CEREBROPLACENTAL RATIO DURING LABOUR

Amy Juliet Wise

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DECLARATION: Student's contribution to the article and agreement of co-authors

I, Amy Juliet Wise, student number 9601677t, declare that this Dissertation is my own work and that I contributed adequately towards research findings published in the article stated below which are being included in my Dissertation.

Signature of Student  **22 day of June month 2021**

Name of Supervisor: Prof Hendrik Lombaard

Signature of Supervisor  **22 day of June month 2021**

Name of Supervisor: Prof Ermos Nicholaou

Signature of Supervisor  **22 day of June month 2021**

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her Dissertation.

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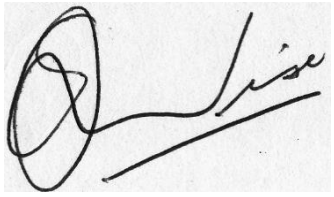
Authors	Name	Signature	Date
1st author	Dr A Wise		11-1-2021
2nd author	Prof E Nicolaou		11-1-2021
3rd author	Prof H Lombaard		11-1-2021

Comments by supervisors: -

DEDICATION

I dedicate this work to all my family, my mom Lynne, sister Laura, my husband Adrian and children Jessica, Thomas and Sarah for their unfailing support and love – thank you.

In memory of my dad, David, I miss you.

PRESENTATIONS ARISING FROM THE STUDY

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PUBLICATIONS ARISING FROM THE STUDY

The use of the cerebroplacental ratio in the latent phase of labour to predict adverse outcomes in a resource-limited setting

A J Wise, MBBCh, FCOG (SA), MMed (O&G), Dip HIV Man (SA), ACHM (FPD), Cert Maternal Fetal Med (SA), E Nicolaou, MD, FCOG (SA), Dip Fet Med (UK), H Lombaard, MBChB, FCOG(SA), MMed (O&G), Pg Dip HSE

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ABSTRACT

To decrease the perinatal mortality rate in South Africa risk stratification of pregnant women needs to improve. Patients requiring referral may go undetected and deliver with the inappropriate level of care. We aimed to determine if the cerebroplacental ratio (CPR) could risk stratify women in early labour. The objectives were to describe the short-term outcomes of fetuses with a normal or abnormal CPR according to the varying definitions in the literature. Two hundred women were prospectively recruited in early labour. Ultrasound was done for biometry and multi-vessel Dopplers, the CPR was calculated. An association was looked for between an abnormal CPR and individual adverse outcomes, a composite score of adverse outcomes or the occurrence of any one adverse outcome. Our results showed that 15(7.7%) participants had a CPR<1.08, 31(16.0%) were <5th centile and 47(24.2%) <10th centile. None of the outcome variables were significantly associated with a CPR<1.08: any adverse event p=0.24, Prior score ≥3 p=0.99, Apgar<7 p=0.30, pH<7 p=0.30, admission p=0.27, fetal compromise p=0.18, resuscitation p=0.70, small for gestational age p=0.24. A CPR<5th centile had no association with a composite score of adverse outcomes (p=0.72). For a CPR cut-off <10th centile there was no association for any variable having an adverse outcome (p=0.46) or a composite score (p=0.31). After adjusting for confounders, there was no association between an abnormal CPR and an adverse outcome. There were no cases of perinatal death or neonatal encephalopathy. An abnormal CPR was not clinically useful in detecting fetuses at risk in early labour regardless of the cut off examined. It was reassuring when normal and may if combined with other parameters still prove useful for risk stratification.

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CONTENTS

LIST OF ABBREVIATIONS

AC abdominal circumference
AEDF absent end diastolic flow
AGA appropriate-for gestational age
AMA advanced maternal age
ANC antenatal clinic
BANC basic antenatal care
BMI body mass index
BPD biparietal diameter
cCTG computerised cardiotocograph
CPR cerebroplacental ratio
CS Caesarean section
CTG cardiotocograph
EFW estimated fetal weight
FGR fetal growth restriction
FIGO Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics)
FL femur length
GA gestational age
HC head circumference
HIV human immunodeficiency virus
ICD-PM International Statistical Classification of Diseases and Related Health Problems – Perinatal Mortality
ISUOG The International Society of Ultrasound in Obstetrics and Gynecology
LNMP last normal menstrual period
MAP mean arterial pressure
MCA middle cerebral artery
MoM multiple of the median
PI pulsatility index
PNMR perinatal mortality rate

REDCap Research Electronic Data Capture

RI resistance index

SASOG The South African Society of Obstetricians and Gynaecologists

SDP single deepest pool

SFH symphysis fundal height

UA umbilical artery

Ut A uterine artery

WHO World Health Organization

WITS University of the Witwatersrand

LIST OF TABLES (in article)

1.0 Introduction

The role of the cerebroplacental ratio (CPR) needs to be more precisely defined as a screening tool for adverse outcomes perinatally and how it should influence management [1, 2]. Its use at various gestational ages, antepartum and intrapartum in low and high risk patients has been investigated[3, 4, 5]. An abnormal CPR is associated with an increased risk of fetal compromise, Caesarean section (CS), meconium stained liquor and an abnormal cardiotocograph (CTG) in appropriate-for gestational age (AGA) fetuses in the latent phase of labour[6]. It is also part of the multi-vessel Doppler assessment in fetuses at risk of late onset growth restriction[7,8].

In a resource-constrained setting, where the perinatal morbidity and mortality rate is unacceptably high, more options to identify at risk fetuses are needed. This opportunity may only arise at the time of parturition. We aimed to describe the percentage of fetuses with an abnormal CPR according to the varying definitions as well as the short-term fetal outcomes and their relationship to an either normal or abnormal CPR in a heterogenous population recruited in early labour. If patients are identified early in labour as being at a higher risk for adverse outcomes, the allocation of resources for monitoring could be adjusted and the risk of a poor outcome may be reduced.

2.0 Literature review

2.1 Intrapartum care based on risk

The decision as to which patients will require more intensive monitoring during labour in a resource restricted setting is complex. The aim is to ensure a good outcome for all mothers and their infants. The Maternal Care Guidelines published in 2015 recommend four hourly monitoring of the fetal heart in the latent phase and half-hourly in the active phase – before and after a contraction with a hand held Doppler device[9]. The disadvantages of intermittent auscultation include the awkward positioning required, and the cost of the device and batteries of the hand-held device[10]. This is appropriate for women considered low-risk who should deliver in a community health care clinic. There are a number of criteria which inform which women should be referred to a higher level of care. In a hospital cardiotocograph (CTG) machines should be available and used for high-risk patients, including those with suspected fetal growth restriction (FGR). The guidelines do not stipulate if the monitoring should be continuous or intermittent for either the latent or active phase or second stage of labour[9]. FIGO reviewed the use of the CTG for monitoring labour, pointing out that despite good evidence to its benefit it is used frequently to monitor low-risk pregnancies, sometimes intermittently[11]. The WITS Obstetric 2017 Protocol Book recommends continuous monitoring for women presenting to a referral hospital unless they are self-referred low-risk women for whom hand-held Doppler assessment is appropriate[12].

2.2 Risk assessment at antenatal clinic

The appropriate stratification of women into low and high risk relies on the assessment of the referring health facility and the timeous presentation of the patient for care. The initial risk assessment is done at the first visit to antenatal clinic (ANC) and a clinic checklist is to be completed. If any concern is noted the patient is to be referred[9]. Further checklists screen for conditions at subsequent visits, a number of these variables can be associated with FGR such as advanced maternal age and chronic medical conditions[9]. Risk stratification does not always occur, as shown in Kwa-Zulu Natal where the documentation of an antenatal care and delivery plan were two of the main areas that were deficient when maternal care records were reviewed[13].

In 2015 in response to the rise in stillbirths seen with the basic antenatal care (BANC) approach to ANC, in which a reduced number of visits were offered to 'low risk' patients, Hofmeyr proposed 'BANC plus' with augmented visits in the third trimester chiefly to identify hypertensive disorders of pregnancy and FGR[14]. He reiterated the WHO's call to initiate ANC early in pregnancy before 12 weeks[15]. A large retrospective cohort in Cape Town showed though that the occurrence of stillbirth at term was not affected by the timing of booking, the quality of care however was not assessed[16].

Gestational age at booking continues to confound attempts to accurately date a pregnancy and thus, has implications for the detection of pregnancies at risk. Statistics South Africa in their review of South Africa's progress in achieving the Millennium Development Goals, report that in 2014, 92.9% of women had had at least one ANC visit and that only 51.8% had presented before 20 weeks gestation. Both of these fell short of the goals of 100% and 63% respectively[17]. In 2016, of the provinces, Gauteng had the lowest ANC attendance at 89.9%[18]. This has the potential to result in women requiring a higher level of care going undetected and to deliver at the inappropriate facility and with inappropriate monitoring.

2.3 Perinatal mortality

In South Africa the perinatal mortality rate (PNMR) was 33.4/1000 total births and in regional hospitals it was 42.7/1000 in 2012-13[19], in 2016 it was reported as 21.0/1000 in South Africa[20]. It is unclear whether this a true reduction as the data sources are different. In Rahima Moosa Mother and Child Hospital (RMMCH) the rate was 28.9/1000 in 2018, as per the departmental statistics prepared by Dr E. Bera (personal communication 5 February 2019)[21]. Unexplained stillbirth is the biggest contributor to the PNMR, which is likely due to undiagnosed fetal growth restriction (FGR), congenital infection, congenital abnormalities and post-maturity. The clinical detection of growth restriction is poor and the availability of ultrasound and skilled sonographers in clinics and district hospitals is very limited. The Saving Babies report goes on to recommend the possible limited use of Doppler to try to detect the fetuses at risk to enable timeous referral[19].

A review of perinatal mortality data from Mpumalanga demonstrated that a significant proportion of late perinatal deaths (25.2%) were below the 10th centile for growth. Macerated stillbirths (MSB) made up a greater proportion of the deaths (38.7%) than the fresh stillbirths (FSB) (21.8%). The other 39.4% were due to the early neonatal deaths (END). Within the MSB and FSB groups the proportion of babies with growth under the 10th centile was 29.7% and 16% respectively. It was noted in this study that a high proportion of mothers were classified as healthy (59%) thus demonstrating the limited ability to detect fetuses at risk with current screening practices[22]. More recently a secondary analysis of the perinatal death data using the WHO ICD-PM (World Health Organization International Statistical Classification of Diseases and Related Health Problems – Perinatal Mortality) codes determined that 68.9% of all perinatal deaths rather than 40.3% were associated with maternal conditions emphasising the need for risk assessment[23].

2.4 Fetal growth restriction

Poorer outcomes are more common in SGA fetuses, especially those with FGR[24]. Diagnosis in the absence of ultrasound is difficult - the Cochrane review found that there was insufficient evidence to conclude that using the symphysis-fundal measurement results in the effective detection of FGR[25]. FGR contributes significantly to the PNMR with 55% of stillbirths weighing less than 2500g[20]. Recently the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) issued guidelines which endorsed the consensus definition on FGR[26, 27] and highlighted the difference in early and late onset FGR. A small for gestational age (SGA) fetus is diagnosed when the estimated fetal weight (EFW) or the fetal abdominal circumference (AC) is less than the tenth centile for the gestational age. Fetal growth restriction is diagnosed when the fetus is SGA as well as having abnormal Dopplers. The early-onset type is identified in the absence of congenital abnormalities at less than 32 weeks gestation. An AC/EFW <3rd centile or absent end diastolic flow (AEDF) in the UA on its own signifies FGR. If the AC/EFW is <10th centile the UA PI and/or the uterine A (Ut A) PI must be >95th centile. From 32 weeks onwards late-onset FGR is defined, in the absence of congenital abnormalities, by an AC/EFW <3rd centile on its own. It can also be characterised by at least two of three findings: AC/EFW <10th centile; AC/EFW crossing centiles > 2 quartiles on growth centiles; CPR <5th centile or UA PI >95th centile[8, 26].

2.5 Consequences of fetal growth restriction

The short-term consequences of FGR include an increased risk of stillbirth and perinatal death, with a worsening adjusted odds ratio as the centiles decrease[28]. The neonates are at an increased risk of bronchopulmonary dysplasia, sepsis and neurodevelopmental delay compared to AGA born at the same GA[29]. Long-term consequences of fetal growth restriction include an adverse effect on their neurodevelopmental outcomes in children – this has been investigated at varying points in childhood, it is more pronounced in those who had cerebral redistribution[30, 31].

2.6 Ultrasound

The use of ultrasound is well established for determining gestational age. It is most accurate when performed between eight and 14 weeks, thereafter it becomes less accurate. In the latter half of pregnancy, the combination of head circumference (HC) and femur length (FL) has been shown to be the most accurate combination in terms of gestational age, with little added benefit from the addition of the biparietal diameter (BPD) and abdominal circumference (AC)[32]. Within the South African setting the availability of ultrasound and skilled sonographers varies. The recommendation is however to do one ultrasound before 24 weeks to assist in dating the pregnancy; and up to 28 weeks if the patient is obese and the dates are unsure[9]. Geerts et al [33] studied patients attending clinics in the Western Cape. They demonstrated that an ultrasound, even if late, is preferable to using the last normal menstrual period (LNMP) or the fundal height measurement when determining the gestational age. Importantly, in this study, scanning doubled the detection rate of SGA fetuses.

2.7 Doppler

The use of the Doppler effect to study the flow of blood in the uterus and fetus to help predict or detect a fetus at risk or affected by growth restriction is well described. Early onset FGR is detected prior to 32 weeks and late onset after 32 weeks gestation[34]. There is however a difference between the early and late onset FGR fetus with respect to their Doppler flows. Early onset FGR tends to affect the umbilical artery (UA) first, usually with an increased pulsatility

index (PI), then absent end diastolic flow (AEDF) and/or reversed end diastolic flow (REDF)[35]. A reduced PI is seen in the middle cerebral artery (MCA) signalling redistribution of blood flow in the fetus [36, 37]. An absent a-wave may also develop in the ductus venosus as part of cardiac dysfunction. The sequence is not always predictable as the PORTO study shows[38]. Late onset FGR may have a normal UA with a decreased MCA PI which then results in an abnormal cerebroplacental ratio (CPR)[39]. The Umbiflow apparatus has been shown in field testing to significantly reduce the rate of stillbirths by detecting an abnormal UA RI in women purported to be low-risk in a low resource setting[22, 40]. Late onset FGR does not always produce an abnormal UA but there may be redistribution with a low MCA PI and CPR <1.08[22, 39, 41]. Thus, those pregnancies at risk of poor perinatal outcomes may still evade detection and continue to contribute to the high PNMR.

2.8 Cerebroplacental ratio

The cerebroplacental ratio (CPR) is a marker of reduced oxygen transfer from the placenta[42]. It was described by Gramellini et al in 1992 using the MCA. The PI of the MCA is divided by the PI of the UA to give a ratio. In their study a single cut-off of 1.08 was defined as normal from 30 weeks gestation onwards[43]. It had also previously been described by Arbeille et al in 1988 using the anterior cerebral artery and a cut-off of >1 for a normal ratio[44]. Ebbing et al has published longitudinal reference ranges for the CPR using the fifth centile as a cut off[45]. Normal ranges for the CPR have been developed in a cross-sectional study by Baschat et al in pregnancies between 20 and 40 weeks[36]; these have been referenced on the Fetal Medicine Barcelona website calculator. The calculator allows the determination of the ratio and the centile, and then reports if it is normal or pathological[36, 46].

The CPR can also be expressed as a Multiple of the Median (MoM). The benefit of using MoM is that it allows standardization between centres, they are easier to derive than centiles and are more stable. Having first being used when describing maternal serum markers, they have now been used for other physiological phenomena[47]. The MoM can be calculated in two different ways when calculating the CPR, the difference in the result (while very small) is most noticeable at higher CPR values[48]. The CPR MoM cut off for FGR is 0.6765 MoM which equates to less than the 5th centile according to the work by Morales-Rosello et al performed on term pregnancies[49].

The sensitivity, specificity and odds ratio for the ability of the CPR to detect an adverse outcome have been calculated. The sensitivity of the CPR, with the PI being the measurement standard, and a cut-off of <1 was 66%, the specificity 85% with an odds ratio of 11.7[50,53]. When the fifth centile was evaluated in a cross-sectional study the sensitivity was 80%, specificity was 60% and odds ratio was 6.2[36, 50,53]. Ebbing et al in a longitudinal study found, with the fifth centile being the measurement standard, the sensitivity is 85%, specificity is 41% and odds ratio is 4.1[45, 50]. The cut-off value has a higher specificity and lower sensitivity than the centile values which have a lower specificity but higher sensitivity. These values refer to the use of the CPR in detecting adverse perinatal outcomes, namely hypoxic ischaemic encephalopathy, periventricular leukomalacia, intraventricular haemorrhages, necrotizing enterocolitis, sepsis, bronchopulmonary dysplasia and death[50]. The CPR has been shown to be predictive of poor perinatal outcome for fetuses at risk of FGR at less than 34 weeks[51]. However as routine screening at 30-34 weeks the detection rate is poor although it did improve if performed in the two weeks prior to delivery[4]. Similarly, routine screening was poor at 35-37 weeks but improved if done in the two weeks prior to delivery[52]. Prior et al prospectively looked at the outcome of low risk women in the United Kingdom. They evaluated the outcome of appropriate-for gestational age (AGA) fetuses in relation to their CPR, which had been measured in the latent phase of labour. They found that the diagnosis of fetal compromise was made significantly more often in those with a CPR below the tenth centile, and they were more likely to have a caesar section, have meconium stained liquor and an abnormal cardiotocograph (CTG). A CPR >90th centile had a 100% negative predictive value for needing a caesarean section for fetal compromise[6].

In early-onset SGA fetuses, the CPR has been shown to be associated with lower mean birthweight, higher chance of a caesarean section and adverse perinatal outcomes[43, 51, 53]. In late-onset SGA fetuses, a CPR <1.08 is associated with an increase in caesarean sections for fetal distress and a lower cord pH[54, 55]. A recently conducted meta-analysis of individual patient data concluded that in term singleton pregnancies the CPR does not offer any benefit over the UA PI, this finding is reflected in the guidelines published in 2020 by ISUOG[56].

2.9 Timing of delivery

While both fetal and maternal well-being are considered, deterioration in the health of the mother may mandate delivery regardless of fetal concerns. As the gestation advances the risks of prematurity related complications to the neonate decrease. Data from the Growth Restriction Intervention Trial (GRIT) study showed that delivery at less than 31 weeks increases the risk of cerebral palsy compared to those born later when looking at cases where there was clinical equipoise[31]. Expectant management can be considered beyond 37w gestation in pregnancies with no features of redistribution, oligohydramnios or hypertensive disorders[57-59]. Most recently ISUOG issued guidelines, using the umbilical artery waveform as a starting point in conjunction with computerised CTG (cCTG). Between 26w0d and 31w6d if there is AEDF or REDF in the UA, the management depends on the ductal waveform – if absent or reversed delivery is indicated. From 34w0d to 37w6d, initially UA PI $\geq 95^{th}$ centile, followed by an AEDF in the UA mandates delivery. At 38w0d and beyond any feature of FGR or redistribution should prompt delivery[8]. The pregnancy should not continue past 39w0d in an SGA fetus[8, 59].

2.10 Mode of delivery

Mode of delivery in a growth restricted fetus, will depend on the obstetrics history of a patient, as well as other obstetric factors that may necessitate a Caesarean delivery. After considering these issues, the mode will depend on the well-being of the current fetus which can be determined by Doppler studies, the biophysical profile and cCTG[58]. Despite an abnormal CPR being associated with an increased need for Caesarean section, the evidence is not currently in favour of it as an indication for a Caesarean delivery[8, 50]. Once the UA has AEDF a Caesarean section is the best option for delivery of the fetus, otherwise an induction of labour is appropriate preferably with continuous fetal monitoring[8].

2.11 Cord blood gas

The umbilical cord blood gas is an important indicator of the metabolic status of the neonate. The pH and base excess are two of the parameters included in Prior's score as markers of an adverse outcome[6]. The normal values of the artery and vein differ slightly – normal arterial pH is 7.24 ± 0,07 and venous pH is 7.33 ± 0.06[60]. Performing a blood gas on cord blood was initially only recommended for high risk deliveries[61], however more recently it has been advised that the cord blood gas is analysed at every delivery despite their being a call to do so for a number of years[62].

The South African Society for Obstetricians and Gynaecologists (SASOG) have come out in support of routine analysis at delivery provided the infrastructure supports it[63]. There are a number of benefits including identifying fetuses which are acidotic despite a 5-minute Apgar score of ≥7[64]. This allows the paediatrician the chance to assess timeously whether further intervention is needed. Neonatal neurological outcome is usually good if the pH > 7.0 and the base excess less acidotic than -12mmol/l[65]. The routine collection of cord gases also improves perinatal outcomes overall by providing immediate biofeedback[62].

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The use of the cerebroplacental ratio in the latent phase of labour to predict adverse outcomes in a resource-limited setting

A J Wise,[1,2] MBBCh, FCOG (SA), MMed (O&G), Dip HIV Man (SA), ACHM (FPD), Cert Maternal Fetal Med (SA); **E Nicolaou,**[3,4,5] MD, FCOG (SA), Dip Fet Med (UK); **H Lombaard**,[1,2] MBChB, FCOG (SA), MMed (O&G), PG Dip HSE
[1] *Department of Obstetrics and Gynaecology, Rahima Moosa Mother and Child Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[2] *Empilweni Services Research Unit, Rahima Moosa Mother and Child Hospital, University of the Witwatersrand, Johannesburg, South Africa*
[3] *Department of Obstetrics and Gynaecology, Chris Hani Baragwanath Academic Hospital; University of the Witwatersrand, Johannesburg, South Africa*
[4] *Morningside Mediclinic, University of the Witwatersrand, Johannesburg, South Africa*
[5] *Department of Obstetrics and Gynaecology, Pavilion for Women, Texas Children's Hospital, Baylor College of Medicine, Houston, USA*
Corresponding author: *A J Wise (amyjulietwise@yahoo.co.uk)*

Background. Risk stratification of pregnant women may decrease the perinatal mortality rate in South Africa. This relies on the assessment of the referring health facility and timeous presentation of the patient. Inaccurate dating affects the ability to detect growth restriction. Patients requiring referral may go undetected and deliver with the inappropriate level of care. Doppler studies can assist in detecting at risk fetuses.
Objectives. To describe the short-term outcomes of fetuses with a normal or abnormal cerebroplacental ratio (CPR) according to the various definitions in the literature.
Methods. A cohort of 200 pregnant women were prospectively recruited while in early labour. Patient history including previous ultrasounds was obtained. Ultrasound was done for biometry, umbilical artery (UA), middle cerebral artery (MCA) and uterine Dopplers, and the CPR was calculated. Labour and delivery details were recorded. An association between an abnormal CPR, adverse outcomes and composite score was determined.
Results. Less than a tenth (7.7%; *n*=15) of the participants had a CPR <1.08. Furthermore, 16.5% (*n*=32) of the participants were <5th centile and 24.2% (*n*=47) were <10th centile. The composite score of adverse outcomes in those with and without a CPR <5th centile was not significant (*p*=0.721). There was no association between adverse outcomes (*p*=0.464) or a composite score (*p*=0.308) and the CPR cut-off of the 10th centile. Moreover, there was no association between an abnormal CPR and adverse outcomes after adjusting for confounders. There were no cases of perinatal death or neonatal encephalopathy.
Conclusion. An abnormal CPR was not clinically useful in detecting fetuses at risk of adverse outcomes in early labour regardless of the CPR cut-off. However, this is reassuring when normal and may if combined with other parameters still prove useful.
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The role of the cerebroplacental ratio (CPR) needs to be more precisely defined as a screening tool for adverse perinatal outcomes and how it could influence management of pregnant women.[1,2] An abnormal CPR is associated with the diagnosis of fetal compromise, caesarean section (CS), meconium stained liquor and an abnormal cardiotocograph (CTG) in appropriate-for-gestational age (AGA) fetuses in the latent phase of labour.[3] It is also part of the multi-vessel Doppler assessment in fetuses at risk of growth restriction.[4]

The decision as to which patients will require more intensive monitoring during labour in a resource-limited setting is complex. In South Africa (SA), fetal heart monitoring with a hand-held Doppler device for low risk women in labour in a community clinic is recommended. In a hospital, CTG machines are used for high-risk patients. Appropriate stratification relies on the assessment by the referring health facility and timeous patient presentation.[5]

Gestational age (GA) at booking and antenatal attendance confound attempts to accurately assess women and has implications for the detection of at-risk pregnancies. The majority of pregnant women (92.9%) visit the antenatal clinic (ANC) at least once, but only 51.8% of women present before 20 weeks in SA.[6] The Gauteng Province had the lowest ANC attendance of 89.9% in 2016.[7] This results in some women who require a higher level of care going undetected.

Unexplained stillbirth is the biggest contributor to the perinatal mortality rate (PNMR). Some stillbirths are due to undiagnosed intrauterine growth restriction (IUGR).[8] The availability of ultrasound and skilled sonographers is limited in clinics and district hospitals, making the diagnosis of IUGR difficult. A Cochrane review found insufficient evidence to conclude that using the symphysis fundal measurement results in effective detection of IUGR.[9]

More options are needed to identify at risk fetuses in resource-limited settings where perinatal morbidity and mortality rate are unacceptably high. We aimed to determine the percentage of fetuses with an abnormal CPR according to the various definitions, as well as the short-term fetal outcomes and their relationship with either a normal or abnormal CPR in a heterogenous population in early labour. If patients are identified early in labour as being at a higher risk for adverse outcomes, the allocation of resources for monitoring could be adjusted and the risk of a poor outcome may be reduced.

Methods

This was a prospective observational cohort study that recruited 200 patients from November 2017 until March 2018. Patients older than 18 years, able to understand and sign consent in English, in the latent phase of a spontaneous labour (<4 cm dilatation) as diagnosed by the attending healthcare worker, and with a normal CTG as judged by the researchers according to local protocol, were included in the study.[10] 17 patients were later found to be in false labour, 11 were induced, they were included in the final analysis since it was not an exclusion criteria. Patients were excluded if the fetus was known to be growth-restricted as per the notes in the file, have a two-vessel cord, a major anomaly, multiple pregnancy and meconium stained liquor or a previous CS.

The study was conducted in a regional academic hospital in Johannesburg, SA. The hospital serves a low-to-middle income area with a diverse population. In 2017, 13 072 babies were delivered at the hospital and a further 405 were born before arrival. The teenage pregnancy rate was 2.2% and advanced maternal age rate was 9.5%. The CS rate was 38.2%, PNMR was 33.4/1 000 births and the stillbirth rate was 21/1 000 births.[11] There are several ANCs in the area but only two have delivery facilities. Hence, a large number of purportedly low risk cases which ordinarily would be managed by a midwife are delivered in hospital.

There is a dedicated ultrasound machine that is available at all times in the labour ward admission area where recruitment took place. We used the SonoScape S12 digital color Doppler ultrasound system (SonoScape, China). CTG machines are available but not in the numbers needed to ensure that each patient can be monitored continuously. Hand-held devices are not always functional and midwife staffing shortages prevent one-on-one monitoring of patients in the active phase of labour.

Ultrasounds were done by the investigators. Patient files were screened in the admission area and patients in the latent phase of labour were approached to participate in the study. If one of the exclusion criteria was detected during the ultrasound, the patient was excluded from the study. Pregnancy was dated using the early ultrasound results, followed by the last normal menstrual period (LNMP) or the late ultrasound and the symphysis fundal height (SFH). The number of fetuses, fetal heart activity, lie, presentation, placental localisation and whether the fetus was intrauterine as well as the number of cord vessels were confirmed. The single deepest pool (SDP) was measured.[12] Estimated fetal weight (EFW) was calculated using biparietal diameter, head circumference, abdominal circumference (AC) and femur length using Hadlock's formula.[13] Uterine artery, umbilical artery (UA) and middle cerebral arteries (MCA), resistance index and pulsatility index (PI) were measured while keeping the angle of insonation as close as possible to 0°. Doppler measurements were performed following the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) Doppler guidelines. CPR was calculated using the Fetal Medicine Barcelona calculator (http://medicinafetalbarcelona.org/calc/.), which calculates the ratio and the centile and then reports it as normal or pathological. If the CPR was <1.08 and/or the centile <5th, it was considered abnormal.[14,15]

The standard of care is to transfer patients to labour ward in the active phase of labour (cervical dilatation >4 cm). Since an abnormal CPR is associated with adverse outcomes, it is prudent to monitor such patients closely when identified. It is not standard practice to immediately offer a CS if the CPR is abnormal. The study was not blinded and recruitment was performed by two people. This assists with consistency; however, it may also result in bias. Ethically, since there is a described association between abnormal Doppler measurements and poor outcomes, it was decided that the patients would be informed of the findings and a request made for continuous monitoring. If no bed was immediately available, continuous fetal monitoring for those with abnormal Doppler measurements was ordered in the admission ward. On-call staff then had to make a decision regarding which patients had priority for access to available resources and manage all further care of the patient as per standard labour and delivery protocols.

At the time of delivery, staff performing the delivery were requested to send an arterial cord blood gas for analysis. While regular reminders were given to staff on the procedure, it is possible that some samples may have been a mix of arterial and venous blood, which would potentially have increased the pH slightly – normal arterial pH (standard deviation (SD)) is 7.24 (0.07) and venous pH is 7.33 (0.06).[16] The patients were informed that only cord blood would be taken for the study. Any other procedures required were part of routine care. These cord blood gas results, delivery details and short-term outcomes of the mother and neonate were collected after discharge.

Since this is a descriptive study and no prior study has been done on a heterogenous population such as ours, no power calculation was done. The decision to recruit 200 patients was based on the availability of the researchers and that at least 10% of the patients were expected to have an abnormal CPR based on the work of Prior *et al.*[3] which assessed low risk women.

As part of the analysis, both the score used by Prior *et al.*[3] and each adverse outcome was compared in patients with a CPR >1.08 and in those with a CPR <1.08 and/or <5th centile. A

score was worked out for all participants who had all variables available including the blood gas (Table 1).

Table 1. Prior's adverse outcome score				
	0	1	2	3
pH	≥7.2	7.1 - <7.2	7.0 - <7.1	<7.0
Base excess	<–8	≥–8 and <–12	≥–12	
Apgar	≥7 at 1 min	<7 at 1 min	<7 at 5 min	
Neonatal unit admission	No	Yes	-	-

Since not all our patients had a gas performed on cord blood, a number of adverse outcome variables were considered to allow for comparison.[17] These adverse outcome variables included a diagnosis of fetal compromise (as per the attending physician), arterial cord blood pH <7.20, Apgar <7 at 5 minutes, need for resuscitation/assistance with breathing, admission to the neonatal unit and a birth weight <10th centile.[17] The Intergrowth 21 growth charts were used to determine birth centiles, the variables entered were the most accurate gestational age (calculated prior to the research ultrasound), neonatal sex and birthweight.[18]

Study data was collected using REDCap (Research Electronic Data Capture), an online database manager hosted at the University of the Witwatersrand.[19] Descriptive statistics were used for categorical and continuous data. This was done to determine the prevalence of the variables as well as means and medians where appropriate. Certain continuous variables were categorised for descriptive and analytical purposes. Analytical statistics were employed to test for any association between the ultrasound findings and fetal outcome. Parametric testing was done with Chi-square tests and Fisher's exact tests. A *p*-value of 0.05 was used to include or exclude the potential of any outcome. Where variables were missing, the denominator was adjusted. The data was analysed with the assistance of a biostatistician. Statistical analysis was performed using Statistica software, version 13.3 (Tibco Software Inc., USA) and R package, version 3.5.1 (RStudio, USA).

Ethics clearance was granted by the University of Witwatersrand Human Research Ethics Committee (ref. no. M170637). The study was registered with the National Health Research Database (ref. no. GP_201709_014). Permission to conduct the study was granted by Rahima Moosa Mother and Child Hospital.

Results

We prospectively recruited 200 patients who consented to participate in the study. We excluded two patients who had undiagnosed twins at the time of the ultrasound and six files went missing. Therefore, we had 96% (*N*=192) of the patients' files available for analysis and 70.5% (*n*=141) of the patients had cord blood gas analysis data.

The minimum age of consent is 18 years; therefore, no comment can be made about the teenage pregnancy rate. More than a tenth of the women (13.3%; *n*=26) were 35 years and older. More than one-third (43.4%; *n*=85) of the patients were primiparous. The majority (97.4%) initiated antenatal care at a local clinic. Furthermore, the majority of the women (73.2%; *n*=142) booked before 24 weeks gestation and 30.4% (*n*=59) were less than 14 weeks pregnant. A third (32.4%) were obese (body mass index (BMI) ≥30 kg/m^2) at their first visit. There was 31.7% (*n*=45) of the women who had mean arterial pressure (MAP) that was >90 mmHg before 24 weeks. MAP was calculated from blood pressure noted in the file and was not done in a standardised manner.

The mean haemoglobin (Hb) of the cohort improved between booking and the time of delivery. At booking, 21.2% (*n*=40) of the patients were anaemic (Hb <11 g/dL) while at the last evaluation, 22.9% (*n*=44) of the patients were anaemic. Medical conditions (excluding HIV) were found in 6.7% (*n*=13) of the patients: 5 had asthma, 4 had hypertension and there was 1 case each of tuberculosis, neurofibromatosis, psychosis and chicken pox during pregnancy.
Blood tests done at booking were Rhesus (Rh) status, Hb, syphilis and HIV serology. Only 2.1% (*n*=4) of the patients were Rh-negative and only one was tested for antibodies, which was also negative. All patients tested negative for syphilis. The prevalence of HIV was 18.0%, with a median (range) $CD4^+$ T cell count of 414 (51 - 815) cells/µL and a HIV viral load of <1 000 copies/mL in 77.1% (*n*=27) of the women. More than a tenth (14.3%; *n*=5) of the patients qualified for prophylaxis for *Pneumocystis jirovecii* pneumonia ($CD4^+$ T cells <200 cells/µL), of which two received the prophylaxis and it was not prescribed for the other three. Sixteen (45.7%) HIV-positive patients were screened for hepatitis B and 2.9% (*n*=1) tested positive.
The self-reported race of each patient was as follows: 83.2% (*n*=163/196) black, 12.8% (*n*=25/196) coloured, 2.0% (*n*=4/196) Asian and 2.0% (*n*=4/196) white (Table 2).

Table 2. Demographics and biophysical data

	N	**Mean (SD)**	**Median**	**Minimum**	**Maximum**
Age (years)	196	27.3 (5.52)	27.0	18.0	41.0
Parity	196	-	0	0	4
Gravidity	196	-	2	1	6
Height (m)	182	159.0 (7.35)	159.0	132.0	178.0
Weight (kg)	193	69.7 (15.21)	66.0	44.0	124.0
BMI (kg/m^2)	182	27.7 (6.10)	26.3	18.1	55.6
MAP at booking (mmHg)	192	84.8 (9.21)	83.6	53.3	110.0
Hb at booking (g/dL)	189	12.0 (1.66)	12.1	6.1	16.2
Hb most recent (g/dL)	192	12.0 (1.59)	12.1	6.7	16.0

SD = standard deviation; BMI = body mass index; MAP = mean arterial pressure; Hb = haemoglobin.

The coloured and white patients were all South African. One Asian patient came from Pakistan. Of the black patients, 53.6% (*n*=105/196) were from SA, and the percentage of non-South Africans was 30.1% (*n*=59). This is lower than our hospital average as some non-South Africans were excluded before recruitment as they were non-English speaking.
There was a significant association between gravidity and BMI of the patient with the mode of delivery (Table 3). A higher gravidity and lower BMI were associated with normal delivery (Table 3). There was no association between mode of delivery and the other variables (Table 3).

Table 3. Mode of delivery			
	Any vaginal delivery (*n*=134)	**Caesarean section (*n*=58)**	
	***n* (%)_**	***n* (%)_**	**p-value**
Age (years), median (IQR)	28 (23 - 32)	26 (22 - 31)	0.276
Race			0.504
Black	109 (81.34)	52 (89.66)	-
Coloured	18 (13.43)	5 (8.62)	-
Asian	4 (2.99)	0 (0.0)	-
White	3 (2.24)	1 (1.72)	-
Parity, median (IQR)	1 (0-2)	0 (0-1)	0.051
Gravidity, median (IQR)	2 (1-3)	1 (1-2)	0.021
BMI (kg/m^2), mean (SD)	26.95 (5.91)	28.89 (6.01)	0.047
MAP at admission (mmHg), mean (SD)	91.72 (8.19)	90.85 (6.93)	0.453
Hb at delivery (g/dL)	11.93 (1.64)	12.29 (1.46)	0.136
IQR = interquartile range; BMI = body mass index; SD = standard deviation; MAP = mean arterial pressure; Hb = haemoglobin. *Unless otherwise specified.			

More than half of the patients (53.1%; *n*=103/194) had a previous ultrasound at a median gestation of 24 weeks. The completeness of information was variable in these reports. One ultrasound appeared completely at odds with other findings and was thus not used to date the pregnancy. The gestational age at recruitment was used to calculate the CPR. The median (range) gestational age at recruitment was 39w3d (33w2d - 44w6d). Although the GA of 44w6d is unlikely, there was no other satisfactory way of dating her pregnancy.

The ultrasound data revealed that 16.5% (*n*=32) of 194 patients had a CPR that was <5th centile and 7.7% (*n*=15) of these patients had a CPR <1.08 (Table 4). A CPR <10th centile has been considered to be abnormal in other studies,[3] but this is not a definition used by the Fetal Medicine Barcelona calculator. In our cohort, 24.2% (*n*=47) of the participants were <10th centile. The umbilical artery (UA) pulsatility index (PI) was in the normal range for gestational age as per the Fetal Medicine Barcelona calculator for all patients (Table 4).

Table 4. Ultrasound data (*N*=194)				
	Mean (SD)	**Median**	**Minimum**	**Maximum**
GA w/d	-	37w2d	34w0d	41w4d
EFW (g)	3220 (409.2)	3196	2202	4489
Liquor – Single deepest pocket (cm)	3.9 (1.93)	3.7	0.4	18.0
LUA PI	0.83 (0.60)	0.75	0.06	2.40
RUA PI	0.91 (0.43_	0.79	0.29	2.57
UA PI	0.84 (0.16)	0.82	0.49	1.27
MCA PI	1.35 (0.29)	1.33	0.61	2.76
CPR	1.65 (0.42)	1.61	0.76	2.83
CPR centile	35.7	32.0	IQR 10.0 - 55.25	
SD = standard deviation; GA = gestational age; EFW = estimated fetal weight; LUA = left uterine artery; PI = pulsatility index; RUA = right uterine artery; UA = umbilical artery; MCA = middle cerebral artery; CPR = cerebroplacental ratio.				

There were no cases of perinatal death or neonatal encephalopathy. Since there was no long-term follow-up, no comment can be made on neurodevelopmental outcomes.
A score out of eight based on Prior's[3] work was calculated for 69.1% (*n*=134) of the patients who had all variables available (Table 5).

Table 5. Prior's score	
Prior's score	***n* (%)**
0	87 (64.9)
1	22 (16.4)
2	9 (6.7)
3	5 (3.7)
4	6 (4.5)
5	2 (1.5)
6	2 (1.5)
7	1 (0.7)
8	-

We found no association between CPR <5th centile and fetal compromise diagnosed at any time during labour (p=0.365), an Apgar score <7 at 5 minutes (p=0.604), cord arterial pH <7.20 (p=0.118), small-for-gestational age (SGA) (p=0.242), neonatal unit admission (p=0.999), bag mask ventilation (BMV) usage/respiratory support (p=0.741) (Table 6). Prior's composite score was not significant (p=0.721). When the CPR cut-off was the 10th centile, there was again no association with any adverse outcome (p=0.495) or Prior's composite score (p=0.308). Moreover, we still found no association between abnormal CPR and adverse outcomes even after adjusting for confounders such as age, race, parity, gravidity, BMI, hemoglobin, blood pressure, growth restriction, mode of delivery, gestational age, sex of the fetus and use of an epidural.
The CPR is reassuring when normal but it is a poor predictor of adverse outcomes when abnormal.(Table 6).

Table 6. Cerebroplacental ratio, PPV and NPV for adverse outcomes						
Adverse outcome	P value	<5th	≥5th	Total	PPV	NPV
Fetal compromise	0.365	10/32	38/162	194	0.21	0.85
Apgar 5 min <7	0.604	1/31	1/158	189	0.50	0.84
Cord pH <7.20	0.118	2/27	25/111	138	0.07	0.77
SGA	0.242	3/31	5/161	192	0.38	0.85
Admission	0.999	3/31	14/161	192	0.18	0.84
BMV/resus	0.741	1/32	7/162	194	0.19	0.84
Any adverse outcome	0.799	13/32	62/162	194	0.17	0.84
PPV = positive predictive value; NPV = negative predictive value; SGA = small-for-gestational age; BMV/resus. = bag mask ventilation/resuscitation.						

Discussion

There is a need to identify modalities that enable the detection of high-risk pregnancies in a resource-limited setting. This is challenging when despite a third (30.4%) of women booking early enough for first trimester screening and two-thirds being eligible for a second trimester anatomy scan,[6] only 53.1% received an ultrasound examination and these were performed by practitioners with varying levels of skill. A study by Geerts *et al.*[20] reported similar findings as our study that 61.3% of their patients booked before 24 weeks; however, they reported that up to 88.9% of their patients had at least one ultrasound.

The population we serve is heterogenous with a number of nationalities (41.4% of deliveries in 2017)[11] and racial groups that differ in proportion to those in the literature, which comments on ethnicity but not on immigration status.[21,22] We found a HIV rate of 18.6%, which is in line with 18.0% reported in the literature.[11] Anaemia is associated with SGA;[23] however, despite a fifth (21.2%) of the patients being anaemic at booking, only three cases of SGA developed (p=0.353). In our study, we found that 7.7% (n=15) of the participants had a CPR <1.08, 16.5% (n=32) were <5th centile and 24.2% (n=47) of the participants were <10th centile. A study by Prior[3] found that 10% of the patients had an abnormal ratio when defined as <10th centile. This was corroborated by a more recent study which showed that 9.6% of the patients who were low risk had a CPR <10th centile.[2]

The CPR has been shown to be predictive of poor outcomes in a variety of settings and gestational ages.[17,24,25] Late onset IUGR may have a normal UA with a decreased MCA PI, which then results in an abnormal CPR.[26] This is of particular interest since the detection of late onset IUGR is difficult without accurate early dating. Our sample is small with 6.8% (n=13) neonates <10th centile for weight and pre-existing IUGR as an exclusion criterion.

The cut-off value of <1.08 has a higher sensitivity and lower specificity than using <5th centile, which has a lower sensitivity but higher specificity in detecting adverse perinatal outcomes such as hypoxic ischaemic encephalopathy, periventricular leukomalacia, intraventricular haemorrhages, necrotising enterocolitis, sepsis, bronchopulmonary dysplasia and death.[25] However, we found no association between any adverse outcomes and the 10th centile as a cut-off (p=0.464).

This may indicate that our designation of some patients as low risk is incorrect and that they should have had an elective delivery earlier rather than awaiting spontaneous labour or more intensive monitoring antepartum and intrapartum. However, in a population studied just prior to induction with a much higher burden of high-risk conditions, the CPR was not shown to perform well in the clinical setting.[22]

More recently, the CPR has been questioned as a stand-alone screening tool due to poor sensitivity and specificity.[22] The PPV was low for all the adverse outcomes. CPR has a very good negative predictive value (NPV) of 0.84 and is reassuring when normal, which is in keeping with the literature.[2,17]
Figueras *et al.*[27] showed that combining CPR with uterine artery Doppler measurements and the EFW or AC <3rd centile improved sensitivity to 82.8 (95% confidence interval (CI) 75.1 - 88.6), and the NPV is clinically relevant at 88.6 (95% CI 83.2 - 92.5). This analysis still has to be done with our data and it will be interesting to see if an association is found. It is also possible that looking at the decline in the CPR over time may be a better predictor of fetuses at risk.[28] However, a study by Kalafat *et al.*[29] showed that a single point estimate was a good predictor. This then does suggest that we could continue to pursue the option of assessment at the time of delivery, which may be our only opportunity to identify at risk fetuses if CPR is assessed in conjunction with other parameters.

Study limitations
Limitations of our work are that the results may not be applicable in a setting where antenatal screening is more rigorous with greater access to technology. However, there are many areas in the world that are similar to ours and where there is an uneven distribution of resources and an heterogenous population with a high burden of hypertension during pregnancy. During this study, there was a concern of bias since the clinicians were not blinded to the Doppler results. There was a protocol in place to request more monitoring as there was evidence of an increased risk of poor outcome. While this may bias the results, in our setting, we cannot afford to increase CS rates without good evidence that it is indicated. The use of CPR is not yet incorporated into our algorithms, yet it was considered ethically wrong to not monitor patients more intensively if possibly at an increased risk.

Conclusion
The aim of this study was to provide new insights on identifying fetuses at risk in a resource-limited environment using available technology. The CPR in early labour is reassuring when normal but there is no statistically significant association with any one particular outcome for a CPR <5th centile. The attempt to improve the sensitivity by including those under the 10th centile was not successful. The use of the CPR alone does not assist sufficiently in mitigating risk in a clinical setting. Recent work has theorised that other pregnancy, labour and maternal characteristics are likely to have a greater impact on the occurrence of adverse outcomes.[22] The recommendation then is not to use CPR for screening despite its good NPV but rather to further elucidate whether it would be useful as part of a more comprehensive risk stratification protocol in early labour. Those with an abnormal CPR should be evaluated for other risk factors at the time of the ultrasound, and the labour and delivery plan adjusted accordingly.
The study showed that the provision of a scan with Doppler measurements around the time of delivery is possible in our setting and does have the benefit of detecting previously undiagnosed conditions immediately relevant to the care of the mother and fetus.

Declaration. This study was done for degree purposes.
Acknowledgements. We would like to thank Prof. E Libhaber and Dr A Izu for assistance with the statistics.

Author contributions. All authors contributed to the protocol. AW and HL collected data. AW wrote the manuscript with inputs from HL and EN. All authors approved the manuscript for publication.

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Conflicts of interest. None.

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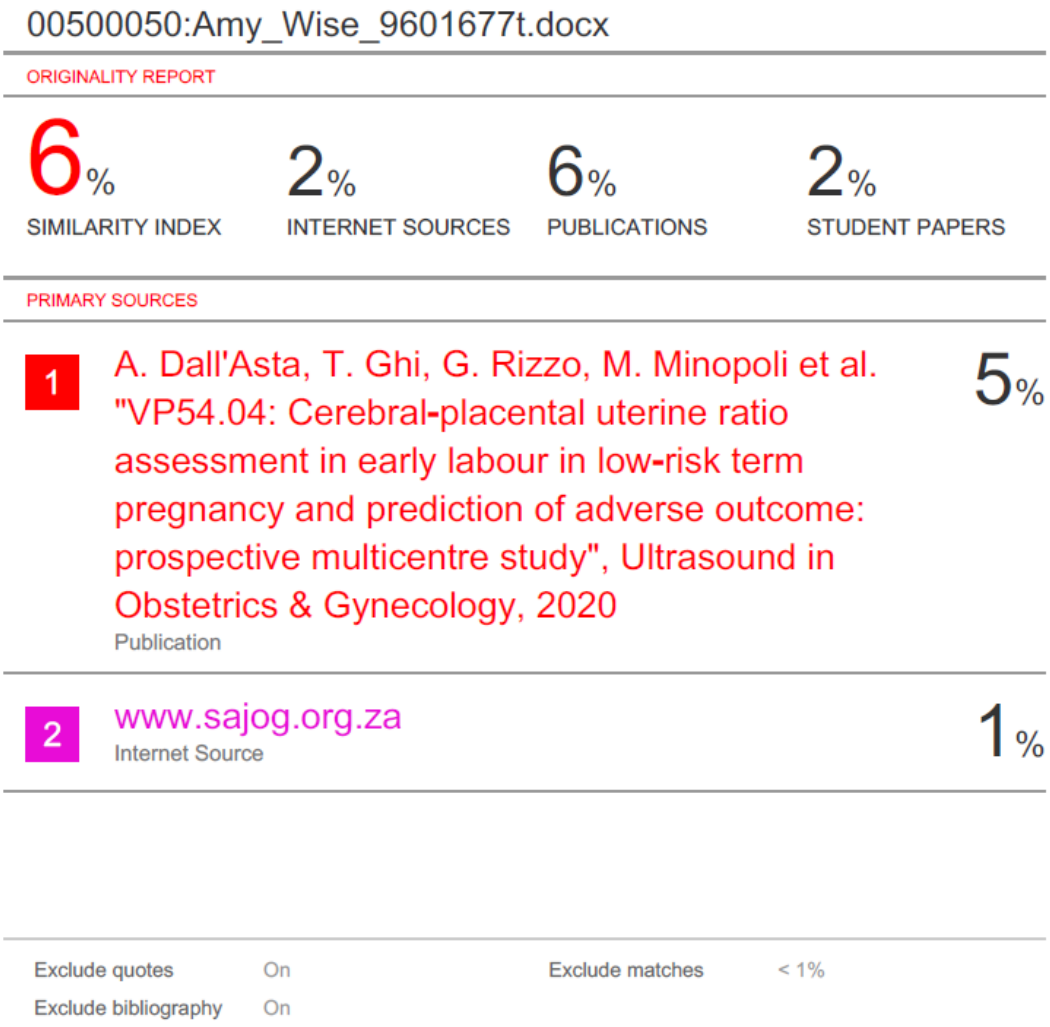
Accepted 6 November 2020.

5.0 Conclusion and recommendations

The motivation behind this study comes from the need to better risk stratify our patients to ensure the appropriate care is rendered with the optimal use of resources. While the use of the cerebroplacental ratio in early labour has not been shown to assist in this regard in our setting there are other lessons that can be taken from the exercise and further analysis is warranted. The use of the uterine artery Doppler to further refine the findings can be considered. The usefulness of the high negative predictive value also needs to be explored as a means of triage.

There were two patients excluded at the time of the ultrasound due to the discovery of a twin pregnancy. Just over half of the patients had ever had an ultrasound thus there was the potential for discovering immediately relevant clinical conditions which would impact the outcome of the pregnancy. While the provision of ultrasound earlier in pregnancy would be preferable, its utility at the time of delivery should be emphasised and training of labour ward staff in the provision of an ultrasound would be beneficial.

Appendix 6.1: Plagiarism report



00500050:Amy_Wise_9601677t.docx

ORIGINALITY REPORT

6%	2%	6%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	A. Dall'Asta, T. Ghi, G. Rizzo, M. Minopoli et al. "VP54.04: Cerebral-placental uterine ratio assessment in early labour in low-risk term pregnancy and prediction of adverse outcome: prospective multicentre study", Ultrasound in Obstetrics & Gynecology, 2020 Publication	5%
2	www.sajog.org.za Internet Source	1%

Exclude quotes	On	Exclude matches	< 1%
Exclude bibliography	On		

The Dall'Asta reference is directly above my abstract (VP 54.05) in the Ultrasound in Obstetrics and Gynaecology Journal 'Ultrasound in Obstetrics & Gynecology 2020; 56 (Suppl. 1): 57–378' and my abstract has been ascribed to them.

Appendix 6.2: Plagiarism declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Dr Amy Wise (Student number: 9601677t) am a student registered for the degree of Master of Science in Medicine in the academic year 2020.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:  Date: 17-1-2021

1

Appendix 6.3: Ethics clearance certificate

R14/49 Dr Amy Wise

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170637

NAME: (Principal Investigator)	Dr Amy Wise
DEPARTMENT:	Obstetrics and Gynaecology - School of Medicine Rahima Moosa Mother and Child Hospital
PROJECT TITLE:	Cerebroplacental Ratio during Labour
DATE CONSIDERED:	30/06/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof H. Lombaard and Prof E. Nicolaou
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	26/07/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

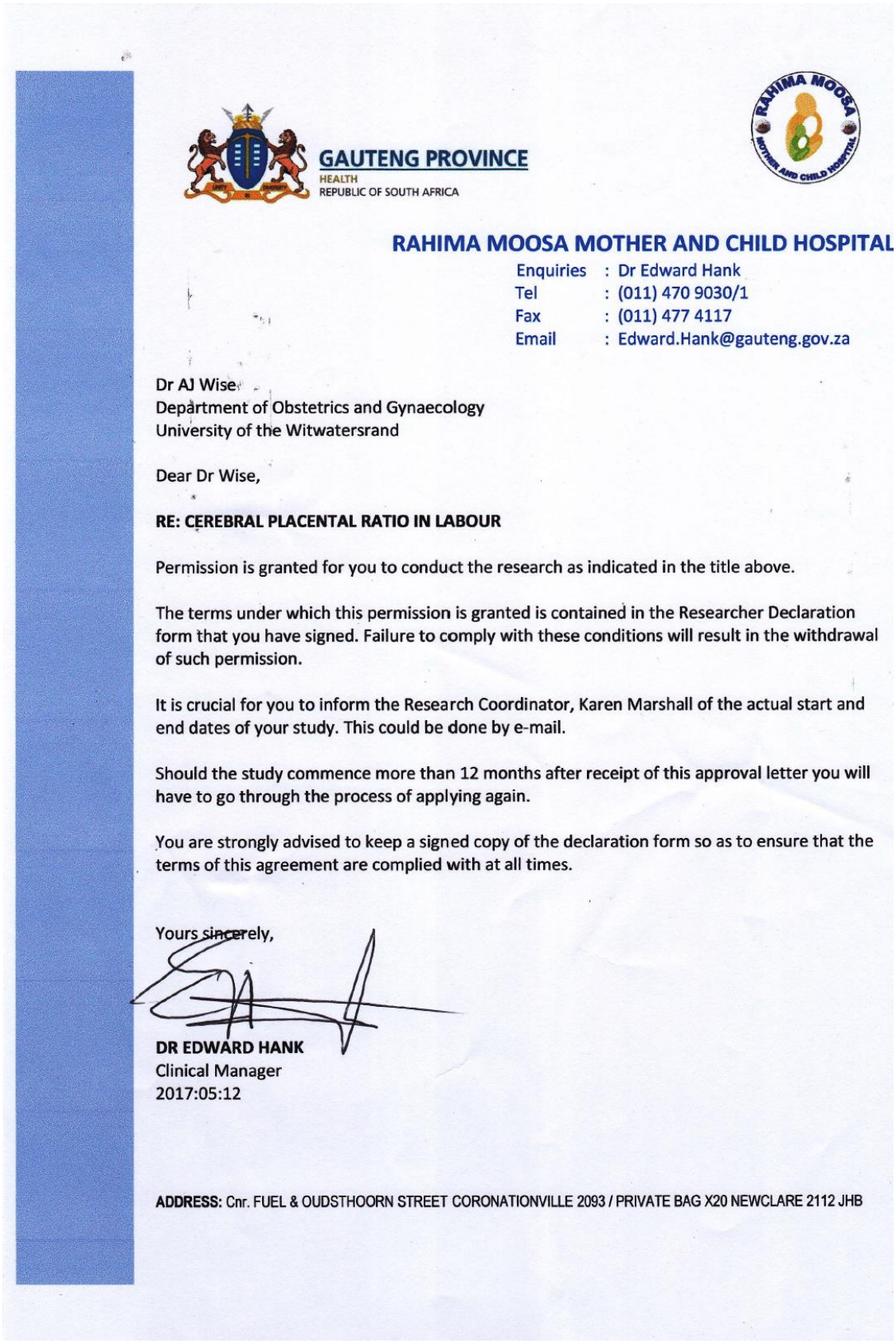
To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in June and will therefore be due in the month of June each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date: 6 August 2017

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 6.4: Rahima Moosa Mother and Child Hospital



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

RAHIMA MOOSA MOTHER AND CHILD HOSPITAL

Enquiries : Dr Edward Hank
Tel : (011) 470 9030/1
Fax : (011) 477 4117
Email : Edward.Hank@gauteng.gov.za

Dr AJ Wise
Department of Obstetrics and Gynaecology
University of the Witwatersrand

Dear Dr Wise,

RE: CEREBRAL PLACENTAL RATIO IN LABOUR

Permission is granted for you to conduct the research as indicated in the title above.

The terms under which this permission is granted is contained in the Researcher Declaration form that you have signed. Failure to comply with these conditions will result in the withdrawal of such permission.

It is crucial for you to inform the Research Coordinator, Karen Marshall of the actual start and end dates of your study. This could be done by e-mail.

Should the study commence more than 12 months after receipt of this approval letter you will have to go through the process of applying again.

You are strongly advised to keep a signed copy of the declaration form so as to ensure that the terms of this agreement are complied with at all times.

Yours sincerely,

DR EDWARD HANK
Clinical Manager
2017:05:12

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

Appendix 6.5: Data sheet

Confidential

Cerebroplacental ratio Form

Study ID _____

Date of Registration _____

Signed informed consent, received patient information sheet
◯ Yes
◯ No

Time of consent _____

Contact Information

First Names _____

Last Name _____

Hospital Number _____

Date of birth _____

Age (years) _____

Race
◯ Asian
◯ Black
◯ Coloured
◯ Mixed Race
◯ White
◯ Other
◯ Unknown
◯ Not Reported

Country of origin
◯ South Africa
◯ Zimbabwe
◯ Mozambique
◯ Lesotho
◯ Nigeria
◯ Ghana
◯ Malawi
◯ Ethiopia
◯ Pakistan
◯ India
◯ Other - specify

Clinic _____

History

Booking date _____

Parity

◯ 0
◯ 1
◯ 2
◯ 3
◯ 4
◯ 5
◯ 6
◯ 7
◯ 8
◯ 9
◯ 10

Gravidity

◯ 1
◯ 2
◯ 3
◯ 4
◯ 5
◯ 6
◯ 7
◯ 8
◯ 9
◯ 10

Obstetric outcome history

	1stT	2ndT IUD< 26	2ndT live< 26	IUD>26	END> 26	LND> 26	ID< 1y	CD< 18y	live26-37	live>37	current preg
1	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
3	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
4	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
6	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
7	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
8	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
9	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Mode of delivery

	NVD	vacuum	forceps	caesar	current pregnancy
1	◯	◯	◯	◯	◯
2	◯	◯	◯	◯	◯
3	◯	◯	◯	◯	◯
4	◯	◯	◯	◯	◯
5	◯	◯	◯	◯	◯
6	◯	◯	◯	◯	◯
7	◯	◯	◯	◯	◯
8	◯	◯	◯	◯	◯
9	◯	◯	◯	◯	◯
10	◯	◯	◯	◯	◯

Height (cm) _____

Weight (kilograms) _____

Date of weight _____

BMI _____

First systolic blood pressure recorded _____ (mmHg)

First diastolic blood pressure recorded _____ (mmHg)

First mean arterial pressure recorded _____ (mmHg)

Last systolic before 24w _____ (mmHg)

Last diastolic before 24w _____ (mmHg)

Last mean arterial pressure before 24w _____ (mmHg)

Medical history

Any medical condition
◯ Yes
◯ No

Medical condition
☐ Diabetes
☐ Epilepsy
☐ Asthma
☐ Cardiac
☐ TB
☐ Hypertension
☐ Connective tissue disorder
☐ Thyroid
☐ Other

	insulin	metformin	diet only
insulin dependent	☐	☐	☐
non-insulin dependent	☐	☐	☐
gestational diabetes	☐	☐	☐

HbA1c

_____
(%)

If epilepsy

- ☐ Carbamazapine (Tegretol)
- ☐ Valproic acid (Epilim)
- ☐ Lamotrigine (Lamictin)
- ☐ Levetiracetam (Keppra)
- ☐ Phenytoin (Epanutin)
- ☐ Clonazapam (Rivotril)
- ☐ Folic acid
- ☐ Other

If epilepsy 'other' - specify

_____

If asthma - chronic use of

- ☐ short acting B2 (Berotec/Ventolin)
- ☐ low-dose controller (Beclate)
- ☐ long-acting B2 (Ventolin/Asthavent)
- ☐ prednisone
- ☐ other

If asthma 'other' - specify

_____

If cardiac condition - specify

_____

Cardiac medication

- ◯ Yes
- ◯ No

Specify cardiac medication

_____
(name,dose,frequency)

Current TB

- ◯ Yes
- ◯ No

Site of TB

- ☐ Pulmonary
- ☐ Brain
- ☐ Spine
- ☐ Abdomen
- ☐ Bone marrow
- ☐ Disseminated
- ☐ Other

TB treatment

- ◯ Rifafour
- ◯ Rifinah
- ◯ Other

If TB treatment other - specify

_____
(MDR/XDR)

Current hypertension diagnosis
- ◯ Chronic hypertension
- ◯ Chronic hypertension with superimposed pre-eclampia
- ◯ Gestational hypertension
- ◯ Mild pre-eclampsia
- ◯ Severe pre-eclampsia
- ◯ Imminent eclampsia
- ◯ Eclampsia

Current chronic hypertensive medication
- ☐ Methyl-dopa
- ☐ Amlodipine
- ☐ Other

If current hypertension medication 'other' - specify

_____

Aspirin use in this pregnancy
- ◯ Yes
- ◯ No

Aspirin start date

_____

Aspirin dose

_____
(mg/d)

Aspirin last taken

_____

Connective tissue disorder - specify
- ☐ Anti Phospholipid Syndrome
- ☐ Systemic Lupus Erythematosis
- ☐ Other

Other CTD- specify

_____

CTD medication
- ☐ Aspirin
- ☐ Enoxaparin daily
- ☐ Enoxaparin bd
- ☐ Chloroquin
- ☐ Other

If CTD medication 'other' - specify

_____

If thyroid disease
- ☐ Initially hypothyroidism
- ☐ Initially hyperthyroidism
- ☐ Goitre
- ☐ Thyroidectomy
- ☐ Radiation
- ☐ Medication

Thyroidectomy - year

_____

Radiation -year

_____

Thyroid medication
- ☐ Neomercazole
- ☐ Propanalol
- ☐ Eltroxin
- ☐ Other
- ☐ None

If thyroid medication 'other' - specify

_____

If medical is 'other' -specify

_____

Surgical history

Any surgery
- ◯ Yes
- ◯ No

Surgical condition
- ☐ Caesarean section x 1
- ☐ Caesarean section x 2
- ☐ Caesarean section x 3 or more
- ☐ Laparotomy for ectopic
- ☐ Evacuation of uterus for POC
- ☐ Myomectomy
- ☐ Cerclage
- ☐ Other

If surgical is 'other' - specify

_____

Booking bloods

Rhesus status
- ◯ positive
- ◯ negative
- ◯ not done

If Rhesus negative - antibodies
- ◯ negative
- ◯ positive
- ◯ not done

If Rhesus antibodies positive

_____
(titre)

Syphilis screening
- ◯ negative
- ◯ positive
- ◯ not done
- ◯ no result

If syphilis screening is positive

_____
(titre)

Bicillin

	yes	no
1st dose	☐	☐
2nd dose	☐	☐
3rd dose	☐	☐

Haemaglobin - booking

_____
(g/dl)

Haemaglobin - most recent

_____
(g/dl)

Date of most recent Hb	_____
HIV - current status	◯ negative ◯ positive ◯ unknown
If positive - date diagnosed	_____
CD4 count done	◯ Yes ◯ No
CD4 count, most recent	_____ (cells/mm3)
CD4 < 200cells/mm3	◯ Yes ◯ No
Bactrim prophylaxis	◯ yes ◯ no ◯ allergic
If CD4 < 100mm3 - CrAg done	◯ Yes ◯ No
If CrAg positive - fluconazole prophylaxis	◯ Yes ◯ No
Viral load done	◯ Yes ◯ No
Viral load - most recent	_____ (copies/ml)
Hepatitis BSAg done	◯ Yes ◯ No
If HepBSAg done	◯ negative ◯ positive ◯ no result
If HepBSAg positive	☐ TDF ☐ 3TC ☐ None
Current HAART	☐ FDC (TDF/FTC/EFV) ☐ TDF ☐ 3TC ☐ EFV ☐ ABC ☐ LPV/r ☐ NVP ☐ AZT ☐ Truvada (TDF/FTC) ☐ None

Gestational Age

Last normal menstrual period known?
- ◯ Yes
- ◯ No

Last Normal Menstrual Period: _____

Certainty of LNMP
- ◯ Yes
- ◯ No

GA by LNMP: _____ (weeks)

Symphysis fundal ht - 1st entry
- ◯ not done
- ◯ mass palpable
- ◯ SF in weeks not plotted
- ◯ SF in cm not plotted
- ◯ SF in cm plotted incorrectly
- ◯ SF in cm plotted correctly

GA by 1st usable entry: _____

GA by Ultrasound

Ultrasound recorded previously
- ◯ Yes
- ◯ No

US - 1st recorded: _____

Rank of user
- ◯ private GP
- ◯ private obstetrician
- ◯ sonographer
- ◯ intern
- ◯ registrar
- ◯ consultant
- ◯ not indicated

Intrauterine pregnancy
- ◯ yes
- ◯ no
- ◯ not recorded

Number of embryos/fetuses
- ◯ 1
- ◯ not recorded

Viability indicated
- ◯ Yes
- ◯ No

Placental position
- ◯ Anterior
- ◯ Posterior
- ◯ Low-lying
- ◯ Not indicated

If low-lying, was a possible praevia later excluded
- ◯ Yes
- ◯ No

Liquor
- ◯ increased
- ◯ decreased
- ◯ normal
- ◯ not indicated

Measurements recorded	☐ CRL ☐ BPD ☐ HC ☐ AC ☐ FL (mm)
1st CRL mm	_____ (mm)
1st CRL weeks	_____ (w/d)
1st BPD mm	_____ (mm)
1st BPD weeks	_____ (w/d)
1st HC mm	_____ (mm)
1st HC weeks	_____ (w/d)
1st AC mm	_____ (mm)
1st AC weeks	_____ (w/d)
1st FL mm	_____ (mm)
1st FL weeks	_____ (w/d)
1st ultrasound GA recorded	◯ Yes ◯ No
1st GA by US	_____ (w/d)
Best option to estimate gestational age	◯ LNMP ◯ 1st palpation ◯ 1st T US pvt ◯ 1st T US junior ◯ 1st T US senior ◯ 14w - 24w T US pvt ◯ 14w - 24w T US junior ◯ 14w - 24w T US senior ◯ >24w US pvt ◯ >24w US junior ◯ >24w US senior
Current GA by best estimation	_____ (weeks)
Best estimate of EDD	_____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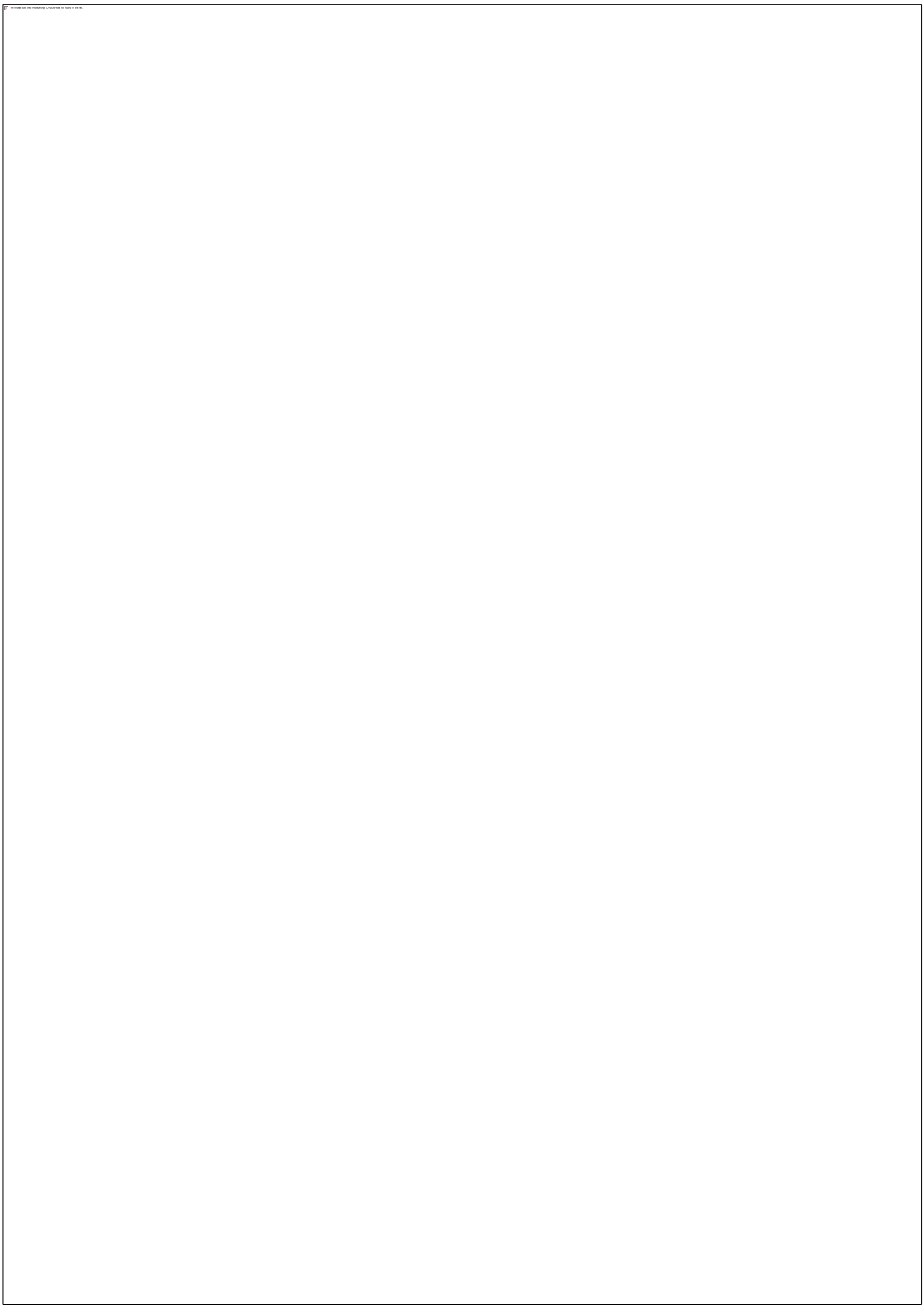
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Appendix 6.6: Patient consent form

INFORMED CONSENT FORM:

Title of Study: Cerebroplacental ratio in labour

I confirm that I have been informed by Dr Wise, about the nature of the study. I have also read/it was read to me and I understood the information sheet and have had the opportunity to ask questions.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

I understand that sections of any of my medical records may be looked at by Dr Wise, Prof Lombaard and Prof Nicolaou. I am aware that I will undergo a sonar and that a sample of blood from the cord of my baby will be taken. Test results, including details such as my medical, surgical, obstetric history, details of my labour, delivery, my baby's health, and my stay in hospital after delivery will be anonymously processed into a computerised system. Data will be kept for two years if published or six years if not published, after this period the data will be destroyed.

Should you wish to contact us at any stage regarding consent, contact Dr Wise at (0731527513) or Professor Lombaard at 0114709090.

I agree to take part in the above-mentioned study. I hereby give consent for my records to be used as per the above-mentioned conditions and for the purposes of research to have a sonar and cord blood taken.

Printed name and surname of patient/participant:

Signature: Date:

Printed name of researcher:

Signature Date:

6.7: Appendix – Copyrights of the publishers of SAJOG

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The editorial team have been informed that the main findings were presented as a poster and published in abstract form.

6.8 Appendix: Additional tables

Appendix 6.8.1: For a CPR <1.08 the association with

	P value	<1.08	≥1.08	Total	PPV	NPV
Fetal compromise	0.181	6/15	42/179	194	0.13	0.94
Apgar <7 at 5min	0.304	1/15	1/174	189	0.5	0.93
Cord bl <7.2	0.913	2/14	25/124	138	0.07	0.89
SGA	0.243	2/15	6/177	192	0.25	0.93
Admission	0.269	3/15	14/177	192	0.18	0.93
BMV/resus	0.695	3/15	24/179	194	0.11	0.93
Any adverse outcome	0.243	8/15	67/179	194	0.11	0.94

Appendix 6.8.2: For a CPR<10th the association with

	P value	<10th	≥10th	Total	PPV	NPV
Fetal compromise	0.594	13/47	35/147	194	0.27	0.77
Apgar <7 at 5min	0.857	1/46	1/143	189	0.50	0.76
Cord bl <7.2	**0.02***	2/36	25/102	138	0.07	0.69
SGA	0.587	3/46	5/146	192	0.38	0.77
Admission	0.765	3/46	14/146	192	0.18	0.75
BMV/resus	0.582	7/47	20/147	194	0.26	0.76
Any adverse outcome	0.464	16/47	59/147	194	0.21	0.74

*The significance of this result is questionable as it implies that those with a CPR ≥10th are more likely to have a Cord pH <7.2.

Appendix: 6.8.3: Prior score PPV and NPV at different cut-offs

Prior Score (n=134)	<5th	≥5th	p-value 5th	PPV	NPV
0 vs 1-7	18/26	69/108	0.625	0.17	0.79
0-1 vs 2-7	24/26	85/108	0.175	0.08	0.78
0-2 vs 3-7	24/26	94/108	0.721	0.13	0.80
0-3 vs 4-7	24/26	99/108	>0.999	0.18	0.80
0-4 vs 5-7	25/26	104/108	>0.999	0.20	0.81
0-5 vs 6-7	25/26	106/108	0.959	0.33	0.81
0-6 vs 7	26/26	107/108	>0.999	0.00	0.80