal Medicine publications committee suggests conservative management until 34 weeks gestation in IUGR fetuses with absent end-diastolic flow in the umbilical artery and conservative management up until 32 weeks gestation where reverse diastolic flow is found, as long as monitoring with NST (non-stress test) remains reassuring, after which delivery should be planned. Dopplers should be done every 1-2 weeks, but if normal, can then be done less regularly (21) .

The Royal College Guidelines on management of a small-for-gestation fetus suggests that a high umbilical artery PI>95th centile with positive end diastolic flows requires twice weekly follow up ultrasounds and if the flow is absent or reduced, daily follow up ultrasounds. This monitoring should be paired with daily NST's, where the beat-to-beat variability has been shown to be the most significant factor to observe. These guidelines do not recommend Biophysical profiles as a monitoring tool. The guideline further recommends that in preterm infants <34 weeks gestation, abnormalities in the Ductus Venosus is an indicator to deliver, not the MCA, and in fetuses above 34 weeks of gestation, redistribution in the MCA is an indication that the fetus must be delivered, as they have the strongest predictive value for poor outcome. It recommends that in fetuses with absent or reversed end-diastolic flow in the umbilical artery, delivery should be at 32 weeks gestation once steroids are complete, or before that if the Ductus Venosus becomes abnormal. (23)

ACOG recommends delivery from 34 weeks onwards if abnormalities are seen in the umbilical artery, or if other risk factors such as oligohydramnios or maternal comorbidities coexist. ACOG also notes to use magnesium sulphate for neuroprotection if delivery is anticipated before 32 weeks of gestation (12). All three above guidelines highlight the fact that IUGR as an isolated finding is not an indication for caesarean section and each case should be individualised according to fetal and maternal indications.

2.6 PERINATAL MORBIDITY AND MORTALITY:

IUGR leads to multiple risks to the fetus, both while intrauterine and in the postnatal period. IUGR has been found to lead to a 7-fold increased risk of death, which increases to a 35.8-fold increased risk of death in the fetus who is less than the 3rd percentile for fetal weight at a given gestation (3). The newborn infant is at an increased risk for complications such as hypothermia, hypoglycaemia and sepsis, to name a few (12).

The PORTO Trial (Prospective Observational Trial to Optimize Paediatric Health in Intrauterine Growth Restriction) was a large prospective trial conducted in Ireland that included more than 1100 singleton pregnancies diagnosed with IUGR (defined as an EFW or AC of <10th centile). Adverse perinatal outcomes were defined as intraventricular haemorrhage, periventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, neonatal sepsis and death. 1 in 20 babies suffered adverse outcomes overall, with an EFW <3rd centile being the most statistically significant and all 8 deaths (4 stillbirths and 4 neonatal deaths) occurred in this group. An abnormal umbilical artery Doppler (specifically absent or reversed flow) had the strongest association with poor outcomes. An estimated fetal weight <5th percentile had a mortality rate of 5, 3%, that increased to 16, 7% when an abnormal Doppler was found. The morbidity rate when the EFW <3rd percentile was 6, 2%, but that was increased to a significant 13% when the fetuses also had abnormal Dopplers. The PORTO Study therefore suggested that an EFW <10th centile with an abnormal umbilical artery Doppler or an EFW <3rd centile is a more adequate definition of IUGR than EFW <10th centile alone. The PORTO study found that oligohydramnios was only a significant finding when compounded by an estimated fetal weight of below the third centile. A low cerebro-placental ratio of <1 was associated with 18% of adverse neonatal outcomes. The PORTO study also saw a 'typical' pattern of progression of Doppler changes in 46% of the IUGR fetuses studied. (43)

Lees et al published the largest prospective randomized control study to date in 2013. The TRUFFLE Study (Trial of Randomized Umbilical and Fetal Flow in Europe) aimed to describe perinatal morbidity and mortality in early-onset IUGR (26-32weeks gestation) in 503 pregnancies, in 20 European perinatal centres over a 5 year period, as well as the Doppler findings in the pregnancies. The intervention was delivery of the fetus and there were three randomization groups according to indication to deliver, namely reduced short-term variability on NST, a Ductus venosus PI that was greater than the 95th percentile or late changes in the Ductus (described as absent or reversal of the a-wave). Defining IUGR as an EFW <10th centile with an umbilical artery Doppler pulsatility index (PI) >95th percentile, overall 2.4% of fetuses died in-utero and a further 5.5% of the 491 livebirths died in the neonatal period. Of the deaths in the neonatal period, 18% died as a result of sepsis, while 10% died as a result of pulmonary dysplasia. (37)

The average gestational age at delivery was just under 31 weeks and 97% of the 490 live births were delivered by caesarean section. Severe mortality was described similarly to in the PORTO Trial above as bronchopulmonary dysplasia, severe cerebral germinal matrix haemorrhage, proven neonatal sepsis, periventricular leukomalacia or necrotizing enterocolitis and 24% of live- born fetuses were affected. 31% of fetuses met the criteria for severe morbidity or mortality. Poorer outcomes were more strongly associated with earlier gestations, lower birthweights and lower APGARS at the time of delivery. Maternal hypertension was found to be a significant risk factor for developing early onset IUGR, with 73% of mothers being hypertensive but it also showed that hypertension was the only maternal comorbidity proven as an independent risk factor for poorer neonatal outcomes. The median time between abnormalities in the Umbilical Artery and the development of fetal heart rate abnormalities on NST was shortened in fetuses whose mothers had hypertensive conditions. (37)

3. PROBLEM STATEMENT:

Intrauterine growth restriction has shown to be a complication associated with preterm labour and poorer perinatal outcomes in many overseas trials, but its burden has not been quantified in our resource-restricted setting. IUGR is diagnosed more commonly at Chris Hani Baragwaneth Academic Hospital (CHBAH) as more patients gain access to ultrasound during pregnancy and a dedicated Fetal Medicine Unit is readily available to assess complicated cases. The aim is to study the outcomes in these babies, as well as the Doppler findings to determine the predictive value for short-term prognosis for abnormal Doppler findings in IUGR at CHBAH. Findings from the study are pivotal in aiding with the counselling of parents with IUGR babies about expected outcomes, specifically in a South African setting.

4. OBJECTIVES FOR THE STUDY

a. To determine the maternal comorbidities associated with IUGR fetuses
b. Determine the perinatal outcomes in fetuses affected by early-onset intrauterine growth restriction at CHBAH
c. Assess the prognostic value of various Doppler findings (PI and changes in waveform) to predict perinatal outcome
    i. Umbilical artery (UA) Doppler
    ii. Middle cerebral artery (MCA) Doppler
    iii. Ductus venosus (DV)

5. METHODOLOGY

5.1 SETTING:

The study took place at the Fetal Medicine Department at CHBAH, a tertiary academic hospital in Soweto, Johannesburg which performs approximately 23 000 deliveries a year. The Maternity Sonar department performed 17838 ultrasounds in 2014, 2430 of which were done by the Fetal Medicine Department (44). Patients requiring specialist sonars are identified by referral from the maternity sonographers and registrars in the obstetrics and gynaecology department, as well as from other referral hospitals in surrounding areas. The fetal medicine team then continues follow up with the patients that are identified as high risk, needing further sonar monitoring.

5.2 STUDY DESIGN:

The study was a prospective cross-sectional descriptive study.

5.3 SAMPLE SIZE:

Data was collected over a fifteen month period from May 2015 to July 2016 in order to achieve a pool of 60 patients.

5.4 STUDY POPULATION:

The study invited all pregnant patients found to have early-onset IUGR to participate. Early-onset IUGR was defined as an abdominal circumference less than the 5^{th} percentile for a

given gestational age and diagnosed between 26 weeks and 0 days and 32 weeks and 0 days of gestation.

5.5 TOOLS:

Sonar machines used were Medison Accuvix V20 and an Aloka Alpha Prosound 10 machines. The growth charts, Doppler charts and estimated fetal growth chart are standardised on the View Point Database version 4.00.05. The specific growth chart used for estimated fetal weight is found in Appendix B. All ultrasounds were performed by fetal medicine subspecialists and fellows in the department.

5.6 ENROLLMENT:

The Fetal Medicine team, comprising of Fetal Medicine Specialists and fellows in Fetal Medicine, enrolled patients into the study at the initial consult when IUGR was diagnosed and after informed consent was obtained. IUGR was defined as per department protocol as an abdominal circumference below the 5th percentile for a given gestational age. At the time of diagnosing IUGR, all patients had level three anatomical assessments of the fetus. Pregnancies were dated by early sonars (done before 20 weeks of gestation, preferably by crown-rump length done from 11-13 weeks of gestation) or if greater than 20 weeks gestation, by last normal menstrual period (LNMP) if sure of dates. If the mothers were unsure of dates or if the pregnancy was an advanced gestation, the pregnancies were dated by transcerebellar diameter (TCD).

Inclusion criteria:

- Women over 18 years of age who have given informed consent
- Singleton pregnancy
- Between 26 weeks and 0 days and 32 weeks and 0 days gestation

- Diagnosed with IUGR (defined as an abdominal circumference below the 5th percentile for a given gestational age)
- Utero-placental insufficiency evidenced by abnormal fetal Doppler studies.

Exclusion criteria:

- Multiple pregnancies
- Chromosomal abnormalities confirmed on invasive genetic testing
- Structural /congenital abnormalities in the fetus (these included all structural abnormalities that may impact on morbidity and mortality)
- Patients who chose not to participate
- Fetuses with ultrasound evidence of intrauterine congenital infection or proven congenital infection on an antenatal TORCH screen or post-natal assessment

Once enrolled in the study, bed letters and antenatal cards were marked with a specific sticker to inform and indicate to all staff members that the patient was a trial participant. These stickers included the researcher's contact details so the study participants could make contact if necessary. Repeat sonars were documented until the timing of delivery and reassessments were individualised at the discretion of the Fetal Medicine consultant depending on the degree of abnormality found and gestational age. Each patient had a printed report at each review and it was requested that the researcher be informed each time the patient was admitted and at the time of delivery. Poster notifications throughout the department and announcements at department academic meetings were used to inform medical staff about the study

Once IUGR was diagnosed, multi-vessel Doppler surveillance was initiated combined with NST's. The department specifically performed the umbilical artery (UA) Doppler, the middle cerebral artery Doppler (MCA) and the ductus venosus (DV) Dopplers as a standard practice

for baseline Doppler studies. The Dopplers were performed according to the recommendations prescribed by the Society of Fetal Medicine. The UA Doppler was taken from a section of cord that was not right near the placental end, as this may reflect greater pressure transmitted from the placental circulation. The MCA was examined in a transverse section of the fetal head at the base of the fetal skull, at 0-degree angle of incidence. The DV was sampled in a transverse section of the fetus at the level of the fetal diaphragm, as it branches from the umbilical vein. (21)

Abnormal Dopplers were defined as:

- Umbilical artery Doppler with a PI >95th percentile ±absent or reversed end diastolic flow
- MCA Doppler PI<5th percentile which indicates redistribution
- Ductus Venosus Doppler that has a PI >95th percentile or changes in the a-wave (absent or reversed)

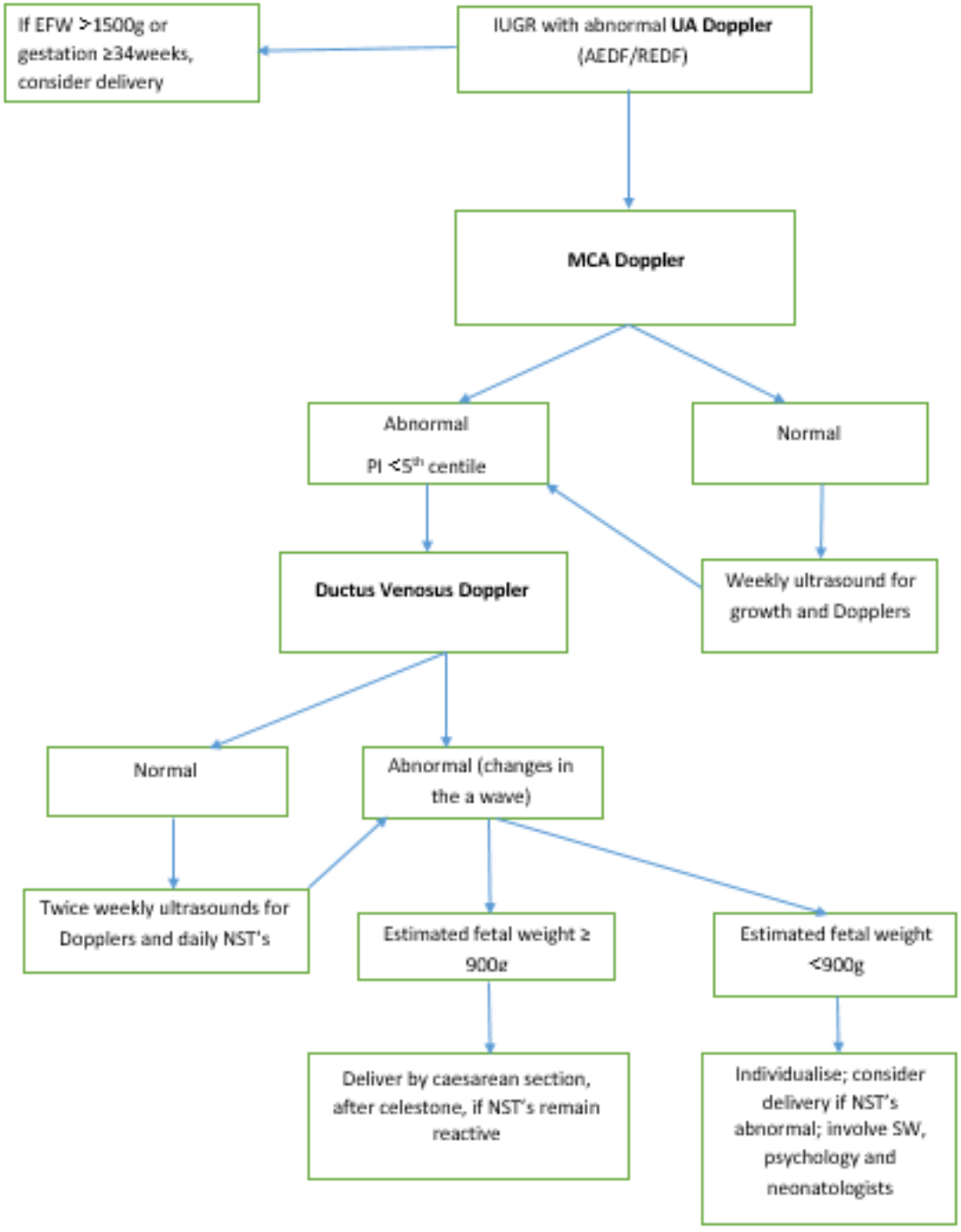
5.7 DATA COLLECTION:

Data was collected prospectively using data sheets (See Appendix A) and completed for all participating patients. No identifying data was recorded on the sheet and an individual study number was assigned to each participant. Maternal, fetal and neonatal data were recorded.

5.8 SURVEILLENCE AND DEFINITIVE MANAGEMENT:

The researcher travelled to CHBAH on a weekly basis and the babies were followed up antenatally, post-delivery and until babies were discharged from hospital. The researcher collected data sheets from the Fetal Medicine department and met with the patients in the ward if they were in patients or contacted them telephonically to introduce herself and provide detailed information about the study.

Existing department surveillance and management protocols for IUGR babies were adhered to for the study and algorithm below summarises the surveillance protocol followed by the department.



Maternal indication for delivery always took precedence over fetal indication but only with maternal informed consent.

NST indication for delivery was any pathological trace, as diagnosed at the discretion of the attending obstetrician at the time. The protocol for NST interpretation at CHBAH are based on the NICE criteria. A reassuring trace was defined as a fetal heart baseline rate between 100 and 160 beats/minute, with baseline variability of at least 5 beats/ minute and no decelerations in the fetal heart rate. Abnormal traces are defined as a baseline above 180 beats/minute or less than 100 beats/minute, a drop in baseline by more than 60 beats/minute for greater than 60 seconds, late decelerations for more than 30 minutes, despite instituting intra-partum resuscitation, or a single prolonged deceleration for greater than 3 minutes. (11)

The department offered all patients diagnosed with IUGR in the pregnancy counselling by a multidisciplinary team comprising Fetal Medicine specialists, obstetricians and neonatologist. All patients with fetuses with borderline weights of 900g or less were counselled by this team regarding possible implications of delivering the fetus at these low birth weights and a possible prolonged hospital stay. They were also referred to the social worker for supportive counselling.

Delivery information was obtained from the caesarean section registers in labour ward theatre or from the labour ward registers if the patients were delivered vaginally. Both labour ward and caesarean section theatre had two registers. One documented maternal admissions such as the date of delivery and indication for delivery and a second documented the babies' weights, apgars and admission ward if admitted.

5.9 PERINATAL FOLLOW UP:

Perinatal outcomes that were assessed included death (in-utero, early neonatal or late neonatal), need for mechanical ventilation and ICU admissions, as well as one or more severe perinatal morbidities.

Severe perinatal morbidity included:

- Intra-ventricular haemorrhage defined as haemorrhage associated with dilatation of the lateral ventricles on cranial ultrasound
- Broncho-pulmonary dysplasia defined as a need for supplementary oxygen to maintain oxygen saturation above 90% after 36 completed weeks of gestation
- Neonatal sepsis proven on blood culture, and
- Necrotizing enterocolitis defined as the presence of pneumatosis or perforation on X-ray or disease confirmed at laparotomy.

Definitions for perinatal death included: (45)

- Intrauterine fetal death (IUFD): death of a fetus while in-utero from 20 weeks of gestation
- Early Neonatal death (END): a live birth where death occurs within the first seven days of life
- Late Neonatal death (LND): a live birth where death occurs after 7 days and before 28 days of life
- Infant death (ID): a live birth where death occurs between 28 and 364 days of life

If intrauterine fetal death or postnatal death occurred, mothers received grievance counselling post-delivery by the social workers assigned to the maternity section of the hospital. Genetic counselling was included in the management if a genetic, congenital or structural abnormality was diagnosed.

Once babies were delivered, they were reviewed by the researcher on a regular basis in the neonatal wards to ascertain if morbidities as described above were diagnosed. The patients' files were reviewed to track their clinical progress and the neonatal registers were checked to determine if the babies were stepped down to another ward, discharged or had demised.

The Neonatal Department's RedCap system was searched for neonates who could not be traced. This is a data-collection system that documented all neonates admitted from labour

ward nursery to either NICU, TICU or Ward 66 (lower risk Neonates) and included information regarding their progress until discharge or death. The neonatal death record books were also checked for evidence of mortality in any of the study babies. Some neonatal files had to be accessed using the mothers' hospital details and a few mothers were contacted telephonically by the researcher to determine outcomes of their babies.

5.11 DATA ANALYSIS:

Categorical variables were described using frequencies and percentages. Continuous variables were described using standard deviations or medians and interquartile ranges. In the event of comparison of outcomes, Kai squares were used to compare categorical variables and the T test was used to compare continuous variables. Data analysis was outsourced to Dr Allison Bentley.

5.12 PERMISSION TO CONDUCT THIS RESEARCH AND ETHICS CLEARANCE:

Permission to conduct research was requested from the CEO of CHBAH and obtained on 10/3/2015. Application to the Human Research Ethics committee (HREC) of the University of Witwatersrand was made in March 2015 and approval was given in May 2015. Clearance certificate number 150350. The research was approved by the Postgraduate Committee of The University of Witwatersrand.

5.13 FUNDING:

All costs of travel, printing and telephones calls were borne by the researcher.

6. RESULTS

A total of 60 women were recruited for the study. One patient was excluded as she did not fit the inclusion criteria in terms of gestational age. Another was excluded as the EFW was not in keeping with the actual birth weight and the baby no longer fitted the criteria for IUGR. A further 5 women were lost to follow up after their recruitment at the first ultrasound, so were excluded from the data analysis. Six study participants had missing data on the final outcome of their babies, but were followed up until admission to the neonatal transitional ICU. The data from these six participants was used to create a survival curve, but was excluded from the final morbidity and mortality analysis. There were therefore 47 patients included in the final analysis.

6.1 MATERNAL DEMOGRAPHICS:

Forty seven women were included. The mean age was 30.8 years (± 6.4). Mean gestational age was 28 weeks and 2 days gestation. Just over 29% of women had a parity of 0, 35.5% had a parity of 1, 22.9% a parity of 2, 6.2% a parity of 3 and 6.2% a parity of 5. Twenty of the 47 women reported previous pregnancy losses. 18.8% of women had a gravidity of 1, 27.1% had a gravidity of 2, 29.2% had a gravidity of 3, 8.3% had a gravidity of 4, 6.2% a gravidity of 5, 8.3% a gravidity of 6, none a gravidity of 7 and 2.1% had a gravidity of 8.

Booking bloods included Rhesus, HIV and RPR result. Forty six were Rhesus positive and one Rhesus result was unknown. Eleven women were HIV positive (all on antiretroviral therapy), 35 women were HIV negative and one result was unknown. All 47 women were RPR negative.

In terms of previous caesarean section for delivery, 70.8% had never had a caesarean section, 21.2% had had one and 6.4% had had 2 previous caesarean sections. Forty five women of the 47 study participants denied any drug use, while one woman was a smoker and one woman reported marujuana use throughout the pregnancy. The body mass index was calculated for 44 of the 47 women due to missing data and the mean (SD) was 31.9 (7.3) kg/m2 .

Five women had no comorbidities and in one patient, the presence of comordidity was not known. Forty one women reported comorbidities, with 7 of these women having more than one comorbidity. Table 1 lists the cormorbidities present in the participants. Hypertensive disorders of varying severity was by far the most common comorbidity, affecting 39 (83%) of the 47 study participants.

Table 1: Maternal comorbidities

Comorbidity:	Number:
Preeclampsia	35
Eclampsia	1
HELLP syndrome	3
Antiphospholipid syndrome	7
Systemic lupus erythematosus	1
Renal failure	2
Multi-fibroid uterus	1
Pulmonary tuberculosis	1
Hyperthyroidism	1

6.2 ULTRASOUND FINDINGS:

Forty seven ultrasound findings were analysed. The range of estimated fetal weight was 500-1557g, with a mean estimated fetal weight of 845.2g. Table 2 below summarises the estimated fetal weight centiles.

Table 2: EFW Centiles

Centile	Number (n=47)	Percentage
<3rd	26	55.3
3rd	18	38.3
5th	1	2.1

10th	1	2.1
50th	1	2.1

The table demonstates that most of the study participants already had severe IUGR at the time of diagnosis, with 55.3% of study participants having an EFW of < 3rd centile.

Four of 47 study participants had anyhydramnios, 36 of the 47 had oligohydramnios while 7 had normal liquor volumes. Seventy nine percent of fetuses were cephalic, while 21% were breech.

Table 3: Doppler Abnormalities

Doppler Abnormality	Number (n=47)	Percentage (%)
AEDF only	10	21.3
AEDF and redistribution (MCA PI on/below the 5th centile)	20	42.6
AEDF + redistribution (MCA PI on/below the 5th centile) + increasing Ductus Venosus PI	7	14.9
AEDF + redistribution (MCA PI on/below the 5th centile) + reversal of flow in the Ductus Venosus PI	3	6.3
REDF + redistribution (MCA PI on/below the 5th centile)	1	2.1
REDF + redistribution (MCA PI on/below the 5th centile)+ abnormal Ductus Venosus Doppler	6	12.7

Table 3 above describes the Doppler changes found on ultrasound. The most common Doppler finding was AEDF in the Umbilical artery with redistibution seen in the MCA. The least commonly found change in the Dopplers was REDF in the UA with redistribution seen on the MCA.

6.3 DELIVERY INFORMATION:

The average gestation at delivery was 29 weeks and 2 days for 47 study participants. The range of birth weights was from 485g to 1455g with a average birth weight of 853.5g. The average time from diagnosis of IUGR with abnormal Dopplers (by ultrasound) to delivery was 6.5 days.

Table 4: A comparison of estimated and actual fetal weights

	Estimated weight	Birth weight
Lowest weight	419	485
25%	698	742
50% (median)	844	830
75%	994	963
Highest weight	1557	1455

As can be seen in Table 4, the estimated weights on sonar and the actual fetal weights were quite similar, also keeping in mind that there was an average delay of 6.5 days from when the EFW was taken until delivery (as noted above).

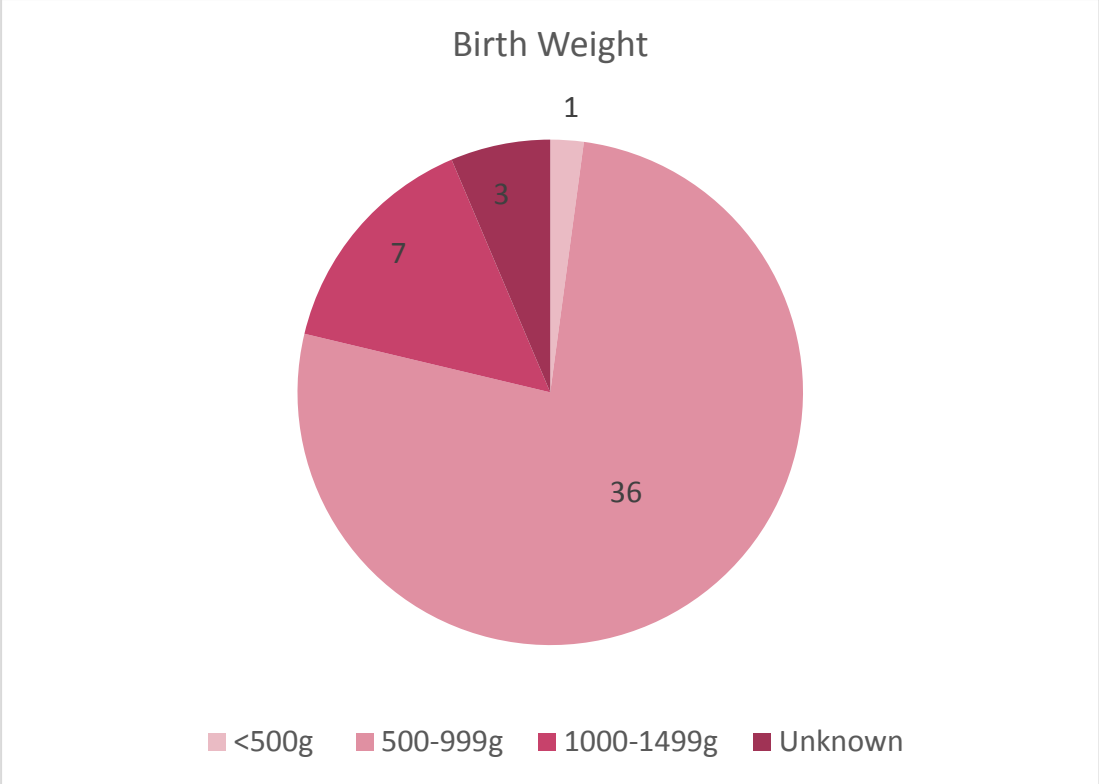


Figure 1: Birth Weight Catergories

Figure 1 demonstartes the birth weight categories for all 47 study participants. Of note is that two IUFD's and one medical TOP did not have the birth weights documented in the labour ward registers. 37 (78.7%) are considered extremely low birth weight with birth weights below one kilogram and 7 (14.9%) and considered very low birth weight, with weights between 1000-1499 grams.

Refer to Table 5. Thirty six of the study participants were delivered by caesarean section for various indications (all with live fetuses when going to theatre), while 11 delivered by NVD. All 11 NVD's were inductions of labour, 9 of which were IUFD's and 2 of which were medical terminations.

Table 5: Indications for caeserean sections as per patient consent forms

Indication:	Number (n=36):	Percentage (%):
Fetal Distress	17	47.2
Severe IUGR	1	2.8
Abnormal Dopplers	10	27.8
Eclampsia	1	2.8
Severe Preeclampsia	1	2.8
HELLP Syndrome	2	5.6
Deteriorating renal function	1	2.8
Unknown (Consent not found; not documented in caeserian book)	3	8.3

Fetal distress was the most common indication (47.2%), with abnormal Dopplers found to be the second most common indication, accounting for 27.8% of the caeserean sections performed.

In the 36 patients who had live fetuses on transfer to theatre, 33 were given a completed course of steroids (12mg Betamethasone IMI BD; two doses) before delivery, 1 patient did not receive steroids (the reason was not clear) and in 2 patients, it was not documented if steroids were given. The Apgars and pH of the babies at delivery were excluded from the analysis due to large amount of missing data.

6.4 NEONATAL ADMISSION DETAILS:

Of the 36 patients who underwent caesarean section, 3 were fresh stillbirths and excluded from neonatal admission data. Of 33 study participants with live-born fetuses, 32 were admitted to TICU (Transitional Intensive Care Unit) and 1 was admitted to Ward 66, which is the lower level of care ward in neonates. Only 1 baby was stepped up to NICU (Neonatal ICU) from TICU and ventilated after a cardiac

arrest in the ward. All other babies did not qualify for ventilation due to their low birth weights.

Surfactant was given to 11 (n=33) babies in TICU, it was not given to 18 babies and was unknown in 4 babies. CPAP (Continuous Positive Airway Pressure) ventilation was administered to 21 babies, it was not given to 11 babies and was unknown in 1 baby.

6.5 PERINATAL MORBIDITY AND MORTALITY:

Perinatal morbidity and mortality only included 47 study participants in which the final outcomes were known. The final outcome was lost for 6 babies after delivery during the neonatal admission, so they were excluded from further anaylsis.

A survival curve was done for all 53 babies that were followed up, including the six that were know in TICU and then lost to further follow up:

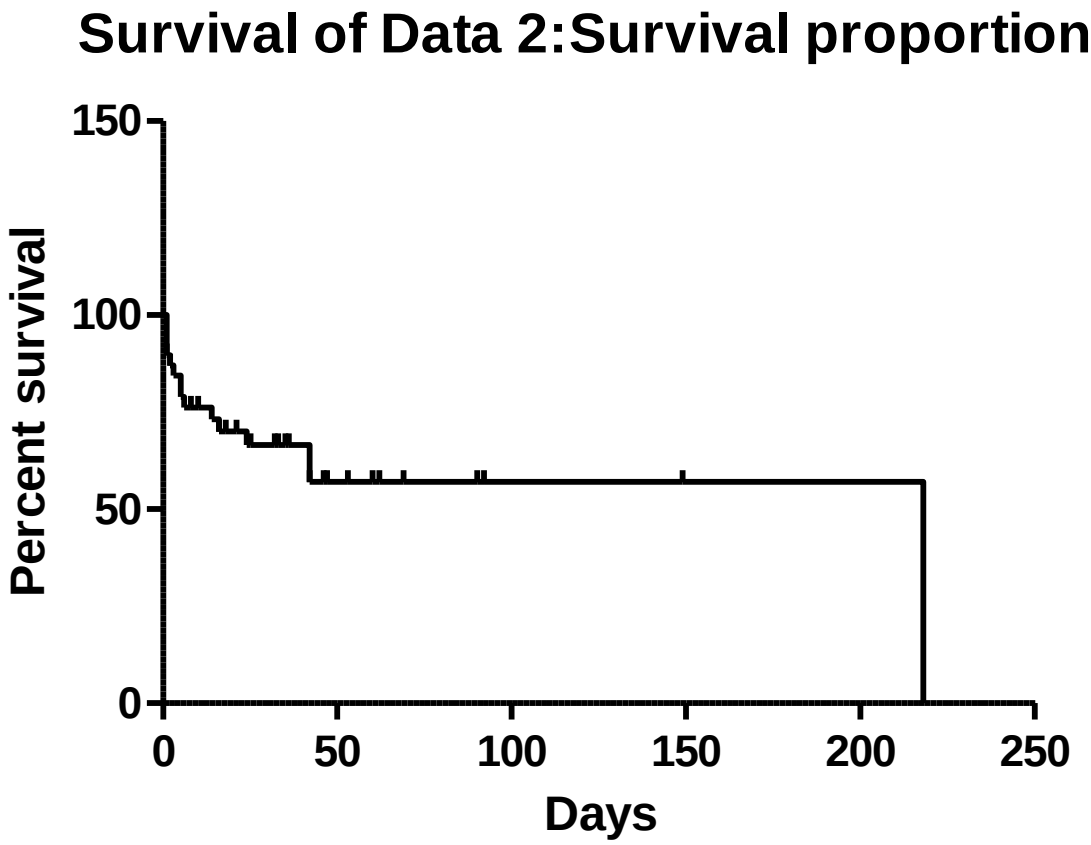


Figure 2: Survival Curve

The median survival was 218 days. At birth (day 0), 14 (26%) babies had demised (IUFD's, Medical TOP's and FSB's). At day 50, only 8 babies were known to be alive. At day 100, 2 were known to be alive. Of note, was that the baby that survived 218 days, was discharged and died two days later at home.

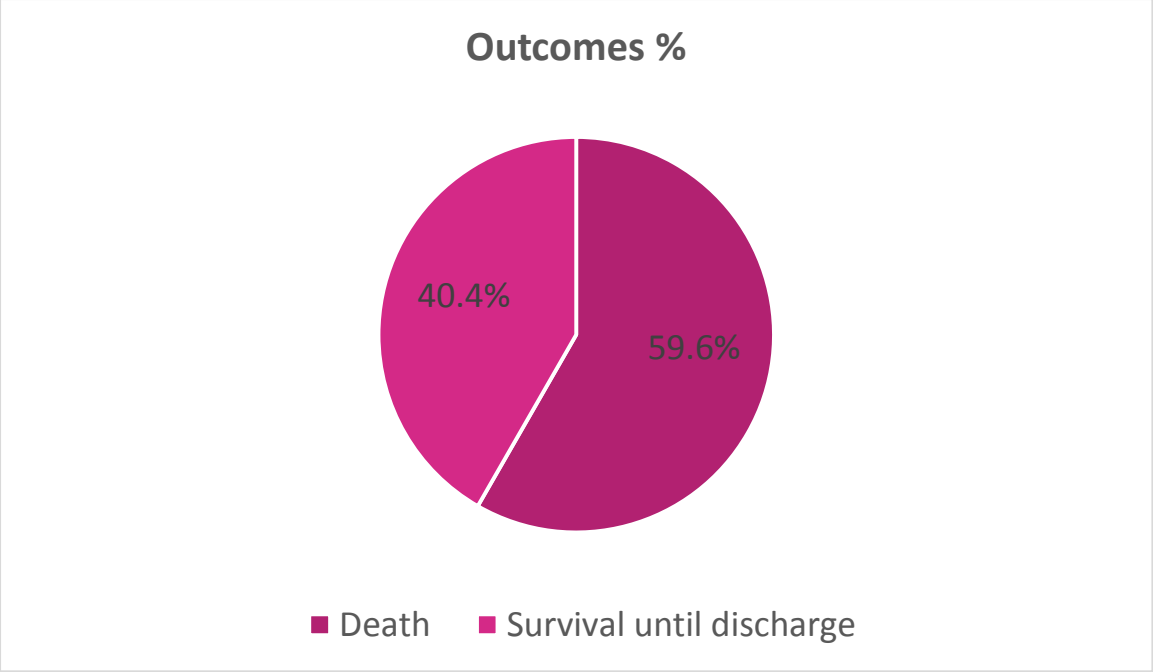
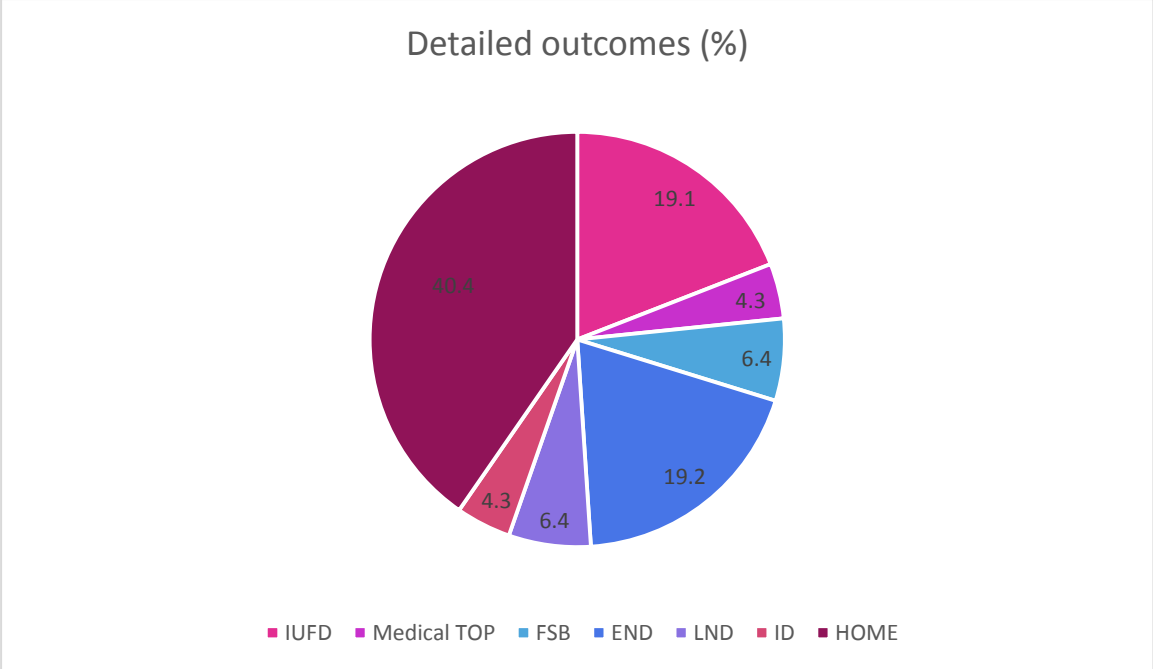


Figure 3: Summary of Outcomes

As can be seen in Figure 3, more than half of the study participants demised before they were discharged home. Ninteen babies survived, while 28 babies demised. Table 5 below summarises the outcomes for all 47 babies.

Table 5: Detailed outcomes

Outcome	Number (n=47)	Percentage (%)
Intrauterine Fetal Death	9	19.1
Medical Termination of Pregnancy	2	4.3
Fresh stillbirth	3	6.4
Early neonatal Death	9	19.1
Late Neonatal Death	3	6.4
Infant Death	2	4.3
Discharged Home	19	40.4



IUFD and END was the most common form of mortality found in the study group.

Table 6 and 7 show the morbidity and mortality by weight category and weight centiles. When the babies that survived were compared to those that did not, it was found that in the survivor group, the average gestational age was 29 weeks and 5 days with a mean birth weight of 969g, while the group that demised had an average gestational age of 28 weeks and 4 days and a mean birth weight of 775.8g. All mortalities were in the 3rd and <3rd centile group. Of note in Table 6, is that 3 birth weights were unknown therefore it summarizes 44 of the study participants. Sixty two percent of babies born below 1000g demised. Birth weight at delivery was shown to be an independent risk factor for perinatal morbidity (p<0001).

Table 6: Comparison between birth weight catergory and survival

Weight	Number Alive	Number Demised
<500g (n=1)	0	1
500-999g (n=36)	14	22
1000-1499g (n=7)	5	2

Table 7: Morbidity and Mortality by Weight Centiles

	<3rd	3rd	5th	10th	50th
Nil M&M	4	3	1	1	1
Morbidity	4	5	0	0	0
Mortality (n=28)	18	10	0	0	0
Percentage of mortalities	64%	36%	0%	0%	0%

Table 8: Morbidity and Mortality by Doppler Abnormality

Doppler Changes	Nil M & M	Morbidity	Mortality	Percentage of overall Mortalities (%) n=28
AEDF only (n=10)	5	2	3	10.7
AEDF + Redistribution (MCA PI on/below 5th centile) (n=21)	4	6	11	39.3
AEDF + Redistribution (MCA PI on/below 5th centile)+ Raised Ductus venosus PI (n=7)	1	1	5	17.9
AEDF + Redistribution (MCA PI on/below 5th centile) + Reversed flow in Ductuc Venosus (n=3)	0	0	3	10.7
REDF + Redistribution (MCA PI on/below 5th	1	0	0	0

centile) (n=1)				
REDF + Redistribution (MCA PI on/below 5th centile)+ Abnormal Ductus Venosus Doppler (n=3)	0	0	6	21.4

Refer to Table 8 above, which summarises the morbidities and mortalities by Doppler findings. The most common Doppler finding in the mortality group was AEDF with redistribution seen in the MCA, but to note is that all babies found to have REDF with redistribution in the MCA and an abnormality in the Ductus Venosus Doppler demised. The prescence of an abnormality of the Ductus Venosus was proven to be statistically significant and was an independent risk factor for perinatal mortality ($p<0.002$).

6.5.1 Intrauterine Fetal Death:

There were 9 IUFD's in the study population. The average time from diagnosis of IUGR on sonar to IUFD was 10.4 days. As above, all were delivered by NVD after induction of labour with oral misprostol. Table 9 summarises the characteristics of the IUFD's.

Table 9: Characteristics of the IUFDs

IUFD	Gestation at Delivery	Weight Centile	Maternal Comorbidity	Doppler	Birth Weight (g)
1	29w2d	<3rd	Preeclampsia	AEDF + redistribution in MCA	803
2	28w5d	<3rd	Nil	AEDF + redistribution in MCA + Raised Ductus	Unknown

3	26w4d	3rd	Preeclampsia	AEDF + redistribution of MCA + Reversed Ductus	750
4	29w5d	<3rd	Preeclampsia	AEDF + redistribution of MCA	720
5	31w4d	<3rd	Preeclampsia	AEDF + redistribution in MCA + raised Ductus	702
6	29w3d	<3rd	HELLP	REDF + redistribution in MCA + Raised Ductus	590
7	29w0d	<3rd	Preeclampsia	AEDF + redistribution in MCA	Unknown
8	28w1d	<3rd	APLS, PTB	AEDF + redistribution in MCA + raised Ductus	485
9	29w1d	<3rd	Preeclampsia	AEDF + redistribution of MCA	790

The average gestational age at diagnosis of IUFD was 29 weeks and 1 day with an average weight of 691.4g at delivery. Eight nine percent were below the 3rd weight centile at a given gestational age. Five babies had evidence of redistribution of the MCA, while four also had changes in the Ductus Venosus Doppler.

6.5.2 Medical Termination of Pregnancy:

Table 10: Characteristics of Medical TOP's

Med TOP	Gestation at Delivery	Weight Centile	Maternal Comorbidity	Doppler	Birth weight (g)	Indication for TOP
1	28w4d	<3rd	Severe PET	AEDF + Redistribution in MCA	515	Mother became Imminently Eclamptic (IE)
2	31w0d	<3rd	APLS, SLE	AEDF	Unknown (EFW=547 g)	Severe IUGR

Table 10 summarises the characteristics of the medical terminations of pregnancy. Both babies has severe IUGR, but the first was done for maternal indications, while the second was for the IUGR.

6.5.3 Fresh Stillbirth:

Table 11: Characteristics of Fresh Stillbirths

FSB	Gestation at Delivery	Weight Centile	Maternal Comorbidity	Doppler	Birth weight (g)	Indication for caeserean
1	27w0d	<3rd	HELLP	AEDF + Redistribution in MCA	678	HELLP Syndrome
2	27w6d	3rd	Severe PET	REDF + redistribution in MCA + Reversed Ductus	735	Severe PET and Severe IUGR
3	27w3d	3rd	Nil	REDF +	786	Abnormal

				redistribution of MCA + reversed Ductus		Dopplers

All freshstillbirths had a positive fetal heartbeat on transfer to theatre. The median gestation was 27 weeksand 3 days and average weight was 786g.

6.5.4 Early Neonatal Death:

Table 12: Characteristics of Early Neonatal Deaths

END	Gestation at Delivery	Weight Centile	Maternal Comorbidity	Doppler	Birth Weight (g)	Documented Cause of Death
1	28w2d	<3rd	Severe preeclampsia	AEDF + redistribution in MCA + reveresed Ductus	580	Severe RDS
2	27w3d	3rd	Preeclampsia	AEDF + redistribution in MCA	816	Severe RDS
3	28w5d	<3rd	Preeclampsia	AEDF + redistribution in MCA + raised Ductus	620	Extreme prematurity
4	28w0d	<3rd	Severe Preeclampsia	AEDF + redistribution in MCA	830	ELBW and RDS
5	26w5d	3rd	Preeclampsia	REDF + redistribution in MCA + raised	680	ELBW and RDS

				Ductus		
6	26w4d	3rd	Preeclampsia	AEDF + redistribution in MCA	700	ELBW and RDS
7	29w1d	3rd	Preeclampsia	AEDF + redistribution of MCA	875	Extreme prematurity
8	32w1d	<3rd	Not documented	AEDF + redistribution of MCA	810	Prematurity
9	27w2d	<3rd	Preeclampsia	REDF + redistribution in MCA + raised Ductus	830	Prematurity

The average gestational age in this group was 28 weeks and 2 days with an average birth weight of 748g. Only one baby had documented morbidity before death, namely NEC I and IVH I (baby 7). The average time from diagnosis of IUGR to delivery was 5.3 days. The average time from birth to death was 2.6 days in this group. Six babies were delivered by caeserean section for the abnormalities found on Doppler, two were delivered for fetal distress and one indication for caeserean section was not documented. Prematurity was the most common documented cause of death.

6.5.5 Late Neonatal Death:

Table 13: Characteristics of Late Neonatal Deaths

LND	Gestation at Delivery	Weight Centile	Maternal Comorbidity	Doppler	Birth Weight (g)	Documented Cause of Death	Morbidity
1	28w1d	3rd	Preeclampsia	AEDF	1010	Severe RDS	Nil
2	28w5d	3rd	Preeclampsia	AEDF +	1095	Severe RDS	Sepsis

			and APLS	redistribution of MCA			
3	28w6d	3rd	Preeclampsia	AEDF + redistribution of MCA	820	Prematurity	NEC I

Table 13 describes the characteristics of the 3 LND's in the study. The average gestational age at delivery in this group was 28 weeks and 4 days. The average birth weight was 975 g. The average time from diagnosis of IUGR to delivery was 3.3 days and average time from delivery to death was 18 days. All three babies were delivered by caesarean section for fetal distress.

6.5.6 Infant Death:

Table 14: Characteristics of Infant Deaths

ID	Gestation at Delivery	Weight Centile	Maternal Comorbidity	Doppler	Birth Weight (g)	Documented Cause of Death	Morbidity
1	28w4d	<3rd	nil	AEDF + redistribution in MCA + reversed Ductus	785	Severe RDS	Sepsis, NEC I, IVH I
2	28w5d	<3rd	Preeclampsia	AEDF	970	Prematurity	Unknown

Refer to Table 14 above. Both babies had EFW of <3rd centile. The average gestation at delivery in the infant death group was 28 weeks and 5 days, with an average bith weight of 877.5g. The average time taken from diagnosis of IUGR to delivery was 1 day and average time from birth to death was 42 days.

6.5.7 Discharged Home:

Table 15: Characteristics of Babies Discharged Home

Baby	Gestation at Delivery	Weight Centile	Maternal Comorbidity	Doppler	Birth Weight (g)	Morbidity	Age at Discharge (days)
1	30w3d	<3rd	PET	AEDF + redistribution oin MCA	945	NEC I; IVH I	42
2	29w1d	3rd	APLS; CHPT	AEDF + redistribution in MCA	935	NEC II; IVH I; Sepsis	90
3	28w5d	3rd	PET	AEDF	870	Nil	35
4	29w2d	3rd	PET	AEDF + Redistribution in MCA	770	BPD; PVED	60
5	30w1d	<3rd	PET	AEDF + redistribution in MCA	1055	Nil	46
6	31w4d	<3rd	Eclampsia	AEDF	1455	Nil	18
7	31w5d	3rd	PET	AEDF + redistribution in MCA	860	BPD; Sepsis	149
8	30w2d	3rd	PET	AEDF + redistribution in MCA	900	NEC I; Sepsis	32
9	28w0d	3rd	Nil	AEDF	785	Nil	62
10	29w0d	10th	PET	AEDF + redistribution of MCA	815	BPD (Note this baby died at home)	216
11	26w6d	3rd	PET	AEDF	1175	Nil	33
12	29w3d	<3rd	PET	AEDF +	965	Nil	53

				redistribution in MCA			
13	29w4d	10th	PET	AEDF + redistribution in MCA + raised Ductus	935	Nil	34
14	30w2d	3rd	PET	AEDF + redistribution in MCA	1320	Nil	21
15	30w1d	3rd	PET	REDF + redistribution of MCA	965	Nil	36
16	30w4d	<3rd	PET	AEDF	1030	NEC I; Sepsis	69
17	31w1d	<3rd	HELLP	AEDF	960	Cardiac arrest	62
18	29w0d	<3rd	PET	AEDF + redistribution in MCA + raised Ductus	775	NEC II; BPD	92
19	28w3d	5th	Eclampsia	AEDF + redistribution in MCA	905	NEC I; Sepsis	39

Table 15 summarises the characteristics of those babiess who were discharged home. The average birth weight was 969.5g in this group with an average gestational age of delivery of 29 weeks and 5 days. Babies were delivered within 4.8 days of diagnosis of IUGR and discharged home after an average of 62.6 days (range of 18-216 days). 52.6% of these babies fulfilled the criteria for major morbidity. One baby was discharged home but died two days later, so did not fit the criteria for mortality for the study. All but one of the mothers suffered from a hypertensive condition.

7. DISCUSSION:

Although the study population was relatively small, this study showed many results that were in keeping with the current literature, as well as raising topics for further studies needed to optimise patient management in IUGR. In this setting, there is a high mortality rate, as well as a high morbidity rate in babies with IUGR that survive to be discharged home.

7.1 MATERNAL DEMOGRAPHICS:

Of note, was the high prevalence of hypertensive conditions found in the mothers registered for the study. Fourty one of 47 women had comorbidities, with 83% of these being hypertensive conditions. Hypertension has been found to have a 8-15% risk of IUGR and was the largest risk factor identified in our study, although it was not statistically significant as a predictor of morbidity or mortality in the study (p=0.1057). In the TRUFFLE study, hypertensive conditions were diagnosed in 73% of study participants and in contast to this study, they were found to be an independent predictor of poorer outcomes in IUGR. This implies that while HPT is a significant risk factor for the development of IUGR, its severity is not necessarily a predictor of pregnancy outcomes in IUGR in this study. Twenty of the 47 study participants also reported prior pregnancy losses, suggesting placental abnormalities may be common in the study group.

7.2 ULTRASOUND FINDINGS:

The average gestational age at registration into the study and diagnosis with IUGR was 28 weeks and 2 days, with an average estimated fetal weight of 845g. If the expected weight is determined for this gestation from the standard growth chart used in the Fetal medicine Department (see Appendix B), 1200g falls on the 50^{th} centile while 1000g is the 3^{rd} centile. This highlights the fact that babies were already severely growth restricted at the time of diagnosis, with 55% of study participants falling below the 3^{rd} centile for a given gestational age. One of the babies were excluded from the study after delivery as the birth weight was 1800g at 31+4 weeks of gestation, which falls on the 50^{th} centile. The estimated fetal weight on ultrasound was 1438g, which is on the 5^{th} centile and thus the patient initially qualified for the study. This is an important factor in counselling patients in the sense that EFW on

ultrasound is not an exact science and may be more or less than the actual delivery weight. Only 10 babies had an isolated Doppler abnormality in the UA, while 78.7% (37/47) already had Doppler abnormalities in more than one vessel, again showing that babies registered for the study had severe IUGR.

Majority of babies also had abnormal liquor volumes, with 40 of 47 babies being diagnosed with either oligohydramnios or anhydramnios. The literature is conflicting, with guidelines published by ACOG stating that liquor volume is of great prognostic value in IUGR (12), where as the Green-top Guideline published by RCOG states that oligohydramnios is of little prognostic value in IUGR (23). This study showed that oligohydramnios and anhydramnios was not statistically significant as an risk factor for a poorer outcome (p=0.1706).

7.3 DELIVERY INFORMATION:

On average, babies were delivered within 6.5 days of being registered for the study. IUGR babies in the study were, in the majority of cases, delivered by caesarean section (76.6%). This is as per institutional protocol that all live IUGR babies known to have abnormal dopplers are delivered by caesarean section. Those not delivered by caesarean, were those women who underwent induction of labour for medical TOP or IUFD. Majority (17 of 36 or 47%) of these were for a fetal distress diagnosed on NST. The concern is that changes in NST are considered late signs in IUGR and a sign of severe compromise in an IUGR fetus, meaning these babies are already acidemic and hypoxic at birth (11). 11 of the 17 babies delivered for fetal distress had poor outcomes, with 7 meeting the criteria of major morbidity (although then being discharged home) and 4 demised. Twenty eight caesarean sections were performed for fetal indications, 5 for maternal indications and in 3 cases, the indication was not known.

7.4 NEONATAL ADMISSIONS:

After excluding the three fresh stillbirths, 32 of the 33 babies were admitted to TICU after delivery and one was admitted to ward 66. The neonatal protocol at CHBAH allows for access to ventilation, if available at the time, to babies over 900g and to cPAP over 800g. This meant

that majority of the babies born from the study did not qualify for ventilation. Only one baby, of 33 babies admitted, received ventilation following a cardiac arrest in TICU and was stepped up to NICU.

7.5 PERINATAL MORBIDITY AND MORTALITY:

More than half of babies registered for the study demised (59.6%). It was shown that babies that survived to discharge home tended to have higher birth weights (969g vs 775.8g) and were born at a later gestation (29 weeks and 2 days vs 28 weeks and 4 days). Birth weight was shown to be an independent predictor of morbidity and mortality ($p<000.1$). Similarly, the TRUFFLE Study also found that poorer outcomes were strongly asscociated with earlier gestations and lower weights at delivery (37). All mortalities in this study had an EFW falling on the 3rd centile or below the 3rd centile, although this was not proven to be statistically significant ($p=0.1586$). The PORTO Study showed that a weight centile <3rd was the most statistically significant predictor of outcomes in their study group, with all 8 mortalities found in that group (43).

Majority of babies born were considered ELBW, with 78.7% weighing less than 1000g. The survival rate in this group was 38.9% (14 of 36 babies). Fifteen percent of babies born were VLBW, weighing less than 1500g and the survival rate in this group was 71.4% (5 of 7 babies). It is important to acknowledge the compounding factor that IUGR plays in perinatal outcomes of preterm fetuses. Prematurity as an isolated factor in itself leads to a greater risk of perinatal morbidity and mortality. Velaphi et al conducted a study at CHBAH looking at 2164 very low birth weight (VLBW) babies born over a two year period and aimed to determine the perinatal morbidity and mortality associated with prematurity of varied weight categories. In total, there were 1566 survivors and 587 mortalities. The overall survival rate of babies born at less than 1500g was 71%, those born at less than 1000g was 32% and there were no survivors in the weight category of less than 600g. The study highlighted that babies born below 1000g were not offered mechanical ventilation at CHBAH and it found that the odds to survival to discharge almost doubled for babies in the weight category of 1000-1099g, when compared to the group of 900-999g. (46)

The study by Velaphi is important to consider as it is in a South African setting, serving the same demographics as this study on IUGR and provides important information about the NICU outcomes in the institute where the study was conducted. The outcomes for survival were in fact very similar, suggesting prematurity being the most important predictor of outcomes, versus intrauterine growth restriction.

The most common mortalities in the study group were intrauterine fetal deaths and early neonatal deaths, each accounting for 19.1% of the 28 mortalities. The overall average time taken from diagnosis of IUGR to delivery was 6.5 days, although speciaifcally in the IUFD group, the average time was longer at 10.4 days, while in the neonatal death groups it was shorter (END was 5.3 days, LND was 3.3 days and ID was 1 day). These findings are in keeping with the GRIT study, where is was found that delaying delivery lead to a greater number of IUFD's, but in the immediate delivery group, there was a higher number of neonatal deaths although not statistically significant (47).

The mortality rate was high. Ninteen of 47 babies with final outcomes known survived until discharge home, but 21.3% (10 of 19) of these babies met the criteria for major morbidity and 80% then also had more than one major morbidity. NEC was diagnosed most commonly, affecting 6 of 10 babies, then sepsis and bronchopulmonary dysplasia each affecting 5 babies and IVH was the least common morbidity diagnosed, only affecting 2 of 10 babies. The PORTO Trial quoted a much lower rate of morbidity, with only 1 in 20 babies meeting the criteria for major morbidity (43).

This study showed that the finding of an abnormal Ductus Venosus Doppler (increased/absent/reveresed) was a statistically significant predictor of morbidity and mortality in IUGR babies born at CHBAH (p=0.002). This may be as a result of changes in the Ductus Venosus already identifying acidotic and severley compromised fetuses, who are then delivered and decompensate more often than babies without changes in the Ductus Venosus. Only AEDF and REDF in the UA have previously been shown to be statistically significant, as seen in the PORTO Trial (48) and in the study by Crimmins et al, which compared the Doppler findings in live versus stillborn IUGR babies (33).

The Ductus Venosus indicates compensatory mechanisms in the fetus whereby there is an increase in right ventricular afterload as blood is shunted via the DV, bypassing the liver and then shunted across the foramen ovale to increase left ventricular afterload. Once there is an accumulation of lactic acid, this mechanism fails and there are changes seen in the a-wave of the DV (31). Turan had shown that once the DV is abnormal, the baby is unlikely to survive longer than a week inutero and that each day delivery was delayed doubled the odds of stillbirth (42).

Babies in this study were shown to have decreased survival once the DV was abnormal. Other indices have been suggested in the literature that may predate changes in the DV. The aortic isthmus is the arterial connection between the placental circulation and the fetal cerebral circulation and its Doppler may be seen as an intermediate step to assess for fetal hypoxia and cardiac decompensation (49). Figueras et al conducted an observational study in 46 fetuses that showed that changes in the aortic isthmus Doppler occurred on average one week before changes in the DV (50). Del-Rio et al showed that reversed flow in the aortic isthmus preceeded changes in the DV by 24-48 hours, although this was also a small study including 51 patients (51). However, correlation of aortic Doppler findings with perinatal outcomes still requires further research. There is insufficient literature presently to justify using the aortic isthmus to determine optimal timing of delivery and to recommend its use in clinical practice.

7.6 LIMITATIONS:

7.6.1 Registration:

The study presented many challenges throughout the study period.

The first and most major limitation was that the researcher was not onsite for the first year of the study period. As per methodology and protocol, the Fetal Medicine team identified, recruited and consented patients but the immediate follow up of the patients by the researcher was not always possible. With the majority of the deliveries occuring within 6.5 days of recruitment, the researcher sometimes only made first contact with the patient after delivery, meaning some study information was gained from records retrospectively.

The emotional distress following the diagnosis of severe IUGR and abnormal dopplers were under-estimated. Patients were overwhelmed with the guarded prognoses for their babies. This was worse in patients who had previous pregnancy losses. To recruit patients at the point of diagnosis was part of the methodology, but more patients declined entry into the study than anticipated.

There was poor referral to the study from other registrars and sonographers. This meant that multiple cases who had sonars in antenatal clinic that may have qualified for the study were missed.

7.6.2 Ultrasound findings:

Due to a common trend of women presenting later in their pregnancies for antenatal care, as well as the poor and late referral to the Fetal Medicine Team for the study as described above, all the patients tended to already have severe IUGR with multiple Doppler abnormalities at the time of registering for the study. There were no early dating sonars due to late booking and unknown last menstrual periods, so accurately dating pregnancies was challenging.

The Fetal Medicine team also reported difficulty with using the trans-cerebellar diameter as a definitive measure of gestational age in advanced gestations. The TCD was often found to be out of keeping with gestational age when the last menstrual period was considered or an early ultrasound was done. The cerebellum was difficult to access in order to assess correctly, especially in cases of oligohydramnios or anhydramnios, which was found in a majority of study participants.

As was proven, women often had higher BMI's (31.9 kg/m2) and this compromised the accuracy of sonars, making dating and general assessment of fetal anatomy more difficult.

7.6.3 Perinatal follow up:

The follow up of babies became very difficult in the postnatal wards, firstly with the researcher being offsite and only going to CHBAH on a weekly basis. Secondly, some babies

were lost to follow up in the wards at various points in their admissions and due to long hopital stays, and poor record-keeping in the admission registers, it was often difficult to follow up the babies. The registers often had the admission details, but it was not always accurately recorded when the babies were sent to other wards or discharged. The system is still all hand-written and not computerised.

The Redcap system was then accessed but only two outcomes could be found on the system as babies records were not updated throughout their hospital stays. Further outcomes were then sourced from the Neonatal Research Unit who kindly assisted with accessing files and discharge summaries. For those few that the outcomes were still not found, attempt were made to reach the mothers telephonically, but majority of the telephone numbers given at the time of registration into the study, were not longer functional or there was no response on multiple attempts.

7.7 AREAS IDENTIFIED FOR FURTHER STUDY:

Ideally, a larger study would allow comparisions between each weight centile and individual Doppler findings. Also, the progression of Doppler changes could be assessed if patients had early ultrasounds and were identified as IUGR earlier in the pregnancy.

A study analysising the NST changes in IUGR fetuses and outcomes associated with various changes would also be beneficial, as NST changes could then be used to assist with timing delivery, especially in very preterm babies where morbidity and mortality may be decreased if allowed more time in utero.

Delivering babies when stage 2 IUGR is diagnosed or the severity has progressed to stage 2 may need to be considered rather than waiting until stage 3 IUGR develops. Babies with a raised ductus venosus doppler may have a better outcome than those with absent or reversed flow.

8. CONCLUSION:

Intrauterine Growth Restriction is a relatively common antenatal problem and has serious implications in our setting at CHBAH. It is associated with a high mortality rate of 59.6% and preterm delivery with the average IUGR baby at CHBAH born at 29 weeks and 2 days, with an average birth weight of 853.5g, which in itself was identified as a strong predictor of poor outcomes in these babies. The benefit of Doppler surveillence in these pregnancies is evident in decreasing unecessary preterm deliveries, while allowing delivery to be timed to decrease that rate of IUFD. The finding of an abnormal Ductus Venosus Doppler is a significant factor that predicts poorer outcomes in IUGR fetuses at CHBAH. These findings can assist in counselling mothers that the prognosis for a baby born with IUGR is guarded, especially the lower the birth weight at the time of delivery. It also suggests that there may be a place to deliver fetuses with a rising PI of the Ductus Venosus, instead of delaying delivery until the DV is absent or reversed.

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APPENDIX A- Data Collection Sheet

Study Number: _____ .

Background:

Age: _____ Parity: _____ Gravidity:_____ .

RH: _____ if negative, atypical antibodies:_____RPR: _____ Hb: ____.

RVD: _____ if reactive, CD4: _____ Treatment: _____ Duration: _____.

Previous pregnancy losses:_____ Details:

.

_____.

Previous c/s: _____ Indications:_____.

Weight:_____ . Height:_____ . BMI:_____.

Current medication:_____ .

Smoking or illicit drug use: _____ .

Comorbidities:_____.

Details (Grade/severity etc):_____.

Ultrasound Findings:

Gestation: _____ by:_____. FH activity: _____.

BPD: _____ AC: _____ FL:_____.

Liquor volume:_____Presentation:_____ Placenta:_____.

General anatomy: _____.

Estimated fetal weight:_____.

Dopplers: Umbilical artery RI:_____ PI: _____ waveform: _____.

Middle cerebral artery RI:_____PI: _____waveform: _____.

Ductus venosus RI:_____ PI: _____ waveform:_____ .

What are the abnormal parameters on the ultrasound at this scan:

.

_____.

Delivery:

Gestation: _____ Mode:_____ .

If c/s, indication: _____ .

NST changes:_____.

If <34weeks gestation, celestone given? _____Dose:_____.

Apgars at 1 min: _____ 5min: _____ 10 min:_____.

Gas at delivery done Y/N pH _____.

Birth weight: _____ EFW on last u/s:_____.

Admission: Y/N Ward: _____Indication: _____.

Age at discharge:_____ .

Respiratory complications:

Intubation Y/N Duration:_____.

Cpap Y/N Duration:_____ .

Surfactant Y/N

Oxygen therapy via nasal prongs: Y/N Duration _____ .

Severe Morbidity:

Neonatal sepsis Y/N Blood culture result: _____.

Bronchopumonary Dysplasia Y/N

NEC Y/N Laparotomy required Y/N

IVH Y/N and Grade_____. Cooling Y/N

Death:

IUFD Y/N if yes, gestation _____ .

Postnatal death Y/N if yes, age: _____.

Cause of death: _____.

Follow up scans:

Baseline Parameters:		**Doppler findings:**			
Gestation			RI	PI	Waveform

FH activity		Umbilical artery			
BPD					
AC		Middle cerebral art			
FL					
AFI		Ductus venosus			
EFW					

APPRENDIX B: The Estimated Fetal weight growth curve

