THE UNIVERSITY OF QUEENSLAND

AUSTRALIA

Maternal and perinatal factors associated with adverse perinatal outcomes at term and the development of a predictive model for identification of at–risk pregnancies.

Christopher John Flatley

BN, GradCertPeriopNurs, MClinEpi

A thesis submitted for the degree of Doctor of Philosophy at

The University of Queensland in 2019

Faculty of Medicine

Abstract

The perinatal period is defined as being between 20 weeks gestation and up to 28 days after birth. Despite advancements in antenatal care, diagnostic tools, interventions and treatments, adverse perinatal outcomes such as stillbirth, fetal growth restriction, preterm birth, hypoxic ischaemic encephalopathy, serious neonatal morbidity and neonatal death still occur. Placental dysfunction is one of the major contributors to these adverse outcomes regardless of gestation. While the majority of fetuses are able to cope with the increase in metabolic requirements in the last few weeks of pregnancy, those with impaired placental function are more susceptible to hypoxic events leading to increased mortality, serious short–term morbidity and long–term neurodevelopmental delays including neonatal encephalopathy and cerebral palsy.

Doppler assessment of fetal blood flow and fetal growth are effective methods to evaluate fetal wellbeing. The umbilical artery pulsatility index can identify growth restriction from suboptimal placentation. The middle cerebral artery pulsatility index can identify the “brain sparing” effect caused by increased perfusion of the fetal brain. The ratio of these two measures (middle cerebral artery pulsatility index/umbilical artery pulsatility index) known as the cerebroplacental ratio has been suggested to be a better predictor than the individual components.

This thesis will investigate the associations between maternal and perinatal factors and adverse perinatal outcomes. It will assess Doppler indices for the identification of fetal growth restricted – small for gestational age fetuses and those at risk of emergency caesarean for non–reassuring fetal status. The creation of accurate reference centiles using the generalised additive model for location, scale and shape approach, will allow for meaningful interpretation of those Doppler measurements. This information will be used to create predictive tools that will enable the clinician to identify pregnancies at risk of adverse perinatal outcomes and emergency caesarean for non–reassuring fetal status.

Declaration by Author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, financial support and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my higher degree by research candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

I acknowledge that an electronic copy of my thesis must be lodged with the University Library and, subject to the policy and procedures of The University of Queensland, the thesis be made available for research and study in accordance with the Copyright Act 1968 unless a period of embargo has been approved by the Dean of the Graduate School.

I acknowledge that copyright of all material contained in my thesis resides with the copyright holder(s) of that material. Where appropriate I have obtained copyright permission from the copyright holder to reproduce material in this thesis and have sought permission from co-authors for any jointly authored works included in the thesis.

Publications During Candidature

First Author Publications

1 Flatley C, Gibbons K, Hurst C and Kumar S. Development of cross–validated model for the prediction of emergency caesarean for intrapartum fetal compromise at term. (Currently under review).

2 Flatley C, Gibbons K, Hurst C, Flenady V, Kumar S. Cross-validated prediction model for severe adverse neonatal outcomes in a term, non-anomalous, singleton cohort. *BMJ Paediatrics Open.* 2019;3(1):e000424.

3 Flatley C and Kumar S. Is the fetal cerebroplacental ratio better that the estimated fetal weight in predicting adverse perinatal outcomes in a low risk cohort? *The journal of maternal–fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians* 2018: 1–7.

4 Flatley C, Kumar S and Greer RM. Reference centiles for the middle cerebral artery and umbilical artery pulsatility index and cerebro–placental ratio from a low–risk population – a Generalised Additive Model for Location, Shape and Scale (GAMLSS) approach. *The journal of maternal–fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians* 2018: 1–8.

5 Flatley C, Greer RM and Kumar S. Magnitude of change in fetal cerebroplacental ratio in third trimester and risk of adverse pregnancy outcome. *Ultrasound in obstetrics & gynecology: the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2017; 50: 514–519.

Other Publications During Candidature

1. Robson D, Daniels S, Flatley C, Kumar S. Obstetric and perinatal outcomes for twin pregnancies in adolescent girls. *Scientific reports.* 2018;8(1):18072.

2. Matta P, Turner J, Flatley C, Kumar S. Prolonged second stage of labour increases maternal morbidity but not neonatal morbidity. *The Australian & New Zealand journal of obstetrics & gynaecology*. 2019;59(4): 555-560.

3. Yi Wen P, Broom E, Flatley C, Kumar S. Maternal demographic and intrapartum antecedents of severe neonatal outcomes at term. *The journal of maternal–fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet.* 2018:1–6. doi: 10.1080/14767058.2018.1540581. [Epub ahead of print]

4. Ho C, Flatley CJ, Kumar S. Emergency caesarean for intrapartum fetal compromise and admission to the neonatal intensive care unit at term is more influenced by fetal weight than the cerebroplacental ratio. *The journal of maternal–fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet.* 2018:1–6. doi: 10.1080/14767058.2018.1526912. [Epub ahead of print]

5. Turner JM, Flatley C, Kumar S. A low fetal cerebroplacental ratio confers a greater risk of intrapartum fetal compromise and adverse neonatal outcomes in low risk multiparous women at term. *European journal of obstetrics, gynecology, and reproductive biology.* 2018;230:15–21.

6. Kean N, Turner J, Flatley C, Kumar S. Maternal age potentiates the impact of operative birth on serious neonatal outcomes. *The journal of maternal–fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet.* 2018:1–8. doi:10.1080/14767058.2018.1498478. [Epub ahead of print]

7. Lui C, Lodge J, Flatley C**,** Gooi A, Ward C, Eagleson K, Kumar S. Obstetric and perinatal outcomes in pregnancies with isolated foetal congenital heart abnormalities. *The Journal of Maternal–Fetal & Neonatal Medicine* 2019;32(18): 2985-2992. doi: 10.1080/14767058.2018.1453799. Epub 2018 Apr 3.

8. Madden JV, Flatley CJ and Kumar S. Term small– for– gestational– age infants from low risk women are at significantly greater risk of adverse neonatal outcomes. *American Journal of Obstetetrics and Gynecology* 2018;218(5): 525 e521-525 e529.

9. Dunn L, Flatley C and Kumar S. Changes in maternal placental growth factor levels during term labour. *Placenta* 2018; 61: 11–16.

10. Thavarajah H, Flatley C and Kumar S. The relationship between the five minute Apgar score, mode of birth and neonatal outcomes. *The Journal of Maternal–Fetal & Neonatal Medicine* 2018; 31: 1335–1341.

11. Li R, Lodge J, Flatley C, Kumar S. The burden of adverse obstetric and perinatal outcomes from maternal smoking in an Australian cohort. *The Australian & New Zealand journal of obstetrics & gynaecology.* 2019;59(3): 356-361.

12. Mendis R, Flatley C, Kumar S. Maternal demographic factors associated with emergency caesarean section for non–reassuring foetal status. *Journal of perinatal medicine.* 2018;46(6):641–7.

13. Michelotti F, Flatley C and Kumar S. Impact of shoulder dystocia, stratified by type of manoeuvre, on severe neonatal outcome and maternal morbidity. *The Australian & New Zealand journal of obstetrics & gynaecology.* 2018;58(3):298–305.

14. Smith A, Flatley C, Kumar S. The risk of preterm birth associated with a low cerebroplacental ratio. *The journal of maternal–fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet.* 2019;32(4): 610-616.

15. Yu J, Flatley C**,** Greer RM and Kumar S. Birth–weight centiles and the risk of serious adverse neonatal outcomes at term. *Journal of perinatal medicine* 2018;46(9): 1048-1056.

16. Jang W, Flatley C, Greer RM and Kumar S. Comparison between public and private sectors of care and disparities in adverse neonatal outcomes following emergency intrapartum cesarean at term – A retrospective cohort study. *PloS one* 2017; 12: e0187040.

17. Daniels S, Robson D, Flatley C and Kumar S. Demographic characteristics and pregnancy outcomes in adolescents – experience from an Australian perinatal centre. *The Australian & New Zealand journal of obstetrics & gynaecology* 2017; 57: 630–635.

18. Rozdarz KM, Flatley CJ and Kumar S. Intrapartum and neonatal outcomes in singleton pregnancies following conception by assisted reproduction techniques. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2017; 57: 588–592.

19. Zhao Y, Flatley C and Kumar S. Intrapartum intervention rates and perinatal outcomes following induction of labour compared to expectant management at term from an Australian perinatal centre. *The Australian & New Zealand journal of obstetrics & gynaecology* 2017; 57: 40–48.

20. Gibbons A, Flatley C and Kumar S. The fetal cerebro–placental ratio in diabetic pregnancies is influenced more by the umbilical artery rather than middle cerebral artery pulsatility index. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2017; 211: 56–61.

21. Lai S, Flatley C and Kumar S. Perinatal risk factors for low and moderate five–minute Apgar scores at term. *European journal of obstetrics, gynecology, and reproductive biology* 2017; 210: 251–256.

22. Dowdall D, Flatley C, Kumar S. Birth weight centiles, risk of intrapartum compromise, and adverse perinatal outcomes in term infants. *The journal of maternal– fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet.* 2017;30(17):2126–32.

23. Gibbons A, Flatley C and Kumar S. Cerebroplacental ratio in pregnancies complicated by gestational diabetes mellitus. *Ultrasound in obstetrics & gynecology: the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2017; 50: 200–206.

24. McGuigan I, Flatley C and Kumar S. Maternal vitamin D levels and the risk of perinatal death. *The journal of maternal–fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians* 2017; 30: 1544–1548.

25. Twomey S, Flatley C and Kumar S. The association between a low cerebro– umbilical ratio at 30– 34 weeks gestation, increased intrapartum operative intervention and adverse perinatal outcomes. *European journal of obstetrics, gynecology, and reproductive biology* 2016; 203: 89–93.

26. Basu A, Flatley C and Kumar S. Intrapartum intervention rates and perinatal outcomes following successful external cephalic version. *Journal of perinatology: official journal of the California Perinatal Association*. 2016; 36: 439–442.

Conference Abstracts – Oral Presentations

1. Flatley C, Kumar S and Greer RM. Reference centiles for the middle cerebral artery and umbilical artery pulsatility index and cerebro–placental ratio from a low–risk population – a Generalised Additive Model for Location, Shape and Scale (GAMLSS) approach. *ISUOG World Congress,* Singapore, October 2018.

2. Flatley C and Kumar S. Is the fetal cerebro–placental ratio better than the estimated fetal weight in predicting adverse perinatal outcomes in a low risk cohort? *RCOG World Congress,* Singapore, March 2018.

3. Flatley C and Kumar S. Is the fetal cerebro–Placental ratio better than the estimated fetal weight in predicting adverse perinatal outcomes in a low risk cohort? *International Postgraduate Symposium in Biomedical Sciences,* University of Queensland, Brisbane, November 2017.

4. Rozdarz KM, Flatley CJ and Kumar S. Intrapartum and neonatal outcomes in singleton pregnancies following conception by Assisted Reproduction Techniques. *RANSCOG Annual Scientific Meeting,* Perth. October 2016.

5. Flatley C, Greer RM and Kumar S. The magnitude of change in the fetal cerebroplacental ratio in the third trimester and the risk of adverse pregnancy outcome. *Queensland Perinatal Consortium (QPaCt).* Brisbane. July 2016.

Conference Abstracts – Poster Presentations

1. Yu J, Flatley C, Greer RM and Kumar S. Birth–weight centiles and the risk of serious adverse neonatal outcomes at term. *RCOG World Congress,* Singapore, March 2018.
2. Michelotti F, Flatley C and Kumar S. The impact of shoulder dystocia on severe neonatal outcome and maternal morbidity specific to the type of manoeuvre: a retrospective review. *RCOG World Congress,* Singapore, March 2018.
3. Dunn L, Flatley C, Kumar S. Changes in maternal placental growth factor levels during term labour. *RCOG World Congress,* Singapore, March 2018.
4. Sherrell H, Flatley C, Kumar S. Maternal and perinatal outcomes after emergency caesarean section at term in nulliparous compared to multiparous women. *RCOG World Congress,* Singapore, March 2018.
5. Turner J, Flatley C, Kumar S. A low fetal cerebroplacental ratio confers a greater risk of intrapartum fetal compromise and adverse neonatal outcomes in low risk multiparous women at term. *RCOG World Congress,* Singapore, March 2018.
6. Smith A, Flatley C, Kumar S. The risk of preterm birth associated with a low cerebroplacental ratio. *RCOG World Congress,* Singapore, March 2018.
7. Flatley C and Kumar S. Retrospective cohort study investigating the role of the cerebroplacental ratio and estimated fetal weight in predicting adverse perinatal outcomes in a low maternal risk cohort. *Queensland Perinatal Consortium (QPaCt) Conference.* Brisbane. July 2017.
8. Flatley C, Greer RM and Kumar S. The magnitude of change in the fetal cerebroplacental ratio in the third trimester and the risk of adverse pregnancy outcome. *International Postgraduate Symposium in Biomedical Sciences.* Brisbane. October 2016.

Publications Included in this Thesis

1 Flatley C and Kumar S. Is the fetal cerebroplacental ratio better that the estimated fetal weight in predicting adverse perinatal outcomes in a low risk cohort? *The journal of maternal–fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians* 2019;32(14): 2380-2386.

Incorporated as Chapter 3

Contributor	Statement of contribution
Flatley C (Candidate)	Conception and design (50%) Analysis and interpretation (70%) Drafting and production (70%)
Kumar S	Conception and design (50%) Analysis and interpretation (30%) Drafting and production (30%)

2 Flatley C, Greer RM and Kumar S. Magnitude of change in fetal cerebroplacental ratio in third trimester and risk of adverse pregnancy outcome. *Ultrasound in obstetrics & gynecology: the official journal of the International Society of Ultrasound in Obstetrics and Gynecology* 2017; 50: 514– 519.

Incorporated as Chapter 4

Contributor	Statement of contribution
Flatley C (Candidate)	Conception and design (40%) Analysis and interpretation (70%) Drafting and production (70%)
Greer R	Conception and design (20%) Analysis and interpretation (15%) Drafting and production (10%)
Kumar S	Conception and design (40%) Analysis and interpretation (15%) Drafting and production (20%)

3 Flatley C, Kumar S and Greer RM. Reference centiles for the middle cerebral artery and umbilical artery pulsatility index and cerebro–placental ratio from a low–risk population – a Generalised Additive Model for Location, Shape and Scale (GAMLSS) approach. *The journal of maternal–fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians* 2019;32(14): 2338-2345.

Incorporated as Chapter 5

Contributor	Statement of contribution
Flatley C (Candidate)	Conception and design (40%) Analysis and interpretation (90%) Drafting and production (70%)
Kumar S	Conception and design (20%) Drafting and production (20%)
Greer R	Conception and design (40%) Analysis and interpretation (10%) Drafting and production (10%)

4 Flatley C, Gibbons K, Hurst C and Kumar S. Development of cross–validated model for the prediction of emergency caesarean for intrapartum fetal compromise at term.

Incorporated as Chapter 6

Contributor	Statement of contribution
Flatley C (Candidate)	Conception and design (60%) Analysis and interpretation (70%) Drafting and production (50%)
Gibbons K	Analysis and interpretation (5%) Drafting and production (10%)
Hurst C	Analysis and interpretation (5%) Drafting and production (10%)
Kumar S	Conception and design (40%) Analysis and interpretation (20%) Drafting and production (30%)

5 Flatley C, Gibbons K, Hurst C, Flenady V, Kumar S. Cross-validated prediction model for severe adverse neonatal outcomes in a term, non-anomalous, singleton cohort. *BMJ Paediatrics Open.* 2019;3(1):e000424.

Incorporated as Chapter 7

Contributor	Statement of contribution
Flatley C (Candidate)	Conception and design (60%) Analysis and interpretation (70%) Drafting and production (55%)
Gibbons K	Analysis and interpretation (5%) Drafting and production (5%)
Hurst C	Analysis and interpretation (5%) Drafting and production (5%)
Flenady V	Drafting and production (5%)
Kumar S	Conception and design (40%) Analysis and interpretation (20%) Drafting and production (30%)

Contributions by Others to the Thesis

Professors Sailesh Kumar and Vicki Flenady provided academic advisory support and guidance for this PhD thesis. Associate Professor Kristen Gibbons academic and statistical advisory support and guidance for this PhD thesis.

Associate Professor Ristan Greer and Cameron Hurst provided additional statistical advice and support.

Data used throughout this thesis was collected by the maternity and obstetric staff at Mater Mothers' Hospitals, Brisbane Australia, and the Maternal and Fetal Medicine department at Mater Mothers' Hospitals.

Statement of parts of the thesis submitted to qualify for the award of another degree

None

Research Involving Human or Animal Subjects Mater Research Institute Human Research and Ethics Committee (EC00332) approvals:

HREC/14/MHS/37

A copy of this approval is included as appendix 1.

Acknowledgements

I would like to express my sincere gratitude to my principle supervisor Professor Sailesh Kumar for his support, guidance, expertise, advice and encouragement. Without your abundance of knowledge, kindness and outstanding work ethic this thesis would not be possible. I would also like to extend my gratitude to my secondary supervisors Professor Vicki Flenady and A/Professor Kristen Gibbons for their advice, support and encouragement throughout my PhD.

I would also like to thank A/Professor Ristan Greer and Cameron Hurst who were kind enough to allow me to tap into their years of experience in clinical epidemiology and statistics.

For my reviewers and chairperson of the three milestones, Professor David McIntyre, Dr Rob Cincotta, Dr Fran Boyle and A/Professor Mamun Abdullah, I thank you for time and kind words during each assessment.

My fellow PhD colleagues in the GENISIS research group, I thank you all for your generosity with your time and your shared knowledge and expertise. I thank all of my co-authors for their contribution to the research and manuscripts.

Professor Glenn Gardiner, I thank you for your years of guidance and for setting me on the path of epidemiology and the wonderful world of statistics.

I would like to acknowledge and am grateful to Mater Research for the financial support they offered during my candidature. Also, the University of Queensland Faculty of Medicine and School of Biomedical Sciences for this wonderful opportunity and their support during my candidature. A special mention for Marilyn Wilckens for her support and guidance.

I would like to thank all of my friends whose support and encouragement has been there for my entire life journey.

I would especially like to thank my dearest family – parents Steve and Jo, brothers Paul and Steve, sister Su and brother-in-law Gav for their support, care and patience with me while I meandered through life and then selfishly took on this research journey and put the rest of my life on hold.

Lastly, I would like to thank with all my heart my beautiful and caring partner, Maki, for her constant patience, empathy, care and support. Without your love and counselling I would never have completed this journey.

This thesis is not the work of a single person or a research group, it is a consequence of a lifetime of support of all my loved ones around me.

Financial Support

Financial support for this research was provided through Mater Research Scholarship along with the Frank Clair Scholarship.

Keywords

cerebroplacental ratio, middle cerebral artery, umbilical artery, estimated fetal weight, epidemiology, reference centiles, GAMLSS, labour obstetric, fetal compromise, fetal hypoxia

Australian and New Zealand Standard Research Classifications (ANZSRC)

ANZSRC code: 111706 Epidemiology, 70%

ANZSRC code: 111402, Obstetrics & Gynaecology, 20%

ANZSRC code: 110320, Radiology and Organ Imaging, 10%

Fields of Research (FoR) Classification

FoR code: 1114, Paediatrics and Reproductive Medicine, 60%

FoR code: 1117, Public Health and Health Services, 30%

FoR code: 1103, Clinical Sciences, 10%

Contents

List of Figures

List of Tables

List of Abbreviations

AGA	Appropriate for gestational age
AIC	Akaike information criterion
AIHW	Australian Institute of Health and Welfare
ANZNN	Australian and New Zealand Neonatal Network
aOR	Adjusted odds ratio
ART	Artificial reproductive technologies
AUC	Area under the curve
BCT	Box-Cox t
BMI	Body mass index
BW	Birth weight
CI	Confidence Interval
CP	Cerebroplacental ratio
CPR	Cerebroplacental ratio
CRS	Clinical reporting system
CS	Caesarean section
DRG	Diagnosis-related group
EM	Emergency
FGR	Fetal growth restriction
GAMLSS	Generalised additive model for location, scale and shape
ICN	Intensive care nursery
IOL	Induction of labour
IQR	Interquartile range
LMS	Lambda-mu-sigma
LBW	Low Birth Weight
MBRD	Mothers and babies research database
MCA PI	Middle cerebral artery pulsatility index
MMH	Mater Mothers' Hospitals
NCCU	Neonatal critical care unit
NICU	Neonatal intensive care unit
NICUS	Neonatal intensive care units
NLR	Negative likelihood ratio
NPV	Negative predictive value
NRFS	Non-reassuring fetal status
OR	Odds ratio
PLR	Positive likelihood ratio
PPV	Positive predictive value
RCD	Routinely collected data
RCT	Randomised control trial
ROC	Receiver operating characteristic
SBC	Schwartz Bayesian criterion
SCN	Special care nursery
SCNO	Serious composite neonatal outcome

SD	Standard deviation
SGA	Small for gestational age
SVD	Spontaneous vaginal delivery
UA PI	Umbilical artery pulsatility index
UR	Unique record

Chapter 1: Introduction

1.1 Background

The perinatal period is defined as being between 20 weeks gestation and up to 28 days after birth (1). Adverse perinatal outcome is a term used to describe poor fetal and neonatal outcomes that occur within this period (1). Improvements in antenatal care and screening techniques have enabled the identification, early intervention and treatment of fetuses at high–risk of these negative outcomes. Despite these improvements, there remains an ongoing risk of perinatal morbidity particularly preterm birth and low birth weight (LBW) (2). More worryingly, there are also seemingly low–risk pregnancies that develop complications leading to the fetus or neonate suffering significant morbidity because of antepartum, intrapartum or postpartum events (3-6).

There are a range of adverse outcomes that can occur during the perinatal period including stillbirth, fetal growth restriction, preterm birth, hypoxic ischaemic encephalopathy, serious neonatal morbidity and neonatal death (2). Some of these events have long term consequences with hypoxic ischaemic encephalopathy being a major risk factor for cerebral palsy. In the majority of pregnancies, the increased demands on vascular perfusion during the last few weeks of pregnancy are tolerated by fetuses with adequate placental function and perfusion of the brain, heart and other vital organs. If placental function is impaired, hypoxic events are more likely to occur and can lead to increased mortality, serious short–term morbidity and long–term neurodevelopmental delays including neonatal encephalopathy and cerebral palsy (7, 8). Despite there being a significant amount of knowledge surrounding maternal and perinatal factors associated with adverse outcomes, the complexity of the relationship between health, disease, environment and human behaviour makes accurate risk prediction complicated (2).

1.2 Fetal Growth Restriction

It is recognised that there are two groups of small fetuses; those that are small for gestational age (SGA) and a subset that are truly growth restricted (3, 4, 9). SGA is often defined as fetuses or infants with an estimated fetal weight (EFW) or birth weight (BW) less than the 10th centile (using either population or customised centiles). Regardless of SGA or growth restriction, being small is associated with increased morbidity (4, 6, 9, 10). Fetal growth restriction (FGR) however, is associated with greater risk compared to infants that are merely SGA without evidence of FGR as a large proportion of SGA fetuses are constitutionally small and healthy, with a normally functioning placenta and normal in utero growth rate (9, 10). Conversely, there are a proportion of fetuses that have impaired growth because of sub optimal placenta function (10-16).

Furthermore, current thinking is that FGR fetuses that have growth restriction may or may not be SGA but have maternal, fetal or placental risk factors that inhibit their potential genetic growth (3, 4, 9, 10, 16, 17). It affects an estimated 5 – 10% of births and is reportedly the second highest cause of perinatal mortality, contributing to 30% of stillbirths (6, 18, 19). It also results in even higher rates of perinatal morbidity and post–natal neurodevelopmental impairment, than seen in those SGA fetuses with normal placental function (4, 5, 9, 10, 16, 17, 20).

FGR can be categorised into two distinct phenotypes with differing onset, Doppler abnormalities and associated morbidities (3, 6, 21). However, at its core, both early and late onset FGR are pathophysiological responses to deteriorating placentation depending on gestation (3-6, 17, 22). Altered fetal Doppler indices are reflective of in utero adaptation with haemodynamic redistribution of cardiac output to vital organs such as the fetal brain, heart and adrenal glands, to counteract the effects of poor placental function (3-5, 10, 21).

For the past 20 years, the standard for identifying FGR has been by Doppler studies in the umbilical artery (3, 4, 20). It has long been accepted that abnormal umbilical artery Doppler indices are associated with adverse consequences in growth restricted fetuses and that prenatal identification of this cohort improves perinatal outcomes (3, 4). Whilst pathological umbilical Doppler indices (absent or reversed end diastolic flow) are reflective of severe placental dysfunction many growth restricted fetuses have umbilical artery Doppler indices within the normal range and are thus missed prenatally (3, 4). This has led to an evolution in research priorities to investigate other parameters to measure the different changes in placental function and the consequent fetal response (3, 4).

The distinction between early and late onset FGR is reflected in the severity of placental disease. These changes are specific to gestation, with a threshold of 32 weeks categorising early or late onset FGR (3, 4, 6, 22, 23).

Although this thesis is primarily concerned with term and near–term fetuses, for thoroughness, a brief exploration of some of the pathophysiology and the effects on feto–placental Doppler indices and placental biomarkers involved in early onset FGR will precede a more complete exploration of the current knowledge of late onset disease.

1.2.1 Early onset FGR

As stated above early onset FGR occurs before 32 weeks gestation and is a consequence of vascular abnormalities of placental tertiary villus vessels. These abnormalities are caused by ineffective trophoblastic cell invasion of the maternal spiral arteries resulting in inadequate vascular remodelling (5, 8, 16, 21, 24-29).

Doppler studies of maternal uterine arteries enable assessment of placental perfusion which in turn reflect inadequate vascular remodelling and placental dysfunction in the form an early diastolic notch (Figure 1.1) (8, 18, 29). If the notch continues after 24 weeks gestation, it is evidence that there is persistent elevated blood flow resistance in the placenta (8, 17, 18, 29). Placental biomarkers such as placental growth factor, pregnancy associated protein A, angioproteins, placental protein 13 and vascular endothelial growth factor, control and correlate with the formation, remodelling and expansion of the placental vascular network (5, 18). Screening studies have shown that the use of these biomarkers early in the first trimester, in combination with uterine artery Doppler and maternal characteristics enhance the detection of specific conditions such as pre–eclampsia and FGR (9, 18, 29-32).

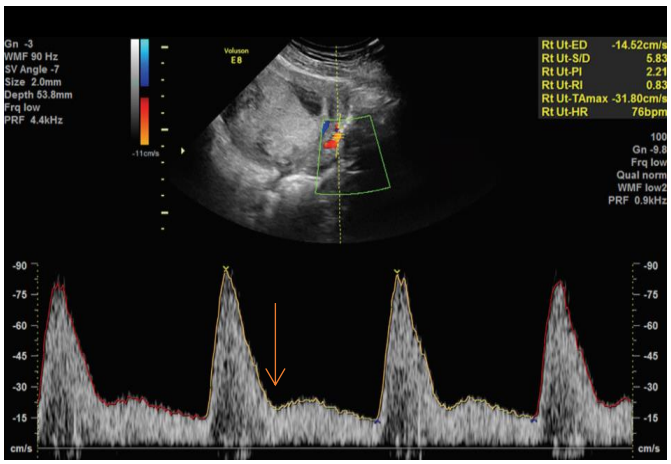

Figure 1-1 Uterine artery doppler with raised pulsatility index & early diastolic notch (red arrow) (29).

1.2.2 Late onset FGR

Whilst early onset FGR occurs in the first and second trimesters, late onset FGR occurs in the third trimester after 32 weeks gestation and is responsible for 70–80% of all cases of FGR (4, 6, 23, 33). Although previously considered a benign and milder form of placental disease, evidence now indicates that late onset FGR contributes to over 50% of unexpected stillbirths and is associated with high levels of adverse perinatal outcomes (3-6, 33-35).

Late onset FGR is suspected when a fetus fails to reach its full growth potential at term after either a slowing or plateauing of its growth trajectory or an increase in the ratio of the head circumference to the abdominal circumference in a fetus that was previously regarded as growing normally (6, 9, 36, 37). In contrast to early onset FGR, late onset FGR presents with less histological changes in the placenta, normal umbilical Doppler indices and a fetus that does not demonstrate the sequential Doppler changes observed in the early onset phenotype (3, 5, 6, 10, 21, 33, 35).

Similar to early onset disease, late onset FGR is due to placental malperfusion, but with different etiology (33). In a 2014 Spanish study, Parra–Saavedra *et al* investigated the placental signs of under–perfusion in 104 singleton term pregnancies with an EFW less than the 10th centile (34). They found that maternal vascular maldevelopment in the form of distal villous hypoplasia was responsible for approximately one quarter of placental under–perfusion and was a result of defective trophoblastic cell invasion and subsequent abnormal vascular remodelling from placental formation early in pregnancy (34). Furthermore, they found that the occurrence of

vascular obstructions late in pregnancy was responsible for approximately half of the lesions that indicate placental under–perfusion (34).

In a 2014 review conducted by Mifsud *et al* on placental pathology in early onset and late onset FGR, they found evidence of an increased number of uteroplacental lesions in late onset FGR fetuses, but a lower incidence than those found in the early onset phenotype and of lesser severity (21). They also found there were some associations with non–vascular pathologies, namely villitis of unknown etiology albeit with varying frequencies (21, 31, 38, 39). In contrast, a 2008 paper by Redline assessing 66 placentas, found that of placental lesions associated with FGR, villitis of unknown etiology was the most common finding in 26% placentas of term fetuses with normotensive FGR (31).

Regardless of the implications of villitis of unknown etiology, the consequences to the fetus of placental insufficiency in near term or term fetuses is vastly different to early onset FGR. Despite not having to cope with the problems associated with prematurity often resulting from early onset FGR, the fetus at term is vulnerable to the aforementioned haemodynamic changes (4, 6). As it approaches term, the fetal brain has an increasingly higher need for oxygen, making it more susceptible hypoxia, especially during the birthing process (4, 6, 8, 40). In common with early onset FGR, late onset cases also demonstrate a similar "brain sparing" autoregulatory redistribution of blood flow in an effort to protect the vital organs such as the fetal brain (6, 8, 10, 22, 37).

1.3 Doppler Indices

1.3.1 Umbilical Artery Pulsatility Index

The umbilical artery Doppler pulsatility index (UA PI) can be used to screen for FGR resulting from suboptimal placentation (7, 8, 17, 18, 25, 41). It is reflective of the increased resistance in the umbilical artery caused by chronic vasoconstriction of the tertiary stem villi resulting from inadequate vascular remodelling (6, 8, 21, 24-27, 29, 42). This abnormal umbilical artery flow is associated with such adverse perinatal outcomes as preterm birth, non–reassuring fetal status, LBW, perinatal mortality, acidosis, hypoglycaemia, respiratory distress and admission to neonatal intensive care unit (NICU) (42-45). However, the predictive ability of the UA PI does not extend to all pregnancies.

In 1999, Farrell *et al* performed a systematic review and meta–analysis, which evaluated 2,700 pregnancies from unselected, low obstetric risk, high obstetric risk and combination populations. They found only minimal predictability of the UA PI in relation to Apgar scores at 1 and 5 minutes, SGA fetuses, heart abnormalities, acidosis and caesarean for non–reassuring fetal distress. Although the authors were concerned about publication bias from some of the included studies, they reached the conclusion that the UA PI has poor predictability of adverse perinatal outcomes (46).

Further investigations show little benefit to routine UA PI assessment in low–risk pregnancies. In 2015, Alfirevic *et al* updated their Cochrane systematic review, assessing data from 14,185 pregnancies in 5 studies (all from the 1990's) and concluded that there was not sufficient evidence that routine umbilical Doppler examination in low–risk or unselected pregnancies would benefit the fetus or the mother (47).

In contrast, however, the same team performed another Cochrane systematic review in 2013, investigating high–risk pregnancies. From analysis of 18 studies and 10,156 pregnancies, the authors concluded that in high–risk pregnancies, there were significant reductions in perinatal mortality in fetuses that had UA PI assessment. Low Apgar scores, stillbirths, emergency caesarean section rates were lower in the cohorts with UA PI assessment, though these did not reach statistical significance. This review was under powered and the authors were concerned about publication bias. Despite these limitations, the authors concluded that umbilical artery Doppler studies should be incorporated into the monitoring of high–risk pregnancies (44).

In 2014, Morales–Rosello *et al* in an analysis of 11,576 fetuses, scanned within 14 days of delivery, found that increases in UA PI were observed in fetuses that were appropriate for gestational age but had not reached their growth potential (14).

The PORTO study in 2013 of 1,100 consecutive pregnancies conducted by Unterscheider *et al*, found that an EFW less than the 10^{th} centile and abnormal umbilical artery Doppler indices (defined as absent or reversed end–diastolic flow or PI >95^{th} centile) was a significantly better predictor of NICU admission and adverse perinatal outcome, than the EFW alone (48).

Though it has been shown that the predictability of the UA PI is limited, it is still an invaluable tool for the assessment of placental function (5, 14, 42, 44, 48). As the increased arterial resistance is a consequence of early placental dysfunction, the elevated UA PI is usually indicative of FGR and thus is considered a risk assessment tool for these fetuses (5, 14, 41, 42).

1.3.2 Middle Cerebral Artery Pulsatility Index

Fetuses at term or near term that have placental under–perfusion and suffer adverse perinatal outcomes, often have a normal UA PI (37). However, because of the "brain sparing" effect there is an increase of perfusion to the fetal brain manifesting itself in a reduced resistance measured by the Doppler pulsatility index of the cerebral vessels (6, 8, 10, 22, 37).

In 2012, Morris *et al* performed a systematic review and meta–analysis investigating the utility of middle cerebral artery pulsatility index (MCA PI) to predict perinatal wellbeing. From a total of 35 studies between 1992 and 2011, 4,025 fetuses were eligible for the meta–analysis. The authors identified that the MCA PI was predictive of adverse perinatal outcome, low Apgar score (<7) at 5 minutes, low Apgar score (<7) at one minute, acidosis (cord pH <7.2), admission to NICU, BW less than the 10th centile and neonatal mortality (Table 1.1). Although these results showed that an abnormal MCA PI is predictive of adverse perinatal outcome, the associations remained weak (49).

Table 1-1: Positive likelihood ratio of MCA PI to predict fetal wellbeing (49).

Outcome	**No. Studies**	**Positive Likelihood Ratio (95% C.I.)**
Apgar @ 5 Minutes <7	10	1.65 (1.07 – 2.52)
Apgar @ 1 Minute <7	4	4.14 (1.52 – 4.57)
Acidosis (Cord pH <7.2)	8	2.04 (1.17 – 3.56)
NICU	7	4.00 (2.16 – 7.40)
BW <10th Centile	12	4.95 (2.81 – 8.72)
Mortality	8	1.36 (1.10 – 1.67)
Adverse Perinatal Outcome	18	2.77 (1.93 – 3.96)

NICU: Neonatal Intensive Care Unit; BW: Birth Weight; C.I.: Confidence Interval

In 2015, Prior *et al* reviewed articles related to the identification of intrapartum fetal compromise (41). They found that in a 2011 paper by Cruz–Martinez *et al*, MCA PI was associated with caesarean section for non–reassuring fetal status and neonatal acidosis (41, 50). This paper investigated 232 singleton fetuses with an EFW less than the 10th centile and a normal UA PI less than the 95th centile who were selected for induction of labour (50). Although associations were found, confidence intervals for the logistic regressions were wide, reflecting an inadequate sample size (50). A 2006 study by Leung *et al*, identified that the MCA PI was

associated with an increased incidence of caesarean for non–reassuring fetal status following a successful external cephalic version (41, 51). There was successful external cephalic version performed on 174 women between 36 – 38 weeks gestation (51). Leung *et al* found a significantly lower MCA PI in fetuses that required caesarean for non–reassuring fetal status 1.30 (Inter–Quartile Range (IQR) 1.22 – 1.55) compared to those who had a spontaneous vaginal birth 1.60 (IQR 1.42 – 1.88) (51).

Although a number of studies have identified associations between the MCA PI and adverse perinatal outcomes in a range of populations, its predictive value is remains weak (42, 49, 52-54).

1.3.3 Cerebroplacental Ratio

Whilst the UA PI has the ability to identify early suboptimal placentation in SGA fetuses and the MCA PI is able to identify cerebral redistribution both have been found to be inadequate predictors of adverse perinatal outcomes (3, 4, 6, 10, 22, 45, 52). The cerebroplacental ratio (CPR) is the ratio of the MCA PI divided by the UA PI, and is suggested to be a better predictor than the individual components (10, 52, 55-59).

Whilst the CPR is often reported as a continuous measure (in its raw form or standardised as either a multiple of the median or a *Z*–score) studies tend to use a cut–off of what is considered to be an abnormal CPR for clinical purposes. There have been however, contrasting opinions when defining the best cut–off values for the CPR. There are some proponents who use a CPR of less than the 10^{th} centile, cut–off of less than 1, others have used 1.08, 1.05 and multiple of the median <0.6765, and whilst each have their merits, further investigation is needed (60-64). One reason for the uncertainty of the best threshold to use is because the CPR evolves throughout the pregnancy, with the point estimate of the mean (or median) as well as the variance depending on the gestational age that the assessment is performed (Figure 1.2) (59, 65).

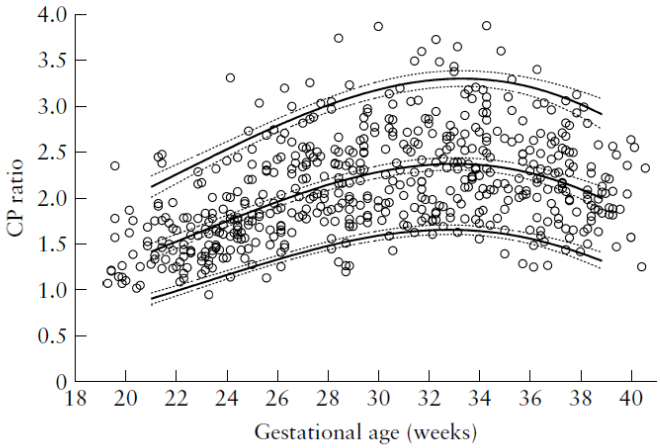

Figure 1-2: Cerebroplacental reference centile curves (66).

*CP ratio; Cerebroplacental Ratio
*Thick lines: 5th, 50th & 95th percentiles with the 95% C.I. (thin lines)

Regardless of the cut–off value, many studies investigating the predictability of the CPR, within different populations, have identified strong associations between abnormal CPR values and various adverse perinatal outcomes (10, 11, 14, 15, 41, 49, 50, 52-54, 56-61, 63, 67-71).

1.3.3.1 CPR in SGA/FGR

Bahado–Singh *et al* investigated 203 fetuses at risk of FGR in their 1999 study (57). The authors reported multiples of the median of the CPR and receiver operating characteristic (ROC) curves with area under the curve (AUC) (57). Multiples of the median were calculated for gestational age against a cross–sectional cohort of 82 normal singleton pregnancies (57). With Doppler indices taken less than three weeks prior to delivery, the authors found the CPR to be predictive of LBW and of a composite of adverse perinatal outcomes which included; 5 minute Apgar score <7, meconium staining, caesarean section for fetal distress, admission to NICU for more than 24 hours, hypoglycaemia or polycythaemia (Table 1.2) (57).

Table 1-2: Cerebroplacental ratio predicting birth weight and adverse perinatal outcomes (57).

Outcome	**AUC**	**P Value**
Birth Weight <10th Percentile	0.758 (0.682 – 0.833)	<0.001
Birth Weight <5th Percentile	0.751 (0.673 – 0.829)	<0.001
Birth Weight <10th Percentile + Composite	0.861 (0.796 – 0.927)	<0.001
Birth Weight <5th Percentile + Composite	0.865 (0.802 – 0.927)	<0.001
Adverse Perinatal Outcome Regardless of Birth Weight	0.736 (0.657 – 0.815)	<0.001

* Birth Weight Cut–offs derived from population reference centiles.

The authors concluded that in a cohort suspected of FGR, not only is an abnormal CPR highly associated with LBW and adverse perinatal outcome, but also superior to the UA PI alone (57).

In a 2005 retrospective study, Odibo *et al* identified 155 cases of FGR fetuses, defined as EFW below the 5th percentile for gestational age (65). This study was the first to utilise the CPR age specific reference centiles calculated on 306 normal singleton fetuses, developed by Baschat and Gembruch in 2003 (65, 72). Using logistic regression, ROC curves and AUC, they measured the CPRs' ability to predict a composite of adverse perinatal outcomes defined as caesarean delivery for non–reassuring fetal status, cord pH <7.0, 5 minute Apgar score <7, respiratory distress, intraventricular haemorrhage >grade 2, periventricular leukomalacia and perinatal death (65). The authors used two definitions of abnormal CPR: <1.08; and <5th percentile defined by the Baschat and Gembruch reference centiles (Table 1.3) (65, 72).

Table 1-3: Cerebroplacental ratio predicting composite adverse perinatal outcome in growth restricted fetuses (65).

CPR Cut–off	**Number**	**Sensitivity**	**Specificity**	**AUC**
CPR <1.08 & FGR <10%	183	72%	62%	0.67
CPR <1.08 & FGR <5%	155	67%	66%	0.67
CPR <5 Percentile & FGR <10%	183	65%	73%	0.69
CPR <5 Percentile & FGR <5%	155	58%	71%	0.68

*CPR: Cerebroplacental Ratio; FGR: Fetal Growth Restriction; AUC: Area Under the Curve

From this the authors concluded that both of the cut–offs of the CPR that were assessed were effective in predicting the composite outcome (65). They were also able to determine that whilst the CPR had an improved sensitivity predicting the composite outcome, the specificity was much lower than that of the UA PI alone (65).

Cruz–Martinez *et al* investigated the association of abnormal CPR with caesarean delivery for non–reassuring fetal status and neonatal acidosis (umbilical artery pH <7.15 or base excess >12) (50). This 2011 prospective study matched 223 SGA fetuses (defined as having an EFW <10th centile) who were to be induced for labour with a normal cohort of singleton pregnancies (50). The normal cohort consisted of fetuses who were also induced for premature rupture of membranes, without signs of chorioamnionitis and whose BW was between the 10th and 90th percentile, according to customised BW standards derived from a 2008 Spanish population by Figueras *et al* (50, 73). Compared to the normal cohort, the authors found that both an abnormal CPR and MCA PI were associated with both caesarean delivery for non–reassuring fetal status and neonatal acidosis (Table 1.4) (50).

Table 1-4: Odds ratio of abnormal cerebroplacental ratio & middle cerebral artery pulsatility index in relation to caesarean delivery for non–reassuring fetal status & neonatal acidosis (50).

Doppler Indices	**Caesarean Delivery for Non–Reassuring Fetal Status**	**Neonatal Acidosis**
	Odds Ratio (95% C.I.)	**Odds Ratio (95% C.I.)**
Abnormal CPR	10.3 (3.22 – 52.8)	5.0 (1.06 – 46.9)
Normal CPR	5.6 (2.13 – 18.6)	2.0 (0.43 – 12.4)
Abnormal MCA PI	18.0 (2.84 – 750)	9.0 (1.25 – 395)
Normal MCA PI	5.1 (2.37 – 12.7)	2.0 (0.62 – 7.46)

C.I.: Confidence Interval; CPR: Cerebroplacental Ratio; MCA PI: Middle Cerebral Artery Pulsatility Index

The authors also found that the CPR had a better sensitivity than the MCA PI in predicting caesarean delivery for non–reassuring fetal status (45.9% c.f. 29.5%) but had worse specificity (78.5% c.f. 91.3%). In light of this they developed a clinical algorithm as a prediction tool that incorporated both the MCA PI and the CPR which allowed an increased sensitivity to 50% preserving a specificity of 76% (50).

In a 2013 review, Hernandez–Andrade *et al* evaluated both human and animal models and found that the CPR has better correlation with hypoxia than its individual components. There were stronger associations with adverse outcome than the middle cerebral artery Doppler and even in

appropriately grown fetuses there were associations with long term neurobehavioral problems (10).

A 2016 systematic review and meta–analysis by Nassr *et al* evaluated the CPRs' role in FGR and its predictability in relation to adverse perinatal outcome (56). They identified seven studies between 1992 and 2014 and 1,428 fetuses were eligible for analysis. The meta–analysis showed that the CPR was associated with emergency caesarean for fetal distress, Apgar score less than 7 at five minutes, and NICU admission (Table 1.5) (56). This systematic review has come under criticism by Morales–Rosello and Khalil due to its grouping both early and late onset FGR fetuses into the same analysis (70). However, as the authors point out, in the past, studies have often failed to stratify their results into early and late onset FGR and when they are distinguished, cut–offs are not universal (74).

Table 1-5: Results from individual studies & meta–analysis (56).

Caesarean Delivery for Fetal Distress				
Study	**Weighting**	**Number**	**Odds Ratio (95% C.I.)**	**Year of Publication**
Gramellini *et al*	11.6%	90	56.00 (11.00 – 285.09)	1992
Bahado– Singh *et al*	14.7%	123	4.46 (1.81 – 10.99)	1999
Makhseed *et al*	14.4%	70	2.56 (0.97 – 6.72)	2000
Dubravko *et al*	14.2%	87	3.56 (1.30 – 9.76)	2003
Rozeta *et al*	16.3%	738	0.88 (0.66 – 1.19)	2010
Monika Singh *et al*	13.5%	50	3.50 (1.07 – 11.48)	2013
Regan *et al*	15.2%	270	10.00 (4.77 – 20.96)	2014
Meta–Analysis		**1,428**	**4.49 (1.63 – 12.42)**	
5–minute Apgar Score <7				
Study	**Weighting**	**Number**	**Odds Ratio (95% C.I.)**	**Year of Publication**
Bahado–Singh *et al*	11.2%	123	3.26 (1.01 – 10.50)	1999
Makhseed *et al*	9.4%	70	2.68 (0.74 – 9.73)	2000
Dubravko *et al*	6.2%	87	20.00 (3.96 – 101.08)	2003
Rozeta *et al*	64.0%	738	3.64 (2.65 – 5.01)	2010
Monika Singh *et al*	9.1%	50	5.23 (1.41 – 19.43)	2013
Meta–Analysis		1,068	**4.01 (2.65 – 6.08)**	
Neonatal Intensive Care Admission				
Study	**Weighting**	**Number**	**Odds Ratio (95% C.I.)**	**Year of Publication**
Gramellini *et al*	15.4%	90	28.00 (7.39 – 106.11)	1992
Bahado– Singh *et al*	16.4%	123	40.50 (13.20 – 124.26)	1999
Makhseed *et al*	16.7%	70	6.30 (2.23 – 17.85)	2000
Rozeta *et al*	19.0%	738	2.00 (1.48 – 2.70)	2010
Monika Singh *et al*	15.0%	50	4.88 (1.17 – 20.26)	2013
Regan *et al*	17.5%	270	14.78 (6.40 – 34.11)	2014
Meta–Analysis		**1,341**	**14.78 (6.40 – 34.11)**	

C.I.: Confidence Interval

Kalafat *et al* developed a predictive model for operative delivery for intrapartum fetal compromise in a cohort of SGA fetuses (75). They included singleton pregnancies that were identified as having an EFW below the 10th centile at a gestational age greater than 36 weeks. In a model that included parity, gestational age, the CPR multiple of the median, induction of labour without augmentation, epidural use, the use of oxytocin for the augmentation of labour and the use of oxytocin used for the augmentation of labour without labour induction they were able to identify the majority of fetuses that have operative delivery for fetal compromise with an AUC of 0.76 (95% CI 0.72 – 0.80), a sensitivity of 70.5%, specificity of 70.0% a positive likelihood ratio of 3.95 (sic)[1] and a negative likelihood ratio of 0.42. Interestingly the authors investigated using the CPR as a continuous variable and found a linear association with the risk of operative delivery for fetal compromise (75). Most studies up to this point have categorised the CPR and utilised cut–offs for patients when assessing the associations with adverse perinatal outcomes despite caution against this approach by Altman and Royston (76).

In another paper by the same group, Kalafat *et al* developed a predictive model for the risk of NICU admission in a SGA cohort (77). Again, they included singleton pregnancies with an EFW less than the 10th centile at 37 weeks gestation or later. Using only the CPR multiple of the median, the EFW centile and the gestational age at delivery, they had an AUC of 0.71 (95% CI 0.63 – 0.79). Using a false positive cut-off of 10%, the model had a sensitivity of 30.9% (95% CI 16.6 – 45.2), positive predictive value of 16.1% (95% CI 9.2 – 26.3), a negative predictive value 95.0% (95% CI 93.2 – 96.1), a positive likelihood ratio 3.09 and a negative likelihood ratio of 0.72 (77).

A 2018 systematic review by Conde-Agudelo *et al* assessed the CPR's ability to predict adverse perinatal outcomes and neurodevelopmental outcomes in FGR (78). Their eligibility criteria included fetuses that were considered growth restricted diagnosed using sonography parameters. For their outcomes they looked at studies that used any form of adverse perinatal composite outcome, perinatal death, caesarean section for fetal distress, low 5-minute Apgar score (<7), acidosis, admission to NICU, neonatal brain lesion, morbidity other than a brain lesion, mechanical ventilation and SGA at birth. Their results indicate that the best utility for CPR is in predicting perinatal death in FGR fetuses with a pooled sensitivity of 93% (95% CI 78 – 98), pooled specificity of 76% (95% CI 74 – 78), positive likelihood ratio 3.9 (95% CI 3.4 – 4.5) and negative likelihood ratio 0.09 (95% CI 0.0 – 0.3). Other than perinatal death, as a standalone test, the CPR performed poorly with low predictability in FGR (Table 1-6) (78).

[1] This should be a positive likelihood ratio of 2.35 (ie: +LR = 0.705/1 – 0.70)

Table 1-6: Accuracy of the cerebroplacental ratio in predicting adverse perinatal outcomes (78).

Outcome	Number of Studies	Women	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio
Perinatal Death	6	1,495	93 (78 – 98)	76 (74 – 78)	3.9 (3.4 – 4.5)	0.09 (0.0 – 0.3)
Adverse Outcome Composite	11	2,658	57 (53 – 61)	77 (75 – 79)	2.5 (2.3 – 2.8)	0.6 (0.5 – 0.6)
Caesarean Section for Fetal Distress	7	1,339	59 (54 – 64)	74 (72 – 77)	2.3 (2.0 – 2.6)	0.6 (0.5 – 0.6)
Apgar@5 <7	6	1,148	54 (42 – 66)	72 (69 – 74)	1.9 (1.5 – 2.4)	0.6 (0.5 – 0.8)
NICU	9	2,206	45 (41 – 49)	79 (77 – 81)	2.2 (1.9 – 2.5)	0.7 (0.6 – 0.8)
Acidosis	5	1,283	48 (38 – 58)	70 (68 – 73)	1.6 (1.3 – 2.0)	0.7 (0.6 – 0.9)
Brain Lesion	5	352	56 (43 – 67)	48 (46 – 54)	1.1 (0.8 – 1.4)	0.9 (0.7 – 1.2)
Morbidity other than Brain Lesion	4	547	78 (67 – 86)	33 (29 – 37)	1.2 (1.0 – 1.3)	0.7 (0.4 – 1.1)
Mechanical Ventilation	1	176	90 (77 – 96)	39 (31 – 47)	1.5 (1.2 – 1.7)	0.3 (0.1 – 0.7)
SGA	2	554	43 (39 – 47)	94 (84 – 98)	7.4 (2.5 – 22.4)	0.6 (0.5 – 0.7)

NICU: Neonatal intensive care unit; SGA: Small for gestational age

1.3.3.2 Appropriate for gestational age fetuses

In a 2013 prospective study, Prior *et al* investigated 400 singleton, normally grown low–risk fetuses (15). The aim was to identify whether a low CPR was associated with an increased risk of compromise during labour. The UA PI, MCA PI and the CPR were all found to be associated with both instrumental vaginal delivery for fetal compromise and caesarean delivery for fetal compromise. ROC analysis was performed and the UA PI had an AUC=0.63, MCA PI AUC=0.64 and CPR AUC=0.69. Fetuses with a CPR <10th percentile had increased odds (OR=6.1; 95% C.I. 3.03 – 12.75) of being delivered via caesarean delivery for fetal compromise. Even after removing fetuses born with a BW <10th percentile, (indicating possible undiagnosed FGR), the association remained (15).

In 2014, Morales–Rosello *et al* investigated the changes in fetal Doppler indices as a marker of failure to reach growth potential at term (14). This retrospective study included 11,576 singleton,

term pregnancies collected over a 10–year period. It demonstrated that high UA PI, low MCA PI and low CPR were all associated with LBW but within the normal range. The authors suggest that the changes in the Doppler indices were reflective of fetal hypoxemia in appropriately grown for gestational age (AGA) fetuses. This is an important finding as it has been previously believed that placental insufficiency (and the subsequent adverse perinatal outcomes resulting from this), had been only associated with SGA fetuses. But these changes in the Doppler indices that Morales–Rosello *et al* detected in this cohort of AGA fetuses, appeared to be similar to that seen in a SGA cohort (14).

In a 2015 Akolekar *et al* performed a screening study of 6,178 AGA and SGA singletons between 35 – 37 weeks gestation. They found that despite there being a higher incidence of adverse outcomes in the SGA cohort, half of the stillbirths and the majority of cases of fetal distress, acidosis, admission to NICU and low Apgar score, occurred in the cohort that were AGA and that the CPR had poor sensitivity (11).

A further investigation by Prior *et al* in 2014, sought to develop a composite risk score for predicting fetal compromise in labour comprising of the UA PI, MCA PI, the CPR and the umbilical vein (58). The authors used a point system to identify the severity of the individual Doppler indices. Over a 24–month period a cohort of 601 singleton pregnancies that had not been diagnosed as having FGR were recruited. Fetuses with the highest composite risk score had an incidence of emergency caesarean for fetal compromise of 53.5% compared to only 3.4% in the fetuses with lowest risk score of 0 – 2. They reported a marked improvement in positive predictive values from 36% observed using the CPR alone, increasing to over 50% when using combining Doppler indices as part of the composite risk score (58).

Miranda *et al* combined maternal characteristics, fetoplacental ultrasound and biochemical markers in the third trimester to investigate adverse perinatal outcomes (79). Between January 2012 and December 2014, 1,590 fetuses were recruited. Adverse perinatal outcome was defined as having suffered from one of the following outcomes; stillbirth, emergency operative delivery (caesarean or instrumental vaginal delivery) for non–reassuring fetal status, 5–minute Apgar score <7 or acidosis (cord pH <7.15 or base excess ≥12). Overall this study found that their combined screening model provided poor predictability for adverse perinatal outcomes, though there was some improvement when assessing SGA fetuses. Whilst individual components of the model indicated associations, the authors report that the sensitivity and positive predictive values were low (79).

In 2015, Khalil *et al* investigated the association between the CPR and intrapartum fetal compromise and admission to the NICU in term fetuses (53). Their study divided the cohort into four groups using a BW cut–off of the 10th centile (adjusted for gender and gestational age) and a CPR cut–off of 0.6765 multiple of the medians against previously published centiles (14, 53). They concluded that the CPR when measured at term is associated with admission to the NICU and emergency operative delivery for fetal compromise, even after adjusting for possible confounding. These associations were found to be higher in fetuses whose weight was AGA than in SGA fetuses with a normal CPR, indicating a stronger relationship between fetal compromise and a low CPR than fetal compromise and BW. The authors suggest that this is supportive of the theory that placental insufficiency leads to fetuses failing to reach their full growth potential regardless if their weights are AGA (53). Also, that irrespective of fetal weight, having a low CPR is independently associated with both admission to the NICU and fetal compromise (53).

In a recent article by Khalil *et al*, they addressed the role of uteroplacental and fetal Doppler in identifying FGR at term (55). They point out the difference in assessing biometric measurements based on fetal growth and fetal size. A single ultrasound is only a point estimate and its only value is in assessment of fetal size. As the majority of SGA fetuses are constitutionally small, there is a need to involve longitudinal measurements of at least two scans. This allows assessment of growth velocity and fetal nutrition which places the measurements in context not only of population references but also in relation to individual's constitution (55).

Using a point estimate of the CPR as a standalone test is unsatisfactory as it has a low sensitivity of approximately 6 – 15% (11). And as pointed out by Khalil *et al*, population reference centiles of Doppler indices are needed to understand placental function in relation to what is considered normal (55). Thus, one aim of this project is to combine the CPR with other Doppler indices as well as known risk factors for adverse perinatal outcomes to devise a more accurate prediction tool.

Morales–Rosello investigated the CPR's ability to detect fetal compromise in AGA fetuses (80). They investigated 569 low–risk fetuses and found that the fetuses who experienced fetal compromise had low CPR measures weeks before birth. They suggested that the evaluation of the CPR alone could identify one third of fetuses that suffer from fetal compromise when they were considered low–risk and AGA (80).

1.4 Reference Centiles for Doppler Indices

1.4.1 Centile Creation for Doppler Indices

Many studies have developed reference ranges or centiles for the UA PI, MCA PI and for the CPR, with just as many different methodologies (12, 13, 57, 66, 72, 81-86). Reference ranges in relation to fetal growth or fetal size pose statistical problems due to the variation in distribution parameters between each gestational week (66).

In 1990, Arduini and Rizzo developed reference limits for the UA PI, the descending aorta, internal carotid artery, MCA PI and renal artery (82). From a cross sectional design, they confirmed 1,556 healthy low–risk pregnancies for the reference creation. The authors report using quadratic regression analysis for umbilical artery, middle cerebral artery and internal carotid artery indices, and linear regression for the descending aorta and renal artery for the construction of the references (82).

Hercher *et al* (1992) created normal ranges for the UA PI, MCA PI and the CPR, to compare AGA and SGA fetal Doppler indices (13). They identified 127 singleton, AGA and with no malformations, to derive their reference ranges from. They found a linear relationship between the UA PI and gestational age and a quadratic relationship between both the MCA PI and CPR, and gestational age. Regressions based on the linear or quadratic relationship were then used to calculate the reference ranges (13).

A 1995 study by Harrington *et al* developed cross–sectional reference ranges to assist in their investigation of the association between Doppler indices and the development of pre–eclampsia/proteinuric pregnancy–induced hypertension (12). The authors identified 167 uncomplicated, appropriately grown; term fetuses and these were used as the basis for the reference centiles. The modelling of the centiles was performed using a polynomial smoothing function. They addressed the changes in skewness across gestational age by including a term in the polynomial, az where a is the gestational age at the scan date and z is the standard normal deviate or Z–score. Model fitting was done using the least squares method, with centiles modelled and subsequent Z–scores derived from those centiles. Goodness of fit was performed on the models by plotting Z–scores against normal centiles and using tests of normality of the Z–scores. All observations taken from the 167 uncomplicated pregnancies were used in the centile creation, meaning there were multiple observations for some fetuses, but this accounted for less than 5% of the raw estimates (12).

Kurmanavicius *et al* designed a study in 1997 specifically aimed to establish reference ranges for various Doppler indices (84). Measurements were obtained for 1,675 "normal" pregnancies, though exclusions based on SGA, prematurity or events that affected the fetus several weeks after the birth were not done retrospectively. Centile creation was done through the use of both linear and polynomial regression at each gestational age. Where residuals were skewed, transformations were used to create normal distributions. Log transformations were applied to the data for the measurements of the umbilical artery, non–placental uterine artery, placental uterine artery and mean resistance index of both uterine arteries, whilst the placenta–cerebral artery ratio was transformed by taking the inverse. These transformations were performed as a result of the assessment of the residuals showing a skewed distribution (84).

Bahlman identified 962 low–risk pregnancies in a 2002 cross–sectional study and developed reference ranges for the MCA PI, the resistance index as well as the systolic, mean and end diastolic velocities (83). The methodology used for the creation of the ranges was suggested by Wellek *et al* using non–linear regression functions and fitting polynomial curves (quadratic) (83, 87).

Two further cross–sectional studies were performed in 2003 and 2004. Baschat and Gembruch aimed to create normative values for the CPR from 306 patients whilst Palacio *et al* derived theirs from 140 patients (72, 86). Baschat and Gembruch found a linear relationship between the UA PI and gestational age and a polynomial quadratic regression model best fitted for the MCA PI and CPR. Whilst Palacio *et al* found that a linear polynomial equation best fit for all parameters (72, 86).

A 2005 longitudinal study by Acharya *et al* collected data on 130 low–risk pregnancies. Each woman had between 3 – 5 ultrasound scans with approximately 4–week intervals between scans, to collect umbilical artery Doppler indices (81). Skewness in the residuals of the data for the Doppler measurements of the UA PI and systolic–diastolic ratio was accounted for using logarithmic transformations and power transformations in the form of a square root was used for the resistance index. To account for the correlation within clusters, multilevel modelling was used, and fractional polynomials fitted for the relationship between gestational age and the Doppler indices (81).

Parra–Cordero *et al* used the fetal artery and venous Doppler measures to create a number of reference ranges (88). They collected data for measures between 23 and 40 weeks gestation and had 172 for the UA PI and 160 measures for the MCA PI. Box–Cox transformation were used, and a weighted model fitted using orthogonal polynomials up to the 4^{th} power. Goodness–of–fit

was assessed using plots of residuals for normality and homoscadacity (not described further nor illustrated) (88).

Ebbing *et al* derived reference ranges for the MCA PI and the UA PI and blood velocities, as well as the CPR (66). Using a longitudinal study design, 161 singleton, low–risk pregnancies were scanned between 3 to 5 times with between 3 to 5 weeks interval between scans. This led to a total of 566 observations recorded between 19–41 weeks gestation. Similar to the Acharya study, multilevel modelling was used to account for within subject correlation. Box–Cox power transformations were used to transform the continuous Doppler indices to normal distributions. Again, fractional polynomial regression models were used to fit centile curves (66). Furthermore, due to the longitudinal study design the authors calculated conditional reference values, where each reference interval is calculated in respect to the previous measurement based on the mean, variance and covariance between the two measurements (66, 89).

Morales–Rosello *et al* created ranges of the vertebral and MCA PI and peak systolic velocity, and the CPR (90). Using 2,323 measures they excluded fetuses with malformations and multiple pregnancies. There appears to be no other exclusion criteria. Little methodology is described except for tests of normality and the use of percentile regression (90).

A 2016 study by Seffah and Swarray–Deen produced ranges of the pulsatility index, the resistive index, the peak systolic velocity and Systolic/Diastolic ratio for the middle cerebral artery, using a prospective cross–sectional study which captured 458 measures between 20 weeks and 40 weeks gestation (91). Other than correlation and regression analyses to evaluate the correlation between the Doppler measures and gestational age, no other statistical methods are described (91).

In the study by Harrington *et al* we start to see the evolution of the centile creation in terms of Doppler indices. They recognised the need to adjust for the changing standard deviations at each gestational age, and also the appropriateness of publishing the results of the assessment of the model fit for the data (12). Kurmanavicius' 1997 study took centile development step further (84). Not only did they adjust for the change in variance at each gestational age, data transformations were used to adjust for the deviations from the normal distribution that were displayed in the assessment of the residuals as functions of gestational age (84). The longitudinal study by Acharya *et al* shows not only the additional statistical considerations that apply to this form of study design but also show a further evolution in centile creation (81). The multilevel modelling accounted for the high correlation that exists within subject measurements and also the use of fractional polynomials is a much more flexible parameterisation of continuous

variables of the Doppler indices. Ebbing *et al* took the calculation of reference centiles even further by using the Box–Cox power transformation that addresses issues with the third parameter of distribution – skewness (92). Also, whilst the multilevel modelling adjusts for the correlation within subjects, using the conditional reference intervals based on Royston's 1995 paper, further addresses the issue of bias and the possibility of unusual patterns arising from repeated measurements (89).

In 2018, Oros *et al* published a systematic review for reference ranges for the UA PI, the MCA PI and the CPR (93). Their search criteria included observational studies aimed at creating reference ranges of the UA PI, MCA PI and the CPR. They identified 2,902 studies of which 38 studies met their inclusion criteria, though their search period ended almost 2 years prior to publication. Their results determined that the studies of Medina Castro *et al*[2] (94), Parra-Cordero *et al* (88), and Arduini *et al* (82) were the highest scoring studies for ranges of the UA PI. Medina Castro *et al*[2] (95), Seffah *et al* (91) and Bahlman *et al* (83) were the highest scoring for the MCA PI. For the CPR they found Morales–Roselle *et al*, Ebbing *et al* (66) and Baschat (72) to be the highest scoring (93). Surprisingly there was no mention or reference to the methodology employed by the WHO for the Intergrowth–21st project which conducted comprehensive research into appropriate methodology for anthropometry. Furthermore, the studies that were identified having the highest score often had poorly described methodologies and in the case of Baschat inadequate sample size with more than half the gestational weeks having less than 15 subjects with the highest number being 25 at 20 weeks gestation (72).

Ciobanu *et al* recently published an article whose aim was to create reference ranges for the UA PI, the MCA PI and the CPR (96). They included all singleton pregnancies with no exclusion criteria and offered scans at 11+0 to 13+6 weeks and at 20+0 to 22+6 weeks. Another scan was then offered at 31+0 to 33+6 weeks between 2011 to 2014 but then change to between 35+0 to 36+6 for the study years 2014 to 2018. A final scan was offered between 41+0 to 41+6 weeks. Median and standard deviation models were fitted to all Doppler parameters. The authors state that the median was obtained by the use of regression analysis and polynomial forms obtained from plots of gestational age against daily medians. The standard deviation was derived from log transformations and then quadratic regression models fitted. Goodness of fit was assessed through q–q plots (96).

This haphazard approach to centile creation goes against what methodologists such as Altman, Royston and Cole have suggested for accurate centile creation (97-104). The authors chose to

[2] Studies published in Spanish and not reviewed in this thesis

measure the indices in gestational groups which not only goes against the most appropriate choice of using the smallest possible time period (ie: gestational age in days) but methodologically is a backwards step (104, 105). Blocking or only using grouped measures in centile creation leads to over–smoothing and less flexible models (105). It ignores the underlying changing distribution across time periods (101). In a time where additive models allow complex data transformations that correct all four parameters of distribution as well as multiple choices of polynomial and other smoothing parameters, these authors have chosen a poor study design and methodological approach.

1.4.2 Study Design for Reference Centile Creation

In the late 1980's and 1990's there were a series of papers written that identified issues in the study design and statistical analysis of data in relation to reference ranges and growth curves for fetal size (89, 97, 98, 102-109). Although there have been advancements in the development of statistical models to refine the accuracy of growth centiles, the principles outlined in those series of papers are still very much relevant and cited in current journal articles on Doppler and general fetal growth centiles (66, 81, 85, 110).

Cole describes a technique of deriving centile charts by providing a set of smoothed centiles that allows consideration of the changing skewness across time points (100). Referred to as the lambda–mu–sigma or LMS method, it involves splitting the outcome variable into a number of groups that is equivalent to the number of time points. Transformation of the data using varying Box–Cox transformations, that are able to use a different power estimation for each time point, results in estimates of generalised means, coefficients of variation and skewness (100). These can then be plotted against the independent variable that is the time points, creating smoothed curves for the mean, standard deviations and power (which provides information regarding the change in skewness). These in turn can be used to generate the smoothed centile curves that cover each time point (100). Whilst the benefit of Cole's LMS method is that it is able to summarise the distribution for each time point of the covariate, it does not adjust for kurtosis in the modelling (100, 111).

In the discussion of Cole's paper, Green identifies the complexity of fitting and smoothing as different stages and separate steps for each of the LMS curves (100, 111). Furthermore, issues surrounding grouping of the covariate, lead Cole and Green to utilise the penalized likelihood method to smooth the centiles (111). This process involves making the smoothing of the LMS curves part of the maximum likelihood and involving roughness penalties (111).

Royston, in 1991 wrote a "cookbook" for "constructing time–specific reference ranges" (102). He identifies that the mean and standard deviation varies when dealing with time–specific variables and must be included in any calculation of reference ranges. In this paper, Royston describes six steps in creating the ranges (102). Within these steps he outlines the importance of starting with a regression model and using a backwards regression method to identify the best fit of the regression model using low order polynomials. He advises to check the distribution of both the raw and residual data across three equal categories of the time dependant variable, transforming the data to adhere to the assumption of normality is essential for his method, and plotting the residuals to check the fit of the data. He suggests using either linear, quadratic or cubic polynomial curves and dealing with non–normal data with logarithmic or Box–Cox power transformations. Assessing the goodness–of–fit should be done using normal plots, Shapiro–Francia W tests and histograms of the residuals (102).

Following Royston's "cookbook", in 1993 Altman published an approach that deals with the varying standard deviation between individual time points (106). Royston's method deals with standard deviation changes when they are linear but it fails to cope with non–linear variation which is often observed between time points in measurements of fetal size. Altman primarily deals with this non–linear trend by assessing the distribution of the outcome variable (*y*) at each individual time point or gestational age (*x*). Under the assumption for the parametric method of creating a reference range, at each *x*, *y* has a normal distribution and subsequently, the residuals at each *x* should also have a normal distribution (106). However, Altman suggests that as the standard deviation varies between each gestational age, testing for normality of the residuals should be performed on the standardised residuals. Standardisation is performed by:

$$\frac{y_i - y_{pred}(x_i)}{s_{pred}\ (x_i)}$$

Where y_{pred} and s_{pred} are the estimated age–specific, mean and standard deviation of y, and y_i and x_i are the subsequent values of *y* and *x* for the i^{th} subject (106). By calculating the reference centiles on each gestational age and using standardised residuals to check for normality of the residuals (i.e. checking the goodness–of–fit of the model), this approach is a simple way to model parametric reference centiles with variation of the standard deviation (106).

Altman co–wrote a study and an opinion piece with Chitty in 1993 and 1994, outlining the methodology of fetal size charts and "design and analysis of studies to derive charts of fetal size" (97, 98). The opinion piece identified several design flaws that were constantly appearing in studies that presented standards of fetal size (97). The most common design flaws identified

were; inappropriate sample selection, unclear methodology surrounding the number of measurements per fetus, unreasonable inclusion/exclusion criteria, small sample sizes, unclear dating of pregnancies and being unclear if the measurements were single measurements or averages of several (97). It aimed to implement the suggestions from the opinion piece in a real world situation (98). This methodology paper, for cross–sectional data, outlined that the study design should be prospective and the sample should be unselected (98). Selection criteria should include only normal fetuses, excluding congenital abnormalities and maternal conditions such as diabetes or renal disease (97, 98). They also suggest including fetuses that die and to only make use of information available at the time of the examination (97, 98). The statistical methodology follows that of the previous 1993 Altman study; modelling the mean by fitting a polynomial regression model, calculating the residuals against gestational age, modelling the variability by using a polynomial regression to model the standard deviation as a function of gestational age, calculating the standard deviation scores and using them to assess goodness–of–fit, and finally obtaining the centiles (98, 106).

Cole's LMS method of centile creation failed to account for kurtosis in his modelling of centiles (100). Royston and Altman's approaches were parametric with the assumption of normal distribution, and while data transformation is an option, it also fails to correct for kurtotic data (102, 106). Cole and Green considered kurtosis a less important contributor to normality than skewness and that it would require fitting a fourth curve at a substantial cost for little benefit (100, 111). This may be the case in relation to a measurement of central tendency but not so when considering measurements of variability – an essential consideration in the creation of growth centiles (112).

Ignoring the effect of kurtosis on the distribution of the data and subsequent effects on the creation of centiles can lead to erroneous modelling and a distortion of the centiles (92). One of the issues previously faced when modelling kurtosis was the use the generalised linear model or generalised additive models where the dispersion parameters of variance, skewness and kurtosis are all modelled through their dependence on the mean and not in terms of the explanatory variable (113).

The World Health Organisation (WHO) devised the Intergrowth–21st project with the aim to develop international standards measuring fetal growth that is determined by ultrasound assessment and fundal height, preterm postnatal growth, newborn size and body composition, maternal weight gain, and 2nd year infant development (114). The authors make the distinction that reference ranges, or centiles, only describe the growth of a particular population during a

specific time and place. While growth standards are derived from a healthy population that are selected so that any constraints of environment, nutrition and health are minimalised and such that the standards report the growth that the fetus should experience. The study was able to develop the standards from more than 4,500 observations that were nested in 59,137 low–risk pregnancies. The populations where the pregnancies were identified had to be free–living with the number of constraints on growth kept to a minimum and also have favourable maternal and perinatal outcomes. The study was able to employ specialised staff that took ultrasound measures every 5 weeks, using standardised techniques on similar ultrasound machines. This amount of quality control as well as the avoidance of potential observer bias by blinding the measurements, enabled the study to ensure a uniform approach resulting in consistency of measurements (114). The robust methodology employed by the WHO to selected population that aims to reduce measurement bias, is an approach that is unrealistic to the vast majority of researchers due to geographical and financial restraints. The authors criticise population specific reference intervals as being "fallacious" due to variations in fetal growth across regions being dictated by their geographical location and that these artificial boundaries nullify within population heterogeneity (114). However, both methodologies are valid but use different approaches to devise different reference charts (115).

Professor Douglas Altman's involvement in the Intergrowth–21st project motivated him to revisit the methodology and study design of growth references and standards (115). Along with Ohuma, the paper discusses many of the recommendations outlined in Altman's previous papers on this subject (97, 98) but in more depth. The authors address the use of cross–sectional data for charts on fetal size and longitudinal data for charts on fetal growth (trajectories) and the choice of data depends on the use for which the charts are intended. They also emphasise the importance of appropriate populations and samples, and the subsequent ability to generalise to the general population for which the charts are intended (115). This point is expanded to discuss the descriptive verses prescriptive approaches to reference charts and the utility of both approaches. The descriptive approach refers to the construction of reference charts at a particular place and time from a given population. They often come from unselected populations with minimal exclusion criteria and while more common than the prescriptive approach the charts are restricted in their generalisability. Conversely, the prescriptive approach is the one used by the Intergrowth–21st project and its aim is derive size or growth standards from a highly selected optimal population (115). While the descriptive approach has greater generalisability and representativeness within the constructed (and similar) populations, the prescriptive approach

comes from more diverse populations which allows comparisons to be made across different populations, e.g. internationally (115).

Discussed within this paper also was the use of routinely collected data. Concerns were raised in regards to the accuracy, standardised collection and documentation as well as the completeness of routinely collected data. However, a study by Villar *et al* (116) showed excellent data quality of antenatal, maternal and neonatal anthropometry data collected in a large obstetric teaching hospital. They tested the agreement between data collected by hospital staff compared to data collected by a physician and social worker that were specifically trained and found the agreement between anthropometric measures to be excellent (115, 116).

There are four factors that Ohuma and Altman considered for appropriate statistical methodology for modelling anthropometry data. They recommend appropriate assessment of normality across gestational ages, accounting for the variability across gestational age by modelling both the mean and standard deviation, provide smooth curves across the centiles by gestational age and graphical goodness–of–fit assessment of the predicted model compared to the raw data (115).

Professor Tim Cole's 2012 paper discussed the progression of anthropometry charts for clinical use. In it he describes the evolution from Count Philibert de Montbeillard's measure of his son's height, to his own development of the LMS method and the more recent adaption and progression to the generalised additive model for location, scale and shape (GAMLSS) developed by Rigby and Stasinopoulos (101, 113). He describes the new methods and the study by Borghi *et al*, who, for the WHO Multicentre Growth Reference Study Group, compared 30 different methodologies for the creation of anthropometry charts and found that the GAMLSS method to be the most appropriate (99, 101).

The GAMLSS method is a semi–parametric univariable regression technique that requires a normal distribution of the response variable but has the flexibility to use non–parametric smoothing functions for the explanatory variable (92, 113, 117). It has the ability to cope with highly skewed and kurtotic data by replacing the exponential family distribution with a more general distribution family for the response variable (117). Using the Box–Cox power exponential distribution with this method, allows modelling of not only positive or negatively skewed data but also accounts for both leptokurtic and platykurtic data (117). This results in better fitting models and subsequently more accurate centile creation. Smoothing between the values of the explanatory variable can be performed using a number of techniques including, (but not restricted to); penalised basis splines, loess, fractional polynomials and cubic splines

(117). Assessment of different models can be done through assessment of the global deviances, generalised Akaike Information Criterion or the Schwartz Bayesian Criterion (117). However, the GAMLSS package offers a comprehensive array of model diagnostic tools, both graphical and quantitative which should be used as the final decision of the goodness–of–fit.

1.5 Thesis Aims and Objectives

1.5.1 Project Aim

Using the Mater Mothers' Hospitals perinatal data set, identify maternal and perinatal factors associated with adverse perinatal outcomes at term and to develop a model for identification of at–risk pregnancies.

The primary aim will be addressed through a number of objectives. The objectives need to investigate the appropriateness of using routinely collected data for research purposes. While epidemiologists often use surveillance data for research purposes, in general, routinely collected data has been avoided due to concerns regarding the integrity. This thesis, therefore, will assess the data integrity and generalisability of the Mater Mothers' Hospitals data through a comparison to Australian national data accessed from the Australian Institute of health and Welfare as well as a trend analysis from 2010 – 2016.

The thesis also aims to use ultrasound–based variables to enhance the accuracy of the prediction models and has dedicated three chapters to investigate the utility of the ultrasound measures of the EFW and the CPR. Initially it investigates whether the diagnostic predictability is enhanced when using both the CPR and EFW. Another chapter investigates whether the utility of the CPR as a predictive variable is enhanced if we measure the change in CPR over time. The final chapter investigating the ultrasound–based variables is dedicated to creating a new set of reference ranges for the UA PI, MCA PI and CPR. This was necessary as the existing reference ranges all suffered from poor methodology and in the case of the CPR, the ranges that have been described as using the most robust methodology we considered too high as 20% of our mothers had a CPR that was less than their 10^{th} centile (66, 93).

Finally, this thesis develops two separate predictive models to identify pregnancies at risk of emergency caesarean section for non–reassuring fetal status and a severe neonatal composite outcome.

1.5.1.1 Primary Objective

Develop two statistical models using the Mater Mothers' Hospitals perinatal data set, that enables clinicians to identify pregnancies that are at risk of emergency caesarean for non–reassuring fetal status and a serious composite neonatal outcome at term.

1.5.1.2 Secondary Objectives

1. Investigate the use of routinely collected data for the purpose of research.
2. Assess data integrity and generalisability of the Mater Mothers' Hospitals data.
3. Describe birth trends and adverse perinatal outcomes over a 6–year period (2010 – 2016) at the Mater Mothers' Hospitals, Brisbane.
4. Investigate the associations of the EFW and CPR and pregnancies that are at risk of emergency caesarean for non–reassuring fetal status and a serious composite neonatal outcome at term.
5. Investigate the relationship between the magnitude of change in CPR in the third trimester of pregnancy and the risk of adverse perinatal outcome.
6. Develop reference centiles for the ultrasound measurements of the UA PI, the MCA PI and the CPR using the GAMLSS approach.
7. Develop a model for the prediction of emergency caesarean section for non–reassuring fetal status at term utilising maternal and ultrasound–based variables.
8. Develop a model for the prediction of a severe neonatal composite outcome comprising of any of the following outcomes: severe acidosis (pH <7.0 or Lactate ≥6mmol/L or Base Excess ≤12), Apgar score at 5 minutes ≤3, admission to NICU or perinatal death, at term utilising maternal and ultrasound–based variables.

Chapter 2: Use of Routinely Collected Data: Birth Trends Between 2010 – 2016

2.1 Introduction

2.1.1 The Use of Routinely Collected Data for the Purpose of Research

Increasingly, hospitals are recognising the value of routinely collecting data that can be used for numerous reasons including health economic analysis, disease surveillance and biomedical research (118, 119). This has led to substantial increases in resources dedicated to the set–up and maintenance of clinical databases as well as the education for staff that collect this data. Pragmatic studies that analyse routinely collected data (RCD) can be an informative and cost–effective way to understand disease progression and the efficacy of treatments in real–world settings. However, studies using RCD can be subject to inherent bias and thus analysis of the data and interpretation of the results must be done with caution (118, 120).

Using RCD is a more pragmatic approach to research that allows assessment of data obtained from a real–world setting that does not interfere with usual care and therefore more accurately reflects clinical practice (121, 122). Research using RCD can be performed on appropriately targeted populations, with large samples over a long time period but at a low cost (123). Historically concerns regarding data integrity meant that studies using RCD tended to be avoided by the majority of clinical epidemiologists (123). While vast improvements have been made to promote accuracy in data collection it is necessary to understand the challenges associated with using RCD and evaluate the data's weakness to interpret the validity of the results.

The RCD cohort's data are collected in the clinical setting under routine conditions, therefore the studies can sacrifice some internal validity but often result in greater generalisability (124, 125). Several factors can influence the validity and generalisability of studies using RCD (119, 122).

A major threat to a study's validity and generalisability is the influence of confounding (122). Confounding can seriously affect the results of a study as fictitious associations between the outcome of interest and exposures may be observed (126). In an RCT, confounders are generally avoided by using randomisation in a highly selected cohort and controlled study environment (125, 127). The randomisation should ensure that any variables, both measured and not measured, that exhibit confounding effects on the outcome are distributed evenly between the

groups (127). In a pragmatic trial using RCD, known confounders can generally be adjusted for using statistical techniques such as multivariable regression or propensity score matching (118). The studies however, are still susceptible to bias through unknown (or unmeasured) confounders which can affect the internal validity of the results (122).

A cohort in an RCT is usually highly selected after being subjected to rigorous inclusion and exclusion criteria. The aim is to maximise the probability that an observed effect can be measured when a treatment is applied, but the study population and environment rarely has the complexity and diversity seen in real–world clinical situations (122, 124). Conversely, a cohort in a pragmatic study is targeted, with the aim to represent the population that the treatment would be applied to in a real–world situation (122). Whilst the later has been shown to often either overestimate or underestimate the effect, it is reflective of what the clinician would observe in routine clinical practice (122).

A benefit to pragmatic studies using RCD is the absence of the "Hawthorne effect". This occurs when a study subject is aware that they are participating in a trial. This knowledge may affect their behaviour, influencing the measurements and the subsequent relationship to the outcome (128-130). This effect can be extended to the trial care providers. Patient care of participants within trials usually exceeds that of usual care and the change in routine behaviour of both care giver and receiver can bias observations and measurements (130).

While routine data collection does not influence usual care or clinical practice, it is governed by the needs of clinical practice. As the primary purpose of the data collection is to support patient care it may lack the necessary detail required for comprehensive or detailed analysis (121). There may also be bias through measurement error due to more variability and missing data within RCD as it is collected by numerous people over a large time period and is often incorporated into the daily tasks of the care givers (118, 121).

The subsequent parts of this chapter will address the following objectives:

1. Assess data integrity and generalisability of the Mater Mothers' Hospitals data.
2. Describe birth trends and adverse perinatal outcomes over a 6–year period (2010 – 2016) at the Mater Mothers' Hospitals, Brisbane.

2.2 Data Sources, Integrity and Generalisability

2.2.1 Data Sources

2.2.1.1 National Australian Institute of Health and Welfare Data

National data was accessed from aggregations of yearly reports of the perinatal data visualisations from the National Perinatal Data Collection, published by the Australian Institute of Health and Welfare (AIHW) for the years 2010 – 2016 (131). The purpose of these data is to report an overview of the mothers and babies that birthed for the corresponding year within Australia. It includes maternal demographics, data from the antenatal period, during labour and birth and for the outcomes of the baby. It is collected for each state and territory within Australia and reported as totals as well as different disaggregation's according to various maternal factors and clinical or policy relevance (131, 132). Each year the data visualisations are published into a report on the key statistics from the AIHW's National Perinatal Data Collection which is a delayed released due to the time required to analyse the data and develop the report (132). All categories used for comparisons between AIHW data and Mater Mothers' Hospitals (MMH) data that are presented in this chapter were based off the data aggregations and categorisations of variables that were presented in the AIHW reports.

2.2.1.1 Mothers and Babies Research Database

The primary data set used throughout this thesis is a refined data set extracted and manipulated from the Mothers and Babies Research Database (MBRD) – a comprehensive Database developed by the Mater Research Institute-University of Queensland (MRI-UQ). The MBRD captures data from the mothers and babies that birthed at MMH in South Brisbane. It contains data from 1st January 1997 until 30th April 2017 which equates to 173,129 births and is an integrated database sourced from several separate entities. It captures routine collected data in relation to obstetric, neonatal and perinatal outcomes as well as some in relation to growth and development and diagnosis– related group (DRG) codes.

2.2.2 Databases that make up MBRD

2.2.2.1 Obstetric Data

The Obstetric Clinical Reporting System (CRS) was the database that was originally the basis for the MBRD. It captured routine obstetric data from 1st January 1997 until 30th April 2007. The Matrix obstetric database superseded CRS from 1st May 2007 until present. These two databases are the source of the vast majority of information held in the MBRD. Data is entered into Matrix by the midwives caring for each patient. Data integrity is checked by a Matrix data team who perform aggregated, by–yearly checks as well as individual random patient checks against patient notes.

2.2.2.2 Neonatal Data

Neonatal data for babies admitted to the Neonatal Critical Care Unit was originally captured in the neonatal intensive care units (NICUS) database which included data on all admissions (that were greater than 24 hours) to special care nursery (SCN) and intensive care nursery (ICN). The NICUS database was used from 1st January 1997 until 31st December 2009. A database known as BadgerNet was implemented to replace the NICUS database but due to multiple technical issues the system was abandoned. In response to the failure of BadgerNet, data regarding neonatal time in ICN and SCU was sourced from the Australian and New Zealand Neonatal Network (ANZNN). However, this only lasted from 1st January 2011 until 31st December 2012. As a result, information regarding treatments in ICN or SCN is limited to the period from 1st January 1997 until 31st December 2012.

Information in relation to perinatal mortality has been sourced from the Perinatal Mortality Database. The Perinatal Mortality Database is a purpose–built database collecting data regarding the date, type and classification of death as well as limited information in relation to whether an autopsy was performed.

2.2.3 Importing and Management of Data in the MBRD

Data were extracted from all sources as comma separated Microsoft excel files and then imported into the STATA statistical package for data merging or appending, cleaning and manipulation. A series of syntax files (“Do” files) created in STATA are run in a sequential order. These files are named and numbered to ensure that the process is systematic and can be easily replicated. Merging or appending files is done using the Maternal Unique Record Number (UR), Fetal UR, Fetal Date of Birth and Birth Order. This ensures that each record is unique.

Duplicated Maternal UR or Fetal UR are checked manually and adjusted accordingly. Once the MBRD is updated a series of STATA "Do" files are run that are designed to cross check variables and check for discrepancies. Further checks of the data's integrity are performed through checking all data fields of a random sample of entries and checked against the original data sources.

2.3 Data Integrity and Generalisability

2.3.1 MMH Study Dataset

Similar to many other data sets of routinely collected data over a substantial time period, there are inconsistencies and periods of missing data within MBRD. Whilst the obstetric and perinatal death data have been consistently collected in the MBRD since 1997, there are major inconsistencies in regard to neonatal data and maternal DRGs.

The data used for this thesis consists primarily of obstetric and perinatal mortality data, with only cause of death attributed to congenital abnormality sourced from ANZNN for 2011– 2012.

The MMH study dataset was collected over a 7 year and 4–month period extracted from the MBRD between the 1st January 2010 to 30th April 2017. Initial data integrity was assessed using a by year analysis and where data was missing, those years were excluded from any analysis including those variables. Where a number of years were missing, or data was of questionable integrity, with sudden drops in numbers that were not due to a change in treatment or policy, further investigation was undertaken in an attempt to understand the discrepancies. After accessing the source data and having discussions with the data custodians, midwives and nurses that had entered data into the databases, as well as the Data Management and Analysis team members from Mater Research, if the discrepancies could not be resolved those variables were excluded from the dataset. Due to the data being collected over an extended period of time as well as changes to the clinical database providing the data required, aggregations and manipulations were done to collapse several categorical variables into dichotomous outcomes. Efforts were made to correct missing or data entry errors through searches of patient records through both Verdi In–Patient Database and Matrix Obstetric Database. Verdi In–Patient Database is a database that captures in–patient information for all admissions to the Mater Adult Hospital and MMH. Where large amounts of data were missing and mainly only outcomes were recorded, missing entries were changed to indicate that the event did not happen. Again, this was

done after accessing the source data, having discussions with the data custodians, midwives and nurses that had entered data into the databases and Data Management and Analysis team members from Mater Research. Only then was it decided that it was reasonable to assume that when entries were incomplete it was because the event had not occurred.

2.3.2 Variable Descriptions

All births between 1st January 2010 and 31st December 2016 were included.

When required, all variables for this analysis were aggregated and/or categorised to reflect the collection and reporting methods that are presented in the data visualisations of the National Perinatal Data Collection (131).

Definitions of the variables investigated were as follows; insurance status were the proportion of mothers that were treated as a privately insured patient or a patient treated in the public health system with no private insurance. Maternal age was categorised into 5 yearly intervals <20 years, 20 – 24 years, 25 – 29 years, 30 – 34 years, 35 – 39 years and ≥40 years of age. Maternal body mass index (BMI) was categorised to reflect those categories reported in the National Perinatal Data Collection (131). The BMI categories are; underweight (BMI <18.5), normal (BMI 18.5 – 24.9), overweight (BMI 25.0 – 29.9), obese 1 (BMI 30.0 – 39.9), obese 2 (BMI 40.0 – 49.9) and obese 3 (BMI ≥50). Australian born was a dichotomous variable indicating whether the mother was born in Australia and Indigenous ethnicity was also a dichotomous variable that indicates if the mother identifies as Aboriginal and/or Torres Strait Islander ethnicity. Smoking reports the proportion of women who self–reported as smoking during pregnancy. Nulliparous is a dichotomous variable that reports whether this was the first pregnancy for each woman. Pre–existing diabetes include women that had diabetes mellitus before getting pregnant. Hypertension also includes women who had hypertension before getting pregnant. Labour is a three–level categorical variable that indicates whether the mother had a spontaneous labour, an induced labour or had no labour and went straight too caesarean section. Method of birth is also a three–level categorical variable of spontaneous vaginal delivery (SVD), instrumental delivery (forceps and/or vacuum deliveries) or caesarean section (either elective or emergency). Of the perinatal outcomes, the gender recorded was male, female and indeterminate gender. Gestational age at birth is a five–level categorical variable reported as; 20+0 – 27+6 weeks, 28+0 – 31+6 weeks, 32+0 – 36+6 weeks, 37+0 – 41+6 weeks and ≥42+0 weeks. Birth weight is also a five–level categorical variable of; <1,500 grams, 1,500 – 2,499 grams, 2,500 – 3,499 grams, 3,500 – 4,499 grams and >4,500 grams. Apgar score at 5 minutes is a categorical

variable with three levels (0 – 3, 4 – 6, 7 – 10). It is derived from an assessment out of 10 of the baby's health status at 5 minutes after birth, based on the heart rate, respiratory effort, muscle tone, reflex irritability and colour (133). The levels of the category reflect the severity of the baby's health with the category of 0 – 3 being severely ill and 7 – 10 reflecting the baby being in good to excellent condition. Neonatal intensive care unit (NICU) or special care nursery (SCN) admission is a dichotomous variable indicating if the babies was admitted to either level of higher–level care. Still born is a dichotomous variable of babies that are born without any signs of life after 24 weeks gestation. Neonatal death is also a dichotomous variable of babies that have died within the first 28 days of being born. Perinatal death is an aggregation of still born and neonatal death.

2.3.3 Statistical Analysis

2.3.3.1 Comparison of MMH to AIHW Data

Data were reported as percentage and number. Due to the large numbers and the purpose of this table being for descriptive purposes only, no hypothesis tested using formal statistical testing was performed. The large numbers mean that trivially small effects would be found to be significantly different if decided using P values (132), therefore significance was interpreted on differences that were deemed to be clinically meaningful.

2.3.3.2 Trend Analysis

Variables are all categorical and as such are reported as percentage (n/N). Tests for trends in both the MMH and AIHW data were assessed using Patrick Royston's User written Stata command – ptrend (134). This command enables the calculation of a chi–square statistic for the regressions or trend of the proportion variables of interest on the year of delivery (134). Due to the large sample size, interpretation will be done with caution with clinical relevance taken into consideration.

2.4 Results

2.4.1 Comparison of AIHW and MMH Data

2.4.1.1 Maternal Demographics

The comparison of the maternal demographics of the AIHW cohort and the MMH cohort are as follows (Table 2.1):

- Insurance Status – There was a greater proportion of public patients in the AIHW data (72.6%) compared to MMH (56.0%).
- Maternal Age –
    - There was a higher proportion of women aged less than 20 years and 20 – 24 years in the AIHW cohort (3.2% & 13.2%) compared to MMH (1.6% and 8.5%).
    - The proportion of women aged 25 – 29 was also higher in the AIHW cohort (27.5%) compared to the MMH cohort (23.3%).
    - Women aged 30 – 34 years were the highest representative age group for both the MMH cohort (37.6%) and the AIHW cohort (33.5%).
    - MMH had 23.1% of women aged 35 – 39, while 18.3% of mothers were the same age in the AIHW cohort.
    - The oldest age group of 40+ years had the highest proportion of women in the MMH cohort (5.9%), with 4.3% of women aged 40+ in the AIHW cohort.
- BMI Categories –
    - There were substantially more underweight women in the MMH cohort with 7.0% of women found to be underweight compared to 3.6% in the AIHW cohort.
    - Of women in the MMH cohort, 59.7% had a normal BMI, while 45.8% of the National AIHW cohort were within the normal BMI range.
    - There was a higher proportion of overweight women found in the AIHW cohort (23.9%) compared to the MMH cohort (19.6%).
    - The AIHW cohort had higher percentages in all three obese categories (15.8%, 2.5% & 0.3%) compared to the MMH (10.9%, 1.7% & 0.2%).
- Australian Born – A higher proportion of women in the AIHW cohort were born in Australia (68.3%) compared to the MMH cohort (62.0%).
- Indigenous Ethnicity – There was a higher proportion of Indigenous women recorded in the AIHW cohort (4.1%) with comparably less recorded in the MMH cohort (1.9%).

- Smoking Status – 14.2% of women within the MMH cohort reported smoking during pregnancy, while 11.5% were reported in the AIHW cohort.
- Nulliparity – There were more nulliparous women in the MMH cohort with 46.6% women never given birth compared to the AIHW cohort of 43.0%.
- Pre–existing Diabetes – there was little difference in the proportion of women who had pre–existing diabetes between the MMH (0.7%) and AIHW cohorts (0.8%).
- Hypertension – there no difference in the proportion of women who had hypertension between the MMH (0.8%) and AIHW cohorts (0.8%).
- Induction of Labour –
    - There was little difference in the number of women having an induction of labour between the MMH cohort and the AIHW cohort (28.4% & 27.5% respectively).
    - There was however, a higher percentage of women that had no labour and went straight to caesarean section within the MMH cohort (25.2%) compared to the AIHW cohort (20.3%).
- Method of Birth –
    - The most prolific method of birth was spontaneous vaginal births for both cohorts with 54.4% in the AIHW cohort and 49.7% at the MMH.
    - The was no difference in the proportion of instrumental deliveries between the AIHW and MMH (12.3% vs 12.7% respectively).
    - The second most common method of birth was via caesarean section with 33.3% of women having a caesarean in the AIHW cohort and 37.6% within the MMH cohort.

Table 2-1: Maternal demographics of women who birthed at Mater Mothers' Hospitals compared to national data from the Australian Institute of Health and Welfare (131).

Maternal Demographics	**AIHW (2010 – 2016)**		**Mater Mothers' Hospitals (2010 – 2016)**	
Insurance Status				
Public	72.6%	1,561,142/2,151,656	56.0%	39,134/69,851
Private	27.4%	590,514/2,151,656	44.0%	30,717/69,851
Maternal Age Category				
<20	3.2%	69,070/2,160,229	1.6%	1,148/69,851
20 – 24	13.2%	284,728/2,160,229	8.5%	5,956/69,851
25 – 29	27.5%	593,721/2,160,229	23.3%	16,252/69,851
30 – 34	33.5%	723,374/2,160,229	37.6%	26,244/69,851
35 – 39	18.3%	395,620/2,160,229	23.1%	16,155/69,851
40+	4.3%	93,286/2,160,229	5.9%	4,096/69,851
BMI Category				
Underweight (<18.5)	3.6%	48,384/1,334,187	7.0%	4,889/69,851
Normal (18.5 – 24.9)	45.8%	611,396/1,334,187	59.7%	41,713/69,851
Overweight (25.0 – 29.9)	23.9%	319,324/1,334,187	19.6%	13,704/69,851
Obese 1 (30.0 – 39.9)	15.8%	210,488/1,334,187	10.9%	7,629/69,851
Obese 2 (40.0 – 49.9)	2.5%	33,173/1,334,187	1.7%	1,191/69,851
Obese 3 (≥50)	0.3%	3,547/1,334,187	0.2%	142/69,851
Australian Born	68.3%	1,474,460/2,160,229	62.0%	43,274/69,851
Indigenous Ethnicity	4.1%	88,456/2,160,229	1.9%	1,337/69,851
Smoking	11.5%	249,387/2,160,229	14.2%	9,897/69,851
Nulliparous	43.0%	913,992/2,127,503	46.7%	32,637/69,851
Pre–existing Diabetes	0.8%	12,913/1,551,302	0.7%	494/69,851
Pre–existing Hypertension	0.8%	12,799/1,551,302	0.9%	612/69,851
Labour				
Spontaneous	52.1%	1,125,433/2,160,229	46.4%	32,421/69,851
Induced	27.5%	595,135/2,160,229	28.4%	19,856/69,851
No Labour – CS Performed	20.3%	439,109/2,160,229	25.2%	17,570/69,851
Method of Birth				
SVD	54.4%	1,174,720/2,160,229	49.7%	34,725/69,851
Instrumental	12.3%	265,349/2,160,229	12.7%	8,835/69,851
Caesarean Section	33.3%	719,866/2,160,229	37.6%	26,290/69,851

BMI: Body Mass Index; AIHW: Australian Institute of Health and Welfare; CS: Caesarean Section; SVD: Spontaneous Vaginal Delivery.
For the AIHW cohort, BMI Categories exclude 2010 data, Birth Weight Categories excludes 2010 data & New South Wales data was not available in 2014 so was also excluded.

2.4.1.2 Perinatal Outcomes

The comparison of the perinatal outcomes of the AIHW cohort and the MMH cohort are as follows (Table 2.2):

- Gender – There was no difference in the distribution of genders between the two cohorts.
- Gestational Age Categories –
    - There was a higher proportion of babies born between 20 – 27 weeks gestation in the MMH cohort, 1.3% compared to 0.9% in the AIHW cohort.
    - For the gestational age between 28 – 31 weeks there was a higher proportion in the MMH cohort compared to the AIHW cohort.
    - There was a higher proportion of babies born between 32 – 36 weeks gestation in the MMH cohort, 8.6% compared to 6.8% in the AIHW cohort.
    - For both cohorts the vast majority of babies were born at term between 37 – 41 weeks gestation – 90.9% AIHW cohort and 87.9% at MMH.
    - There was a slightly higher proportion of late term births in the AIHW cohort (0.6% v 0.4%).
- Birth Weight Categories –
    - MMH had higher proportion of underweight babies with 2.8% of those born <1,500 grams compared to 1.5% AIHW.
    - MMH had 6.8% born between 1,500 – 2,499 grams compared to 5.4% for the AIHW cohort.
    - The majority of babies had a BW between 2,500 grams and 3,499 grams with little difference between the two cohorts (52.0% AIHW v 51.8% MMH).
    - The second highest proportion of babies were born within the 3,500 – 4,499 gram weight range, with 39.5% in the AIHW cohort and 37.3% in the MMH cohort.
    - There was no difference in the proportion of babies born >4,500 grams 1.5% within the AIHW cohort and 1.3% at MMH.
- Apgar Score at 5 Minutes categories –
    - There was little difference in the very low Apgar scores of 0 – 3 between MMH (0.5%) and the AIHW cohort (0.5%).
    - Little difference was also found in the low Apgar score of between 4 – 6 with 1.4% in the AIHW cohort and 1.5% in the MMH cohort.
- NICU/SCN Admission – There was no difference in proportion of babies admitted to the NICU/SCU at MMH (15.7%) and the AIHW cohort (15.7%).

- Stillbirth, Neonatal and Perinatal Death –
    - There was no difference in the recorded proportions of stillbirths between MMH (0.7%) and AIHW (0.7%).
    - There was a higher proportion of neonatal deaths at MMH (0.6%) compared to AIHW (0.3%)
    - There was a higher proportion of perinatal deaths reported within the MMH cohort (1.3%) compared to the AIHW cohort (1.0%).

Table 2-2: Perinatal outcomes of babies born at Mater Mothers' Hospitals compared to data from the Australian Institute of Health and Welfare (131).

Perinatal Outcomes	**AIHW (2010 – 2016)**		**Mater Mothers Hospital (2010 – 2016)**	
Gender				
Male	51.4%	1,109,728/2,160,229	51.3%	35,817/69,851
Female	48.6%	1,049,461/2,160,229	48.7%	34,019/69,851
Indeterminate	0.05%	1,040/2,160,229	0.02%	15/69,851
Gestational Age Categories				
20 – 27 weeks	0.9%	18,762/2,160,229	1.3%	937/69,851
28 – 31 weeks	0.8%	16,805/2,160,229	1.9%	1,293/69,851
32 – 36 weeks	6.8%	147,852/2,160,229	8.6%	5,978/69,851
37 – 41 weeks	90.9%	1,963,529/2,160,229	87.9%	61,371/69,851
≥42 weeks	0.6%	12,447/2,160,229	0.4%	261/69,851
Birth Weight Categories				
<1,500 grams	1.5%	32,227/2,160,229	2.8%	1,965/69,851
1,500 – 2,499	5.4%	116,410/2,160,229	6.8%	4,726/69,851
2,500 – 3,499	52.0%	1,123,615/2,160,229	51.8%	36,199/69,851
3,500 – 4,499	39.5%	853,269/2,160,229	37.3%	26,020/69,851
≥4,500	1.5%	33,248/2,160,229	1.3%	934/69,851
Apgar Score at 5 Minutes				
0 – 3	0.3%	7,210/2,144,781	0.5%	313/69,851
4 – 6	1.4%	30,842/2,144,781	1.5%	1,057/69,851
7 – 10	98.0%	2,102,722/2,144,781	96.8%	67,647/69,851
NICU/SCN Admission	15.7%	298,366/1,903,056	15.7%	10,944/69,851
Stillborn	0.7%	15,344/2,160,229	0.7%	495/69,851
Neonatal Death	0.3%	5,481/2,160,229	0.6%	382/69,851
Perinatal Death	1.0%	20,825/2,160,229	1.3%	877/69,851

*NICU: Neonatal Intensive Care Unit; SCU: Special Care Unit

2.4.2 Trend Analysis

The trend analysis for the AIHW cohort and the MMH cohort between 2010 and 2016 are as follows (Table 2.3):

- Maternal Age –
    - There was a trend of decreasing proportions of young mothers <20 years of age for both the AIHW and MMH cohorts.
    - For the maternal age of 20 – 24 there was also a trend of reducing proportions of births within this age category for both the AIHW and MMH cohorts.
    - The trends of decreased proportions were also in the age category of 25 – 29, though it was more pronounced in the MMH cohort, and the trend in the AIHW cohort is unlikely to be clinically significant.
    - In the 30 – 34 age category there was an increasing trend for births in both AIHW and MMH cohorts.
    - There was a decreasing trend in the proportion of births for women aged between 35 – 39 years in both the AIHW and MMH cohorts, though the trend in the AIHW cohort is unlikely to be clinically significant.
    - For the cohort of women aged 40+ years there was an increasing trend in the proportion of births for both the AIHW and MMH cohorts, though again the trend in the AIHW cohort is unlikely to be clinically significant.
- Maternal BMI –
    - There was a slight increase in the in the proportion of underweight women in the AIHW cohort, though this is unlikely to be clinically significant. While there was no change found in the MMH cohort.
    - There was an increase in the proportion of women who were classified as being in the normal BMI category for both the AIHW and MMH cohorts, though the trend in the MMH cohort is unlikely to be clinically significant.
    - There was an increase in the proportion of women classified as being overweight in the AIHW cohort while the MMH cohort had no difference.
    - The obese 1, obese 2 and obese 3 categories all had increases in the proportions of women for the AIHW cohort, though this is unlikely to be clinically significant. There was no difference in the MMH cohort for all obesity categories.

- Australian Born – The proportion of Australian born women giving birth had a decreasing trend for both cohorts.
- Indigenous Ethnicity – there was a trend of increasing proportion of Indigenous women giving birth in both the AIHW and MMH cohorts.
- Smoking Status – There was decreasing trend in women who reported smoking during pregnancy, however this was much more pronounced in the MMH cohort.
- Nulliparity – There was an increasing trend in the proportion of nulliparous women in the AIHW cohort, though this trend is unlikely to be clinically significant. There was no difference detected in the MMH cohort.
- Pre–existing Diabetes – There was an increasing trend in the proportion of women with pre–existing diabetes in the AIHW cohort. The MMH cohort had a decreasing trend in the proportion of pre–existing diabetes, though this is unlikely to be clinically significant.
- Pre–existing Hypertension – There was no difference in the proportion of hypertensive women in the MMH cohort or AIHW cohort.
- Induction of Labour –
    - There were decreasing trends in both the AIHW and MMH cohorts for women who had spontaneous births.
    - Increases in the proportion of labours that were induced were seen in the MMH and AIHW cohorts.
    - There was an increase in the proportion of women that had no labour and went straight to caesarean section for the AIHW cohort, while the MMH cohort had a decrease in the proportion of women that went straight to caesarean section.
- Method of Birth –
    - There was a slight decrease in the proportion of spontaneous vaginal delivery in the AIHW cohort but a slight increase in the MMH cohort.
    - There was an increase in the proportion of instrumental deliveries for both cohorts, though these are unlikely to be clinically significant.
    - There was an increase in the proportion of caesarean section deliveries in the AIHW cohort, while the MMH cohort had a decreasing trend.

- Gestational Age at Birth –
    - The proportion of extremely preterm births (20 – 27 weeks gestation) remained consistent in both cohorts.
    - For the gestational age of 28 – 31 weeks, both the AIHW and MMH cohorts had a decreasing trend, though this is unlikely to be significant in the AIHW cohort.
    - For the gestational age of 32 – 36 weeks the AIHW cohort had an increasing trend, though again this is unlikely to be clinically significant, while the MMH cohort had no difference.
    - There was no difference in the proportion of term babies (37 – 41 weeks gestation) born in the AIHW cohort and an increase in the proportion of term babies born in the MMH cohort, though this is unlikely to be clinically significant.
    - There was no difference in the proportion of post term (+41 weeks gestation) babies born in the MMH cohort and a decreasing trend of in the AIHW cohort, though this is unlikely to be clinically significant.
- Birth Weight –
    - There was a decreasing trend in babies born <1,500 grams in both the AIHW and MMH cohorts, though this is unlikely to be clinically significant in the AIHW cohort.
    - For babies born between 1,500 – 2,499 grams there was an increasing trend for the AIHW cohort, but again this is unlikely to be clinically significant, while there was no difference in the proportions for the MMH cohort.
    - There was an increase in the proportion of babies born with a BW between 2,500 – 3,499 for both the AIHW and MMH cohorts.
    - There was a decreasing trend of babies born with BWs between 3,500 – 4,499 in both the AIHW and MMH cohorts.
    - There was a decrease in the proportion of babies born with a BW of ≥4,500 for both the AIHW and MMH cohorts.

- Apgar Score at 5 Minutes –
    - There was no difference in the proportion of babies born with very low Apgar scores at 5 minutes (Apgar@ 5 minutes 0 – 3) in both the AIHW and MMH cohorts.
    - There was an increase in the proportion of babies born with a low Apgar score at 5 minutes (Apgar@ 5 minutes 4 – 6) for both the AIHW and MMH cohorts.
    - There was a decrease in the trend of babies born with Apgar scores between 7 – 10 at 5 minutes for both cohorts, though this is unlikely to be clinically significant.
- NICU/SCN Admission – There was an increasing trend for NICU/SCN admissions in the AIHW cohort but no difference in the MMH cohort.
- Stillbirths – There was no difference in the percentage of stillbirths in the MMH cohort and an increasing trend in the AIHW cohort, though this is unlikely to be clinically significant.
- Neonatal Deaths – There was a decreasing trend in the proportion of neonatal deaths for both the MMH and AIHW cohorts.
- Perinatal Death – There was a decreasing trend in the proportion of overall perinatal deaths in both the MMH and AIHW cohorts, though these are unlikely to be clinically significant.

Table 2-3: Trend analysis for Mater Mothers' Hospitals and Australian Institute of Health and Welfare from 2010 – 2016 (131).

Year of Delivery		**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**P Value**
Maternal Age Category									
<20	AIHW	3.8% (11,455/300,215)	3.7% (11,106/302,025)	3.6% (11,135/312,251)	3.3% (10,263/309,489)	3.0% (9,394/312,548)	2.7% (8,268/308,887)	2.4% (7,449/314,814)	<0.001
	Mater	2.6% (252/9,563)	2.4% (223/9,496)	1.7% (169/10,189)	1.3% (132/10,095)	1.3% (132/9,943)	1.3% (135/10,427)	1.0% (105/10,138)	<0.001
20 – 24	AIHW	14.1% (42,283/300,215)	13.8% (41,536/302,025)	13.5% (42,264/312,251)	13.4% (41,621/309,489)	12.9% (40,330/312,548)	12.6% (38,893/308,887)	12.0% (37,801/314,814)	<0.001
	Mater	10.3% (988/9,563)	9.4% (891/9,496)	8.4% (854/10,189)	7.9% (799/10,095)	7.9% (781/9,943)	7.8% (815/10,427)	8.2% (828/10,138)	<0.001
25 – 29	AIHW	27.5% (82,577/300,215)	27.9% (84,276/302,025)	27.8% (86,705/312,251)	27.5% (85,051/309,489)	27.6% (86,401/312,548)	27.2% (83,959/308,887)	26.9% (84,752/314,814)	<0.001
	Mater	25.1% (2,400/9,563)	24.7% (2,348/9,496)	23.8% (2,424/10,189)	23.1% (2,335/10,095)	22.5% (2,237/9,943)	22.3% (2,329/10,427)	21.5% (2,179/10,138)	<0.001
30 – 34	AIHW	31.4% (94,340/300,215)	31.8% (96,192/302,025)	32.5% (101,618/312,251)	33.4% (103,242/309,489)	34.2% (106,991/312,548)	35.1% (108,400/308,887)	35.8% (112,591/314,814)	<0.001
	Mater	35.2% (3,363/9,563)	35.9% (3,410/9,496)	36.5% (3,716/10,189)	38.3% (3,869/10,095)	38.6% (3,842/9,943)	39.0% (4,070/10,427)	39.2% (3,974/10,138)	<0.001
35 – 39	AIHW	19.0% (57,095/300,215)	18.4% (55,680/302,025)	18.2% (56,807/312,251)	17.9% (55,512/309,489)	17.9% (55,927/312,548)	18.2% (56,080/308,887)	18.6% (58,519/314,814)	<0.001
	Mater	22.0% (2,103/9,563)	22.5% (2,137/9,496)	23.3% (2,376/10,189)	23.2% (2,339/10,095)	23.2% (2,303/9,943)	23.5% (2,449/10,427)	24.2% (2,448/10,138)	<0.001
40+	AIHW	4.1% (12,369/300,215)	4.3% (13,118/302,025)	4.4% (13,655/312,251)	4.4% (13,738/309,489)	4.3% (13,482/312,548)	4.3% (13,265/308,887)	4.3% (13,659/314,814)	0.01
	Mater	4.8% (457/9,563)	5.1% (487/9,496)	6.4% (650/10,189)	6.2% (621/10,095)	6.5% (648/9,943)	6.0% (629/10,427)	6.0% (604/10,138)	<0.001
BMI Category									
Underweight (<18.5)	AIHW	Not Recorded	3.1% (5,945/192,066)	3.4% (7,084/205,449)	3.5% (7,156/205,224)	3.8% (8,054/211,921)	3.8% (7,933/209,280)	3.9% (12,212/310,247)	<0.001
	Mater	7.2% (673/9,345)	6.9% (651/9,430)	7.1% (715/10,107)	7.2% (722/10,007)	7.4% (737/9,911)	6.9% (717/10,379)	6.7% (674/10,089)	0.37
Normal (18.5 – 24.9)	AIHW	Not Recorded	37.9% (72,782/192,066)	44.6% (91,627/205,449)	45.8% (93,945/205,224)	47.1% (99,715/211,921)	48.4% (101,305/209,280)	49.0% (152/022/310,247)	<0.001
	Mater	59.3% (5,539/9,345)	59.4% (5,602/9,430)	60.1% (6,072/10,107)	60.9% (6,097/10,007)	60.8% (6,025/9,911)	60.4% (6,270/10,379)	60.5% (6,108/10,089)	0.01
Overweight (25.0 – 29.9)	AIHW	Not Recorded	21.1% (40,591/192,066)	24.0% (49,390/205,449)	24.2% (49,649/205,224)	24.2% (51,332/211,921)	25.0% (52,343/209,280)	24.5% (76,019/310,247)	<0.001
	Mater	20.2% (1,884/9,345)	20.5% (1,933/9,430)	19.9% (2,015/10,107)	19.7% (1,975/10,007)	19.0% (1,886/9,911)	19.4% (2,016/10,379)	19.8% (1,995/10,089)	0.05

Obese 1 (30.0 – 39.9)	AIHW	Not Recorded	14.0% (26,933/192,066)	16.1% (33,018/205,449)	16.0% (32,774/205,224)	16.1% (34,041/211,921)	16.3% (34,129/209,280)	16.0% (49,593/310,247)	<0.001
	Mater	11.3% (1,054/9,345)	11.3% (1,069/9,430)	11.0% (1,109/10,107)	10.5% (1,046/10,007)	10.8% (1,067/9,911)	11.3% (1,174/10,379)	11.0% (1,110/10,089)	0.55
Obese 2 (40.0 – 49.9)	AIHW	Not Recorded	2.2% (4,267/192,066)	2.5% (5,079/205,449)	2.5% (5,067/205,224)	2.5% (5,305/211,921)	2.6% (5,511/209,280)	2.6% (7,944/310,247)	<0.001
	Mater	1.8% (171/9,345)	1.7% (160/9,430)	1.7% (175/10,107)	1.5% (149/10,007)	1.8% (177/9,911)	1.7% (181/10,379)	1.8% (178/10,089)	0.97
Obese 3 (≥50)	AIHW	Not Recorded	0.2% (456/192,066)	0.2% (512/205,449)	0.3% (530/205,224)	0.3% (605/211,921)	0.3% (626/209,280)	0.3% (818/310,247)	0.004
	Mater	0.3% (24/9,345)	0.2% (15/9,430)	0.2% (21/10,107)	0.2% (18/10,007)	0.2% (19/9,911)	0.2% (21/10,379)	0.2% (24/10,089)	0.93
Australian Born	AIHW	71.4% (214,457/300,215)	70.5% (212,860/302,025)	68.9% (215,009/312,251)	68.5% (211,905/309,489)	66.9% (209,188/312,548)	66.6% (205,817/308,887)	65.2% (205,224/314,814)	<0.001
	Mater	66.6% (6364/9,563)	67.3% (6,387/9,496)	61.7% (6,286/10,185)	62.2% (6,274/10,089)	59.3% (5,893/9,939)	59.4% (6,187/10,414)	58.1% (5,883/10,124)	<0.001
Indigenous Ethnicity	AIHW	3.9% (11,633/300,215)	3.9% (11,897/302,025)	4.0% (12,454/312,251)	4.1% (12,541/30,489)	4.2% (12,978/312,548)	4.3% (13,204/308,887)	4.4% (13,749/314,814)	<0.001
	Mater	1.9% (179/9,563)	1.8% (174/9,496)	1.7% (173/10,189)	1.7% (174/10,095)	1.9% (185/9,943)	2.0% (211/10,427)	2.4% (241/10,138)	0.004
Smoking	AIHW	13.5% (40,455/300,215)	13.0% (39,300/302,025)	12.2% (38,220/312,251)	11.5% (35,446/309,489)	10.8% (33,767/312,548)	10.3% (31,674/308,887)	9.7% (30,525/314,814)	<0.001
	Mater	23.0% (2,200/9,563)	22.5% (2,132/9,496)	18.3% (1,864/10,189)	10.6% (1,071/10,095)	9.9% (986/9,943)	8.3% (864/10,427)	7.7% (780/10,138)	<0.001
Nulliparous	AIHW	42.5% (125,568/295,456)	43.0% (127,815/297,343)	42.5% (130,566/307,569)	43.6% (132,797/304,776)	43.5% (133,867/307,844)	42.9% (130,537/304,268)	42.8% (132,842/310,247)	<0.001
	Mater	46.8% (4,468/9,558)	47.1% (4,468/9,496)	46.6% (4,750/10,187)	47.3% (4,766/10,085)	47.0% (4,676/9,942)	46.5% (4,849/10,420)	46.0% (4,660/10,129)	0.28
Pre–existing Diabetes	AIHW	0.7% (1,469/216,177)	0.7% (1,530/224,404)	0.7% (1,610/230,400)	1.0% (1,890/193,727)	1.0% (2,296/229,923)	1.1% (2,428/226,134)	0.7% (1,690/230,537)	<0.001
	Mater	0.7% (66/9,563)	0.8% (79/9,496)	0.8% (83/10,189)	0.8% (82/10,095)	0.8% (79/9,943)	0.5% (47/10,427)	0.6% (58/10,138)	0.01
Pre–existing Hypertension	AIHW	0.8% (1,819/300,215)	0.9% (1,966/224,404)	0.8% (1,923/230,400)	0.8% (1,460/193,727)	0.8% (1,898/229,923)	0.8% (1,840/226,134)	0.8% (1,893/230,537)	0.06
	Mater	0.8% (80/9,563)	1.1% (100/9,496)	0.9% (93/10,189)	0.9% (90/10,095)	0.8% (81/9,943)	0.9% (90/10,427)	0.8% (78/10,138)	0.17
Labour									
Spontaneous	AIHW	55.6% (166,910/300,215)	54.4% (164,417/302,025)	53.8% (168,050/312,251)	52.3% (161,840/309,489)	50.9% (159,039/312,548)	49.8% (153,705/308,887)	48.1% (151,472/314,814)	<0.001
	Mater	50.4% (4,822/9,563)	47.4% (4,502/9,495)	47.9% (4,884/10,189)	46.2% (4,662/10,093)	46.2% (4,595/9,943)	44.3% (4,616/10,427)	42.8% (4,340/10,137)	<0.001
Induced	AIHW	25.1% (75,460/300,215)	25.9% (78,314/302,025)	26.3% (81,982/312,251)	27.5% (85,079/309,489)	28.3% (88,425/312,548)	29.2% (90,297/308,887)	30.4% (95,578/314,814)	<0.001

	Mater	24.3% (2,320/9,563)	25.8% (2,447/9,495)	26.2% (2,669/10,189)	28.0% (2,829/10,093)	29.0% (2,885/9,943)	32.4% (3,382/10,427)	32.8% (3,324/10,137)	<0.001
No Labour – CS Performed	AIHW	19.3% (57,798/300,215)	19.6% (59,212/302,025)	19.9% (62,131/312,251)	20.2% (62,501/309,489)	20.8% (65,033/312,548)	21.0% (64,857/308,887)	21.5% (67,577/314,814)	<0.001
	Mater	25.3% (2,421/9,563)	26.8% (2,546/9,495)	25.9% (2,636/10,189)	25.8% (2,602/10,093)	24.8% (2,463/9,943)	23.3% (2,429/10,427)	24.4% (2,473/10,137)	<0.001
Method of Birth									
SVD	AIHW	55.8% (167,517/300,215)	55.1% (166,429/302,025)	54.8% (171,021/312,251)	54.3% (168,157/309,489)	54.0% (168,680/312,548)	53.8% (166,073/308,887)	53.0% (166,843/314,814)	<0.001
	Mater	48.8% (4,664/9,563)	48.7% (4,624/9,496)	49.7% (5,066/10,189)	50.0% (5,046/10,095)	50.1% (4,979/9,943)	50.5% (5,263/10,427)	50.1% (5,083/10,137)	0.003
Instrumental	AIHW	11.9% (35,833/300,215)	12.0% (36,286/302,205)	12.3% (38,425/312,251)	12.3% (38,080/309,489)	12.4% (38,692/312/548)	12.4% (38,201/308,887)	12.7% (39,832/314,814)	<0.001
	Mater	12.5% (1,197/9,563)	11.6% (1,104/9,496)	11.9% (1,214/10,189)	12.3% (1,245/10,095)	13.3% (1,325/9,943)	13.5% (1,402/10,427)	13.3% (1,348/10,137)	<0.001
Caesarean Section	AIHW	32.2% (96,794/300,215)	32.9% (99,246/302,025)	32.9% (102,782/312,251)	33.3% (103,191/309,489)	33.6% (105,154/312,548)	33.9% (104,604/308,887)	34.3% (108,095/314,814)	<0.001
	Mater	38.7% (3,702/9,563)	39.7% (3,768/9,496)	38.4% (3,909/10,189)	37.7% (3,804/10,095)	36.6% (3,639/9,943)	36.1% (3,762/10,427)	36.6% (3,706/10,137)	<0.001
Gestational Age									
20 – 27 weeks	AIHW	0.8% (2,446/295,456)	0.8% (2,497/297,343)	0.8% (2,413/307,570)	0.8% (2,499/304,777)	0.8% (2,401/307,844)	0.8% (2,418/304,268)	0.8% (2,542/310,247)	0.17
	Mater	1.4% (134/9,563)	1.5% (141/9,495)	1.3% (131/10,186)	1.3% (131/10,093)	1.4% (138/9,943)	1.2% (124/10,426)	1.4% (138/10,134)	0.32
28 – 31 weeks	AIHW	0.7% (2,057/295,456)	0.7% (2,012/297,343)	0.7% (2,110/307,570)	0.7% (2,061/304,777)	0.7% (2,110/307,844)	0.7% (2,040/304,268)	0.6% (1,987/310,247)	0.02
	Mater	2.4% (227/9,563)	2.1% (199/9,495)	2.1% (218/10,186)	1.9% (192/10,093)	1.7% (167/9,943)	1.4% (149/10,426)	1.4% (141/10,134)	<0.001
32 – 36 weeks	AIHW	5.9% (17,543/295,456)	6.0% (17,878/297,343)	6.2% (19,131/307,570)	6.2% (18,931/304,777)	6.3% (19,305/307,844)	6.4% (19,370/304,268)	6.2% (19,297/310,247)	<0.001
	Mater	8.5% (808/9,563)	9.2% (871/9,495)	9.0% (912/10,186)	8.5% (858/10,093)	8.4% (831/9,943)	8.1% (848/10,426)	8.4% (850/10,134)	0.05
37 – 41 weeks	AIHW	91.7% (270,986/295,456)	91.7% (272,776/297,343)	91.7% (281,970/307,507)	91.8% (279,634/304,777)	91.7% (282,313/307,844)	91.8% (279,167/304,268)	91.7% (284,395/310,247)	0.70
	Mater	87.5% (8,371/9,563)	86.9% (8,252/9,495)	87.1% (8,872/10,186)	87.9% (8,876/10,093)	88.2% (8,766/9,943)	88.9% (9,263/10,426)	88.5% (8,971/10,134)	<0.001
≥42 weeks	AIHW	0.8% (2,358/295,456)	0.7% (2,088/297,343)	0.6% (1,891/307,570)	0.5% (1,608/304,777)	0.5% (1,501/307,844)	0.4% (1,216/304,268)	0.6% (1,782/310,247)	<0.001
	Mater	0.2% (23/9,563)	0.3% (32/9,495)	0.5% (53/10,186)	0.4% (36/10,093)	0.4% (41/9,943)	0.4% (42/10,426)	0.3% (34/10,134)	0.37
Birth Weight Categories									

<1,500 grams	AIHW	1.5% (4,566/300,215)	1.5% (4,639/302,025)	1.5% (4,584/312,251)	1.5% (4,651/309,489)	1.5% (4,670/312,548)	1.4% (4,467/308,887)	1.5% (4,650/314,814)	0.01
	Mater	3.1% (300/9,562)	3.2% (301/9,496)	3.0% (308/10,188)	2.8% (283/10,095)	2.7% (272/9,943)	2.4% (247/10,422)	2.5% (254/10,138)	<0.001
1,500 – 2,499	AIHW	5.2% (15,697/300,215)	5.3% (15,965/302,025)	5.3% (16,450/312,251)	5.4% (16,718/309,489)	5.4% (16,915/312,548)	5.5% (17,136/308,887)	5.6% (17,529/314,814)	<0.001
	Mater	6.7% (637/9,562)	7.3% (689/9,496)	6.8% (693/10,188)	6.6% (661/10,095)	6.6% (652/9,943)	6.7% (700/10,422)	6.9% (694/10,138)	0.58
2,500 – 3,499	AIHW	50.9% (152,767/300,215)	50.9% (153,832/302,025)	51.3% (160,246/312,251)	52.0% (160,881/309,489)	52.6% (164,330/312,548)	52.9% (163,446/308,887)	53.4% (168,113/314,814)	<0.001
	Mater	49.9% (4,770/9,562)	49.1% (4,664/9,496)	49.9% (5,084/10,188)	52.2% (5,269/10,095)	53.1% (5,278/9,943)	53.8% (5,607/10,422)	54.5% (5,527/10,138)	<0.001
3,500 – 4,499	AIHW	40.5% (121,618/300,215)	40.5% (12,262/302,025)	40.2% (125,507/312,251)	39.5% (122,234/309,489)	39.0% (121,850/312,548)	38.7% (119,425/308,887)	38.2% (120,373/314,814)	<0.001
	Mater	38.6% (3,693/9,562)	39.0% (3,699/9,496)	38.5% (3,919/10,188)	37.3% (3,765/10,095)	36.4% (3,622/9,943)	36.0% (3,753/10,422)	35.2% (3,569/10,138)	<0.001
≥4,500	AIHW	1.8% (5,288/300,215)	1.7% (5,062/302,025)	1.7% (5,263/312,251)	1.6% (4,799/309,489)	1.5% (4,592/312,548)	1.4% (4,271/308,887)	1.3% (3,973/314,814)	<0.001
	Mater	1.7% (162/9,562)	1.5% (143/9,496)	1.8% (184/10,188)	1.2% (117/10,095)	1.2% (119/9,943)	1.1% (115/10,422)	0.9% (94/10,138)	<0.001
Apgar Score at 5 Minutes									
0 – 3	AIHW	0.3% (1,042/298,014)	0.3% (979/299,793)	0.3% (989/309,959)	0.3% (1,048/307,277)	0.3% (1,047/310,330)	0.3% (969/306,725)	0.4% (1,136/312,683)	0.46
	Mater	0.6% (57/9,456)	0.4% (38/9,390)	0.4% (43/10,070)	0.4% (42/9,976)	0.5% (47/9,817)	0.4% (41/10,298)	0.5% (45/10,010)	0.25
4 – 6	AIHW	1.3% (3,749/298,014)	1.3% (3,965/299,793)	1.4% (4,335/309,959)	1.5% (4,622/307,277)	1.5% (4,662/310,330)	1.5% (4,627/306,725)	1.6% (4,882/312,683)	<0.001
	Mater	1.4% (128/9,456)	1.4% (127/9,390)	1.1% (109/10,070)	1.6% (159/9,976)	1.8% (181/9,817)	1.5% (157/10,298)	2.0% (196/10,010)	<0.001
7 – 10	AIHW	98.2% (292,670/298,014)	98.1% (294,212/299,793)	98.1% (304,167/309,959)	98.0% (301,255/307,277)	98.0% (304,091/310,330)	98.0% (300,534/306,725)	97.8% (305,793/312,683)	<0.001
	Mater	98.0% (9,271/9,456)	98.2% (9,225/9,390)	98.5% (9,918/10,070)	98.0% (9,775/9,976)	97.7% (9,589/9,817)	98.1% (10,100/10,298)	97.6% (9,769/10,010)	<0.001
NICU/SCN Admission	AIHW	15.0% (44,694/298,014)	15.3% (45,761/299,793)	15.4% (47,766/309,959)	16.0% (43,159/269,069)	15.4% (42,422/275,374)	15.9% (43,348/271,966)	17.5% (31,216/178,881)	<0.001
	Mater	16.4% (1,568/9,563)	15.5% (1,471/9,496)	15.4% (1,571/10,189)	15.0% (1,511/10,095)	16.1% (1,604/9,943)	15.2% (1,582/10,427)	16.6% (1,687/10,138)	0.65
Stillborn	AIHW	0.7% (2,201/300,215)	0.7% (2,230/302,025)	0.7% (2,255/312,251)	0.7% (2,191/309,489)	0.7% (2,200/312,548)	0.7% (2,160/308,887)	0.7% (2,107/314,814)	<0.001
	Mater	0.7% (67/9,563)	0.8% (71/9,496)	0.8% (82/10,189)	0.7% (69/10,095)	0.7% (67/9,943)	0.7% (70/10,427)	0.7% (69/10,138)	0.43
Neonatal Death	AIHW	0.3% (876/300,215)	0.3% (843/302,025)	0.2% (738/312,251)	0.3% (807/309,489)	0.3% (786/312,548)	0.2% (689/308,887)	0.2% (742/314,814)	<0.001

	Mater	0.8% (73/9,563)	0.6% (55/9,496)	0.4% (41/10,189)	0.7% (70/10,095)	0.6% (64/9,943)	0.4% (37/10,427)	0.4% (42/10,138)	0.001
Perinatal Death	AIHW	1.0% (3,077/300,215)	1.0% (3,073/302,025)	1.0% (2,993/312,251)	1.0% (2,998/309,489)	1.0% (2,986/312,548)	0.9% (2,849/308,887)	0.9% (2,849/314,814)	<0.001
	Mater	1.5% (140/9,563)	1.3% (126/9,496)	1.2% (123/10,189)	1.4% (139/10,095)	1.3% (131/9,943)	1.0% (107/10,427)	1.1% (111/10,138)	0.01

BMI: Body Mass Index; SVD: Spontaneous Vaginal Delivery; NICU: Neonatal Intensive Care Unit; SCN: Special Care Nursery
Data Reported as % (N)

2.5 Discussion

The MMH is a major tertiary hospital and one of the largest maternity hospitals in the southern hemisphere. It is likely to be representative of other metropolitan hospitals throughout Australia. There were few differences observed in the maternal demographics between the two cohorts and it is important to note that the proportion of smoking, nulliparity and importantly pre–existing diabetes and hypertension are very similar between the two cohorts. For the vast majority of perinatal outcomes there were no clinically significant differences. The exception to this though is the very preterm infants that were born before 32 weeks gestation. The MMH cohort had higher proportions of 20 – 27 weeks gestation births and twice the proportion of 28 – 31 weeks gestation than observed in the AIHW cohort. This is due to it being a major tertiary centre and therefore the most appropriate place for those infants to be born. These higher proportion of very preterm births is also likely the reason for the difference in neonatal deaths. Overall the perinatal outcomes are similar between the two cohorts and illustrates that the MMH study cohort is representative of this level of hospital and therefore generalisable to the other metropolitan hospitals in Australia.

The trend analysis also showed that for the vast number of measures the trend directions and size were very similar for the two cohorts. When differences were detected they were likely to be due to the large sample size and not of any clinical significance.

The purpose of this chapter was not only checking the generalisability of the study data from the MMH but also to check the data integrity, accuracy and to illustrate that the missing data was handled appropriately. The similarities of the proportions of the demographics and perinatal outcomes between the two cohorts demonstrated the appropriateness of the study cohort. The similarities and lack of abnormal trends or spikes in data from the trend analysis shows the appropriateness of the data aggregations and manipulations.

Chapter 3: Is the fetal cerebroplacental ratio better that the estimated fetal weight in predicting adverse perinatal outcomes in a low risk cohort?

Christopher Flatley[1] and Sailesh Kumar[1,2]

1. Mater Research Institute, University of Queensland, Brisbane, Australia
2. School of Medicine, University of Queensland, Brisbane, Australia

This chapter addresses the secondary objective:

Investigate the associations of the EFW and CPR and pregnancies that are at risk of emergency caesarean for non–reassuring fetal status and a serious composite neonatal outcome at term.

Published in The Journal of Maternal – Fetal & Neonatal Medicine

Citation

Flatley C and Kumar S. Is the fetal cerebroplacental ratio better that the estimated fetal weight in predicting adverse perinatal outcomes in a low risk cohort? The journal of maternal– fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 2018: 1– 7. DOI: 10.1080/14767058.2018.1438394

DOI

https://doi.org/10.1080/14767058.2018.1438394

3.1 Abstract

Objective: In high–risk pregnancies combining the cerebroplacental ratio (CPR) with the estimated fetal weight (EFW) improves the identification of vulnerable fetuses. The purpose of this study was to assess the CPR and EFW's ability to predict adverse obstetric and perinatal outcomes in a low–risk pregnancy, when measured late in gestation.

Methods: This was a retrospective study of women who birthed at Mater Mothers Hospitals, Brisbane, Australia between 2010 and 2015. We included all non–anomalous singleton pregnancies that had an ultrasound scan performed between 36+0 and 38+6 weeks gestation. Excluded was any major congenital abnormality, aneuploidy, multiple pregnancy, preterm birth, maternal hypertension, or diabetes. The primary outcome was a severe composite neonatal outcome (SCNO) defined as severe acidosis (umbilical cord artery pH <7.0, cord lactate ≥6 mmol/L, cord base excess ≤–12 mmol/L) Apgar score ≤3 at 5 minutes, admission to the neonatal intensive care unit (NICU), and death. A low CPR was defined as <10th centile for gestation and small for gestational age (SGA) was defined as an EFW <10th centile and appropriate for gestational age (AGA) was defined as EFW ≥10th centile.

Results: Of 2,425 pregnancies, 13.2% (321/2,425) had a fetus with a CPR <10th centile and 13.7% (332/2,425) with an EFW <10th centile. Both a low CPR and SGA predicted the SCNO. Individually a low CPR and SGA had sensitivity for detection of SCNO of 23.3% and 24.7%, respectively which increased to 36.7% when combined. Both were associated with emergency caesarean for non–reassuring fetal status (NRFS), as well as early–term birth and admission to NICU. Stratifying the population into EFW <10th centile and EFW ≥10th centile, a low CPR maintained its association with the SCNO, early–term birth and emergency caesarean for NRFS in the cohort with an EFW <10th centile but SCNO lost its association with a low CPR in the EFW >10th cohort. Stratifying the population into CPR <10th centile and CPR >10th centile, a low EFW was associated with early–term birth, induction of labour, admission to NICU, and the SCNO.

Conclusions: In a low–risk cohort both the CPR and EFW individually and in combination predicts adverse obstetric and perinatal outcomes when measured late in pregnancy. However, the predictive value was enhanced when both were used in combination.

3.2 Introduction

A low fetal cerebroplacental ratio (CPR) is associated with suboptimal fetal growth and poor placental function (135, 136) and reflects compensatory fetal circulatory changes as a consequence of an adverse intrauterine environment (137). There is now good evidence that the CPR is more strongly correlated with adverse perinatal outcomes than its individual components (138-143).

Much of the evidence for the utility of the CPR as a screening test for adverse outcomes comes from retrospective studies (11) with cohorts that comprise both high and low risk populations with many different maternal co–morbidities such as diabetes mellitus and hypertension. These co–morbidities can increase the risk of aberrant fetal growth and/or adverse perinatal outcomes. More recently, a large North American study (144) clearly demonstrated that amongst a cohort of uncomplicated low–risk women at term, small for gestational age (SGA) newborns had a significantly higher likelihood of composite neonatal morbidity, stillbirth and neonatal mortality compared to appropriate for gestational age (AGA) babies. These investigators strongly recommended that further research is needed to determine if improved detection of SGA babies amongst uncomplicated pregnancies could reduce morbidity and mortality. Despite this laudable aim, identification of these at–risk fetuses remains problematic. Although there is a clear association with adverse outcomes, the detection rate that the CPR offers remains poor (11, 15, 71, 145) and clinicians are increasingly incorporating it into routine care despite its relatively poor performance as a screening test, particularly in a low–risk population.

Given its correlation with fetal growth, should the CPR alone rather than the estimated fetal weight (EFW), be used to identify vulnerable fetuses or should they be used in combination as suggested by some investigators (69, 79).

Thus, the purpose of this study was to assess the CPR's and/or the EFW's ability to predict adverse obstetric and perinatal outcomes when measured late in pregnancy in a low–risk cohort of women.

3.3 Methods

This was a retrospective cohort study of women giving birth at the Mater Mother's Hospital in Brisbane, Australia between 2010 and 2015. With approximately 10,000 births per year, the Mater Mother's Hospital is the largest tertiary maternity hospital in Australia. Maternal demographic data was collected from the institution's maternal database and cross referenced with the maternal and fetal and neonatal databases. The study protocol was approved by the hospital's Human Research Ethics Committee (Reference number HREC/14/MHS/37).

The study cohort included women with a non–anomalous singleton fetus who had an ultrasound scan performed between 36+0 – 38+6 weeks gestation with data recorded for the middle cerebral artery pulsatility index (MCA PI), the umbilical artery pulsatility index (UA PI) and EFW. Calculation of the gestational age was based using the last menstrual period or earliest ultrasound examination or by correlation with both. Exclusion criteria included any major congenital abnormality, aneuploidy, multiple pregnancy, preterm birth (<37 weeks gestation), non– recorded UA PI, MCA PI or EFW, maternal hypertension and diabetes mellitus.

The cerebroplacental ratio (CPR) was calculated by dividing the MCA PI by the UA PI. The 10^{th} centile for the EFW was calculated for gestational age against reference centiles created by Hadlock *et al* (146). The 10^{th} centile for the CPR was calculated by gestation against previously published reference centiles (145).

The two primary outcomes were a severe composite neonatal outcome (SCNO) [defined as acidosis (umbilical cord artery pH <7.0, cord lactate ≥6 mmol/L, cord base excess ≤–12 mmol/L) and/or Apgar score ≤3 at 5 minutes and/or admission to the neonatal intensive care unit (NICU) and/or death] and emergency caesarean section for non–reassuring fetal status (NRFS)**.** A low CPR was defined as <10^{th} centile for gestation and SGA was defined as an EFW <10^{th} centile and AGA was defined as EFW ≥10^{th} centile.

3.4 Statistical Analysis

Distributions of the continuous variable were assessed. Parametric data was reported as mean ± standard deviation and differences assessed using a *t*–test. Non–parametric data were reported as median and interquartile range with differences assessed using a Wilcoxon Rank– Sum test. Differences in proportions were analysed using Chi square test and *Z* test for two proportions. To account for women having more than one birth within the study period, generalised estimating equations were used to generate unadjusted and adjusted Odds ratios. Data analysis was performed using Stata/SE 14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.). Statistical significance was defined as $p < 0.05$. Preparation of this manuscript was in accordance with the STROBE guidelines for observational studies.

3.5 Results

Over the study period, we identified 2,425 women who met the inclusion criteria. Of these women, 13.2% (321/2,425) had a fetus with a CPR <10th centile and 13.7% (332/2,425) with an EFW <10th centile (Table 3.1). Of the SGA cohort, 29.5% (98/332) had a low CPR whilst AGA fetuses, 10.7% (223/2,093) had a low CPR. Conversely, of fetuses with a low CPR, 30.5% (98/321) were SGA and those with a CPR $\geq$10th centile, 11.1% (234/2,104) were SGA.

Women with fetuses that had a low CPR had lower body mass index (BMI) and were more likely to be nulliparous (Table 3.1). Women with SGA fetuses were younger and had a lower BMI. They were also less likely to be Caucasian but more likely to be of Asian ethnicity. There were higher rates of nulliparity in both groups and maternal smoking in the SGA cohort (Table 3.1).

Table 3-1: Maternal demographic and pregnancy factors associated with CPR <10th centile & EFW <10th centile.

	CPR >10th Centile	**CPR <10th Centile**	**P– Value**	**EFW >10th Centile**	**EFW <10th Centile**	**P– Value**
Age#	30.4 (5.6)	29.8 (5.7)	0.06	30.5 (5.6)	29.5 (6.2)	0.004
BMI*	22.3 (20.0 – 26.0)	21.8 (19.5 – 25.1)	0.01	22.6 (20.1 – 26.5)	20.8 (18.7 – 23.1)	<0.001
Ethnicity						
Caucasian^	55.6% (1,169/2,104)	51.9% (166/320)	0.22	56.5% (1,183/2,093)	45.9% (152/331)	<0.001
Indigenous^	3.1% (66/2,104)	4.4% (14/320)	0.25	3.2% (67/2,093)	3.9% (13/331)	0.49
Asian^	22.3% (469/2,104)	27.2% (87/320)	0.05	21.6% (452/2,093)	31.4% (104/331)	<0.001
Other^	19.0% (400/2,104)	16.6% (53/320)	0.29	18.7% (391/2,093)	18.7% (62/331)	0.98
Nulliparous	48.0% (1,009/2,103)	65.4% (210/321)	<0.001	48.1% (1,007/2,092)	63.9% (212/332)	<0.001
Smoking‡	15.9% (334/2,104)	19.3% (62/321)	0.12	15.6% (327/2,093)	20.8% (69/332)	0.02

BMI: body Mass Index; CPR: Cerebroplacental Ratio; EFW: Estimated Fetal Weight
#Mean (SD) – (*t*-test)
* Median Interquartile Range (Wilcoxon Rank Sum Test)
^ *Z* Test for Two Proportions
‡ Chi Square Test

Analysing the CPR, the SCNO was associated with a low CPR even after adjusting for parity, maternal body mass index and delivery via emergency caesarean for NRFS (except for modes of birth analyses) (aOR 1.78, 95% C.I. 1.30 – 2.43). Fetuses with a low CPR were more likely to be born at 37 and 38 weeks gestation and by emergency caesarean for NRFS. This cohort of women were also more likely to have babies with birth weights, $<5^{th}$ and $<10^{th}$ centiles and be admitted to NICU (Table 3.2).

Analysing the EFW, the SCNO was associated with an EFW $<10^{th}$ centile (aOR 1.96, 95% C.I. 1.43 – 2.67), after adjusting for parity, maternal body mass index and delivery via emergency caesarean for NRFS (except for modes of birth analyses). SGA fetuses were also more likely to be born at 37 and 38 weeks gestation, to be induced, admitted to NICU and delivered by emergency caesarean for NRFS (Table 3.2).

Table 3-2: Gestational distribution, intrapartum and neonatal outcomes for CPR <10th centile and EFW <10th centile.

	CPR >10th Centile	CPR <10th Centile	Adjusted OR (95% C.I.)	P Value	EFW >10th Centile	EFW <10th Centile	Adjusted OR (95% C.I.)	P Value
Gestation								
37 weeks*	11.8% (248/2,104)	24.3% (78/321)	2.41 (1.79 – 3.24)	<0.001	11.0% (230/2,093)	28.9% (96/332)	3.44 (2.58 – 4.58)	<0.001
38 weeks*	24.6% (517/2,104)	30.2% (97/321)	1.43 (1.10 – 1.87)	0.01	23.6% (494/2,093)	36.1% (120/332)	2.03 (1.57 – 2.61)	<0.001
39 weeks*	33.3% (700/2,104)	24.6% (79/321)	0.69 (0.52 – 0.90)	0.01	33.2% (695/2,093)	25.3% (84/332)	0.71 (0.54 – 0.93)	0.01
40 weeks*	20.3% (428/2,104)	15.9% (51/321)	0.73 (0.53 – 1.00)	0.05	21.6% (452/2,093)	8.1% (27/332)	0.30 (0.20 – 0.45)	<0.001
>40 weeks*	10.0% (211/2,104)	5.0% (16/321)	0.39 (0.23 – 0.67)	0.001	10.6% (222/2,093)	1.5% (5/332)	0.11 (0.05 – 0.27)	<0.001
Method of Birth								
SVD#	56.5% (1,189/2,104)	48.6% (156/321)	0.81 (0.63 – 1.03)	0.08	55.7% (1,165/2,093)	54.2% (180/332)	1.01 (0.80 – 1.29)	0.92
Instrumental#	12.6% (266/2,104)	13.7% (44/321)	0.84 (0.59 – 1.19)	0.32	12.7% (266/2,093)	13.3% (44/332)	0.77 (0.54 – 1.11)	0.16
Elective CS#	16.8% (353/2,104)	15.0% (48/321)	1.00 (0.72 – 1.39)	0.99	16.7% (349/2,093)	15.7% (52/332)	1.04 (0.75 – 1.44)	0.83
EM CS#	14.1% (296/2,104)	22.7% (73/321)	1.64 (1.21 – 2.21)	0.001	15.0% (313/2,093)	16.9% (56/332)	1.15 (0.84 – 1.60)	0.38
EM CS NRFS#	5.2% (109/2,104)	14.6% (47/321)	2.86 (1.97 – 4.16)	<0.001	5.7% (119/2,093)	11.1% (37/332)	2.04 (1.36 – 3.07)	0.001
EM CS Other#	8.9% (187/2,104)	8.1% (26/321)	0.80 (0.51 – 1.25)	0.33	9.3% (194/2,093)	5.7% (19/332)	0.59 (0.36 – 0.98)	0.04
Labour Induced*	39.5% (830/2,104)	46.4% (149/321)	1.14 (0.89 – 1.46)	0.30	37.8% (792/2,093)	56.3% (187/332)	2.17 (1.69 – 2.77)	<0.001
Birth Weight*	3253.1 ±527.7	2874.9 ±532.7			NA	NA	NA	NA
BWT <5th Centile*	11.5% (242/2,104)	33.6% (108/321)	3.13 (2.36 – 4.16)	<0.001	NA	NA	NA	NA
BWT <10th Centile*	22.4% (471/2,104)	45.5% (146/321)	2.36 (1.83 – 3.06)	<0.001	NA	NA	NA	NA
Acidosis*	5.6% (117/2,104)	10.6% (34/321)	1.50 (0.99 – 2.28)	0.06	5.8% (121/2,093)	9.0% (30/332)	1.29 (0.83 – 2.00)	0.25
Apgar Score ≤3 at 5 Minutes*	0.3% (7/2,095)	0% (0/321)	1	NA	0.3% (7/2,084)	0% (0/331)	1	NA
Admission to NICU*	6.2% (131/2,104)	12.8% (41/321)	1.82 (1.23 – 2.68)	0.003	5.8% (121/2,093)	15.4% (51/332)	2.60 (1.80 – 3.77)	<0.001
Perinatal Death*	0.2% (4/2,104)	0.6% (2/321)	2.61 (0.44 – 15.67)	0.29	0.2% (5/2,093)	0.3% (1/332)	1.09 (0.12 – 10.17)	0.93
SCNO*	10.9% (230/2,104)	22.8% (70/321)	1.78 (1.30 – 2.43)	<0.001	10.8% (226/2,093)	22.3% (74/332)	1.96 (1.43 – 2.67)	<0.001

SVD: Spontaneous Vaginal Delivery; EM: Emergency; CS: Caesarean Section; BWT: Birth Weight; CPR: Cerebroplacental Ratio; EFW: Estimated Fetal Weight; SCNO: Serious Composite Neonatal Outcome; OR: Odds Ratio C.I.: Confidence Interval

*Adjusted for Parity, Maternal Body Mass Index and Delivery via Emergency Caesarean for Non–Reassuring Fetal Status

Adjusted for Parity & Maternal Body Mass Index

The EFW <10th centile had a sensitivity of 24.7% (95% C.I. 19.9 – 29.9) and the CPR <10th centile had a sensitivity of 23.3% (95% C.I. 18.7 – 28.5) for the SCNO respectively. When the EFW <10th centile and the CPR <10th centile was used in combination the sensitivity increased to 36.7% (95% C.I. 31.2 – 42.4) (Table 3.3). For emergency caesarean for NRFS, the EFW <10th centile had a sensitivity of 23.7% (95% C.I. 17.3 – 31.2) and the CPR <10th centile had a sensitivity of 30.1% (23.1 – 38.0) respectively, whilst both combined, increased the sensitivity to 40.4% (95% C.I. 32.6 – 48.5). Additional performance characteristics of various thresholds for EFW and CPR respectively are presented in Table 3.3. The highest positive likelihood ratio (PLR 5.11) for SCNO was achieved using EFW <3rd centile cut–off while the highest PLR for emergency caesarean for NRFS was seen with a CPR <5th centile albeit for both outcomes this came at a cost of reduced sensitivity.

Table 3-3: Diagnostic value of EFW <10th centile and CPR <10th centile for fetuses with composite outcome and emergency caesarean for non–reassuring fetal status.

	Probability Cut–off	Sensitivity (95% C.I.)	Specificity (95% C.I.)	AUC (95% C.I.)	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio
Serious Composite Neonatal Outcome								
CPR <10th	0.15	23.3% (18.7 – 28.5)	88.2% (86.7 – 89.5)	0.56 (0.53 – 0.58)	21.8%	89.1%	1.98	0.87
CPR <5th	0.15	16.0% (12.0 – 20.6)	93.2% (92.0 – 94.2)	0.55 (0.52 – 0.57)	24.9%	88.7%	2.34	0.90
EFW <10th	0.15	24.7% (19.9 – 29.9)	87.9% (86.4 – 89.2)	0.56 (0.54 – 0.59)	22.3%	89.2%	2.03	0.86
EFW <3rd	0.15	10.3% (7.1 – 14.3)	98.0% (97.2 – 98.5)	0.54 (0.52 – 0.56)	41.9%	88.6%	5.11	0.92
CPR <10th or EFW <10th	0.15	36.7% (31.2 – 42.4)	79.1% (77.2 – 80.8)	0.58 (0.55 – 0.61)	19.8%	89.8%	1.75	0.80
Emergency Caesarean for Non–Reassuring Fetal Status								
CPR <10th	0.10	30.1% (23.1 – 38.0)	87.9% (86.5 – 89.2)	0.59 (0.55 – 0.63)	14.6%	94.8%	2.49	0.79
CPR <5th	0.10	19.2% (13.4 – 26.3)	92.8% (91.7 – 93.8)	0.56 (0.53 – 0.59)	15.5%	94.4%	2.68	0.87
EFW<10th	0.10	23.7% (17.3 – 31.2)	87.0% (85.5 – 88.4)	0.55 (0.52 – 0.59)	11.1%	94.3%	1.82	0.88
EFW <3rd	0.10	6.4% (3.1 – 11.5)	97.2% (96.4 – 97.8)	0.52 (0.50 – 0.54)	13.5%	93.8%	2.27	0.96
CPR <10th or EFW <10th	0.10	40.4% (32.6 – 48.5)	78.3% (76.6 – 80.0)	0.59 (0.55 – 0.63)	11.4%	95.0%	1.86	0.76

CPR: Cerebroplacental Ratio; EFW: Estimated Fetal; AUC: Area Under the Curve; C.I.: Confidence Interval

Figures 3.1 and 3.2 illustrate the different individuals within the cohort that the CPR and the EFW identify for fetuses that had the SCNO and emergency caesarean for NRFS respectively. For SGA fetuses with a low CPR there was an increased risk of being born at 37 weeks gestation and emergency caesarean for NRFS. They were also more likely to have been admitted to NICU and have the SCNO (Table 3.4). Of the AGA cohort, a low CPR was also associated with birth at 37 weeks gestation and emergency caesarean for NRFS (Table 3.4).

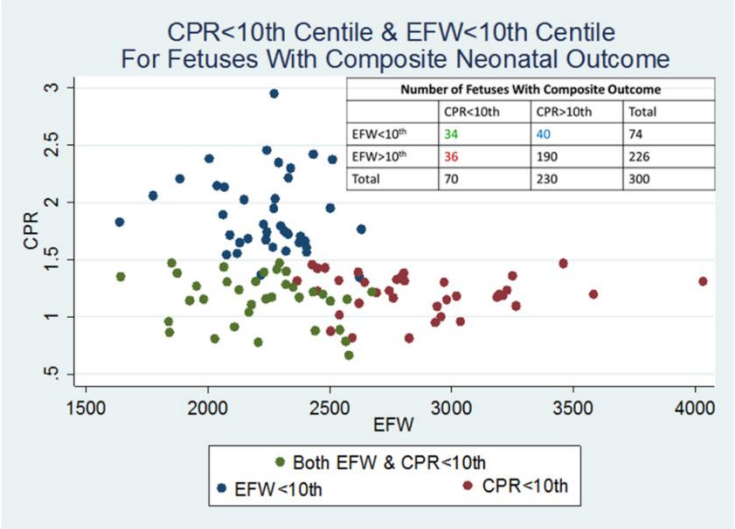

Figure 3-1: CPR <10th centile and EFW <10th centile for fetuses who had the composite neonatal outcome.

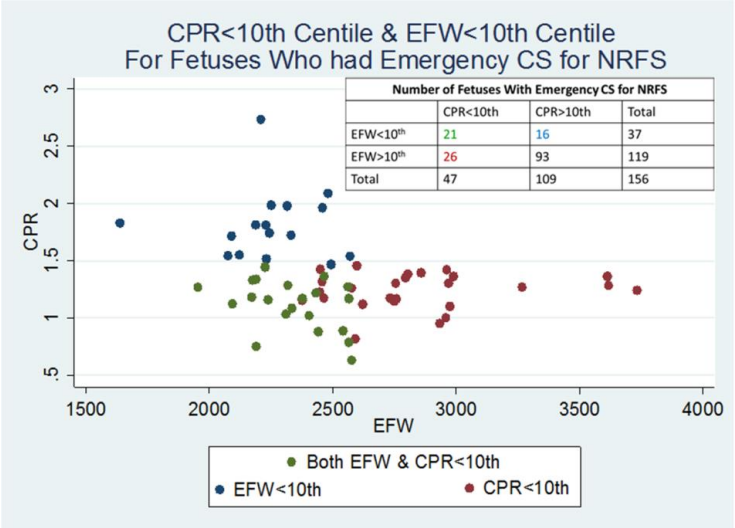

Figure 3-2: CPR <10th centile and EFW <10th centile for fetuses who had an emergency caesarean for non–reassuring fetal status.

Table 3-4: Outcomes related to the cerebroplacental ratio stratified by estimated fetal weight.

	EFW <10th Centile				**EFW >10th Centile**			
	CPR >10th centile	**CPR <10th centile**	**Adjusted OR (95% C.I.)**	**P Value**	**CPR >10th centile**	**CPR <10th centile**	**Adjusted OR (95% C.I.)**	**P Value**
Gestation								
37 weeks*	23.9% (56/234)	40.8% (40/98)	2.28 (1.33 – 3.92)	0.003	10.3% (192/1,870)	17.0% (38/223)	1.84 (1.25 – 2.71)	0.002
38 weeks*	33.8% (79/234)	41.8% (41/98)	1.26 (0.76 – 2.10)	0.38	23.4% (438/1,870)	25.1% (56/223)	1.21 (0.87 – 1.67)	0.26
39 weeks*	30.8% (72/234)	12.2% (12/98)	0.34 (0.17 – 0.66)	0.001	33.6% (628/1,870)	30.0% (67/223)	0.87 (0.64 – 1.18)	0.35
40 weeks*	9.4% (22/234)	5.1% (5/98)	0.56 (0.20 – 1.55)	0.26	21.7% (406/1,870)	20.6% (46/223)	0.90 (0.64 – 1.27)	0.56
>40 weeks*	2.1% (5/234)	0% (0/98)	1	NA	11.0% (206/1,870)	7.2% (16/223)	0.53 (0.31 – 0.91)	0.02
Method of Birth								
SVD#	58.6% (137/234)	43.9% (43/98)	0.70 (0.43 – 1.16)	0.16	56.3% (1,052/1,870)	50.7% (113/223)	0.86 (0.65 – 1.14)	0.29
Instrumental#	13.3% (31/234)	13.3% (13/98)	0.77 (0.37 – 1.58)	0.47	12.6% (235/1,870)	13.9% (31/223)	0.90 (0.60 – 1.37)	0.64
Elective CS#	16.7% (39/234)	13.3% (13/98)	0.76 (0.38 – 1.53)	0.44	16.8% (314/1,870)	15.7% (35/223)	1.02 (0.70 – 1.51)	0.89
EM CS#	11.5% (27/234)	29.6% (29/98)	2.57 (1.39 – 4.74)	0.003	14.4% (269/1,870)	19.7% (44/223)	1.38 (0.96 – 1.98)	0.09
EM CS NRFS#	6.8% (16/234)	21.4% (21/98)	3.16 (1.54 – 6.49)	0.002	5.0% (93/1,870)	11.7% (26/223)	2.42 (1.52 – 3.85)	<0.001
EM CS Other#	4.7% (11/234)	8.2% (8/98)	1.27 (0.46 – 3.50)	0.64	9.4% (176/1,870)	8.1% (18/223)	0.78 (0.46 – 1.31)	0.35
Labour Induced*	51.7% (121/234)	67.4% (66/98)	1.57 (0.93 – 2.67)	0.09	37.9% (709/1,870)	37.2% (83/223)	0.89 (0.66 – 1.20)	0.43
Acidosis*	6.8% (16/234)	14.3% (14/98)	1.80 (0.80 – 4.02)	0.16	5.4% (101/1,870)	9.0% (20/223)	1.38 (0.82 – 2.32)	0.22
Apgar Score ≤3 at 5 Minutes*	0% (0/233)	0% (0/98)	1	NA	0.4% (7/1,862)	0% (0/222)	1	NA
Admission to NICU*	11.1% (26/234)	25.5% (25/98)	2.18 (1.13 – 4.21)	0.02	5.6% (105/1,870)	7.2% (16/223)	1.15 (0.66 – 2.01)	0.62
Perinatal Death*	0.4% (1/234)	0% (0/98)	1	NA	0.2% (3/1,870)	0.9% (2/223)	4.23 (0.66 – 26.99)	0.13
SCNO*	17.1% (40/234)	34.7% (34/98)	2.04 (1.14 – 3.63)	0.02	10.2% (190/1,870)	16.1% (36/223)	1.43 (0.96 – 2.13)	0.08

SVD: Spontaneous Vaginal Delivery; CS; Caesarean Section; BWT: Birth Weight; NICU: Neonatal Intensive Care Unit; CPR: Cerebroplacental Ratio; EFW: Estimated Fetal Weight; OR: Odds Ratio; C.I.: Confidence Interval; SCNO: Serious Composite Neonatal Outcome

*Adjusted for Parity, Maternal Body Mass Index and Delivery via Emergency Caesarean for Non–Reassuring Fetal Status

Adjusted for Parity & Maternal Body Mass Index

For the cohort that had a low CPR and an EFW <10th centile there was a higher risk of birth at 37 and 38 weeks gestation, emergency caesarean for NRFS, IOL, admission to NICU and the SCNO (Table 3.5). Of the cohort with a CPR >10th centile but an EFW <10th centile there was a similarly increased risk of being born at 37 and 38 weeks gestation, IOL, admission to NICU and the SCNO.

Table 3-5: Outcomes related to estimated fetal weight stratified by the cerebroplacental ratio.

	CPR <10th Centile				**CPR >10th Centile**			
	EFW >10th Centile	**EFW <10th Centile**	**Adjusted OR (95% C.I.)**	**P Value**	**EFW >10th Centile**	**EFW <10th Centile**	**Adjusted OR (95% C.I.)**	**P Value**
Gestation								
37 weeks*	17.0% (38/223)	40.8% (40/98)	3.98 (2.24 – 7.09)	<0.001	10.3% (192/1,870)	23.9% (56/234)	2.84 (2.01 – 4.02)	<0.001
38 weeks*	25.1% (56/223)	41.8% (41/98)	2.08 (1.23 – 3.49)	0.01	23.4% (438/1,870)	33.8% (79/234)	1.84 (1.37 – 2.48)	<0.001
39 weeks*	30.0% (67/223)	12.2% (12/98)	0.36 (0.18 – 0.72)	0.003	33.6% (628/1,870)	30.8% (72/234)	0.88 (0.66 – 1.19)	0.41
40 weeks*	20.6% (46/223)	5.1% (5/98)	0.19 (0.07 – 0.51)	0.001	21.7% (406/1,870)	9.4% (22/234)	0.35 (0.22 – 0.55)	<0.001
>40 weeks*	7.2% (16/223)	0% (0/98)	1	NA	11.0% (206/1,870)	2.1% (5/234)	0.16 (0.06 – 0. 39)	<0.001
Method of Birth								
SVD#	50.7% (113/223)	43.9% (43/98)	0.87 (0.53 – 1.43)	0.58	56.3% (1,052/1,870)	58.6% (137/234)	1.13 (0.85 – 1.51)	0.38
Instrumental#	13.9% (31/223)	13.3% (13/98)	0.68 (0.33 – 1.40)	0.29	12.6% (235/1,870)	13.3% (31/234)	0.84 (0.55 – 1.28)	0.41
Elective CS#	15.7% (35/223)	13.3% (13/98)	0.98 (0.48 – 1.99)	0.95	16.8% (314/1,870)	16.7% (39/234)	1.06 (0.73 – 1.54)	0.77
Emergency CS#	19.7% (44/223)	29.6% (29/98)	1.60 (0.90 – 2.82)	0.11	14.4% (269/1,870)	11.5% (27/234)	0.84 (0.54 – 1.29)	0.42
Emerg CS NRFS#	11.7% (26/223)	21.4% (21/98)	1.93 (1.00 – 3.70)	0.049	5.0% (93/1,870)	6.8% (16/234)	1.48 (0.84 – 2.60)	0.18
Emerg CS Other#	8.1% (18/223)	8.2% (8/98)	0.92 (0.36 – 2.36)	0.87	9.4% (176/1,870)	4.7% (11/234)	0.52 (0.28 – 0.98)	0.04
Labour Induced*	37.2% (83/223)	67.4% (66/98)	3.31 (1.94 – 5.66)	<0.001	37.9% (709/1,870)	51.7% (121/234)	1.92 (1.44 – 2.54)	<0.001
Acidosis*	9.0% (20/223)	14.3% (14/98)	1.44 (0.67 – 3.09)	0.36	5.4% (101/1,870)	6.8% (16/234)	1.11 (0.63 – 1.96)	0.72
Apgar Score ≤3 at 5 Minutes*	0% (0/222)	0% (0/98)	1	NA	0.4% (7/1,862)	0% (0/233)	1	NA
Admission to NICU*	7.2% (16/223)	25.5% (25/98)	4.29 (2.10 – 8.77)	<0.001	5.6% (105/1,870)	11.1% (26/234)	1.92 (1.19 – 3.08)	0.01
Perinatal Death*	0.9% (2/223)	0% (0/98)	1	NA	0.2% (3/1,870)	0.4% (1/234)	3.09 (0.30 – 31.95)	0.34
SCNO*	16.1% (36/223)	34.7% (34/98)	2.39 (1.34 – 4.25)	0.003	10.2% (190/1,870)	17.1% (40/234)	1.16 (1.08 – 2.37)	0.02

SVD: Spontaneous Vaginal Delivery; CS; Caesarean Section; BWT: Birth Weight; NICU: Neonatal Intensive Care Unit; CPR: Cerebroplacental Ratio; EFW: Estimated Fetal Weight; OR: Odds Ratio; C.I.: Confidence Interval; SCNO: Serious Composite Neonatal Outcome

*Adjusted for Parity, Maternal Body Mass Index and Delivery via Emergency Caesarean for Non–Reassuring Fetal Status

Adjusted for Parity & Maternal Body Mass Index

3.6 Discussion

The results from this study indicate that there is no difference in the ability to predict the SCNO using either EFW <10th centile (23.3%) or CPR <10th centile (22.8%) (aOR 1.78, 95% C.I. 1.30 – 2.43 vs. 1.96, 95% C.I. 1.43– 2.67, p=0.41) thresholds individually. However, when used in combination the sensitivity increased to 36.7% (95% C.I. 31.2 – 42.4) suggesting that the EFW identifies a cohort of fetuses at risk of SCNO that is separate from that identified by the CPR alone (Figure 1). Our results thus support the incorporation of both the CPR and the EFW into any risk stratification model.

We also show that in SGA fetuses, a low CPR is associated with early term birth and emergency caesarean for NRFS. The association with these outcomes with a low CPR were also found in AGA fetuses although this was slightly weaker. In fetuses with a low CPR, being SGA was associated with early term birth, IOL, admission to NICU and SCNO. Again, these associations extended to the CPR >10th centile cohort with albeit weaker correlation.

Our stratified analysis of both the CPR and EFW suggest that a low CPR is associated with emergency caesarean for NRFS regardless of the EFW even in a low risk cohort as in this study. The congruent association of emergency caesarean for NRFS with a low CPR regardless of fetal weight is likely to be indicative of the relationship between placental function, aberrations in fetal growth and intrapartum fetal compromise. Our findings concur with that shown by Khalil *et al* in a mixed risk cohort (147).

Induction of labour was associated with a low EFW in both the low CPR (aOR 3.31, 95% C.I. 1.94 – 5.66) and normal CPR cohorts (aOR 1.92, 95% C.I. 1.44 – 2.54). The difference in odds ratios between both these groups is likely to be secondary to the low EFW being the primary indication for IOL.

The results from this study are in concordance to recent studies by Sirico *et al* and Mendez–Figeroa *et al* (144, 148). Sirico *et al* found that there was an inverse correlation between the CPR and the development of pathological fetal heart rates in labour (148). They also demonstrated that a low CPR showed stronger associations with adverse outcomes in an SGA cohort (148). Mendez–Figeroa *et al* showed that when compared to an AGA cohort, SGA babies had a significantly greater risk of morbidity and mortality (144). In contrast our study shows that in a low risk cohort, being SGA was not associated with increased odds for emergency caesarean for NRFS in contrast to a low CPR which was strongly correlated regardless of EFW. Furthermore, even though we demonstrated that the association with adverse outcomes were stronger in the

SGA cohort, there was still a reasonably strong association between a low CPR and SCNO even in the AGA group suggesting that screening in this cohort may also be worthwhile.

The strengths of this study lie in the large cohort of EFW and CPR measurements obtained from a single tertiary centre. We chose a composite of serious neonatal outcomes that are linked to poorer longer– term sequelae such as cerebral palsy (149) and still found a significant association with a low CPR even in a low risk population. The limitations are those that are inherent to retrospective studies. Although we excluded women with medical co–morbidities (diabetes mellitus and hypertension) these women were referred for a clinically indicated ultrasound assessment of the fetus and hence may not be truly low risk. Furthermore, as the EFW was available to clinicians as part of the ultrasound report it is likely that in a proportion of women it may have influenced the decision for or timing of birth. Nevertheless, despite these limitations, in our view our findings are interesting and highlight the importance of incorporating both the CPR and the EFW into risk assessment at term.

It is probably fair to say that there is equipoise amongst clinicians as to the benefits of a late pregnancy scan. Currently, Cochrane reviews do not support the use of either routine late pregnancy ultrasound or umbilical artery Doppler assessment in low–risk populations (150, 151). However, these reviews are limited by small sample size, use of surrogate outcomes, and most importantly, ultrasound scans that were often performed too remote from term, thereby potentially missing late onset growth restriction. A recent prospective observational cohort study showed that late pregnancy ultrasound in low risk women tripled the detection rate for SGA babies at term (152). However, this study was limited by the lack of middle cerebral artery (MCA) Dopplers (and thus the CPR measurement) once an SGA fetus was detected. It is possible that detection rates for SGA and other vulnerable babies may have been further improved if the CPR had been included. This omission is important because in term fetuses, umbilical artery (UA) Dopplers are usually normal and thus would not identify an at–risk fetus (153).

Chapter 4: The magnitude of change in the fetal cerebroplacental ratio in the third trimester and the risk of adverse pregnancy outcome

Christopher Flatley[1], Ristan M Greer[1,2], Sailesh Kumar[1,2]

1. Mater Research Institute, University of Queensland, Brisbane, Australia.
2. School of Medicine, The University of Queensland, Queensland, Australia.

This chapter addresses the secondary objective:

Investigate the relationship between the magnitude of change in CPR in the third trimester of pregnancy and the risk of adverse perinatal outcome.

Published in Ultrasound in Obstetrics and Gynecology

Citation

Flatley C, Greer RM and Kumar S. Magnitude of change in fetal cerebroplacental ratio in third trimester and risk of adverse pregnancy outcome. Ultrasound in obstetrics & gynecology: the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2017; 50: 514– 519. DOI 10.1002/uog.17371

DOI

https://doi.org/10.1002/uog.17371

4.1 Abstract

Objectives: To evaluate whether the magnitude of change in the cerebroplacental ratio (CPR) after 30 weeks' gestation is a better predictor of adverse pregnancy outcome compared with a single CPR measurement at 35 – 37 weeks. A secondary aim was to evaluate whether the utility of CPR at 35 – 37 weeks was enhanced after adjusting for change in gestational age.

Methods: This was a retrospective cohort study of women who had at least two ultrasound scans between 30 and 37 weeks gestation, with the final scan at 35 – 37 weeks. Exclusion criteria were major congenital abnormality, aneuploidy, multiple pregnancy and unknown middle cerebral artery pulsatility index or umbilical artery pulsatility index. A normal reference range for CPR was derived from a separate cohort of women with normal outcome and a Generalised Additive Model for Location, Scale and Shape was fitted to derive standardized centiles. These reference centiles were then used to calculate *Z*-scores for the study cohort. Logistic regression models and receiver–operating characteristics (ROC) curves were used to evaluate the predictive utility of CPR *Z*–score at last CPR measurement and the change in CPR on mode of delivery, neonatal outcome and composite neonatal outcome. The area under the ROC curve (AUC) for each model was compared before and after adjustment for parity, hypertension, diabetes, body mass index and smoking status.

Results: A total of 1,860 women met the inclusion criteria. There was no association between the magnitude of change in CPR and composite adverse pregnancy outcome ($P = 0.92$). Of the outcomes that made up the composite, an increase in CPR *Z*–score over time was associated with a lower risk for emergency caesarean delivery ($P < 0.001$) and emergency caesarean delivery for non–reassuring fetal status ($P = 0.02$). It was also associated with a lower risk of birth weight $<10^{th}$ centile ($P = 0.01$) and hypoglycaemia ($P = 0.001$). There was no significant difference between the AUCs of last CPR *Z*–score and last CPR *Z*–score adjusted for the change in gestational age in predicting pregnancies at risk for adverse outcome.

Conclusions: Our results suggest that both the individual CPR *Z*–score and the magnitude and direction of change in CPR *Z*–score can identify pregnancies at risk of various adverse perinatal outcomes. However, the CPR *Z*–score at 35 – 37 weeks gestation appears to be a better predictor.

4.2 Introduction

Deterioration in placental function during pregnancy results in compensatory hemodynamic changes in the fetus, with increased blood flow to the brain and other essential organs (8, 57). This redistribution of cardiac output is typically seen in small for gestational age fetuses, or indeed, any fetus that fails to reach its growth potential regardless of gestation (40, 154), and is associated with an increased risk of adverse perinatal and long–term neurodevelopmental outcomes (155-157).

The ratio of the middle cerebral artery pulsatility index (MCA PI) to the umbilical artery PI (UA PI) is referred to as the cerebroplacental ratio (CPR) and is reflective of the severity of cerebral redistribution. However, CPR changes during gestation and is proportionate to relative fetal growth (66). We and others have shown previously that the CPR at 35 – 37 weeks gestation is associated with intrapartum fetal compromise, poor acid–base status at birth and an increased risk of admission to the neonatal critical care unit (NCCU) at term (11, 15, 53, 58, 60, 67, 68). However, despite this, its sensitivity as a predictor of adverse outcome is unimpressive, at 6 – 15% (11).

The primary aim of this study was to see if the magnitude of change in CPR after 30 weeks gestation was a better predictor of adverse pregnancy outcome compared with a single CPR measurement later in pregnancy. A secondary aim was to evaluate whether the accuracy of CPR at 35 – 37 weeks to detect adverse pregnancy outcomes was enhanced after adjusting for the gestational age change in CPR.

4.3 Methods

This was a retrospective cohort study in women attending the Mater Mother's Hospital in Brisbane, Australia, between 2013 and 2015. The Mater Mother's Hospital is a major tertiary centre in the state of Queensland and the largest maternity hospital in Australia, with approximately 10,000 births per annum. Previous prospectively collected maternal demographic data from the institution's maternal database were cross–referenced against the institution's ultrasound and neonatal databases. The study protocol was approved by the hospital's human research ethics committee (Reference number HREC/14/MHS/37).

The study cohort included pregnant women with a non-anomalous singleton fetus who had at least two ultrasound scans between 30 + 0 and 37 + 6 weeks gestation, with the final scan at 35 – 37 weeks, with data recorded for both MCA PI and UA PI for the calculation of CPR. Gestational age was calculated using the last menstrual period or earliest ultrasound examination, or by correlation with both. Exclusion criteria included any major congenital abnormality, aneuploidy, multiple pregnancy and unknown UA PI or MCA PI. Demographic data collected included maternal age, insurance status, body mass index (BMI), ethnicity, smoking history, presence of hypertension and diabetes mellitus, and parity. Ultrasound data recorded included gestational age at ultrasound, UA PI and either the left or right MCA PI.

For recording ultrasound data, we used an automated tracing method that incorporated at least three waveforms and was repeated three times in order to obtain the mean PI. The angle of insonation was maintained at <30°. The MCA was imaged using colour Doppler and its waveform recorded from the proximal third of the vessel, distal to its origin from the circle of Willis. Depending on the quality of the waveform, either the left or right MCA PI was measured. The UA Doppler waveforms were recorded from a free loop of the umbilical cord, and CPR was calculated by dividing MCA PI by UA PI.

A normal reference range for CPR was created using ultrasound data between 22 and 42 weeks gestation derived from a separate cohort of women with a normal pregnancy outcome. Specific obstetric and perinatal exclusion criteria for this cohort included any mode of delivery other than spontaneous vaginal delivery, preterm birth (<37 weeks), multiple pregnancy, presence of hypertension or diabetes mellitus, major congenital abnormality, aneuploidy, indeterminate fetal gender, perinatal death, admission to the NCCU, hypoglycaemia (defined as clinically significant hypoglycaemia in the first 24 h after delivery), acidosis at birth (defined as cord blood pH <7.1 and lactate >6 mmol/L), respiratory distress (defined as the need for prolonged

ventilatory assistance), resuscitation (defined as the need for respiratory and/or cardiopulmonary resuscitation) and 5–min Apgar score <7. A Generalized Additive Model for Location, Scale and Shape (GAMLSS) using Box–Cox transformation was fitted to the data to create standardized centiles by gender and gestational age at ultrasound (117). These were then used to calculate *Z*–scores for the study cohort: ((measured CPR − mean reference CPR)/SD of reference CPR) (Figure 4.1).

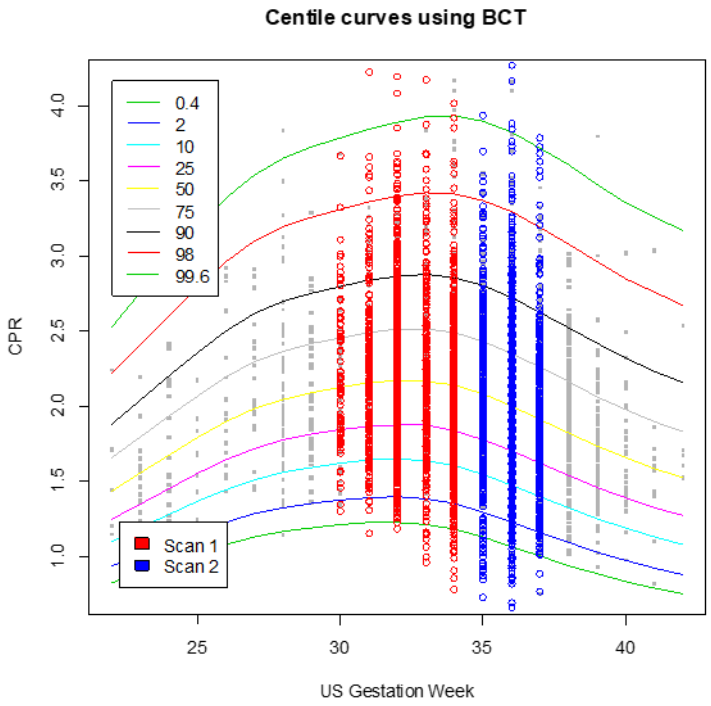

Figure 4-1: Cerebroplacental ratios of study cohort plotted over reference standardised centiles.

BCT: Box–Cox t distribution; CPR: Cerebroplacental Ratio

Scan 1 (Red) and Scan 2 (Blue)

The change in CPR *Z*–score per week was obtained by subtracting the CPR *Z*–score obtained from the second ultrasound scan from that of the first and dividing it by the number of weeks between the first and second scans ((CPR *Z*–score Scan 2 − CPR *Z*–score Scan 1)/(gestational age at Scan 2 − gestational age at Scan 1)), thus accounting for any variation in the interval between the first and second scans. Using the change in CPR per week allowed analysis of the magnitude and direction of change in CPR.

The primary outcome of this study was a composite measure of any adverse neonatal outcome, defined as perinatal death, emergency caesarean delivery for non–reassuring fetal status, NCCU

admission (including admission to the special care nursery, intensive care nursery and intensive care unit), severe respiratory distress, 5–min Apgar score <7, hypoglycaemia or acidosis at birth. Other outcomes assessed included mode of, and indication for delivery, gestational age at delivery and delivery before 37 weeks gestation, birth weight *Z*–score (calculated with reference to Australian birth weight percentiles for gestational age and gender) (4) and duration of labour. Mode of delivery was defined as spontaneous vaginal, instrumental (forceps and vacuum), elective caesarean section or emergency caesarean section. Emergency caesarean section was further stratified into those indicated for non–reassuring fetal status and those indicated for all other reasons.

4.4 Statistical Analysis

Distributions for continuous data were assessed. Correlations between continuous variables were assessed using Pearson's correlation coefficient for parametric data and Spearman's correlation coefficient for non–parametric data. For normally distributed data, differences between means were assessed using an independent sample *t*–test (and Wilcoxon rank–sum test for non–parametric data). Differences in proportions were tested using the *Z*–test for two proportions. Logistic regression models and receiver operating characteristics (ROC) curves were used to evaluate the predictive utility of CPR *Z*–score, calculated from the last CPR measurement, and the change in CPR on mode of delivery, neonatal outcome and composite neonatal outcome. The areas under the ROC curves (AUCs) for each model were compared, before and after adjustment for parity, hypertension, diabetes, BMI and smoking status.

Summary statistics are reported as mean ± SD or median (interquartile range), as appropriate. Data analysis was performed using Stata/SE 13.1 (Statacorp, College Station, TX, USA) and R Version 3.1.1 (R Core Team (2014); R Foundation for Statistical Computing, Vienna, Austria; http://www.R– project.org/). Statistical significance was defined as $P < 0.05$.

4.5 Results

During the study period, 1,693 women met the inclusion criteria for the reference cohort and 1,860 for the study group. Characteristics of the reference and study groups are shown in Table 4.1. In the study cohort, mean CPR *Z*–score for the first ultrasound scan (at mean 5.5 ± 1.9 weeks prior to delivery and mean 32.6 ± 1.2 weeks gestation) was –0.11 ± 1.09, while mean CPR *Z*–score for the second ultrasound scan (at mean 2.1 ± 1.3 weeks prior to delivery and mean 36.0 ± 0.7 weeks gestation) was –0.16 ± 1.13. The mean change in CPR *Z*–score per week was –0.02 ± 0.46; the mean interval between scans was 3.4 ± 1.3 weeks.

Table 4-1: Maternal demographics of study and reference cohorts.

	Study Cohort N=1,860	**Reference Cohort N=1,693**	**P Value**
Age*¶	31.3 (5.8)	30.3 (5.8)	<0.001
BMI (kg/m^2) †‡	23.9 (20.8 – 28.9)	22.7 (20.0 – 26.6)	<0.001
Nulliparous	774 (41.6%)	630 (37.2%)	0.01
Ethnicity			
Caucasian	994 (53.4%)	907 (53.6%)	0.94
Indigenous	61 (3.3%)	61 (3.6%)	0.60
Asian	302 (16.2%)	287 (17.0%)	0.57
Indian	159 (8.6%)	89 (5.3%)	<0.001
Other	344 (18.5%)	348 (20.6%)	0.12
Hypertension	214 (11.5%)	101 (6.0%)	<0.001
Diabetes	666 (35.8%)	234 (13.9%)	<0.001
Smoking	272 (14.6%)	276 (16.3%)	0.16

BMI: Body Mass Index
Demographic characteristics are reported as number (percentage) unless otherwise indicated.
Comparisons made using *Z*–test for two proportions unless otherwise indicated.
* Mean (Standard Deviation)
† Median (Interquartile Range)
¶ *t*–test
‡ Wilcoxon Rank Sum Test

There was no difference in the change in CPR *Z*–score according to maternal age, BMI, parity, ethnicity, diabetes or smoking status. CPR *Z*–score decreased during the third trimester in women diagnosed with hypertension, compared with no significant change in those without hypertension (Table 4.2). CPR *Z*–score at the second ultrasound scan correlated positively with maternal BMI, was higher in women with diabetes (−0.07 ± 1.16 *vs* −0.21 ± 1.11) and lower in nulliparous women (−0.27 ± 1.11 *vs* −0.08 ± 1.14) and smokers (−0.30 ± 1.12 *vs* −0.14 ± 1.12). There was, however, no difference in last CPR *Z*–score according to maternal age, ethnicity or hypertension (Table 4.2).

Table 4-2: Maternal demographics by change in CPR Z–score/week and last CPR Z–score.

		Change in CPR *Z*–score/Week		**Last CPR *Z*–score (35 – 37 Weeks)**	
	N=1,860	Change in CPR *Z*–score/Week	P Value	Last CPR *Z*–score	P Value
Age*	31.3 (5.8)	0.013¶	0.59	0.027¶	0.24
BMI (kg/m^2) †	23.9 (20.8 – 28.9)	0.029‡	0.22	0.070‡	0.003
Nulliparous	774 (41.6%)	– 0.05 (0.45)	0.07	– 0.27 (1.11)	<0.001
Ethnicity					
Caucasian	994 (53.4%)	– 0.01 (0.49)	0.25	– 0.13 (1.09)	0.16
Indigenous	61 (3.3%)	– 0.08 (0.42)	0.34	– 0.35 (1.20)	0.18
Asian	302 (16.2%)	0.003 (0.40)	0.29	– 0.07 (1.05)	0.13
Indian	159 (8.6%)	– 0.07 (0.43)	0.16	– 0.29 (1.18)	0.13
Other	344 (18.5%)	– 0.04 (0.43)	0.31	– 0.24 (1.25)	0.13
Hypertension	214 (11.5%)	– 0.09 (0.48)	0.03	– 0.25 (1.14)	0.24
Diabetes	666 (35.8%)	– 0.02 (0.43)	0.76	– 0.07 (1.16)	0.01
Smoking	272 (14.6%)	– 0.07 (0.50)	0.07	– 0.30 (1.12)	0.03

CPR: Cerebroplacental ratio, BMI: Body Mass Index
Demographic characteristics are reported as number (percentage) unless otherwise indicated.
Change in CPR *Z*–score/Week and Last CPR *Z*–score is reported as Mean (Standard Deviation) unless otherwise indicated.
Comparisons are made using *t*–test unless otherwise indicated.
¶ Pearson's Correlation Coefficient
‡ Spearman's Rho Rank Correlation Coefficient
* Mean (Standard Deviation)
† Median (Interquartile Range)

Univariable logistic regression confirmed that there was no association between the change in CPR per week and composite adverse pregnancy outcome. Of the outcomes that made up the composite, an increase in CPR *Z*–score over time was associated with a lower risk of emergency caesarean delivery and was protective in the subset requiring emergency caesarean delivery for non-reassuring fetal status (Table 4.3).

An increase in CPR *Z*-score over time was also associated with a lower risk of preterm delivery before 37 weeks, birth weight <10th centile and hypoglycaemia (Table 4.3). A higher CPR *Z*–score at 35 – 37 weeks was similarly associated with a lower risk of composite adverse pregnancy outcome. Of the outcomes that made up the composite, a higher CPR *Z*–score at 35 – 37 weeks was associated with a lower risk of emergency caesarean delivery, including the subgroup delivered for non–reassuring fetal status. A higher CPR *Z*–score at the second ultrasound scan was also associated with a lower risk of preterm delivery before 37 weeks, birth weight <10th centile, 5–min Apgar score <7, admission to the NCCU or perinatal death. A higher final CPR *Z*–score was a risk factor for birth weight > 90th centile (Table 4.3).

The composite adverse pregnancy outcome, 5–min Apgar score <7, admission to the NCCU and perinatal death were all associated with a low mean CPR *Z*-score (≤ –0.4) at the 35 – 37 week scan, yet there was only a minimal change in CPR *Z*–score from the initial scan, indicating a consistently low CPR with limited room for any further decrease. In particular, perinatal death had a consistently low mean CPR *Z*–score, decreasing by only 0.05 per week to a mean CPR *Z*–score of –0.84 ± 1.28 (Figure 4.2 and Table 4.3).

Table 4-3: Neonatal outcomes by change in CPR Z–score/week and last CPR Z–score.

	Change in CPR *Z*–score/Week			**Last CPR *Z*–score (35 – 37 Weeks)**		
	Change in CPR *Z*–score/Week	**OR (95% C.I.)**	**P Value**	**CPR *Z*–score Scan 2**	**OR (95% C.I.)**	**P Value**
Male	– 0.01 (0.45)			– 0.13 (1.10)		
Female	– 0.03 (0.46)	NA	0.48	– 0.19 (1.16)	NA	0.30
Length of Labour (min) n=1,269	0.001‡	NA	0.97	0.029‡	NA	0.30
Mode of Delivery						
SVD	– 0.01 (0.44)	1.08 (0.89 – 1.33)	0.40	– 0.12 (1.07)	1.07 (0.98 – 1.16)	0.12
Instrumental	0.01 (0.43)	1.20 (0.88 – 1.65)	0.25	– 0.15 (1.15)	1.01 (0.89 – 1.15)	0.85
Elective CS	0.01 (0.47)	1.23 (0.96 – 1.58)	0.10	– 0.04 (1.08)	1.13 (1.02 – 1.24)	0.02
Emergency CS	– 0.10 (0.50)	0.63 (0.49 – 0.81)	<0.001	– 0.40 (1.26)	0.79 (0.72 – 0.88)	<0.001
NRFS	– 0.12 (0.50)	0.61 (0.41 – 0.91)	0.02	– 0.80 (1.44)	0.62 (0.53 – 0.72)	<0.001
Other	– 0.01 (0.45)	0.68 (0.51 – 0.91)	0.01	– 0.23 (1.14)	0.94 (0.84 – 1.06)	0.33
Preterm (<37 Weeks)	– 0.20 (0.76)	0.40 (0.30 – 0.55)	<0.001	– 0.81 (1.41)	0.58 (0.51 – 0.66)	<0.001
BWT <10th centile	– 0.07 (0.49)	0.73 (0.57 – 0.94)	0.01	– 0.65 (1.19)	0.61 (0.56 – 0.69)	<0.001
BWT >90th centile	0.03 (0.49)	1.35 (0.99 – 1.85)	0.06	0.33 (1.13)	1.62 (1.41 – 1.86)	<0.001
Apgar <7 at 5 min	– 0.05 (0.48)	0.89 (0.45 – 1.77)	0.74	– 0.52 (1.35)	0.76 (0.59 – 0.99)	0.04
NCCU	0.01 (0.58)	1.20 (0.91 – 1.59)	0.19	– 0.43 (1.33)	0.79 (0.70 – 0.88)	<0.001
Respiratory Distress	0.03 (0.61)	1.30 (0.94 – 1.78)	0.11	– 0.26 (1.31)	0.92 (0.81 – 1.04)	0.16
Perinatal Death	– 0.05 (0.58)	0.90 (0.35 – 2.33)	0.82	– 0.84 (1.28)	0.62 (0.45 – 0.87)	0.01
Hypoglycaemia	– 0.45 (0.94)	0.24 (0.10 – 0.57)	0.001	– 0.56 (1.45)	0.75 (0.46 – 1.21)	0.23
Acidosis	0.01 (0.54)	1.17 (0.77 – 1.77)	0.46	– 0.20 (1.38)	0.96 (0.82 – 1.13)	0.67
Composite Adverse Neonatal Outcome	– 0.02 (0.56)	0.99 (0.79 – 1.24)	0.92	– 0.40 (1.28)	0.77 (0.70 – 0.84)	<0.001

CPR: Cerebroplacental ratio, SVD: Spontaneous vaginal delivery, CS: Caesarean section, NRFS: Emergency caesarean indicated for non–reassuring fetal status, BWT: Birth weight, NCCU: Neonatal critical care unit, Composite adverse neonatal outcome: Defined as perinatal death, birth by emergency caesarean for non–reassuring fetal status, NCCU admission, severe respiratory distress, Apgar score <7 at 5 minutes, hypoglycaemia, or acidosis at birth.
Change in CPR *Z*–score/Week and Last CPR *Z*–score is reported as Mean (Standard Deviation) unless otherwise indicated.
Univariable Logistic Regression: Odds ratios are reported unless otherwise indicated.
‡ Spearman's Rho Rank Correlation Coefficient

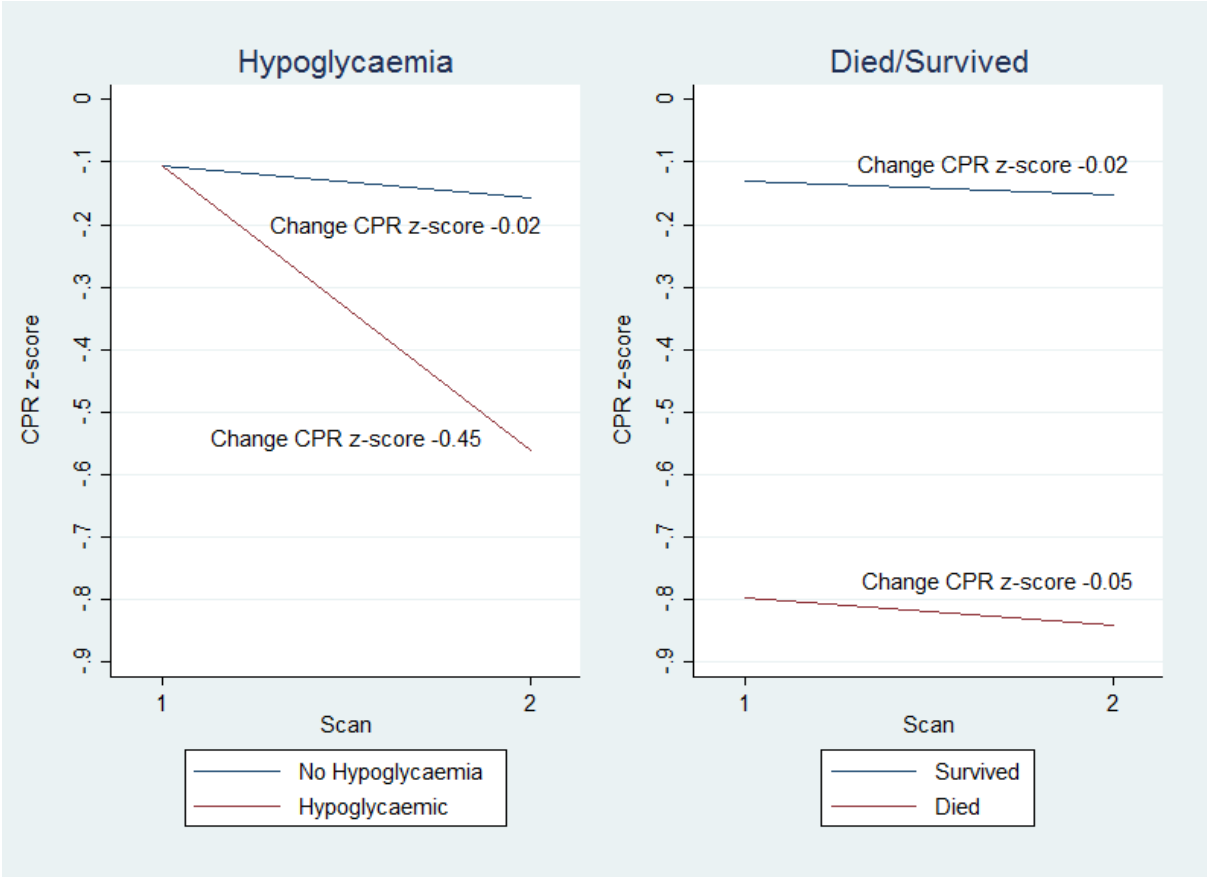

Figure 4-2: Change in CPR between scan 1 and scan 2 of hypoglycaemic compared to non–hypoglycaemic fetuses and fetuses that died compared to fetuses that survived.

CPR: Cerebroplacental Ratio

The AUCs derived from univariable logistic regression indicated that CPR *Z*–score at 35 – 37 weeks was a better predictor than was the change in CPR *Z*–score for the majority of adverse neonatal outcomes, although the AUC was <0.7 for all outcomes.

After adjusting for the change in CPR *Z*–scores, there was no improvement in the predictive value of CPR when measured at 35 – 37 weeks gestation (AUC <0.69 for all outcomes). Comparison of ROC curves derived from multivariable logistic regression, adjusted for any potential confounding effects of parity, maternal hypertension, diabetes, BMI and smoking status, indicated no significant improvement in any of the models (Table 4.4).

Table 4-4: Adjusted area under the curve for neonatal outcomes.

	Last CPR *Z*–score (35 – 37 Weeks)	**Change in CPR *Z*–score/Week**	**Last CPR *Z*–score & Change in CPR/Week**	**Last CPR AUC c.f. Last & Change in CPR/Week AUC**
	AUC (95% C.I.)	AUC (95% C.I.)	AUC (95% C.I.)	P value
SVD	0.627 (0.602 – 0.652)	0.626 (0.601 – 0.652)	0.627 (0.602 – 0.652)	0.68
Instrumental	0.740 (0.705 – 0.775)	0.743 (0.708 – 0.777)	0.743 (0.708 – 0.777)	0.56
Elective CS	0.642 (0.612 – 0.672)	0.640 (0.609 – 0.670)	0.642 (0.611 – 0.672)	0.88
Emergency CS	0.659 (0.627 – 0.691)	0.657 (0.625 – 0.689)	0.662 (0.630 – 0.694)	0.28
NRFS	0.736 (0.686 – 0.785)	0.700 (0.652 – 0.748)	0.734 (0.684 – 0.784)	0.65
Other	0.624 (0.585 – 0.662)	0.629 (0.590 – 0.667)	0.629 (0.591 – 0.668)	0.45
Preterm (<37 Weeks)	0.687 (0.645 – 0.728)	0.634 (0.585 – 0.682)	0.683 (0.640 – 0.726)	0.43
BWT <10th centile	0.765 (0.731 – 0.800)	0.716 (0.678 – 0.753)	0.770 (0.735 – 0.804)	0.37
Apgar <7 at 5 min	0.658 (0.567 – 0.748)	0.604 (0.501 – 0.706)	0.663 (0.570 – 0.756)	0.75
NCCU	0.614 (0.577 – 0.651)	0.596 (0.559 – 0.634)	0.639 (0.602 – 0.676)	0.05
Respiratory Distress	0.576 (0.533 – 0.618)	0.586 (0.543– 0.628)	0.603 (0.560 – 0.646)	0.12
Perinatal Death	0.753 (0.640 – 0.866)	0.710 (0.606 – 0.814)	0.762 (0.638 – 0.885)	0.65
Hypoglycaemia	0.716 (0.546 – 0.886)	0.770 (0.583 – 0.957)	0.765 (0.580 – 0.949)	0.48
Acidosis	0.681 (0.630 – 0.732)	0.680 (0.628 – 0.731)	0.679 (0.627 – 0.731)	0.72
Composite	0.619 (0.590 – 0.649)	0.593 (0.564 – 0.622)	0.630 (0.600 – 0.660)	0.11

*Adjusted for parity, hypertension, diabetes, body mass index and smoking status
BWT: Birth weight; SVD: Spontaneous vaginal delivery; CS: Caesarean Section; NRFS: Emergency Caesarean Indicated for Non–Reassuring Fetal Status; NCCU: Neonatal Critical Care Unit; CPR: Cerebroplacental ratio; AUC: area under Curve

Composite Adverse Neonatal Outcome: defined as perinatal death, birth by emergency caesarean for non–reassuring fetal status, NCCU admission, severe respiratory distress, Apgar score <7 at 5 minutes, hypoglycaemia, or acidosis at birth.

4.6 Discussion

The results of our study suggest that the CPR *Z*–score measured at 35 – 37 weeks gestation is associated with a better predictive value for adverse pregnancy outcome than is the magnitude of change in CPR *Z*–score over time. We found that the greatest reduction in CPR *Z*–score over time was associated with an increased risk of having an emergency caesarean section, particularly for non-reassuring fetal status. It was also associated with preterm delivery before 37 weeks, birth weight <10th centile and neonatal hypoglycaemia. Although these adverse outcomes are also associated with a low CPR at 35 – 37 weeks, what is interesting is that the risks of these complications were higher when the CPR *Z*–score reduction was greatest. In particular, the greatest decrease in CPR *Z*–score over time was seen in the cohort of pregnancies that had significant neonatal hypoglycaemia. Our findings also suggest that preterm delivery before 37 weeks is associated with a mean decline of 0.2 SD per week.

The reduction in CPR *Z*–score over time was also greater in neonates with a birth weight <10th centile than in those with a birth weight ≥10th centile, although the magnitude of the reduction in mean CPR *Z*–score was not as large as that observed for preterm or hypoglycaemic fetuses. However, this cohort of fetuses, as well as those with composite adverse neonatal outcome, already had a very low mean CPR *Z*–score at the first scan, suggesting significantly poorer placental function and thus limited capacity for further decrease in CPR *Z*–score (Figure 4.2).

As with previous studies(4, 11, 15, 40, 57, 60, 67, 157, 158), our results indicate that a low CPR measured late in the third trimester is associated with adverse perinatal outcome. However, by measuring the change in CPR *Z*–score over time, it may be possible to identify fetuses whose hemodynamic status is in more rapid decline, increasing their risk of adverse perinatal outcome, in particular hypoglycaemia, preterm birth and emergency caesarean section for non–reassuring fetal status.

Allam and Maarouf (159) found, in a group of 201 women in Egypt, that a low CPR at 31 – 42 weeks gestation was more common in women with hypertension, and in their meta–analysis Bramham *et al*. (160) found that women with chronic hypertension had a significant risk of developing superimposed pre–eclampsia and worse perinatal outcome, such as low birth weight, preterm birth, caesarean section, perinatal death and admission to the neonatal intensive care unit. In contrast, we found no difference in CPR *Z*–score at the second scan in hypertensive

compared with normotensive women. However, we did find a significant difference in the change in CPR *Z*–score over time between these two groups.

Although a number of previous studies have assessed the relationship between a single low CPR measured at various gestational timepoints and adverse outcome (4, 11, 15, 40, 57, 60, 67, 157, 158), there have been no studies assessing the impact of the magnitude of change in the CPR and its association with adverse pregnancy outcome. This study attempts to address this paucity of data. However, comparison of CPR *Z*–scores at different timepoints poses statistical problems as well as problems of interpretation. The variability in gestational age at which the CPR was measured presents a problem, as a raw change in CPR value can be misleading. Furthermore, the interval between the scans was variable and the gestational age at which each scan was performed influenced the size of the difference in the CPR. Differences in mean CPR between gestational weeks makes a valid comparison of scans between two or more timepoints difficult. To address these limitations, using the GAMLSS model and Box–Cox transformation to obtain standardized centiles, we were able to create gestational-age reference ranges of CPR *Z*–scores (Figure 4.1) using a truly representative cohort of uncomplicated vaginal deliveries, without any adverse perinatal outcome. By dividing the change in CPR by the change in gestational age between scans, we were able to undertake a comparison of the change in CPR *Z*–score over time, adjusting for discrepancies in time between scans.

The limitations of this study include those inherent to its retrospective nature. The study cohort was clearly not an unselected population, with ultrasound scans performed for various clinical indications, including previous obstetric history, maternal medical conditions, such as diabetes or hypertension, and uncertainty regarding fetal size. However, our reference cohort all had normal pregnancies and normal perinatal outcomes, and thus provided a realistic sample with which to compare those who had adverse outcomes.

Our results suggest that both the individual CPR *Z*–score and the magnitude and direction of change in CPR *Z*–score can identify pregnancies at risk of various adverse perinatal outcomes; however, the CPR *Z*–score at 35 – 37 weeks gestation appears to be a better indicator of outcome.

Chapter 5: Reference centiles for the middle cerebral artery and umbilical artery pulsatility index and cerebroplacental ratio from a low–risk population – a Generalised Additive Model for Location, shape and Scale (GAMLSS) approach

Christopher Flatley[1], Sailesh Kumar[1,2] and Ristan M. Greer[1,2]

1. Mater Research Institute, University of Queensland, Brisbane, Australia.
2. School of Medicine, University of Queensland, Queensland, Australia.

This chapter addresses the secondary objective:

Develop reference centiles for the ultrasound measurements of the UA PI, the MCA PI and the CPR using the GAMLSS approach.

Published in The Journal of Maternal – Fetal & Neonatal Medicine

Citation

Christopher Flatley, Sailesh Kumar & Ristan M. Greer (2018): Reference centiles for the middle cerebral artery and umbilical artery pulsatility index and cerebroplacental ratio from a low–risk population – a Generalised Additive Model for Location, Shape and Scale (GAMLSS) approach, The Journal of Maternal–Fetal & Neonatal Medicine, DOI: 10.1080/14767058.2018.1432590

DOI: https://doi.org/10.1080/14767058.2018.1432590

5.1 Abstract

Objectives: The primary aim of this study was to create reference ranges for the fetal Middle Cerebral artery Pulsatility Index (MCA PI), Umbilical Artery Pulsatility Index (UA PI) and the Cerebroplacental Ratio (CPR) in a clearly defined low–risk cohort using the Generalised Additive Model for Location, Shape and Scale (GAMLSS) method.

Methods: Prospectively collected cross–sectional biometry and Doppler data from low–risk women attending the Mater Mother's Hospital, Maternal and Fetal Medicine Department in Brisbane, Australia between January 2010 and April 2017 were used to derive gestation specific centiles for the MCA PI, UA PI and CPR. All ultrasound scans were performed between 18+0 and 41+6 weeks gestation with recorded data for the MCA PI and/or UA PI. The GAMLSS method was used for the calculation of gestational age–adjusted centiles. Distributions and additive terms were assessed, and the final model was chosen on the basis of the Global Deviance, Akaike information criterion (AIC) and Schwartz Bayesian criterion (SBC), along with the results of the model and residual diagnostics as well as visual assessment of the centiles themselves.

Results: Over the study period 6,013 women met the inclusion criteria. The MCA PI was recorded in 4,473 fetuses, the UA PI in 6,008 fetuses and the CPR was able to be calculated in 4,464 cases. The centiles for the MCA PI used a fractional polynomial additive term and Box–Cox t (BCT) distribution. Centiles for the UA PI used a cubic spline additive term with BCT distribution and the CPR used a fractional polynomial additive term and a BCT distribution.

Conclusion: We have created gestational centile reference ranges for the MCA PI, UA PI and CPR from a large low–risk cohort that supports their applicability and generalisability.

5.2 Introduction

The fetal Cerebroplacental Ratio (CPR) is the ratio of the Middle Cerebral Artery Pulsatility Index (MCA PI) to the Umbilical Artery Pulsatility Index (UA PI) that shows promise as a tool for the identification of fetuses at risk of a variety of intrapartum and neonatal complications particularly in late pregnancy (8, 15, 53, 57, 58, 60, 67). More recently a low CPR has also been shown to be predictive of perinatal loss at term (161).

Given the increasing use of the CPR in clinical management, it is vital that any CPR value is interpreted with respect to standardised reference centiles that have been created using appropriately rigorous statistical methodology and are broadly applicable to different populations. Although there have been several publications detailing reference centiles for the MCA PI (72, 83), UA PI (72, 82) and CPR (57, 72), these are potentially limited by methodological constraints such as small sample size, suboptimal modelling and lack of reporting of model diagnostics or subsequent goodness–of–fit evaluation (83). The statistical techniques, characteristics of the study population used for creating the centiles as well as inclusion and exclusion criteria used to define a "normal cohort" will also undoubtedly influence the generalisability of the centiles developed.

The methodology for the creation of size and growth reference centiles has expanded greatly since the first simple height and growth curves were published in the eighteenth century to the more recent development of the Lambda, Mu and Sigma methods introduced by Cole (100, 162). The World Health Organization in 2006 published detailed description of the statistical techniques used to develop child growth curves and after a review of 30 different methods, the authors recommended that the Generalised Additive Model for Location, Scale and Shape (GAMLSS) was the most appropriate for this purpose (99, 101).

The GAMLSS model, first developed by Rigby and Stasinopoulos offers a highly robust and flexible approach to modelling data that are highly skewed and kurtotic (113, 117, 163). It is currently the only method that is able to model all forms of kurtosis – lepto, platy and mesokurtosis and is able to model all four parameters of distribution (mean, standard deviation, skewness and kurtosis) for the response variable as smooth nonparametric functions within each group of the explanatory variable (92, 106, 113, 117, 163).

As ultrasound and Doppler data are rarely normally distributed, the GAMLSS approach, because of its parametric and nonparametric functionality, offers a suitable method to model the four parameters of distribution.

Our aim was thus to develop reference centiles for the MCA PI, UA PI and CPR using the GAMLSS technique in a large sample of low–risk women.

5.3 Methods

Prospectively collected, cross–sectional biometry and Doppler data from women attending the Mater Mother's Hospital, Maternal and Fetal Medicine Department in Brisbane, Australia between January 2010 and April 2017 were used to derive gestation specific centiles for MCA PI, UA PI and CPR. The Mater Mother's Hospital is a major tertiary centre in the state of Queensland and the largest maternity hospital in Australia with approximately 10,000 births per year. Maternal demographic data from the institution's obstetric database was cross– referenced against the ultrasound and neonatal databases to construct the study cohort. The study protocol was approved by the hospital's Human Research Ethics Committee (reference number HREC/14/MHS/37).

For measurement of the MCA PI and UA PI, an automated tracing method was used, which incorporated at least three waveforms and repeated three times to obtain the mean Pulsatility Index. The angle of insonation for both vessels was usually <10° and not greater than 30° for all measurements. The MCA was imaged using colour Doppler and its waveform recorded from the proximal third of the vessel, distal to its origin from the circle of Willis. The UA Doppler waveform was recorded from a free loop of cord and the CPR was calculated by dividing the MCA PI by the UA PI. Gestational age was calculated using the crown–rump length measured in the first trimester.

Inclusion criteria were women aged between 18 – 40 years with a single non–anomalous fetus who delivered at term. Women who had undergone assisted reproduction techniques (ART), Body Mass Index (BMI) ≥35 kg/m^2, had diabetes mellitus, chronic or pregnancy induced hypertension, preeclampsia, respiratory, thyroid or heart disease or had known fetal growth restriction (FGR) were excluded from the study cohort, as the aim was to create appropriate centiles in a clearly defined low–risk population. All ultrasound scans were performed between 18+0 and 41+6 weeks gestation with recorded data for the MCA PI and/or UA PI.

5.4 Statistical Analysis

The GAMLSS method (117, 163) was used for the calculation of gestational age– adjusted centiles. Penalised Basis Spline, Cubic Spline, Polynomial and Fractional Polynomial smoothing were assessed on the basis of the Global Deviance, Akaike information criterion (AIC) and Schwartz Bayesian criterion (SBC). Normal, Gamma, Inverse Gamma, Gumbel, Reverse Gumbel, Logistic, Cole and Green Box–Cox, Power Exponential, t Family, Box–Cox t (BCT) and Box–Cox Power Exponential distributions were all assessed using the AIC and SBC to select the best fit model. Model diagnostics were also performed to assess the fit of the model using worm plots, Q–Q plots (163, 164), and a detrended transformed Owen's plot (163, 165). The final model was chosen on the basis of the AIC and SBC along with the results of the model and residual diagnostics as well as visual assessment of the centiles themselves.

Summary statistics are reported as percentage (number), mean (SD) or median (interquartile range, IQR) as appropriate. Data analysis was performed using StataCorp. 2015. Stata statistical software: Release 14. College Station, TX: Stata Corp LP. The GAMLSS algorithm was implemented using R software (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.r– project.org/) and the GAMLSS package by Rigby RA and Stasinopoulos DM (113).

5.5 Results

Over the study period, 23,152 women were identified as having had an ultrasound scan between 18+0 and 41+6 weeks gestation with recorded data for the MCA PI and/or UA PI. Of these 17,139 women were excluded as they did not fulfil the inclusion criteria leaving 6,013 women in the final cohort. Characteristics of the study population are presented in Table 5.1. The MCA PI was recorded in 4,473 fetuses; the UA PI was recorded in 6,008 fetuses and the CPR was able to be calculated in 4,464 cases. Characteristics of the study cohort are outlined in Table 5.1.

Table 5-1: Characteristics of the study population (n=4,630).

Characteristics	
Maternal Age*	30.5 (4.9)
Nulliparous	46.4% (2,788/6,013)
BMI‡	22.3 (20.1 – 25.4)
Ethnicity	
Caucasian	50.2% (3,019/6,013)
Indigenous	1.4% (84/6,013)
Asian	29.0% (1,746/6,013)
Other	19.4% (1,164/6,013)
IOL	32.1% (1,927/6,013)
Birthweight*	3,419 (444)
Gender	
Male	50.9% (3,062 /6013)
Female	49.1% (2,951 /6,013)
Gestation at Birth	39 (38 – 40)
Method of Birth	
Spontaneous Vaginal Birth	54.7% (3,288/6,013)
Instrumental	14.3% (862/6,013)
Elective Caesarean	15.2% (913/6,013)
Emergency Caesarean	15.8% (950/6,013)
Emergency CS NRFS	4.2% (252/6,013)
NICU admission	4.8% (288/6,013)
Acidosis	6.2% (375/6,013)
Apgar <7 at 5 minutes	1.5% (89/6,013)
Died (stillbirth and neonatal death)	0.1% (8/6,013)

* Mean (Standard Deviation)
‡ Median (Interquartile Range)
IOL: Induction of Labour, BMI: Body Mass Index, CS NRFS: Emergency Caesarean Non–Reassuring Fetal Status, NICU: Neonatal Intensive Care Unit, Acidosis (Arterial Cord pH <7.0 or Lactate >6.0mmol/L or Base Excess $\leq$12mmol/L)

5.5.1 Middle Cerebral Artery Pulsatility Index

After assessment of the smoothing and transformation parameters, the best fit model for the MCA PI was a fractional polynomial additive term and BCT distribution for the calculation of the centiles. Centile threshold values according to gestational age for the MCA PI are reported in Table 5.2 with the centiles presented in Figure 5.1.

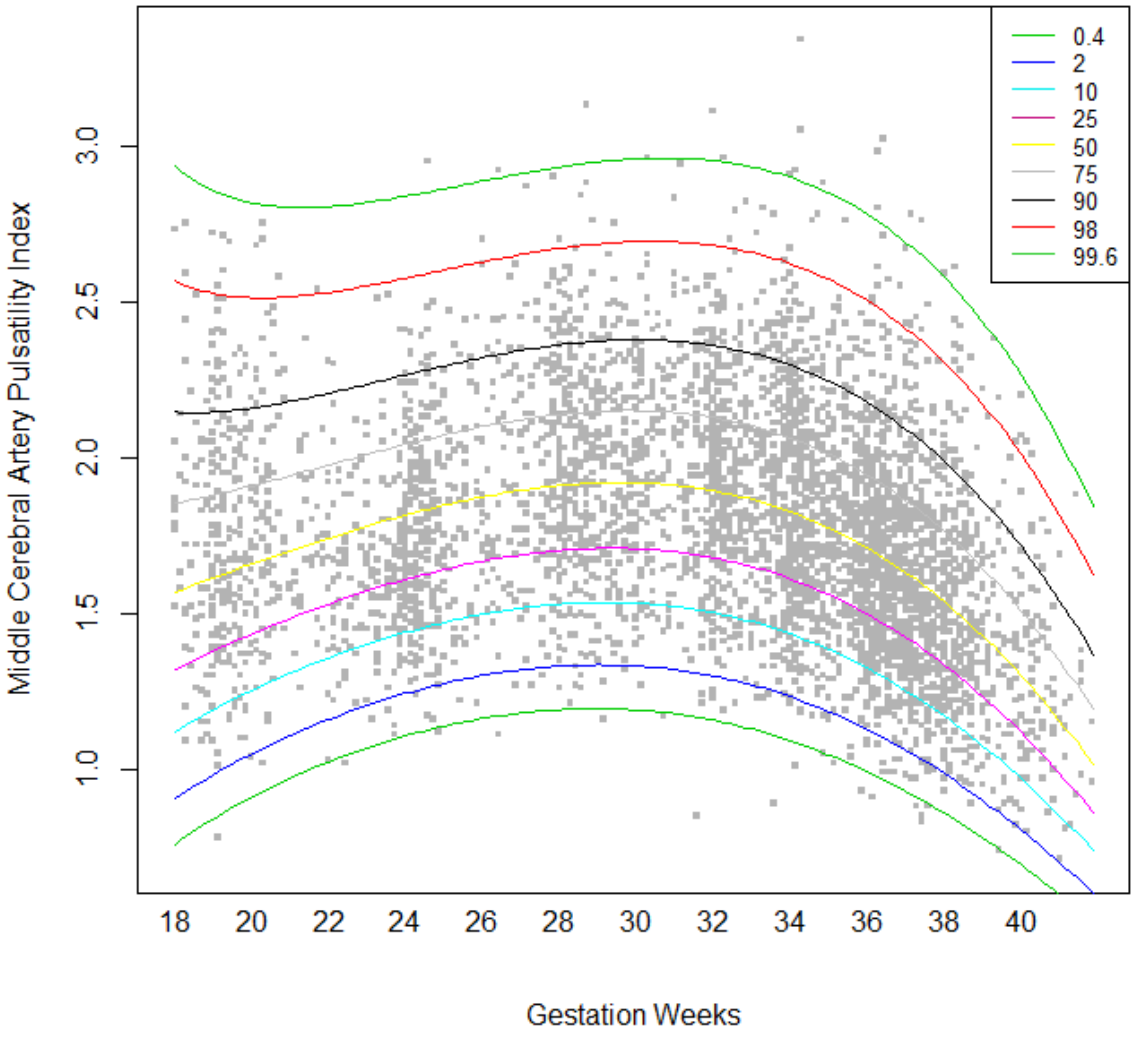

Figure 5-1: Middle cerebral artery pulsatility index centile curves using BCT.

Table 5-2: Middle cerebral artery pulsatility index centiles.

Gestational (Week)	0.4th	2nd	5th	10th	25th	50th	75th	90th	95th	98th	99.6th	Number
18	0.76	0.90	1.01	1.12	1.32	1.57	1.85	2.15	2.34	2.57	2.93	64
19	0.84	0.98	1.09	1.19	1.38	1.61	1.88	2.15	2.32	2.53	2.86	193
20	0.91	1.05	1.15	1.25	1.43	1.66	1.91	2.16	2.32	2.51	2.82	106
21	0.97	1.11	1.21	1.31	1.48	1.70	1.94	2.18	2.33	2.52	2.80	41
22	1.02	1.16	1.26	1.36	1.53	1.74	1.98	2.21	2.35	2.53	2.80	65
23	1.07	1.21	1.31	1.40	1.57	1.78	2.01	2.24	2.38	2.55	2.82	110
24	1.11	1.24	1.34	1.44	1.61	1.82	2.04	2.27	2.41	2.58	2.84	265
25	1.14	1.28	1.38	1.47	1.64	1.85	2.07	2.29	2.44	2.60	2.86	74
26	1.16	1.30	1.40	1.50	1.67	1.87	2.10	2.32	2.46	2.63	2.89	74
27	1.18	1.32	1.42	1.52	1.69	1.90	2.12	2.34	2.48	2.65	2.91	105
28	1.19	1.33	1.43	1.53	1.70	1.91	2.14	2.36	2.50	2.67	2.93	279
29	1.19	1.33	1.44	1.54	1.71	1.92	2.15	2.37	2.52	2.69	2.95	146
30	1.19	1.33	1.44	1.53	1.71	1.92	2.15	2.38	2.52	2.69	2.96	141
31	1.18	1.32	1.42	1.52	1.70	1.91	2.14	2.37	2.52	2.69	2.96	132
32	1.16	1.30	1.40	1.50	1.68	1.89	2.13	2.36	2.51	2.68	2.95	315
33	1.13	1.27	1.37	1.47	1.65	1.86	2.10	2.33	2.48	2.66	2.93	223
34	1.09	1.23	1.34	1.43	1.61	1.83	2.06	2.30	2.44	2.62	2.90	419
35	1.05	1.18	1.29	1.38	1.56	1.77	2.01	2.24	2.39	2.57	2.85	297
36	0.99	1.13	1.23	1.32	1.50	1.71	1.94	2.18	2.33	2.50	2.78	523
37	0.93	1.06	1.16	1.25	1.42	1.63	1.86	2.09	2.24	2.41	2.69	435
38	0.86	0.99	1.08	1.17	1.33	1.54	1.76	1.99	2.13	2.30	2.58	260
39	0.78	0.90	0.99	1.08	1.23	1.43	1.64	1.86	2.00	2.17	2.44	107
40	0.69	0.80	0.89	0.97	1.12	1.30	1.51	1.71	1.85	2.01	2.26	80
41	0.60	0.70	0.78	0.85	0.99	1.16	1.35	1.54	1.67	1.82	2.06	19

Model diagnostics show the plots of residuals are normally distributed around zero, as well as the density and Q–Q plot (Figure 5.2).

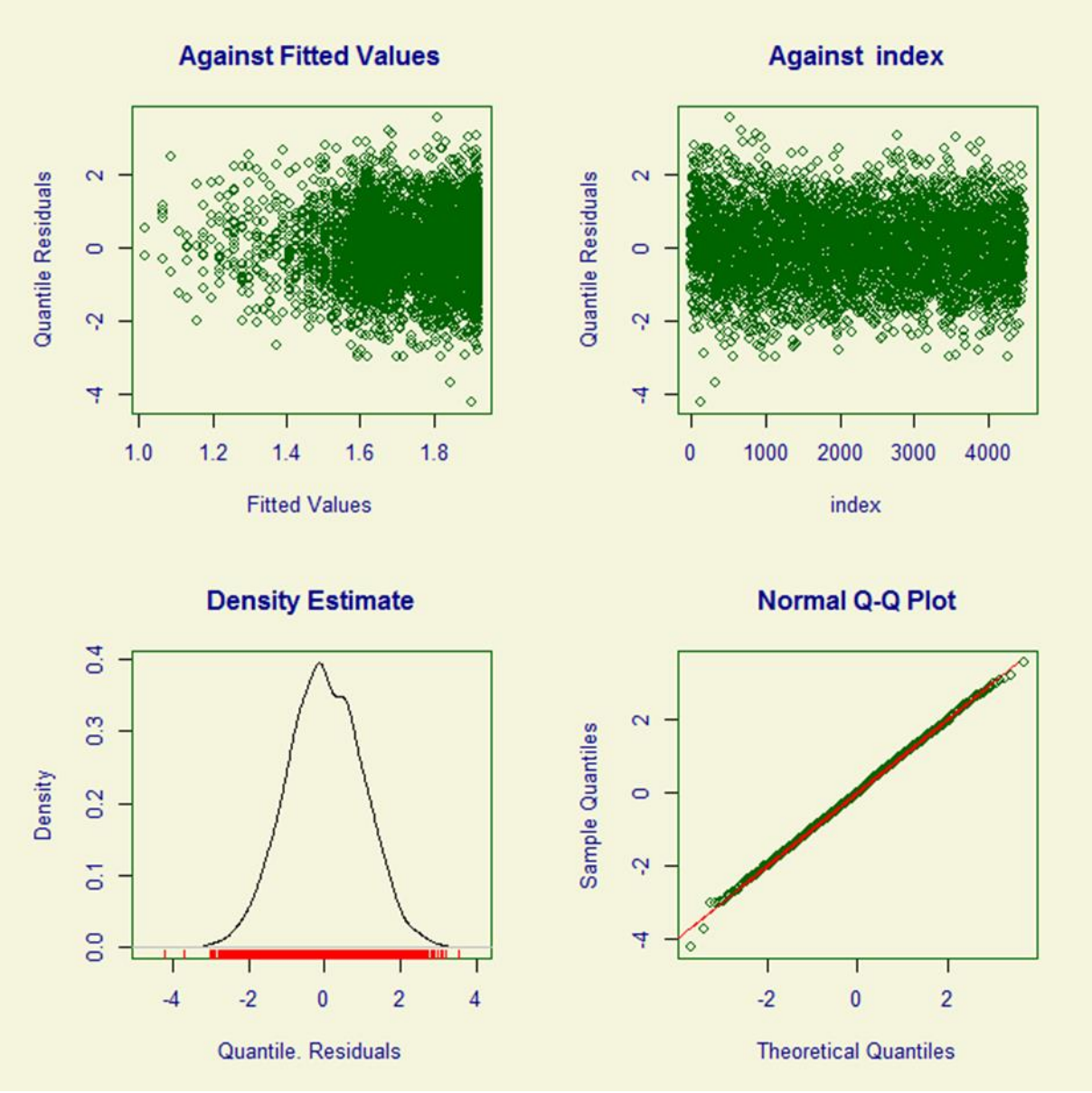

Figure 5-2: Residual plots of the middle cerebral artery pulsatility index centile curves.

Summary of the quantile residuals show the mean is 0.002, the variance is 1.0002, coefficient of skewness is – 0.01 and the coefficient of kurtosis is 2.94. The worm plot indicates that the fitted mean is appropriate as there is very slight deviation from the origin (Figure 5.3).

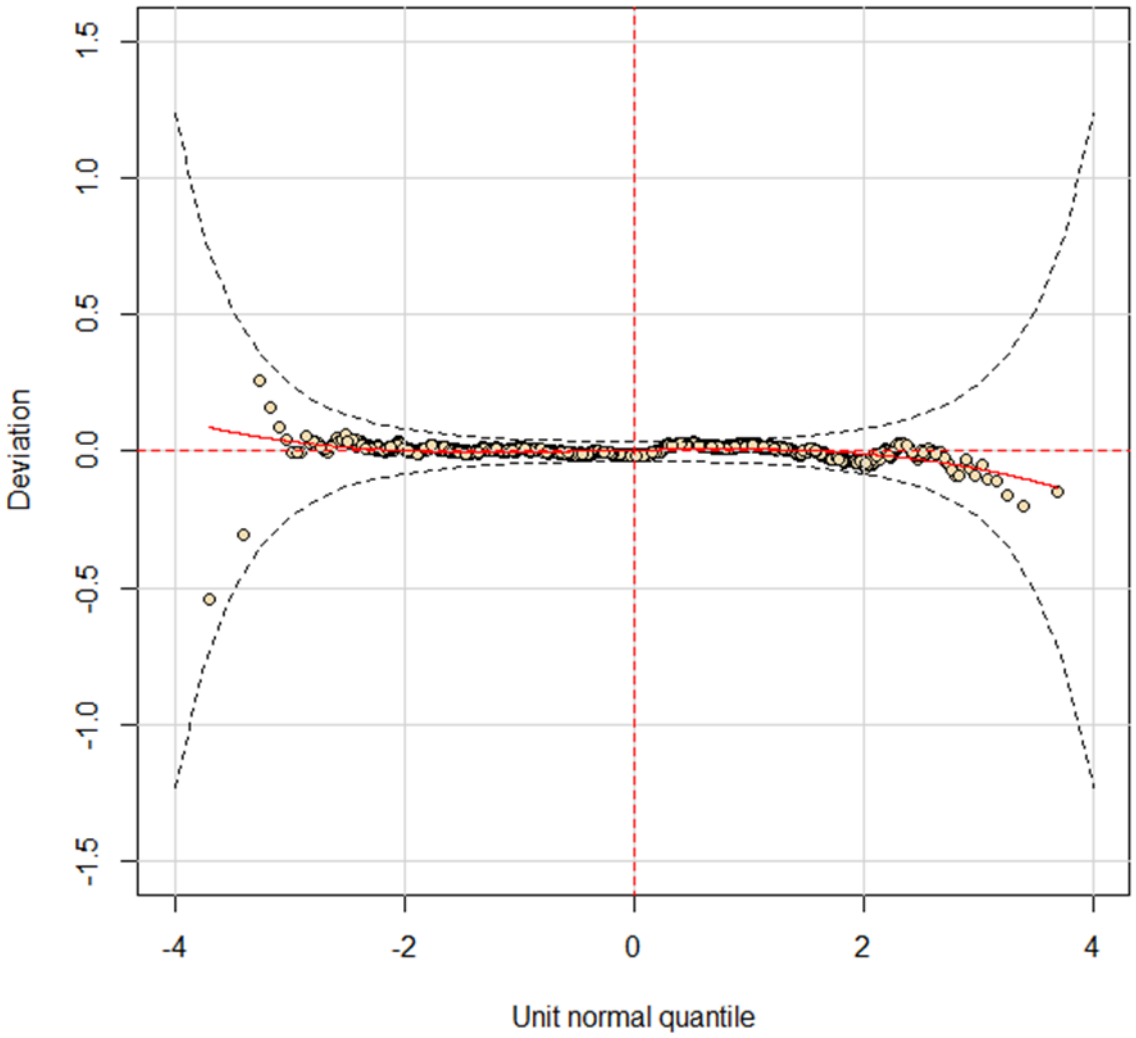

Figure 5-3: Worm plot of the middle cerebral artery pulsatility index centile curves.

There is appropriate fitting of the variance and no apparent skewness indicating the fitted distribution is appropriate. The detrended transformed Owen's plot shows that the horizontal line is within the confidence interval of the plot indicating that the normalised residuals have come from a normal distribution and therefore the model is a reasonable fit for the data (Figure 5.4).

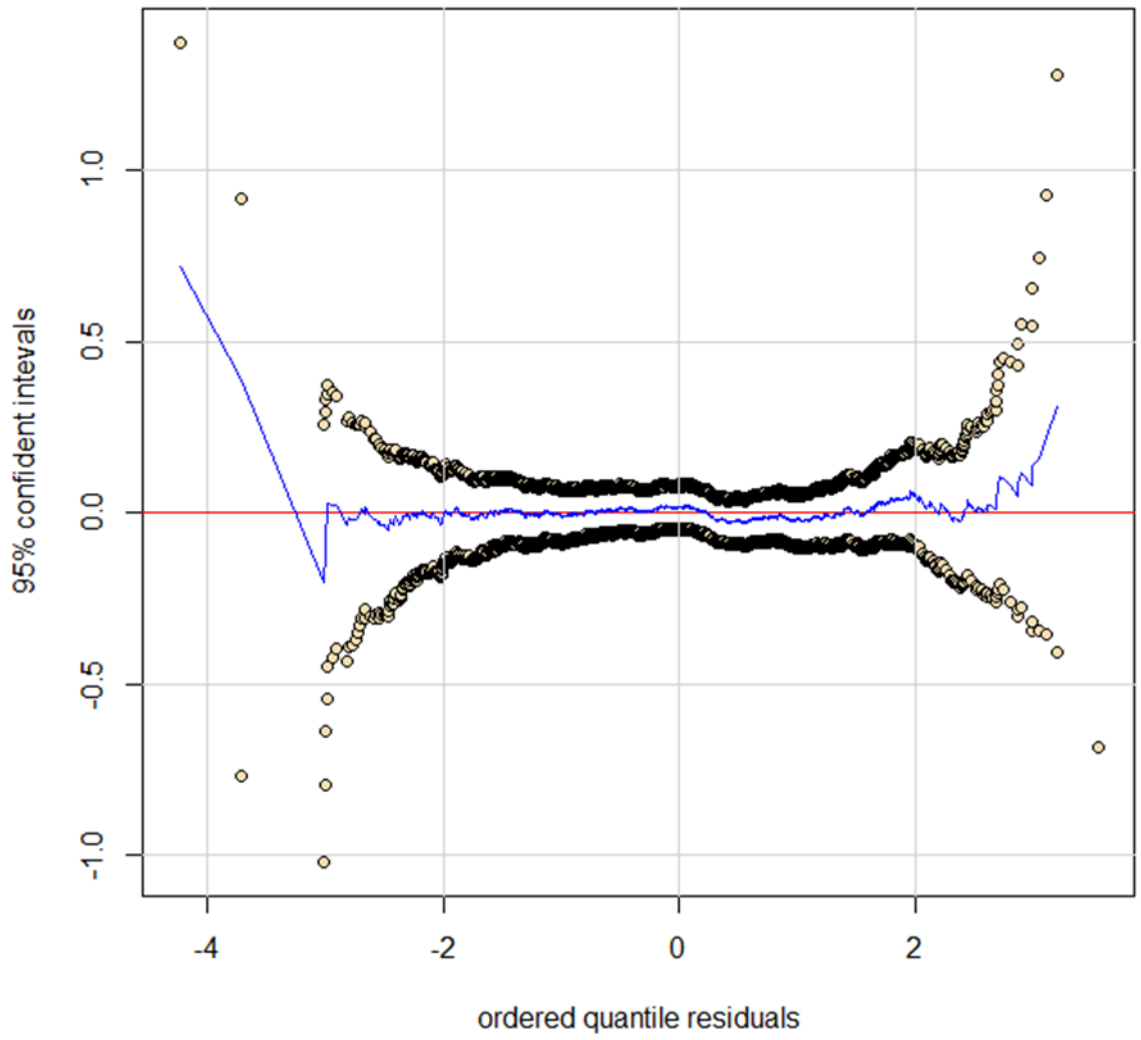

Figure 5-4: De–trended Owen's plot of the middle cerebral artery pulsatility index centile curves.

5.5.2 Umbilical Artery Pulsatility Index

For the UA PI the best fit was a cubic spline additive term with BCT distribution. Gestational age centile thresholds are detailed in Table 3 with the centiles graphed in Figure 5.5.

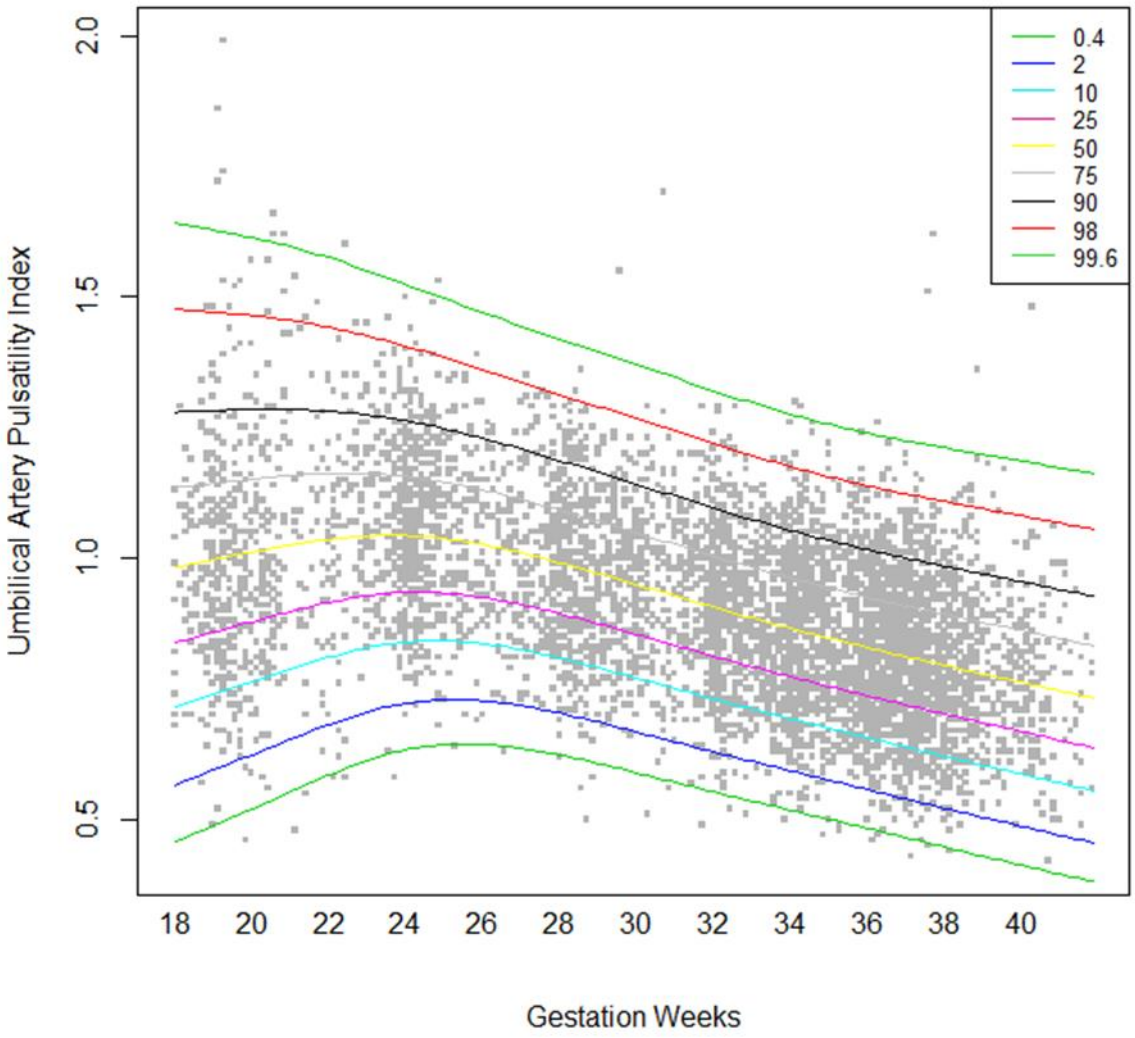

Figure 5-5: Umbilical artery pulsatility index centile curves using BCT.

Table 5-3: Umbilical artery pulsatility index centiles.

Gestation (Week)	0.4th	2nd	5th	10th	25th	50th	75th	90th	95th	98th	99.6th	Number
18	0.46	0.57	0.64	0.72	0.84	0.98	1.14	1.28	1.37	1.48	1.64	82
19	0.49	0.60	0.67	0.74	0.86	1.00	1.14	1.28	1.37	1.47	1.63	256
20	0.52	0.62	0.70	0.76	0.88	1.01	1.15	1.28	1.37	1.46	1.61	140
21	0.55	0.65	0.72	0.79	0.90	1.03	1.16	1.28	1.36	1.46	1.60	50
22	0.59	0.68	0.75	0.81	0.92	1.04	1.16	1.28	1.36	1.44	1.58	88
23	0.61	0.71	0.77	0.83	0.93	1.04	1.16	1.27	1.34	1.43	1.55	179
24	0.63	0.72	0.78	0.84	0.93	1.04	1.16	1.26	1.33	1.41	1.52	389
25	0.64	0.73	0.79	0.84	0.93	1.04	1.15	1.25	1.31	1.38	1.50	123
26	0.64	0.73	0.78	0.84	0.93	1.03	1.13	1.23	1.29	1.36	1.47	112
27	0.64	0.72	0.77	0.83	0.91	1.01	1.11	1.21	1.27	1.34	1.44	143
28	0.62	0.70	0.76	0.81	0.89	0.99	1.09	1.19	1.25	1.31	1.42	367
29	0.61	0.69	0.74	0.79	0.88	0.97	1.07	1.16	1.22	1.29	1.39	182
30	0.59	0.67	0.72	0.77	0.85	0.95	1.05	1.14	1.20	1.27	1.37	181
31	0.57	0.65	0.70	0.75	0.83	0.93	1.03	1.12	1.18	1.24	1.35	188
32	0.55	0.63	0.68	0.73	0.81	0.91	1.00	1.10	1.15	1.22	1.32	449
33	0.54	0.61	0.66	0.71	0.79	0.89	0.98	1.07	1.13	1.20	1.30	288
34	0.52	0.59	0.65	0.69	0.77	0.87	0.96	1.05	1.11	1.18	1.28	546
35	0.50	0.58	0.63	0.67	0.76	0.85	0.94	1.03	1.09	1.16	1.26	377
36	0.48	0.56	0.61	0.66	0.74	0.83	0.93	1.02	1.07	1.14	1.24	676
37	0.47	0.54	0.59	0.64	0.72	0.81	0.91	1.00	1.06	1.12	1.22	618
38	0.45	0.52	0.57	0.62	0.70	0.80	0.89	0.98	1.04	1.11	1.21	316
39	0.43	0.50	0.56	0.60	0.69	0.78	0.88	0.97	1.03	1.10	1.20	125
40	0.41	0.49	0.54	0.59	0.67	0.76	0.86	0.96	1.01	1.08	1.19	102
41	0.40	0.47	0.52	0.57	0.65	0.75	0.85	0.94	1.00	1.07	1.17	31

Model diagnostics show the plots of most of the residuals are normally distributed around zero. The density and Q–Q plot however, indicate that the data is slightly skewed to the right (Figure 5.6).

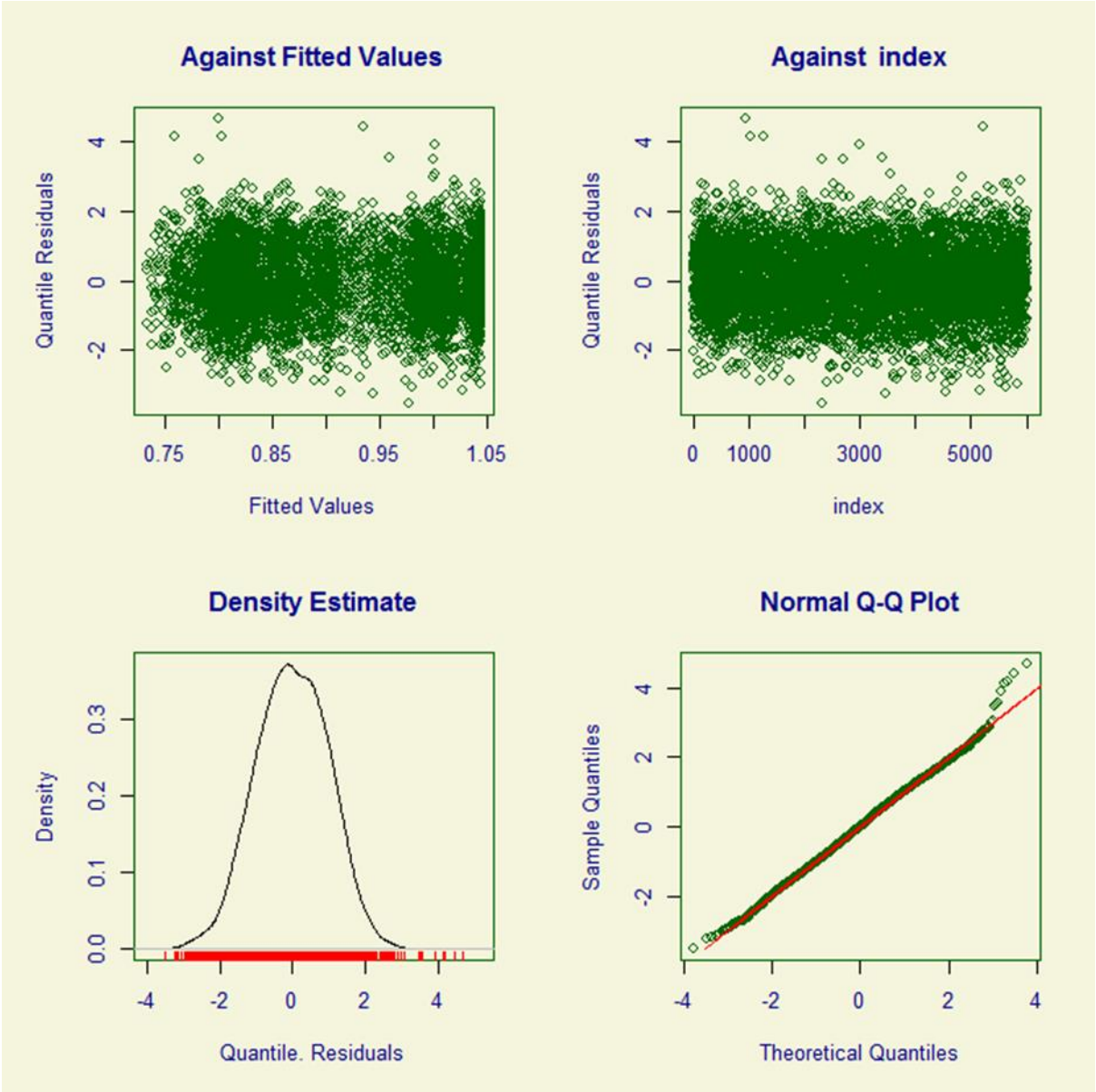

Figure 5-6: Residual plots of the umbilical artery pulsatility index centile curves.

The summary of the quantile residuals shows the mean is – 0.002, the variance is 1.0001, coefficient of skewness is – 0.01 and the coefficient of kurtosis is 3.001. The worm plot deviates and slightly passes below the origin with a very slight negative slope – a possible indication that the fitted mean and variance is too large. However, the deviation is unlikely to be of consequence due to the very small magnitude. There is no apparent skewness and excessive kurtosis is also absent indicating appropriate fitting of the distribution of the tails (Figure 5.7).

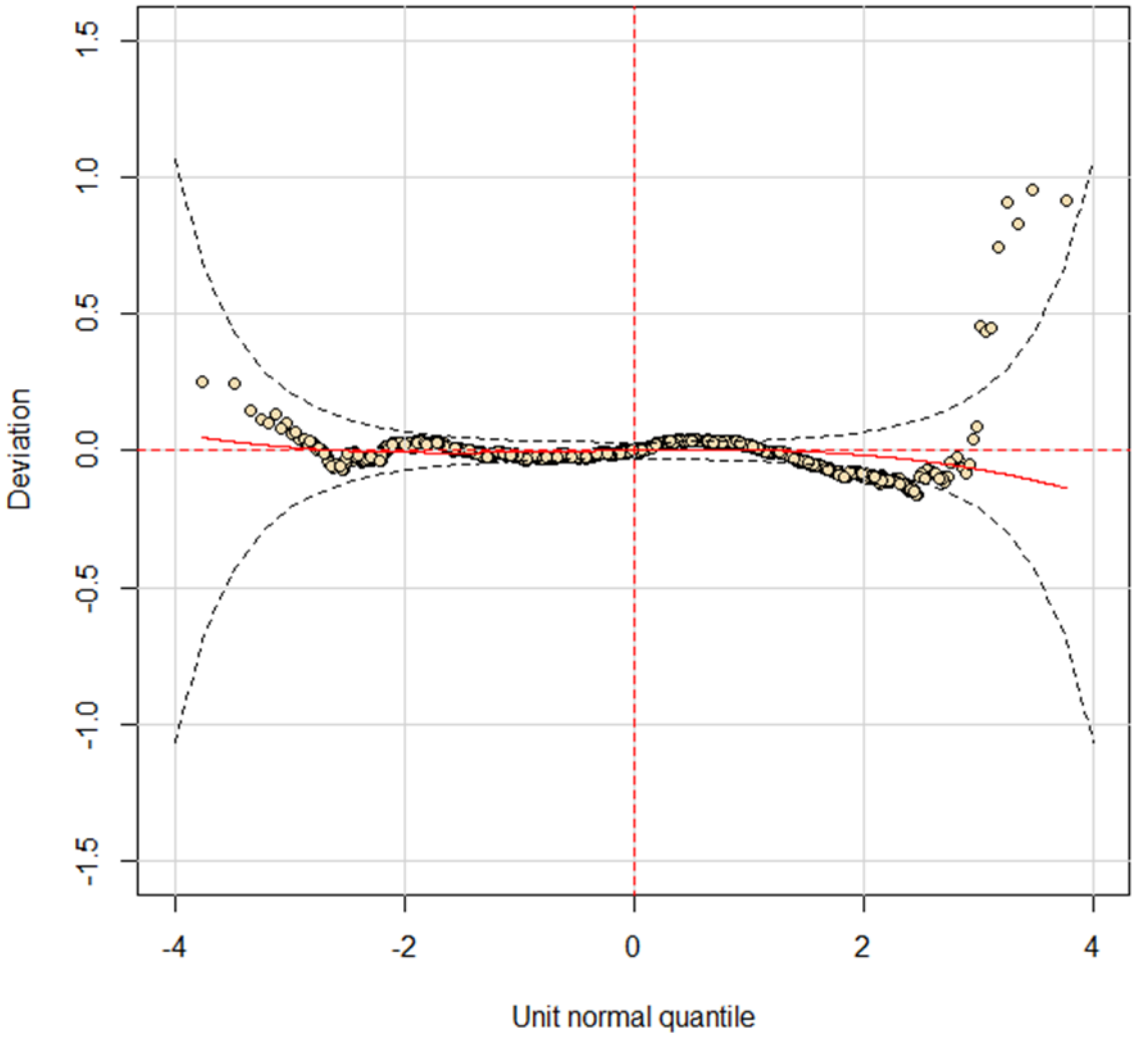

Figure 5-7: Worm plot of the umbilical artery pulsatility index centile curves.

The detrended transformed Owen's plot demonstrates that although the normalised residuals may have a long right sided tail it still indicates that the model is a reasonable fit for the data (Figure 5.8).

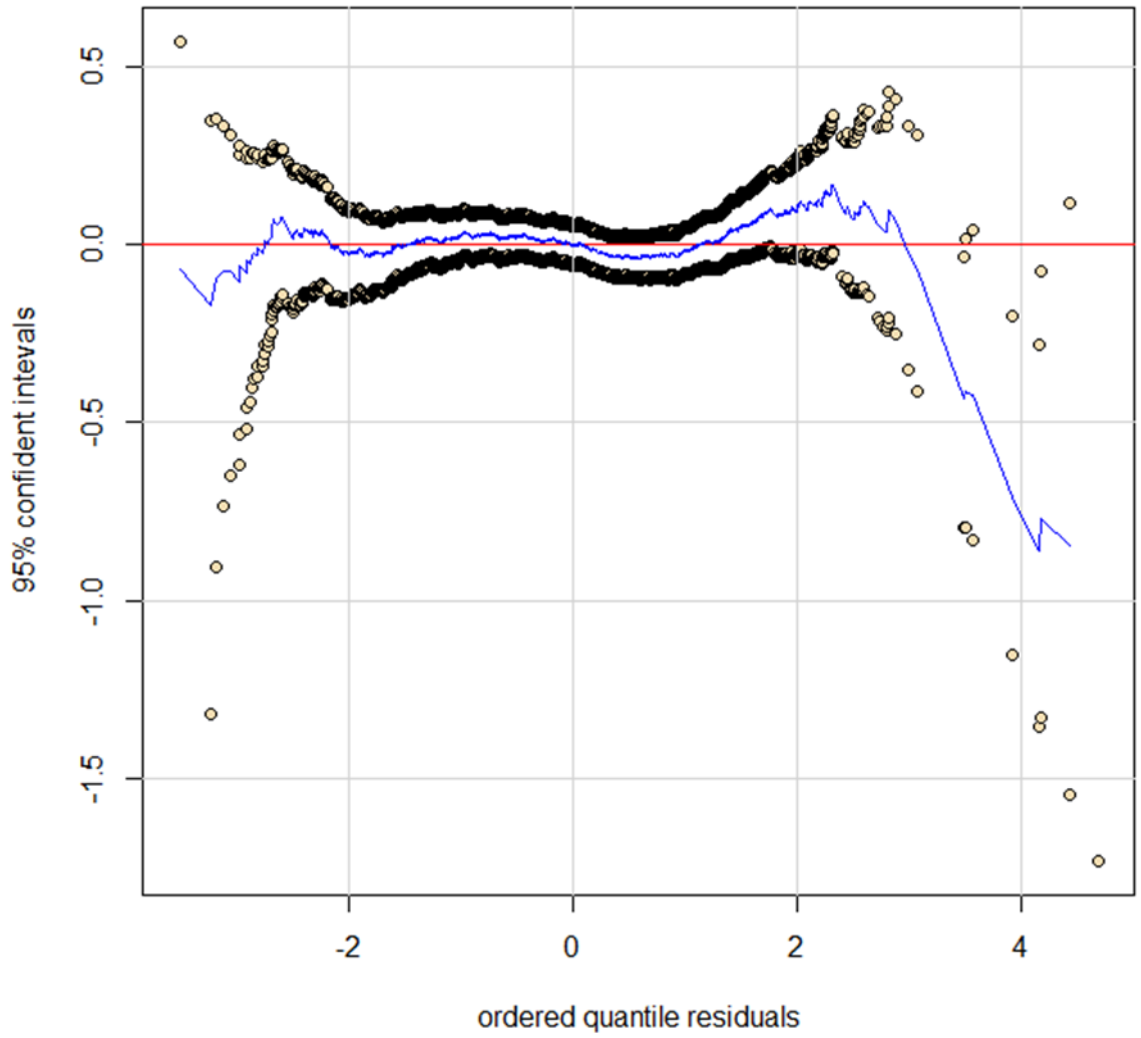

Figure 5-8: De–trended Owen's plot of the umbilical artery pulsatility index centile curves.

5.5.3 Cerebroplacental Ratio

The centiles for the CPR used a fractional polynomial additive term and a BCT distribution. Gestational age centile thresholds are outlined in Table 5.4 with the centiles presented in Figure 5.9.

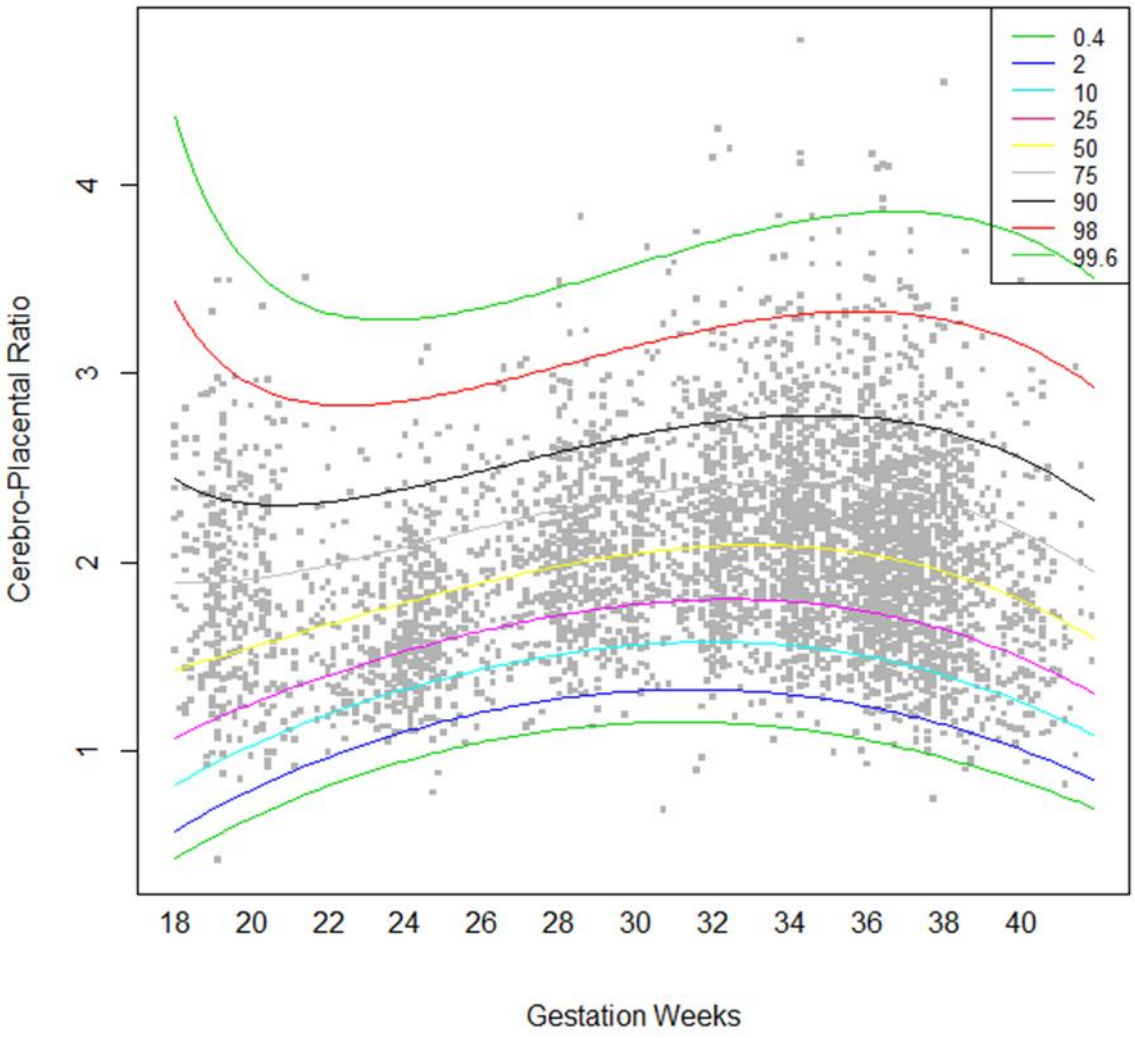

Figure 5-9: Cerebroplacental ratio centile curves using BCT.

Table 5-4: Cerebroplacental ratio centiles.

Gestation (Week)	0.4th	2nd	5th	10th	25th	50th	75th	90th	95th	98th	99.6th	Number
18	0.43	0.58	0.70	0.82	1.07	1.43	1.90	2.45	2.85	3.38	4.36	59
19	0.54	0.69	0.81	0.93	1.17	1.49	1.89	2.35	2.67	3.10	3.85	180
20	0.65	0.80	0.91	1.03	1.25	1.55	1.91	2.31	2.59	2.94	3.56	102
21	0.74	0.89	1.00	1.12	1.33	1.61	1.95	2.31	2.55	2.87	3.40	40
22	0.82	0.97	1.08	1.20	1.40	1.67	1.99	2.32	2.55	2.84	3.32	62
23	0.89	1.04	1.15	1.27	1.47	1.73	2.03	2.35	2.57	2.84	3.29	114
24	0.95	1.10	1.22	1.33	1.53	1.79	2.08	2.39	2.60	2.86	3.29	265
25	1.00	1.16	1.27	1.38	1.59	1.84	2.13	2.44	2.64	2.89	3.31	75
26	1.05	1.21	1.32	1.43	1.64	1.89	2.18	2.49	2.69	2.94	3.35	75
27	1.09	1.25	1.36	1.48	1.68	1.94	2.23	2.54	2.74	2.99	3.40	106
28	1.11	1.28	1.40	1.51	1.72	1.98	2.28	2.59	2.79	3.04	3.46	283
29	1.14	1.30	1.42	1.54	1.75	2.02	2.32	2.63	2.84	3.09	3.52	146
30	1.15	1.32	1.44	1.56	1.78	2.05	2.36	2.67	2.89	3.15	3.58	141
31	1.15	1.33	1.45	1.57	1.80	2.07	2.39	2.71	2.93	3.20	3.64	132
32	1.15	1.33	1.46	1.58	1.80	2.09	2.41	2.74	2.97	3.24	3.70	314
33	1.14	1.32	1.45	1.57	1.80	2.09	2.42	2.77	3.00	3.28	3.75	223
34	1.12	1.30	1.43	1.56	1.79	2.09	2.43	2.78	3.02	3.31	3.80	422
35	1.09	1.27	1.41	1.54	1.77	2.07	2.42	2.78	3.02	3.33	3.83	299
36	1.06	1.24	1.37	1.50	1.74	2.05	2.40	2.77	3.02	3.33	3.85	523
37	1.01	1.19	1.33	1.46	1.70	2.01	2.36	2.74	3.00	3.32	3.86	437
38	0.96	1.14	1.27	1.40	1.64	1.95	2.32	2.70	2.96	3.29	3.84	260
39	0.90	1.08	1.21	1.34	1.58	1.88	2.25	2.64	2.90	3.24	3.80	107
40	0.84	1.01	1.14	1.26	1.49	1.80	2.16	2.55	2.82	3.16	3.73	80
41	0.77	0.93	1.05	1.17	1.40	1.70	2.06	2.44	2.71	3.05	3.63	19

Model diagnostics show the plots of residuals are normally distributed around zero, as well as the density and Q–Q plot (Figure 5.10).

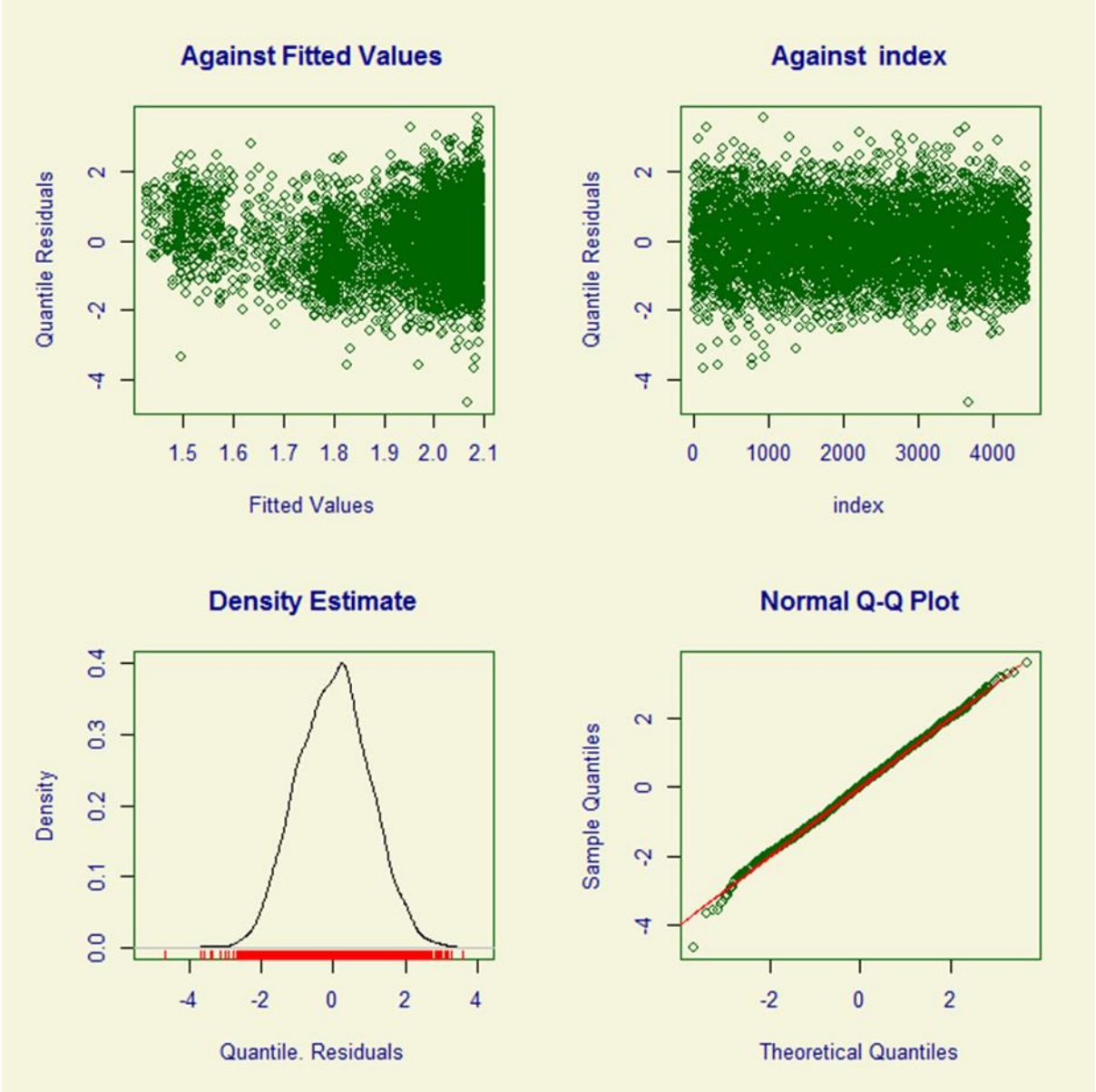

Figure 5-10: Residual plots of the cerebroplacental ratio centile curves.

Summary of the Quantile residuals show the mean is 0.001, the variance is 1.0002, coefficient of skewness is – 0.008 and the coefficient of kurtosis is 3.01 indicating normal distribution of the residuals and adequate model fit. The worm plot indicates that the fitted mean is appropriate for the model as there is no deviation from the origin and the fitted distribution is appropriate with no apparent skewness or excessive kurtosis (Figure 5.11).

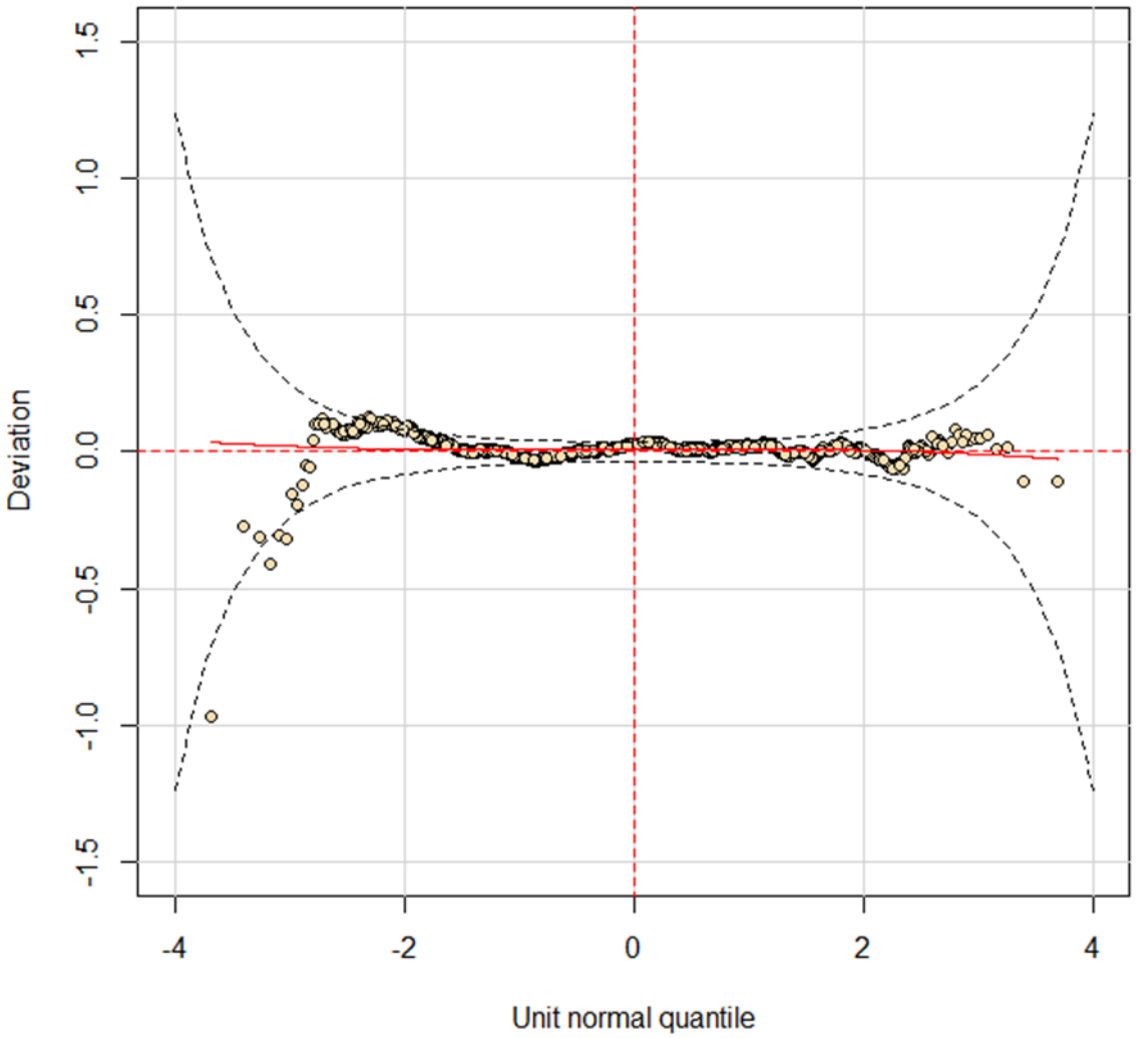

Figure 5-11: Worm plot of the cerebroplacental ratio centile curves.

The detrended transformed Owen's plot demonstrates that the normalised residuals have come from a normal distribution and that therefore the model is a reasonable fit for the data (Figure 5.12).

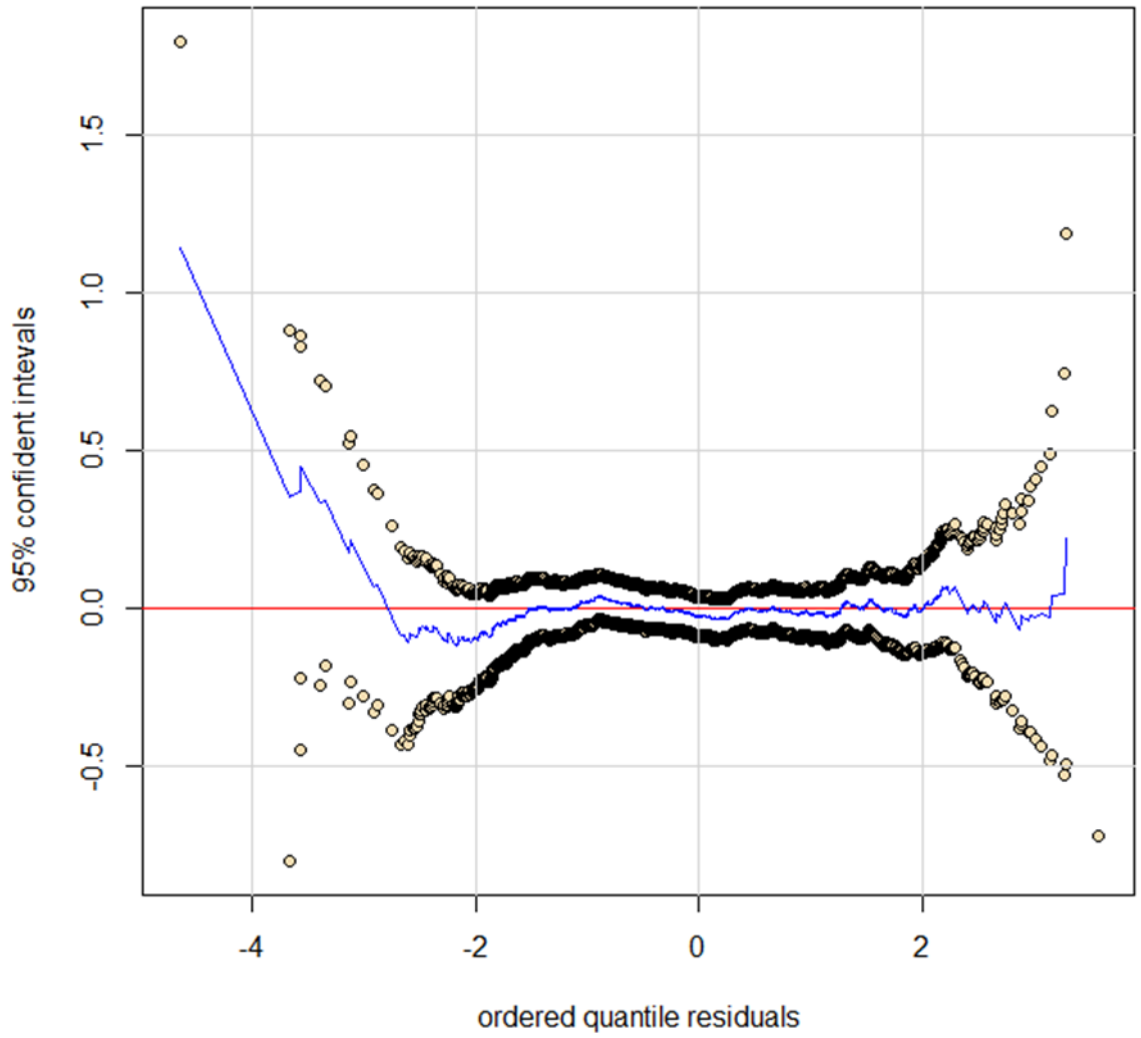

Figure 5-12: De–trended Owen's plot of the cerebroplacental ratio centile curves.

5.6 Discussion

Principal Findings

In this paper we report reference centiles for the MCA PI, UA PI and CPR from a large low–risk cohort using the GAMLSS technique incorporating cubic splines and fractional polynomials for smoothing and BCT for data distribution. The GAMLSS technique enables us to model the parameters of location, scale, skewness and leptokurtosis resulting in a more accurate model fit for the data then previously available (92, 117). The GAMLSS technique is a preferable statistical method particularly because data related to Doppler indices often do not follow a Gaussian distribution and hence for accurate centile creation require concordance between the distribution of data and the modelling technique utilising appropriately rigorous distributional assumptions (99).

It is critical that the creation of centiles takes into account the different parameters of data distribution (97, 98, 102, 104, 106). When the distribution is skewed and kurtotic, centiles and subsequent corresponding *Z*–scores do not have a valid interpretation (166). Although kurtosis is often thought of as less important than skewness when assessing normality of data (111), it has components of both tailedness and peakedness of a distribution (167). It is a measure of how the density of the study observations is different from the density of a normal distribution (112). Both the flatter platykurtotic and peakier leptokurtotic data densities cross the normal distribution curves twice on each side of the mean (167). The importance of correcting these deviations from normality becomes important when generalising the reference intervals (centiles) to the general population (112). The GAMLSS method used in this paper meets all these requirements.

Our centiles are derived from a large low–risk population of 6,013 women with clear inclusion criteria. The UA PI and MCA PI centiles were created using 6,008 and 4,473 data points, respectively, while the CPR centiles incorporated 4,464 data points. In our view, the characteristics of study population and the large numbers used to formulate the centiles together with robust and comprehensive statistical modelling clearly define these centiles as appropriate references. Indeed, previously publications (57, 72) report centiles derived from very small populations. Other publications (57, 72, 82, 83) also either fail to take into account or do not adequately report the methods used to correct for all parameters of distribution and provide little evidence of the appropriateness of their methodology or graphical representation of their model assessment (57, 72, 82, 83). One of the most commonly cited references (66) of CPR centiles

uses longitudinal measurements (66). However, Altman and Chitty have identified a number of deficiencies when using longitudinal data for the creation of reference charts, namely, repeated measures correlation and loss of variability (97, 98). Whilst Ebbing et al. addressed the methodological issues of repeated measures correlation and loss of variability by calculating conditional reference intervals using multilevel modelling (66, 97, 98), longitudinal studies are highly susceptible to selection and differential dropout bias.

The CPR is increasingly being used, particularly in late pregnancy, as an adjunct to standard fetal biometry and Dopplers for the identification of suboptimal fetal growth and fetuses at risk of adverse intrapartum and perinatal outcomes. Unlike women with known risk factors (hypertension, diabetes mellitus, previous fetal growth restriction, etc.), routine ultrasound to assess fetal wellbeing is generally not performed in low–risk women unless there are concerns about fetal size on clinical examination. From a healthcare burden perspective, the vast majority of SGA infants are born to women with uncomplicated, low–risk pregnancies (168). The difficulty, however, is defining what constitutes a "low–risk" cohort as there are many maternal medical, demographic and psychosocial factors that are associated with an increased risk of adverse outcomes. Clearly if this population were to be defined by the absence of all possible risk factors this would result in an artificially low number of women that would be considered "normal" or "low–risk". Such an approach would be divorced from clinical reality. Notwithstanding the difficulty in defining this cohort, some investigators have suggested that excluding women with diabetes mellitus and hypertension is reasonable given their relatively high prevalence in pregnancy (169).

Implications for Practice

Our centiles for the MCA PI, the UA PI and CPR are all slightly lower than those calculated by Ebbing et al. (66). While we would expect some differences due to methodology used, the differences could also be due to a number of other factors, principally the fact that they were generated from a low–risk cohort of women with many of the conventionally accepted risk factors (extremes of maternal age, severe obesity, diabetes mellitus, hypertension and other medical disorders, smoking, etc.) excluded. In our view, the centiles we present in this manuscript are also likely to have greater generalisability as they were derived from a more ethnically diverse cohort compared to Ebbing et al.'s study (66) which was comprised almost entirely of Nordic women.

Conclusion

In conclusion, we have created gestational centile reference ranges for the MCA PI, UA PI and CPR using statistically robust techniques and a biologically and clinically plausible low–risk cohort. Currently the CPR is being used to guide management particularly in late pregnancy without good evidence of its efficacy. It is, therefore, important that obstetricians use appropriate reference thresholds with confidence.

Chapter 6: Development of cross–validated model for the prediction of emergency caesarean for intrapartum fetal compromise at term

Christopher Flatley[1], Kristen Stacey Gibbons[1], Cameron Hurst[2], Sailesh Kumar[1,3]

1. Mater Research Institute, University of Queensland, Brisbane, Queensland, Australia.
2. QIMR Berghofer Medical Research Institute, Queensland, Australia.
3. School of Medicine, The University of Queensland, Queensland, Australia.

This chapter addresses the secondary objective:

Develop a model for the prediction of emergency caesarean section for non–reassuring fetal status at term utilising maternal and ultrasound–based variables.

This paper is currently under review.

6.1 Abstract

Objectives: The aim of this study was to develop a predictive model for emergency caesarean for fetal distress at term using a combination of maternal and late pregnancy ultrasound parameters measured at ≥36 weeks gestation.

Methods: This was a cohort study using prospectively collected data from singleton, non–anomalous births at the Mater Mother's Hospital, Brisbane, Australia between January 2010 and April 2017. Ultrasound recordings were performed between 36 – 38 weeks gestation for the estimated fetal weight, umbilical artery and middle cerebral artery pulsatility indices and cerebroplacental ratio. Standardisation of the ultrasound measures were performed using *Z*–scores accounting for gestational age at ultrasound against published reference centiles. Mixed effects generalised linear models were used to generate univariable and multivariable models. Variables for the predictive model were selected using a backward elimination technique based on the Akaike information criterion. Diagnostic accuracy of the final model was performed through calculations of receiver operating characteristic curves, positive and negative likelihood ratios and positive and negative predictive values. Validation of the model was performed using the K–fold cross validation technique.

Results: Over the study period 5,439 women met the inclusion criteria of which 4.2% underwent emergency caesarean for fetal distress. There were a significantly higher proportion of induced and nulliparous women in the emergency caesarean cohort ($p<0.001$). Infants in this group had lower *Z*–scores for estimated fetal weight, cerebroplacental ratio and middle cerebral artery pulsatility index and higher scores for the umbilical artery pulsatility index ($p<0.001$). Ethnicity, nulliparity, induction of labour, estimated fetal weight *Z*–score and cerebroplacental ratio *Z*–score, were all included in the final model. The model showed moderate to high accuracy with an area under the characteristic curve of 0.77 (95% CI 0.74 – 0.80).

Conclusions: The results of our study show that a prediction model that combines the continuous standardised measures of the cerebroplacental ratio, estimated fetal weight and several maternal factors is able to identify emergency cesarean for fetal distress with improved accuracy.

6.2 Introduction

Whilst some cases of intrapartum fetal hypoxia at term arise because of acute catastrophic events such as cord prolapse, placental abruption or uterine rupture, the majority do not, and hypoxia in these cases develops as a gradual process due to the inability of the fetus to tolerate the stress of parturition – i.e. reduced feto-placental reserve before labour commences (155, 170, 171). Why some term babies are more prone to intra-partum compromise is not entirely clear although growth restriction is implicated in many cases (172). Indeed, up to 63% of babies who become distressed and suffer oxygen deprivation in labour have no apparent prior risk factors (173). If not delivered rapidly enough, these babies are at risk of hypoxic brain injury and subsequent disability with hypoxic ischaemic encephalopathy being the strongest and most consistent risk factor for cerebral palsy in term infants (170). In Australia, hypoxic peripartum death (stillbirth or neonatal death of mature infants after the onset of labour in an otherwise healthy pregnancy) is one of the top three causes of mortality in singletons ≥37 weeks (174).

The fetal cerebroplacental ratio (CPR) is the ratio of the Middle Cerebral Artery Pulsatility Index (MCA PI) to the Umbilical Artery Pulsatility Index (UA PI). Increased cerebral blood flow is a fetal adaptive response to hypoxia and this is reflected by a reduction in MCA PI and thereby a reduction in the CPR. A low CPR appears to be an independent predictor of intrapartum fetal compromise, acidosis at birth and neonatal unit admission in term babies that are not small for gestational age (SGA) (15, 147, 171). Nevertheless, based on the best available evidence, there is currently no reliable test for intrapartum fetal compromise ("fetal distress").

The aim of this study thus was to develop a predictive model for emergency caesarean for fetal distress (ECFD) using a combination of maternal and late pregnancy ultrasound parameters measured ≥36 weeks gestation.

6.3 Methods

Maternal demographic, obstetric, ultrasound and perinatal data from women that birthed at term (≥37 weeks gestation) at the Mater Mother's Hospital in Australia between January 2010 and April 2017 were used to develop a predictive model for ECFD. Institutional ethical approval was obtained (HREC/14/MHS/37).

Only ultrasound data from singleton, non–anomalous fetuses obtained between 36 – 38 weeks gestation were included. The CPR was calculated as a ratio of the Middle Cerebral Artery Pulsatility Index (MCA PI) to the Umbilical Artery Pulsatility Index (UA PI) as previously reported (72). The estimated fetal weight (EFW) was calculated using Hadlock's formula (146).

To ensure accurate dating of the pregnancy, only cases where the gestational age was confirmed using a first trimester ultrasound examination were used in the analysis. The following variables were considered to be potentially clinically relevant to the primary outcome and therefore included in the initial analysis: maternal age, body mass index (BMI), ethnicity, parity, smoking status, alcohol consumption, use of illicit drugs, diabetes mellitus (gestational, type 1 or type 2), hypertension (gestational, chronic or pre–eclampsia), assisted reproductive techniques (ART) and Socio–Economic Indexes for Areas (SEIFA) score. The SEIFA score is an Australian measure of an individual's socioeconomic status where the average score is 1,000 and a lower score is indicative of greater social disadvantage (175). Intrapartum data included induction of labor (IOL), fetal gender and gestational age at birth. Intrapartum fetal compromise was diagnosed contemporaneously by the treating obstetric team based on an abnormal fetal heart pattern, fetal scalp pH or lactate. The primary outcome was ECFD.

6.4 Statistical Analysis

Categorical variables were reported as number and percentage and differences assessed using chi square test. Continuous variables were reported as mean and standard deviation with differences assessed using a *t*–test due to the large sample size and in accordance with the central limit theorem (176). Because of the change in the central tendency (mean/median) and dispersion (variance/interquartile range) over gestational age for the CPR, UA PI, MCA PI and EFW, standardisation was performed using *Z*–scores against previously published reference centiles (177, 178).

To account for the correlation of observations from women who birthed more than once during the study period, mixed effects generalised linear models were used to generate univariable and multivariable models. For the multivariable model building, all variables with a P value <0.2 were included in the initial model. This was done in consideration of both the sample size and number of events to satisfy the 10 events per variable rule to avoid overfitting the model (179-181).

Variables in the model were selected using a backward elimination technique as described by Sauerbrei *et al* (181). Using this technique variables are removed one by one based on the highest P value and subsequent model improvement assessed through a decrease in the Akaike information criterion (AIC), a widely used measure of model fit that also penalizes for model complexity (181, 182). All variables that were removed throughout the backward elimination process were reinserted into the final model and assessed if there was any improvement in the model using the AIC.

Initial evaluation of diagnostic accuracy of the final model was performed through calculations of receiver operating characteristic (ROC) curves. Further diagnostic evaluation of the model was performed with calculations of the sensitivity, specificity, percentage of cases correctly classified, positive and negative likelihood ratios (PLR and NLR) and positive and negative predictive values (PPV and NPV).

Validation of the model was performed using the K–fold cross validation technique using 50 folds (183, 184). Evaluations of the predictions from the cross–validation model and the original predictive model was performed through the use of confusion matrices that compared predicted outcomes against true outcomes along with examination of diagnostic accuracies, using the optimum threshold (i.e. the highest sensitivity and specificity) according to the ROC of the original predictive model. All statistical analysis was performed using Stata statistical software, StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.

6.5 Results

Over the study period we identified 5,439 women that met the inclusion criteria. Of these, 4.2% (230/5,439) underwent an ECFD. Characteristics of the study cohort and descriptive statistics are outlined in Table 6.1. ECFD was less likely to occur to Caucasian women (41.7% vs. 51.1%, p=0.01) and more likely to women from “Other” ethnicities (22.2% vs. 16.2%, p=0.02). A higher proportion of women in the ECFD group underwent IOL (73.5% vs. 43.1%, p<0.001) and

were nulliparous (78.3% vs. 44.3%, p<0.001). Fetuses in the ECFD group had a lower mean EFW (2,841g vs. 2,974g, p<0.001), CPR (1.77 vs. 2.00, p<0.001), MCA PI (1.50 vs 1.61, p<0.001) and a higher UA PI (0.88 vs. 0.83, p<0.001). After standardisation, the ECFD fetuses had lower *Z*–scores for EFW (0.09 vs. 0.45, p<0.001), CPR (-0.63 vs. -0.13, p<0.001), and MCA PI (-0.50 vs. -0.13, p<0.001), whilst the UA PI *Z*–score was higher (0.39 vs. 0.08, p<0.001).

Table 6-1: Descriptive Statistics

	Total Cohort	Emergency Caesarean Fetal Distress		
	Total (5,439)	No (n=5,209)	Yes (n=230)	P Value
Age	31.0 (5.5)	31.0 (5.5)	30.6 (5.5)	0.31
BMI	25.0 (6.5)	25.0 (6.6)	24.8 (5.6)	0.69
Ethnicity				
Caucasian	50.7% (2,756/5,439)	51.1% (2,660/5,209)	41.7% (96/230)	0.01
Indigenous	3.3% (180/5,439)	3.3% (170/5,209)	4.4% (10/230)	0.37
Asian	29.6% (1,608/5,439)	29.5% (1,535/5,209)	31.7% (73/230)	0.46
Other	16.5% (895/5,439)	16.2% (844/5,209)	22.2% (51/230)	0.02
SEIFA Score	1,017 (74)	1,017 (73)	1,014 (78)	0.53
Diabetes Mellitus	23.9% (1,298/5,439)	24.0% (1,248/5,209)	21.7% (50/230)	0.44
Hypertension	8.3% (449/5,439)	8.3% (431/5,209)	7.8% (18/230)	0.81
ART	4.9% (264/5,439)	4.8% (249/5,209)	6.5% (15/230)	0.23
Smoking	13.5% (733/5,439)	13.5% (702/5,209)	13.5% (31/230)	1.00
Alcohol Consumption	4.8% (259/5,439)	4.7% (247/5,209)	5.2% (12/230)	0.74
Illicit Drug Use	10.6% (578/5,439)	10.6% (553/5,209)	10.9% (25/230)	0.90
Nulliparous	45.8% (2,489/5,439)	44.3% (2,309/5,209)	78.3% (180/230)	<0.001
IOL	44.4% (2,415/5,439)	43.1% (2,246/5,209)	73.5% (169/230)	<0.001
Gestational Age at Birth	38.7 (1.1)	38.7 (1.1)	38.8 (1.3)	0.41
Gender (female)	50.4% (2,740/5,439)	50.4% (2,626/5,209)	49.6% (114/230)	0.80
EFW	2,969 (458)	2,974 (456)	2,841 (484)	<0.001
CPR	1.99 (0.51)	2.00 (0.50)	1.77 (0.50)	<0.001
UA PI	0.83 (0.15)	0.83 (0.15)	0.88 (0.18)	<0.001
MCA PI	1.61 (0.33)	1.61 (0.32)	1.50 (0.31)	<0.001
EFW *Z*-score	0.43 (1.10)	0.45 (1.10)	0.09 (1.23)	<0.001
CPR *Z*-score	-0.15 (1.02)	-0.13 (1.01)	-0.63 (1.11)	<0.001
UA PI *Z*-score	-0.09 (1.04)	0.08 (1.02)	0.39 (1.20)	<0.001
MCA PI *Z*-score	-0.15 (0.98)	-0.13 (0.98)	-0.50 (0.98)	<0.001

Data are reported as % (n) for categorical data (Chi Square test) and mean (Standard deviation) (*t*-test) for continuous data. BMI: Body Mass Index; SEIFA: Socio-Economic Indexes for Areas; SVD: Spontaneous Vaginal Delivery; CS: Caesarean Section; EFW: Estimated Fetal Weight; CPR: Cerebroplacental Ratio; UA PI: Umbilical Artery Pulsatility Index; MCA PI: Middle Cerebral Artery Pulsatility Index

The univariable generalised linear mixed models showed significant associations between ECFD and "Other" ethnicity (OR 1.67, 95% CI 1.18 – 2.37, p=0.004), IOL (OR 3.65, 95% CI 2.71 – 4.92, p<0.001), and nulliparity (OR 4.52, 95% CI 3.29 – 6.21, p<0.001). The standardised scores of the ultrasound variables showed that the EFW (OR 0.73, 95% CI 0.65 – 0.83, p<0.001), CPR (OR 0.63, 95% CI 0.55 – 0.71, p<0.001), UA PI (OR 1.33, 95% CI 1.17 – 1.51, p<0.001) and MCA PI (OR 0.68, 95% CI 0.59 – 0.78, p<0.001) *Z*–scores all being significantly associated with ECFD (Table 6.2).

Table 6-2: Univariable analysis.

	Total Cohort	**Emergency Cesarean Fetal Distress**			
	Total (5,439)	**No (n=5,209)**	**Yes (n=230)**	**Odds Ratio (95% C.I.)**	**P Value**
Age	31.0 (5.5)	31.0 (5.5)	30.6 (5.5)	0.99 (0.96 – 1.01)	0.31
BMI	25.0 (6.5)	25.0 (6.6)	24.8 (5.6)	1.00 (0.98 – 1.02)	0.69
Ethnicity					
Caucasian	50.7% (2,756/5,439)	51.1% (2,660/5,209)	41.7% (96/230)	1	
Indigenous	3.3% (180/5,439)	3.3% (170/5,209)	4.4% (10/230)	1.63 (0.83 – 3.18)	0.15
Asian	29.6% (1,608/5,439)	29.5% (1,535/5,209)	31.7% (73/230)	1.32 (0.97 – 1.80)	0.08
Other	16.5% (895/5,439)	16.2% (844/5,209)	22.2% (51/230)	1.67 (1.18 – 2.37)	0.004
SEIFA Score	1,017 (74)	1,017 (73)	1,014 (78)	0.999 (0.998 – 1.00)	0.53
Diabetes Mellitus	23.9% (1,298/5,439)	24.0% (1,248/5,209)	21.7% (50/230)	0.88 (0.64 – 1.21)	0.44
Hypertension	8.3% (449/5,439)	8.3% (431/5,209)	7.8% (18/230)	0.94 (0.58 – 1.54)	0.81
ART	4.9% (264/5,439)	4.8% (249/5,209)	6.5% (15/230)	1.39 (0.81 – 2.38)	0.23
Smoking	13.5% (733/5,439)	13.5% (702/5,209)	13.5% (31/230)	1.00 (0.68 – 1.47)	1.00
Alcohol Consumption	4.8% (259/5,439)	4.7% (247/5,209)	5.2% (12/230)	1.11 (0.61 – 2.00)	0.74
Illicit Drug Use	10.6% (578/5,439)	10.6% (553/5,209)	10.9% (25/230)	1.03 (0.67 – 1.57)	0.90
Nulliparous	45.8% (2,489/5,439)	44.3% (2,309/5,209)	78.3% (180/230)	4.52 (3.29 – 6.21)	<0.001
IOL	44.4% (2,415/5,439)	43.1% (2,246/5,209)	73.5% (169/230)	3.65 (2.71 – 4.92)	<0.001
Gestational Age at Birth	38.7 (1.1)	38.7 (1.1)	38.8 (1.3)	1.05 (0.94 – 1.18)	0.41
Gender (female)	50.4% (2,740/5,439)	50.4% (2,626/5,209)	49.6% (114/230)	0.97 (0.74 – 1.26)	0.80
EFW	2,969 (458)	2,974 (456)	2,841 (484)	0.999 (0.999 – 0.9996)	<0.001
CPR	1.99 (0.51)	2.00 (0.50)	1.77 (0.50)	0.37 (0.27 – 0.49)	<0.001
UA PI	0.83 (0.15)	0.83 (0.15)	0.88 (0.18)	7.29 (3.13 – 16.96)	<0.001
MCA PI	1.61 (0.33)	1.61 (0.32)	1.50 (0.31)	0.30 (0.19 – 0.46)	<0.001
EFW *Z*-score	0.43 (1.10)	0.45 (1.10)	0.09 (1.23)	0.73 (0.65 – 0.83)	<0.001
CPR *Z*-score	-0.15 (1.02)	-0.13 (1.01)	-0.63 (1.11)	0.63 (0.55 – 0.71)	<0.001
UA PI *Z*-score	-0.09 (1.04)	0.08 (1.02)	0.39 (1.20)	1.33 (1.17 – 1.51)	<0.001
MCA PI *Z*-score	-0.15 (0.98)	-0.13 (0.98)	-0.50 (0.98)	0.68 (0.59 – 0.78)	<0.001
Gestational Age at Ultrasound	36.6 (0.72)	36.6 (0.72)	36.6 (0.71)	1.02 (0.85 – 1.23)	0.83
Time from Ultrasound to Birth	15.3 (8.6)	15.3 (8.5)	15.6 (9.2)	1.00 (0.99 – 1.02)	0.61

Data are reported as % (n) for categorical data and mean (Standard deviation) for continuous data.
BMI: Body Mass Index; ART: Artificial Reproductive Technologies; SEIFA: Socio-Economic Indexes for Areas; IOL: Induction of Labour; EFW: Estimated Fetal Weight; CPR: Cerebroplacental Ratio; UA PI: Umbilical Artery Pulsatility Index; MCA PI: Middle Cerebral Artery Pulsatility Index

Model selection was performed with the initial model consisting of all variables that had a P value <0.20 in the univariable analysis as previously described, with the exception of UA PI *Z*–score and MCA PI *Z*–score which were omitted due to their association with the CPR *Z*–score. Backwards elimination of variables was performed using the AIC until the final parameters were established. The generalised linear mixed model that was determined to be the best fit consisted of ethnicity [Caucasian – reference, Indigenous (aOR 1.47, 95% CI 0.73 – 2.96, p=0.28), Asian (aOR 1.10, 95% CI 0.79 – 1.51, p=0.58), Other (aOR 1.93, 95% CI 1.35 – 2.77, p<0.001)], nulliparity (aOR 3.78, 95% CI 2.73 – 5.24, p<0.001), IOL (aOR 3.16, 95% CI 2.33 – 4.27, p<0.001), EFW *Z*–score (aOR 0.86, 95% CI 0.76 – 0.98, p=0.03) and CPR *Z*–score (aOR 0.72, 95% CI 0.63 – 0.82, p<0.001) (Table 6.3).

Table 6-3: Final predictive model.

Emergency Caesarean Fetal Distress		
	Odds Ratio (95% C.I.)	**P Value**
Ethnicity		
Caucasian	1	
Indigenous	1.47 (0.73 – 2.96)	0.28
Asian	1.10 (0.79 – 1.51)	0.58
Other	1.93 (1.35 – 2.77)	<0.001
Nulliparous	3.78 (2.73 – 5.24)	<0.001
IOL	3.16 (2.33 – 4.27)	<0.001
Estimated Fetal Weight Z–score	0.86 (0.76 – 0.98)	0.03
CPR Z–score	0.72 (0.63 – 0.82)	<0.001

C.I.: Confidence Interval; IOL: Induction of Labour; CPR: Cerebroplacental Ratio

The predictive accuracy of the final model showed an AUC 0.77 (95% CI 0.74 – 0.80) (Figure 6.1). The final model had a sensitivity of 70.9% (95% CI 64.5 – 76.7), specificity of 70.6% (95% CI 69.3 – 71.8), PLR 2.5 (95% CI 2.2 – 2.7), NLR 0.41 (95% CI 0.34 – 0.50), PPV 9.6% (95% CI 8.2 – 11.1) and NPV 98.3% (95% CI 97.8 – 98.6) (Table 6.4). Using a false positive rate of 10% the sensitivity was 45.2% (95% CI 38.7 – 51.9), the PLR increased to 4.53 (95% CI 3.84 – 5.34), NLR 0.61 (95% CI 0.54 – 0.69), PPV 16.7% (95% CI 13.8 – 19.8) and NPV 97.4% (95% CI 96.9 – 97.8).

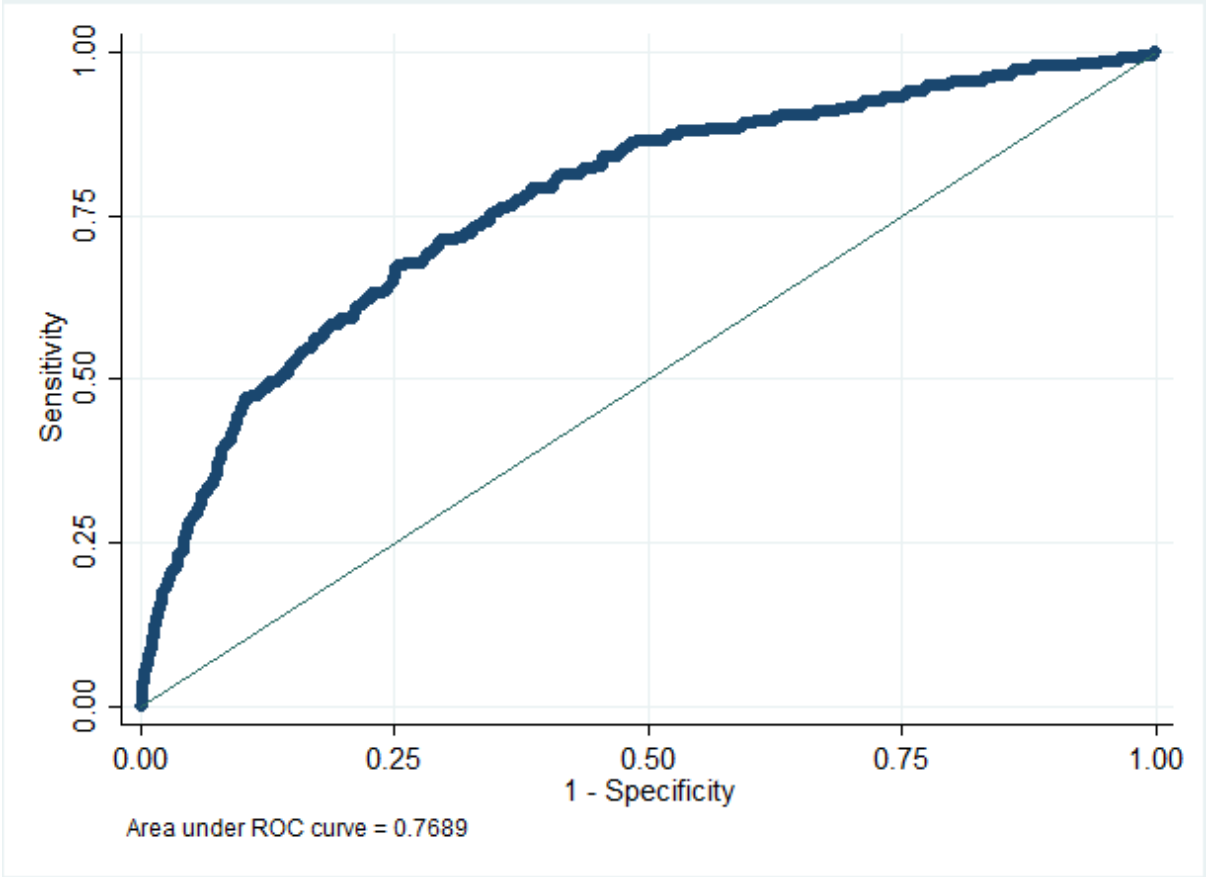

Figure 6-1: Receiver–operating characteristics for prediction of emergency caesarean for fetal distress.

Table 6-4: Diagnostic evaluation.

	AUC (95% C.I.)	**Sensitivity**	**Specificity**	**Correctly Classified**	**PLR**	**NLR**	**PPV**	**NPV**
Final Model	0.77 (0.74 – 0.80)	70.9% (64.5 – 76.7)	70.6% (69.3 – 71.8)	70.6%	2.5 (2.2 – 2.7)	0.41 (0.34 – 0.50)	9.6% (8.2 – 11.1)	98.3% (97.8 – 98.6)
Cohort CPR <10th	0.77 (0.71 – 0.82)	70.6% (58.3 – 81.0)	70.6% (67.1 – 73.9)	70.6%	2.4 (2.0 – 2.9)	0.42 (0.29 – 0.60)	18.5% (14.1 – 23.8)	96.2% (94.2 – 97.7)
Cohort EFW <10th	0.80 (0.73 – 0.87)	76.0% (61.8 – 86.9)	75.6% (71.5 – 79.4)	75.7%	3.1 (2.5 – 3.9)	0.32 (0.19 – 0.52)	24.4% (17.9 – 31.9)	96.8% (94.5 – 98.3)
Cohort with CPR <10th & EFW <10th	0.79 (0.70 – 0.87)	74.1% (53.7 – 88.9)	70.5% (61.9 – 78.2)	71.2%	2.5 (1.8 – 3.6)	0.37 (0.19 – 0.70)	34.5% (22.5 – 48.1)	92.9% (85.8 – 97.1)
Cohort with CPR <10th or EFW <10th	0.76 (0.70 – 0.81)	70.3% (59.8 – 79.5)	69.3% (66.5 – 72.1)	70.3%	2.3 (2.0 – 2.7)	0.43 (0.31 – 0.59)	16.3% (12.8 – 20.3)	96.5% (94.9 – 97.7)

AUC: Area Under the Curve; FPR: False Positive Rate; PLR: Positive Likelihood Ratio; NLR: Negative Likelihood Ratio; PPV: Positive Predictive Value; NPV: Negative Predictive Value; ECFD: Emergency Caesarean for Fetal Destress; CPR: Cerebroplacental Ratio; EFW: Estimated Fetal Weight

Testing the model on higher risk cohorts, the final model indicated improved accuracy. In a cohort that had a CPR <10th centile the PPV increased to 18.5% (95% CI 14.1 – 23.8). In a cohort with an EFW <10th centile there were improvements in the AUC 0.80 (95% CI 0.73 – 0.87), sensitivity 76.0% (95% CI 61.8 – 86.9), specificity 75.6% (95% CI 71.5 – 79.4), correctly classified 75.7%, PLR 3.1 (95% CI 2.5 – 3.9), NLR 0.32 (95% CI 0.19 – 0.52), PPV 24.4% (95% CI 17.9 – 31.9) and NPV 96.8% (95% CI 94.5 – 98.3). Comparisons of the diagnostic value of the model in each cohort can be found in Table 6.4.

There was little difference between the final model [AUC 0.77 (95% CI 0.74 – 0.80)] and the cross–validation model [AUC 0.76 (95% CI 0.73 – 0.79)] indicating accurate and robust model performance. Both the Delong's test and the Hanley and McNeil test suggested there is a significant difference between the AUC of the two models ($p<0.001$), however due to the near identical confidence intervals of the AUC and diagnostic accuracies as well as the identical graphical representation of both AUCs, the tests were deemed to be overpowered and a common sense, clinically relevant interpretation was applied. Comparisons of predicted and true outcome of ECFD for the final model and the cross–validation model are presented in Table 6.5 and Figure 6.2, with comparison of diagnostic accuracy of the final model and the cross–validation model shown in Table 6.6.

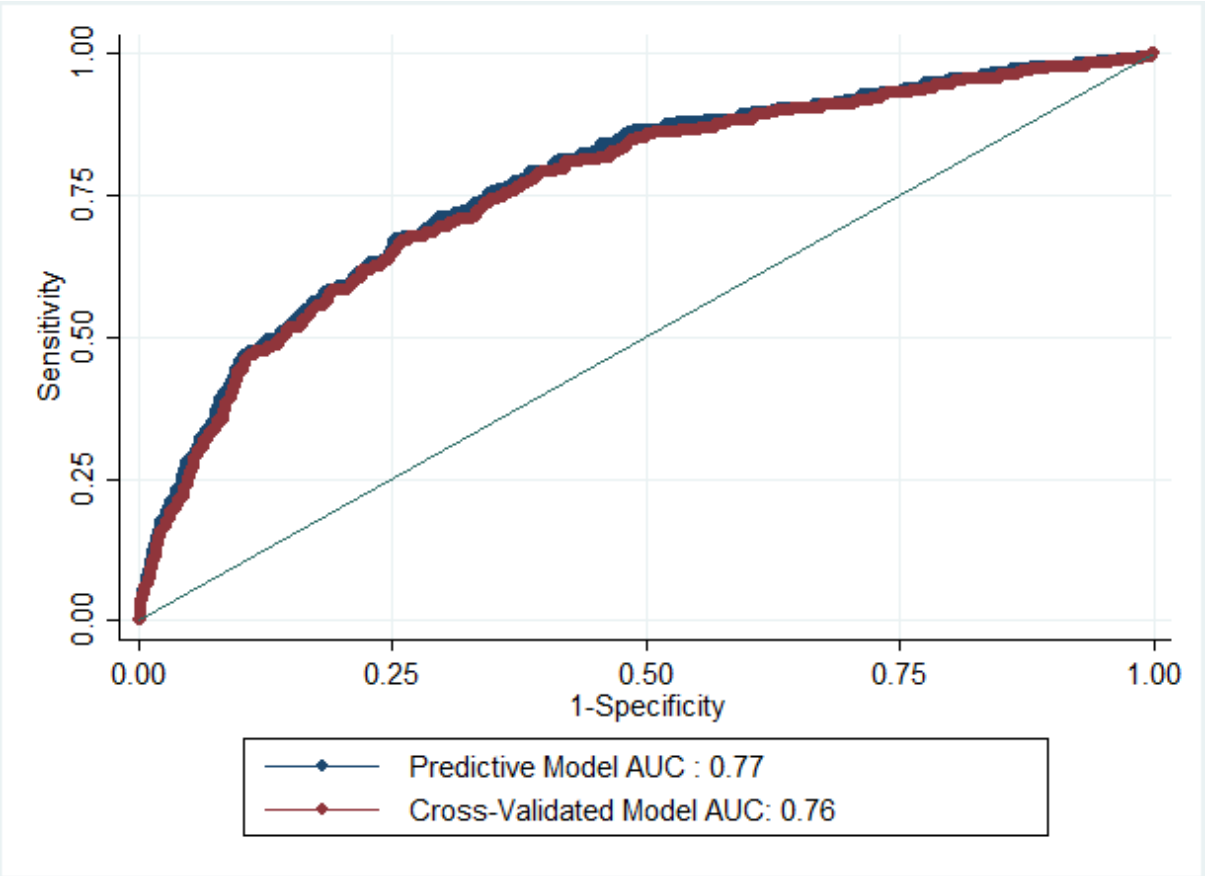

Figure 6-2: Comparison of predictive model and cross–validated model.

Table 6-5: Predictive model and cross–validation model confusion matrix using the optimal threshold of sensitivity and specificity.

Predicted Outcome	**True Outcome**		
Final Model	**ECFD**	**No ECFD**	**Total**
ECFD	163	1,534	1,697
No ECFD	67	3,675	3,742
Total	230	5,209	5,439
Cross-Validation Model	**ECFD**	**No ECFD**	**Total**
ECFD	160	1,543	1,703
No ECFD	70	3,666	3,736
Total	230	5,209	5,439

ECFD: Emergency Caesarean for Fetal Distress

Table 6-6: Predictive model and cross–validation model diagnostic evaluation using the optimal threshold of sensitivity and specificity.

	Final Model	**Cross-Validation Model**
Sensitivity	70.9% (64.5 – 76.7)	69.6% (63.2 – 75.4)
Specificity	71.1% (69.8 – 72.3)	70.4% (69.1 – 71.6)
PPV	9.6% (8.2 – 11.1)	9.4% (8.1 – 10.9)
NPV	98.3% (97.8 – 98.6)	98.1% (97.6 – 98.5)
PLR	2.5 (2.2 – 2.7)	2.4 (2.1 – 2.6)
NLR	0.41 (0.34 – 0.50)	0.43 (0.36 – 0.53)
Correctly Classified	70.6%	70.3%
AUC	0.77 (0.74 – 0.80)	0.76 (0.73 – 0.79)

AUC: Area Under the Receiver Operating Characteristic Curve; PLR: Positive Likelihood Ratio; NLR: Negative Likelihood Ratio; PPV: Positive Predictive Value; NPV: Negative Predictive Value

6.6 Discussion

Principal findings

The results of our study from a general obstetric population show that a model that combines the CPR, EFW and several maternal factors is able to identify with improved accuracy, term fetuses that develop intrapartum fetal compromise and require emergency caesarean for delivery. Furthermore, our cross–validation analysis for internal fidelity of the model demonstrates that it is highly calibrated (Figure 6.2), with a strong ability to discriminate fetuses at risk. Our model appears to have better performance characteristics than other models developed for the same purpose (75, 80, 185). Indeed, a recently published model for intrapartum fetal compromise showed an AUROC Curve of AUC 0.76 (95% CI 0.72 – 0.80) (75) with the authors explaining that this relatively high figure reflected the high–risk nature of their study population (small for gestational age (SGA) fetuses). Our model however, showed similar diagnostic accuracy in a general cohort and when applied to a similar high–risk cohort, there were improvements in all diagnostic accuracies (75). Another similar study from Holland (185) showed that a model incorporating only antenatal variables achieved an AUROC Curve of 0.70 (95% CI 0.66 – 0.73) whilst addition of intrapartum characteristics increased this figure to 0.73 (95% CI 0.70 – 0.76). The study by Schuit *et al* however did not include ultrasound variables. We have previously

shown that the CPR and EFW are able to identify separate cohorts of fetuses at risk of intrapartum compromise and using them in combination enhances their predictive capability (186). In this study we extend our previous findings to develop a model that accurately identifies fetuses at risk.

Strengths and limitations of the study

The strengths of this study include the large cohort of accurately dated term pregnancies, the short interval between ultrasound and birth and strict criteria used to define intrapartum fetal compromise. The tertiary centre focus of the study with universal intrapartum fetal heart rate monitoring, use of evidence–based guidelines and consistent intrapartum care for all women are further strengths. Additionally, all obstetric caregivers were blinded to the CPR so this would not have influenced any decisions regarding obstetric or intrapartum management. Furthermore, we did not include birthweight as a variable as our aim was to develop a model that used only prenatal and ultrasound variables rather than intrapartum factors. This would allow the model to be used in a clinically meaningful and potentially timely manner. Furthermore, we used all ultrasound measures as continuous variables rather than predetermined cut–offs. Whilst using thresholds to define an at–risk cohort may be convenient, it is unsound statistically as information is lost, limiting the power hence the accuracy of any predictive model. The use of thresholds and by extension the dichotomisation of outcomes underestimates the impact these variables may have when close to the chosen cut–off (76). Figure 6.3 illustrates the linear relationship between ECFD and the ultrasound measures of the EFW and CPR after adjusting for the confounding effects of the other variables within our model.

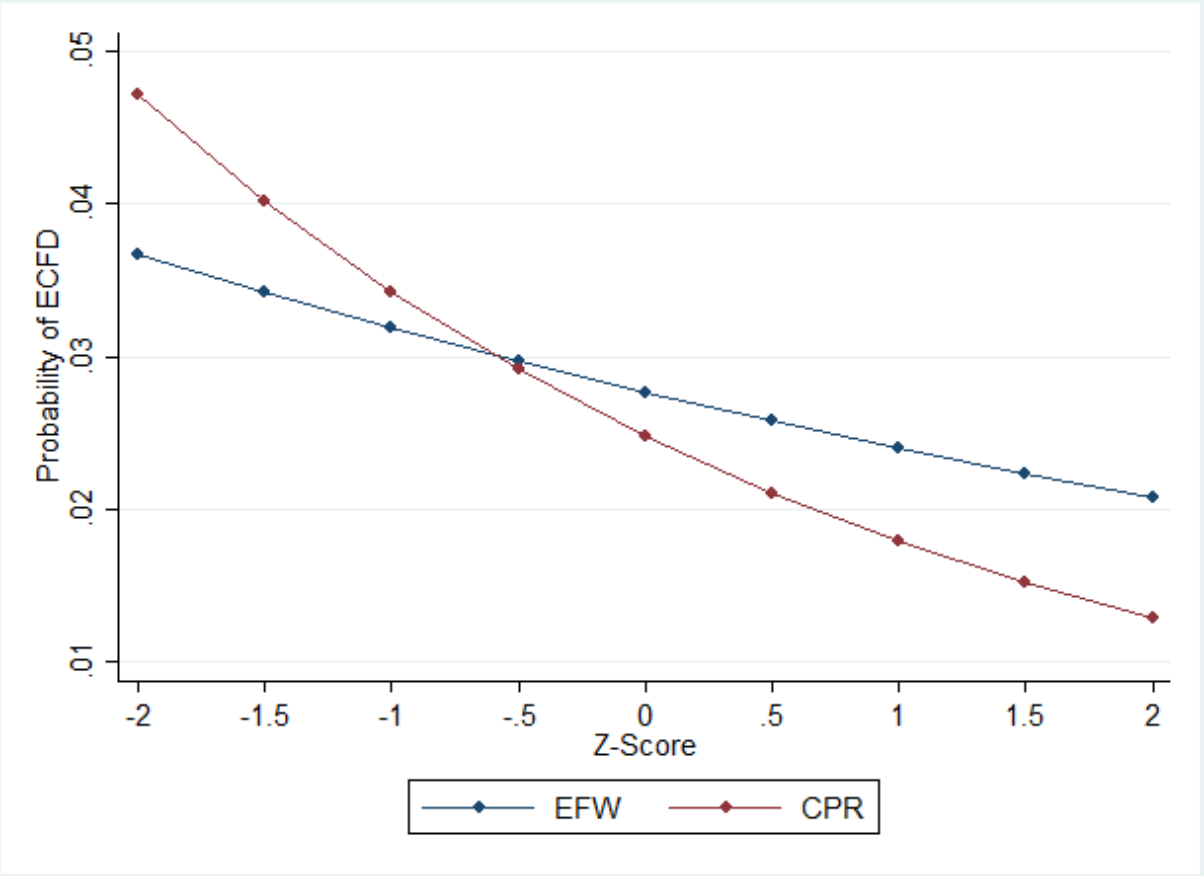

Figure 6-3: Adjusted probabilities of emergency caesarean for fetal distress for estimated fetal weight and cerebroplacental ratio Z–score.

Although there was no external validation performed, the similarities of the confusion matrices and the diagnostic evaluations between the predictive model and the cross–validation model demonstrates the appropriateness of the final model with no overfitting of the variables. The limitations of this study relate to the use of routinely collected data. The indications for IOL varied over the study period and could have influenced intrapartum outcomes. Although the CPR was not reported, the EFW and UA PI were, and this could have played a part in the clinical decision–making process and subsequent obstetric management. Furthermore, we acknowledge that the diagnosis of "fetal distress" is not a precise one, lacks a "gold standard" and management is influenced by a number of human factors.

Conclusions and implications for clinical practice

Our model offers a prediction tool that could help identify term fetuses at risk of ECFD with improved accuracy, and thus facilitate informed decision making for women and clinical management for obstetric caregivers. For example, when clinicians are considering IOL, this model allows them the opportunity to evaluate the probability of ECFD occurring as an outcome depending if IOL is undertaken. Our combined model offers far greater predictive accuracy than the CPR, EFW, UA PI or, MCA PI as standalone measures or even the use of a combination of these variables. Furthermore, we have achieved this accuracy without dichotomising the cohort into high–risk sub–groups on the basis of either a low CPR or EFW threshold. Whilst SGA infants or those with a low CPR are at risk of operative birth for fetal compromise, both these thresholds actually have relatively poor performance as a screening test for adverse outcomes (78). Indeed, whilst there is an increased risk of SGA infant having ECFD, the probability decreases in a linear fashion as the EFW increases. It is also common to use cut–offs for the CPR, but similar to another study by Kalafat *et al* we have been able to illustrate that the CPR has a linear association with ECFD and dichotomising would, at best discount useful information and at worst, may be misleading (75). Therefore, using the ultrasound measures as continuous variables within our model offers a more accurate and meaningful approach to prognosis within term fetuses. We were able to show that for those fetuses that are considered to be within the high–risk groups of low CPR and or low EFW our model performance improves, without the use of stratification. Furthermore, our model performs better than previous models constructed in specific high risk cohorts and by incorporating the use of EFW and CPR *Z*–scores as continuous measures we were able to show that the model performs well in a general cohort and improves in accuracy in the higher risk cohorts (75). There is also now evidence that the use of placental biomarkers such as placental growth factor may be useful for identifying vulnerable fetuses and future work needs to elucidate what role such biomarkers may have in similar models (187).

However, whilst our prediction model identifies important risk factors and the influence of their confounding effects for the outcome of ECFD and offers the possibility of identifying at–risk fetuses we acknowledge that a post–test management algorithm is yet to be determined. There are indeed many factors to consider, generalisability of the model including risk thresholds that may influence the need for intrapartum fetal monitoring, timing, place and mode of birth. Additionally, the acceptability to women in late pregnancy and its cost effectiveness are important issues to consider. Finally, and perhaps most critically, is the potential for harm, particularly the possibility of increased IOL rates and elective caesarean section at early term

gestations. Nevertheless, notwithstanding these concerns, our work demonstrates the possibility of accurate late pregnancy risk stratification for ECFD.

Chapter 7: Cross–validated prediction model for severe adverse neonatal outcomes in a term, non–anomalous, singleton cohort

Christopher Flatley[1], Kristen Stacey Gibbons[1], Cameron Hurst[2], Vicki Flenady[1,3,4], Sailesh Kumar[1,3,4]

1. Mater Research Institute, University of Queensland, Brisbane, Queensland, Australia.
2. QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia.
3. Centre for Research Excellence in Stillbirth, Mater Research Institute-University of Queensland, Queensland, Australia.
4. School of Medicine, The University of Queensland, Herston, Queensland, Australia.

This chapter addresses the secondary objective:

Develop a model for the prediction of a severe neonatal composite outcome comprising of any of the following outcomes: severe acidosis (pH <7.0 or Lactate ≥6mmol/L or Base Excess ≤12), Apgar score at 5 minutes ≤3, admission to NICU or perinatal death, at term utilising maternal and ultrasound–based variables.

Published in BMJ Paediatrics Open.

Citation:

Flatley C, Gibbons K, Hurst C, Flenady V and Kumar S.: Cross-validated prediction model for severe adverse neonatal outcomes in a term, non-anomalous, singleton cohort. *BMJ Paediatrics Open* 2019;**3:**e000424. doi: 10.1136/bmjpo-2018-000424

DOI: http://dx.doi.org/10.1136/bmjpo-2018-000424

7.1 Abstract

Objective

The aim of this study was to develop a predictive model utilising maternal, intrapartum and ultrasound variables for a composite of severe adverse neonatal outcomes (SANO) in term infants.

Design

Prospectively collected observational study. Mixed effects generalised linear models were used for modelling. Internal validation was performed using the K–fold cross validation technique.

Setting

This was a study of women that birthed at the Mater Mothers' Hospitals in Brisbane, Australia between January 2010 and April 2017.

Patients

We included all term, non–anomalous singleton pregnancies that had an ultrasound performed between 36–38 weeks gestation and had recordings for the umbilical artery pulsatility index, middle cerebral artery pulsatility index and the estimated fetal weight.

Main Outcome Measures

The components of the SANO were: severe acidosis arterial, admission to the neonatal intensive care unit, Apgar score of ≤3 at 5 minutes or perinatal death.

Results

There were 5,439 women identified during the study period that met the inclusion criteria, with 11.7% of this cohort having SANO. The final generalised linear mixed model consisted of the following variables: maternal ethnicity, socioeconomic score, nulliparity, induction of labour, method of birth and *Z*–scores for EFW and CPR. The final model had an area under the receiver operating characteristic curve of 0.71.

Conclusions

The results of this study demonstrate it is possible to predict infants that are at risk of SANO at term with moderate accuracy using a combination of maternal, intrapartum and ultrasound variables. Cross–validation analysis suggests a high calibration of the model.

7.2 Introduction

Globally, hypoxia remains a major contributor to stillbirth, hypoxic ischemic encephalopathy and cerebral palsy. For parents and families, the psychosocial and financial impact of these complications are profound and long-lasting. The majority of these catastrophic events occur despite a lack of obvious risk factors (173). This problem is significant and pressing, with the Royal College of Obstetricians & Gynaecologists, Gates Foundation, The Lancet and the World Health Organisation (WHO) urging focused research in this area. Indeed, a recent major 2017 UK report ("Each Baby Counts") of stillbirths, neonatal deaths and perinatal brain injury occurring has set an ambitious 50% reduction target by 2020 (188).

One prerequisite of any strategy to reduce adverse outcomes is the need to identify an at–risk population of fetuses. However, there is often lack of clarity of the population being screened and the perinatal outcomes chosen. Furthermore, clinically plausible and accurate interpretation of the relationship between risk variables and health outcomes is vital to ensure the robustness of any predictive model (179). The development of risk algorithms and predictive models utilising both ultrasound and demographic variables to enable risk stratification and individualised care is an increasing focus of research to reduce stillbirth and other adverse outcomes in high income contry settings (189). The accuracy of these models depends on careful consideration of not only the association between risk factors and outcomes, but importantly also how these factors interact with and on occasion, confound each other.

The cerebroplacental ratio (CPR) is the ratio of the middle cerebral artery pulsatility index (MCA PI) divided by the umbilical artery pulsatility index (UA PI) and is now shown to be a possible marker of sub–optimal fetal growth regardless of gestation (14, 40, 72). A low CPR is associated with a variety of adverse perinatal outcomes including stillbirth, intrapartum fetal compromise, and acidosis at birth, a low Apgar score and neonatal unit admission regardless of gestational age or weight (15, 78, 171, 190). The CPR is now increasingly being incorporated into clinical practice despite its relatively poor performance as a screening test for adverse perinatal outcomes (11, 15, 71, 145). Previously we have shown that both the CPR and estimated fetal weight (EFW) identified distinct at–risk cohorts and that a model incorporating both these factors improved the predictive capability for adverse perinatal outcomes (186). Others, (77, 80) have used a larger number of variables including the CPR, fetal gender, parity, maternal age, EFW and gestational age at birth to develop models for prediction of adverse pregnancy outcomes.

The aim of this study was to develop a predictive model utilising a range of maternal, pregnancy, intrapartum and ultrasound variables for a composite of severe adverse neonatal outcomes (SANO) for term infants.

7.3 Methods

This study utilised information from clinical records of women that birthed at the Mater Mothers' Hospitals in Brisbane, Australia between January 2010 and April 2017. The predictive model was developed using routine prospectively collected demographic, ultrasound, intrapartum and perinatal data.

We included all term (≥37 weeks gestation), non-anomalous singleton pregnancies that had an ultrasound performed between 36–38 weeks gestation and had recordings for the UA PI, MCA PI and the EFW. Gestational age was determined using a first trimester ultrasound examination. Fetal biometry and estimated fetal weight was measured and calculated using Hadlock's formula (146).

The following maternal demographic, pregnancy and birth variables were extracted for the analysis: maternal age, body mass index (BMI), ethnicity, parity, smoking status, alcohol consumption, use of illicit drugs, diabetes mellitus (gestational, type 1 or type 2), hypertension (gestational, chronic or pre-eclampsia), assisted reproductive techniques (ART), induction of labour (IOL), fetal gender, mode of birth, gestational age at birth and socio–economic index for areas (SEIFA) score. The SEIFA score is an Australian measure of an individual's socioeconomic status where the average score is 1,000 and a lower score represents relative socioeconomic deprivation (175).

The components of the SANO were: severe acidosis (cord artery pH<7.0, lactate >6mmol/L and/or base excess ≤-12mmol/L), admission to the neonatal intensive care unit (NICU), Apgar score of ≤3 at 5 minutes and/or perinatal death. Perinatal death was defined as stillbirth that occurred after ≥ 37 weeks gestation or neonatal death within 28 days of birth.

This study had full institutional ethical approval (Reference number HREC/14/MHS/37).

7.4 Statistical Analysis

Due to the change in the mean and standard deviation over gestation for the measures of the CPR, UA PI, MCA PI and EFW, *Z*–scores were first calculated for each gestational age when the ultrasound scan was performed, using previously published reference centiles (177, 178).

Data measured on a continuous scale are reported as mean (standard deviation). Proportions are reported as a percentage and number of observations. Mixed effects generalised linear models with a binomial distribution were used to account for the correlation of observations from women having more than one birth within the study period. Univariable analysis was performed and all variables with a P value <0.20 were included in the initial model. This was done in consideration of the prevailing consensus opinion that at least 10 events per variable are required to avoid overfitting the model (179-181).

Model building was performed using the backwards stepwise approach as previously described by Sauerbrei *et al* (181). Variables were removed based on the highest P value and subsequent model improvement assessed through a decrease in the Akaike information criterion (AIC), a widely used criterion to assess model goodness of fit and parsimony (182). All variables removed were individually re–inserted into the model and reassessed for any model improvement.

Receiver operating characteristic (ROC) curves, sensitivity, percentage of cases correctly classified, positive and negative likelihood ratios (PLR and NLR) and positive and negative predictive values (PPV and NPV) were used to evaluate the diagnostic accuracy of the final model.

Internal validation of the model was performed using the K–fold cross validation technique using 50 folds (183, 184). The number of SANO outcomes were compared to the number of SANO predicted by the model through the use of cross tabulation of actual and predicted outcomes (a.k.a confusion matrix) for the cross–validation model versus the original predictive model, and comparison of diagnostic accuracies using the original predictive model's optimum threshold from the ROC curves.

Statistical analysis was performed using Stata statistical software, StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.

7.5 Results

There were 5,439 women during the study period that met the inclusion criteria, with 11.7% (639/5,439) of this cohort having the SANO. Infants with the composite SANO were more likely to be born to women who were younger (30.3 vs. 31.0, p=0.001), nulliparous (63.9% vs. 43.4%, p<0.001), had lower SEIFA score (1,011 vs. 1,018, p=0.03) and were less likely to be female (46.5% vs. 50.9%, p=0.04). These women were more likely to be induced (54.5% vs. 43.1%, p<0.001) and have an operative delivery, [instrumental delivery (30.7% vs. 10.8%) and emergency caesarean (25.7% vs. 15.1%), p<0.001]. For the ultrasound variables, fetuses in the SANO cohort had lower mean EFW (2,911g vs. 2,976g, p<0.001), lower mean CPR (1.93 vs. 2.00, p<0.001) and higher mean UA PI (0.86 vs. 0.83, p<0.001). There was however, no difference in the mean MCA PI (1.59 vs 1.61, p=0.19). After standardisation, *Z*–scores for the EFW (0.32 vs. 0.45, p=0.01), CPR (-0.31 vs -0.13, p<0.001) and MCA PI (-0.23 vs. -0.14, p=0.03) were all lower in the SANO cohort whilst the UA PI was higher (0.25 vs. 0.07, p<0.001). There was no difference in the time from ultrasound to delivery between the two groups.

Table 7-1: Descriptive Statistics

	Total Cohort (5,439)	**Severe Adverse Neonatal Outcome**		
		No (n=4,800)	**Yes (n=639)**	**P Value**
Age	31.0 (5.5)	31.0 (5.5)	30.3 (5.5)	0.001
BMI	25.0 (6.5)	25.0 (6.5)	25.1 (6.6)	0.60
Ethnicity				
Caucasian	50.7% (2,756/5,439)	50.3% (2,413/4,800)	53.7% (343/639)	0.11
Indigenous	3.3% (180/5,439)	3.3% (156/4,800)	3.8% (24/639)	0.51
Asian	29.6% (1,608/5,439)	29.8% (1,428/4,800)	28.2% (180/639)	0.41
Other	16.5% (895/5,439)	16.7% (803/4,800)	14.4% (92/639)	0.14
SEIFA Score	1,017 (74)	1,018 (73)	1,011 (76)	0.03
Diabetes Mellitus	23.9% (1,298/5,439)	23.9% (1,149/4,800)	23.3% (149/639)	0.73
Hypertension	8.3% (449/5,439)	8.3% (400/4,800)	7.7% (49/639)	0.57
ART	4.9% (264/5,439)	4.9% (235/4,800)	4.5% (29/639)	0.69
Smokes	13.5% (733/5,439)	13.5% (648/4,800)	13.3% (85/639)	0.89
Alcohol	4.8% (259/5,439)	4.7% (227/4,800)	5.0% (32/639)	0.76
Illicit Drug Use	10.6% (578/5,439)	10.4% (497/4,800)	12.7% (81/639)	0.07
Nulliparous	45.8% (2,489/5,439)	43.4% (2,081/4,800)	63.9% (408/639)	<0.001
IOL	44.4% (2,415/5,439)	43.1% (2,067/4,800)	54.5% (348/639)	<0.001
Gestation	38.7 (1.1)	38.7 (1.1)	38.7 (1.3)	0.38
Gender (female)	50.4% (2,740/5,439)	50.9% (2,443/4,800)	46.5% (297/639)	0.04
Method of Birth				
SVD	53.2% (2,895/5,439)	56.0% (2,687/4,800)	32.6% (2089/639)	<0.001
Instrumental	13.2% (716/5,439)	10.8% (520/4,800)	30.7% (196/639)	<0.001
Emergency CS	16.4% (890/5,439)	15.1% (726/4,800)	25.7% (164/639)	<0.001
Elective CS	17.3% (938/5,439)	18.1% (867/4,800)	11.1% (71/639)	<0.001
US Gestation	36.6 (0.72)	36.6 (0.7)	36.5 (0.7)	0.01
Time from Ultrasound to Birth (Days)	15.3 (8.6)	15.3 (8.4)	15.4 (9.5)	0.70
EFW	2,969 (458)	2,976 (452)	2,911 (503)	<0.001
CPR	1.99 (0.51)	2.00 (0.50)	1.93 (0.55)	<0.001
UA PI	0.83 (0.15)	0.83 (0.15)	0.86 (0.16)	<0.001
MCA PI	1.61 (0.33)	1.61 (0.32)	1.59 (0.34)	0.19
EFW *Z*–score	0.43 (1.10)	0.45 (1.08)	0.32 (1.24)	0.01
CPR *Z*–score	-0.15 (1.02)	-0.13 (1.0)	-0.31 (1.12)	<0.001
UA PI *Z*–score	0.09 (1.03)	0.07 (1.02)	0.25 (1.13)	<0.001
MCA PI *Z*–score	-0.15 (0.98)	-0.14 (0.97)	-0.23 (1.03)	0.03

Data are reported as % (n) for categorical data (Chi Square test) and mean (Standard deviation) (*t*-test) for continuous data. BMI: Body Mass Index; SEIFA: Socio-Economic Indexes for Areas; ART: Artificial Reproductive Technologies; IOL: Induction of Labour; SVD: Spontaneous Vaginal Delivery; CS: Caesarean Section; US: Ultrasound; EFW: Estimated Fetal Weight; CPR: Cerebroplacental Ratio; UA PI: Umbilical Artery Pulsatility Index; MCA PI: Middle Cerebral Artery Pulsatility Index

After univariable analysis, associations between the SANO and maternal age (OR 0.97, 95% CI 0.96 – 0.99, p=0.003), SEIFA score (OR 0.999, 95% CI 0.997 – 0.999, p=0.04), nulliparity (OR 2.50, 95% CI 1.89 – 3.13, p<0.001), IOL (OR 1.67, 95% CI 1.33 – 2.11, p<0.001) and female gender (OR 0.83, 95% CI 0.69 – 0.99, p=0.04) were identified. The composite outcome was also associated with instrumental birth (OR 5.97, 95% CI 3.52 – 10.13, p<0.001) and emergency caesarean (OR 3.28, 95% CI 2.26 – 4.76, p<0.001) as well as *Z*–scores for EFW (OR 0.89, 95% CI 0.82 – 0.97, p=0.01), CPR (OR 0.83, 95% CI 0.75 – 0.91, p<0.001), UA PI (OR 1.20, 95% CI 1.09 – 1.32, P<0.001) and MCA PI *Z*–score (OR 0.90, 95% CI 0.82 – 0.99, p=0.04) (Table 7.2).

Table 7-2: Univariable analysis.

	Total Cohort (5,439)	Severe Adverse Neonatal Outcome			
		No (n=4,800)	Yes (n=639)	Odds Ratio (95% C.I.)	P Value
Age	31.0 (5.5)	31.0 (5.5)	30.3 (5.5)	0.97 (0.96 – 0.99)	0.003
BMI	25.0 (6.5)	25.0 (6.5)	25.1 (6.6)	1.00 (0.99 – 1.02)	0.60
Ethnicity					
Caucasian	50.7% (2,756/5,439)	50.3% (2,413/4,800)	53.7% (343/639)	1	
Indigenous	3.3% (180/5,439)	3.3% (156/4,800)	3.8% (24/639)	1.08 (0.66 – 1.77)	0.76
Asian	29.6% (1,608/5,439)	29.8% (1,428/4,800)	28.2% (180/639)	0.88 (0.71 – 1.08)	0.22
Other	16.5% (895/5,439)	16.7% (803/4,800)	14.4% (92/639)	0.79 (0.60 – 1.04)	0.09
SEIFA Score	1,017 (74)	1,018 (73)	1,011 (76)	0.999 (0.997 – 0.9999)	0.04
Diabetes Mellitus	23.9% (1,298/5,439)	23.9% (1,149/4,800)	23.3% (149/639)	0.96 (0.77 – 1.20)	0.73
Hypertension	8.3% (449/5,439)	8.3% (400/4,800)	7.7% (49/639)	0.91 (0.65 – 1.28)	0.58
ART	4.9% (264/5,439)	4.9% (235/4,800)	4.5% (29/639)	0.90 (0.58 – 1.41)	0.66
Smokes	13.5% (733/5,439)	13.5% (648/4,800)	13.3% (85/639)	0.98 (0.75 – 1.29)	0.89
Alcohol	4.8% (259/5,439)	4.7% (227/4,800)	5.0% (32/639)	1.07 (0.70 – 1.63)	0.76
Illicit Drug Use	10.6% (578/5,439)	10.4% (497/4,800)	12.7% (81/639)	1.30 (0.97 – 1.74)	0.08
Nulliparous	45.8% (2,489/5,439)	43.4% (2,081/4,800)	63.9% (408/639)	2.50 (1.89 – 3.13)	<0.001
IOL	44.4% (2,415/5,439)	43.1% (2,067/4,800)	54.5% (348/639)	1.67 (1.33 – 2.11)	<0.001
Gestation	38.7 (1.1)	38.7 (1.1)	38.7 (1.3)	0.97 (0.89 – 1.05)	0.41
Gender (female)	50.4% (2,740/5,439)	50.9% (2,443/4,800)	46.5% (297/639)	0.83 (0.69 – 0.99)	0.04
Method of Birth					
SVD	53.2% (2,895/5,439)	56.0% (2,687/4,800)	32.6% (2089/639)	1	
Instrumental	13.2% (716/5,439)	10.8% (520/4,800)	30.7% (196/639)	5.97 (3.52 – 10.13)	<0.001
Emergency CS	16.4% (890/5,439)	15.1% (726/4,800)	25.7% (164/639)	3.28 (2.26 – 4.76)	<0.001
Elective CS	17.3% (938/5,439)	18.1% (867/4,800)	11.1% (71/639)	1.07 (0.79 – 1.45)	0.68
US Gestation	36.6 (0.72)	36.6 (0.7)	36.5 (0.7)	0.85 (0.74 – 0.97)	0.02
Time from Ultrasound to Birth (Days)	15.3 (8.6)	15.3 (8.4)	15.4 (9.5)	1.00 (0.99 – 1.01)	0.69
EFW	2,969 (458)	2,976 (452)	2,911 (503)	0.9997 (0.999 – 0.9999)	0.002
CPR	1.99 (0.51)	2.00 (0.50)	1.93 (0.55)	0.73 (0.61 – 0.89)	0.001
UA PI	0.83 (0.15)	0.83 (0.15)	0.86 (0.16)	3.89 (1.98 – 7.65)	<0.001
MCA PI	1.61 (0.33)	1.61 (0.32)	1.59 (0.34)	0.83 (0.63 – 1.10)	0.20
EFW *Z*–score	0.43 (1.10)	0.45 (1.08)	0.32 (1.24)	0.89 (0.82 – 0.97)	0.01
CPR *Z*–score	-0.15 (1.02)	-0.13 (1.0)	-0.31 (1.12)	0.83 (0.75 – 0.91)	<0.001
UA PI *Z*–score	0.09 (1.03)	0.07 (1.02)	0.25 (1.13)	1.20 (1.09 – 1.32)	<0.001
MCA PI *Z*–score	-0.15 (0.98)	-0.14 (0.97)	-0.23 (1.03)	0.90 (0.82 – 0.99)	0.04

Data are reported as % (n) for categorical data and mean (Standard deviation) for continuous data.

BMI: Body Mass Index; SEIFA: Socio-Economic Indexes for Areas; ART: Artificial Reproductive Technologies; IOL: Induction of Labour; SVD: Spontaneous Vaginal Delivery; CS: Caesarean Section; US: Ultrasound; EFW: Estimated Fetal Weight; CPR: Cerebroplacental Ratio; UA PI: Umbilical Artery Pulsatility Index; MCA PI: Middle Cerebral Artery Pulsatility Index

The initial multivariable model consisted of maternal age, ethnicity, SEIFA score, illicit drug use, nulliparity, IOL, gender, method of birth, EFW *Z*–score and CPR *Z*–score. The UA PI and MCA PI *Z*–scores were not included due to the association with the CPR *Z*–score. Model selection was performed as previously described. The final generalised linear mixed model consisted of maternal ethnicity [Caucasian – reference, Indigenous (aOR 1.03, 95% CI 0.60 – 1.79, p=0.91), Asian (aOR 0.66, 95% CI 0.51 – 0.86, p=0.002), Other (aOR 0.73, 95% CI 0.54 – 1.00, p=0.049)], SEIFA score (aOR 0.998, 95% CI 0.996 – 0.999, p=0.003), nulliparity (aOR 1.50, 95% CI 1.18 – 1.90, p=0.001), IOL (aOR 1.34, 95% CI 1.07 – 1.69, p=0.01), method of birth [Spontaneous Vaginal Delivery (SVD) – reference, instrumental (aOR 5.69, 95% CI 3.41 – 9.49, p<0.001), emergency caesarean (aOR 3.15, 95% CI 2.17 – 4.57, p<0.001), elective caesarean (aOR 1.33, 95% CI 0.94 – 1.88, p=0.11)] and *Z*–scores for EFW (aOR 0.88, 95% CI 0.79 – 0.97, p=0.01) and CPR (aOR 0.88, 95% CI 0.79 – 0.98, p=0.02) (Table 7.3).

Table 7-3: Final model - severe adverse neonatal outcome.

	Odds Ratio (95% C.I.)	**P Value**
Ethnicity		
Caucasian	1	
Indigenous	1.03 (0.60 – 1.79)	0.91
Asian	0.66 (0.51 – 0.86)	0.002
Other	0.73 (0.54 – 1.00)	0.049
SEIFA Score	0.998 (0.996 – 0.999)	0.003
Nulliparous	1.50 (1.18 – 1.90)	0.001
IOL	1.34 (1.07 – 1.69)	0.01
Method of Birth		
SVD	1	
Instrumental	5.69 (3.41 – 9.49)	<0.001
Emergency CS	3.15 (2.17 – 4.57)	<0.001
Elective CS	1.33 (0.94 – 1.88)	0.11
EFW *Z*–score	0.88 (0.79 – 0.97)	0.01
CPR *Z*–score	0.88 (0.79 – 0.98)	0.02

C.I.: Confidence Interval; IOL: Induction of Labour; SVD: Spontaneous Vaginal Delivery; CS: Caesarean Section; EFW: Estimated Fetal Weight; CPR: Cerebroplacental Ratio

The final model had an area under the receiver operating characteristic (AUROC) curve of 0.71 (95% CI 0.69 – 0.73) (Figure 7.1).

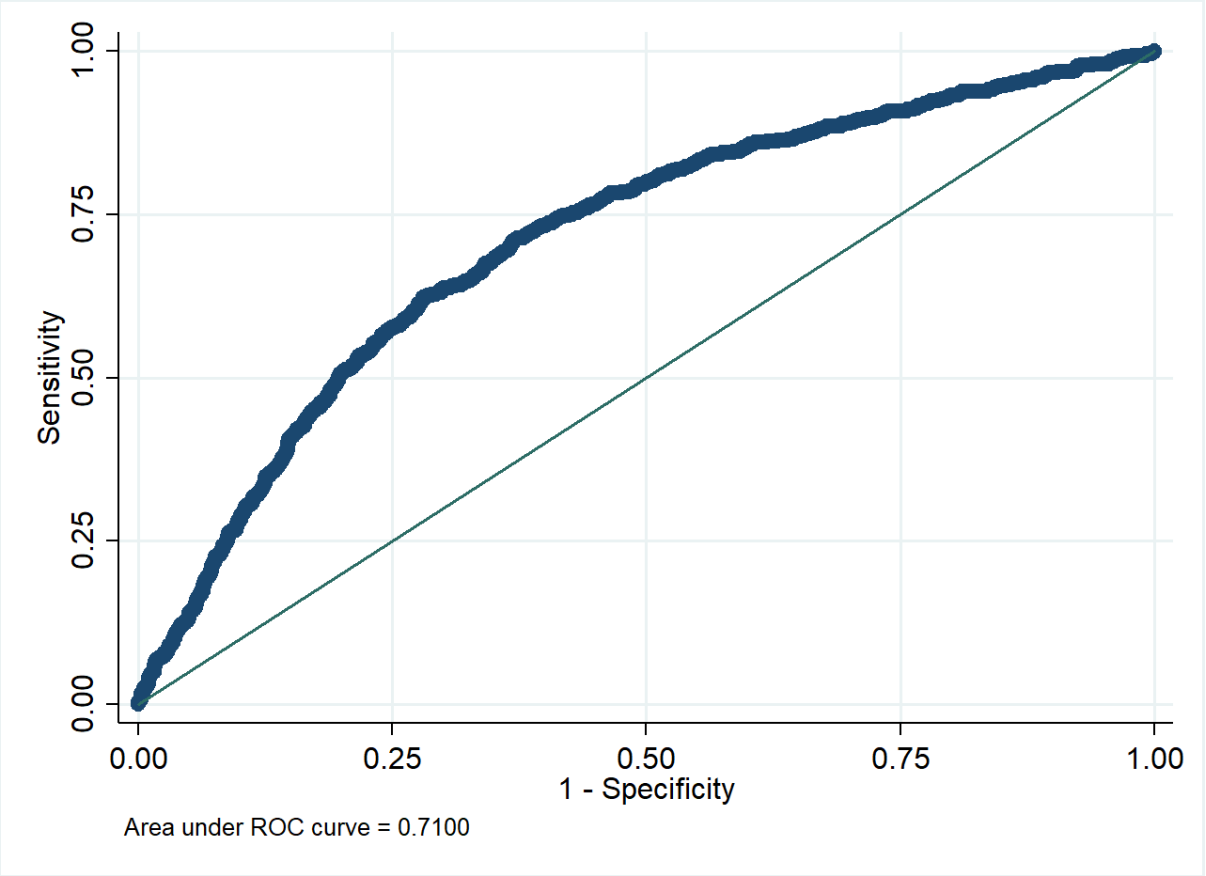

Figure 7-1: Receiver–operating characteristics for prediction of severe adverse neonatal outcome.

Using a fixed false positive cut–off of 10%, the model demonstrated a sensitivity of 28.2% (95% CI 24.7 – 31.8), a PLR of 2.8 (95% CI 2.4 – 3.3) and NLR of 0.80 (95% CI 0.76 – 0.84). The PPV was 27.3% (95% CI 23.9 – 30.8), NPV of 90.4% (95% CI 89.5 – 91.2).

We also assessed the performance of the model in high–risk cohorts (EFW <10th centile and CPR <10th centile). Overall, there was negligible improvement in performance in any of the AUROC curves, but there was substantial improvement in the PPV for a cohort with an EFW <10th centile as well as those with both an EFW <10th centile and CPR <10th centile. There was also improvement in the PLR observed in the EFW <10th centile cohort (Table 7.4).

Table 7-4: Diagnostic evaluation.

	AUC (95% C.I.)	**Sensitivity (95% C.I.)**	**Specificity (95% C.I.)**	**Correctly Classified**	**PLR (95% C.I.)**	**NLR (95% C.I.)**	**PPV (95% C.I.)**	**NPV (95% C.I.)**
Final Model	0.71 (0.69 – 0.73)	66.0% (62.2 – 69.7)	66.4% (65.1 – 67.8)	66.2%	1.97 (1.84 – 2.11)	0.51 (0.46 – 0.57)	20.7% (19.0 – 22.6)	93.6% (92.8 – 94.4)
Cohort CPR<10th	0.70 (0.65 – 0.75)	65.9% (56.9 – 74.1)	65.9% (62.1 – 69.5)	65.4%	1.93 (1.64 – 2.27)	0.52 (0.40 – 0.66)	26.9% (22.0 – 32.2)	91.0% (88.1 – 93.4)
Cohort EFW<10th	0.73 (0.67 – 0.78)	67.6% (57.9 – 76.3)	68.5% (63.9 – 72.9)	68.5%	2.15 (1.77 – 2.60)	0.47 (0.36 – 0.63)	35.3% (28.8 – 42.2)	89.3% (85.4 – 92.4)
Cohort with CPR<10th & EFW<10th	0.74 (0.65 – 0.83)	64.4% (48.8 – 78.1)	65.5% (56.0 – 74.2)	65.4%	1.87 (1.34 – 2.61)	0.54 (0.36 – 0.82)	42.6% (30.7 – 55.2)	82.2% (72.7 – 89.5)
Cohort with CPR<10th or EFW<10th	0.69 (0.65 – 0.73)	63.5% (56.2 – 70.4)	63.8% (60.7 – 66.8)	63.4%	1.75 (1.53 – 2.01)	0.57 (0.47 – 0.70)	25.4% (21.5 – 29.5)	90.0% (87.5 – 92.1)

AUC: Area Under the Curve; FPR: False Positive Rate; PLR: Positive Likelihood Ratio; NLR: Negative Likelihood Ratio; PPV: Positive Predictive Value; NPV: Negative Predictive Value; CPR: Cerebroplacental Ratio; EFW: Estimated Fetal Weight

Cross–validation of the model showed accurate and robust performance of the model with little difference between the final model (AUROC curve 0.71, 95% CI 0.69 – 0.73) compared to the cross–validation model (AUROC curve 0.70, 95% CI 0.68 – 0.72) (Figure 7.2). Confusion matrices of the comparisons of predicted and true outcome of the SANO for the final and cross–validation model can be found in Table 7.5, with diagnostic accuracies presented in Table 7.6. The Delong's test and the Hanley and McNeil test both suggested a significant difference between the models AUC ($p<0.001$), however this was in contradiction to the confidence intervals of the AUC and the diagnostic accuracies, negligible differences in the confusion matrices and the graphical comparison of the models, suggesting the study is overpowered for these formal tests. Again, clinical relevance and common sense was used for interpretation for the comparison of the predictive and cross–validation models.

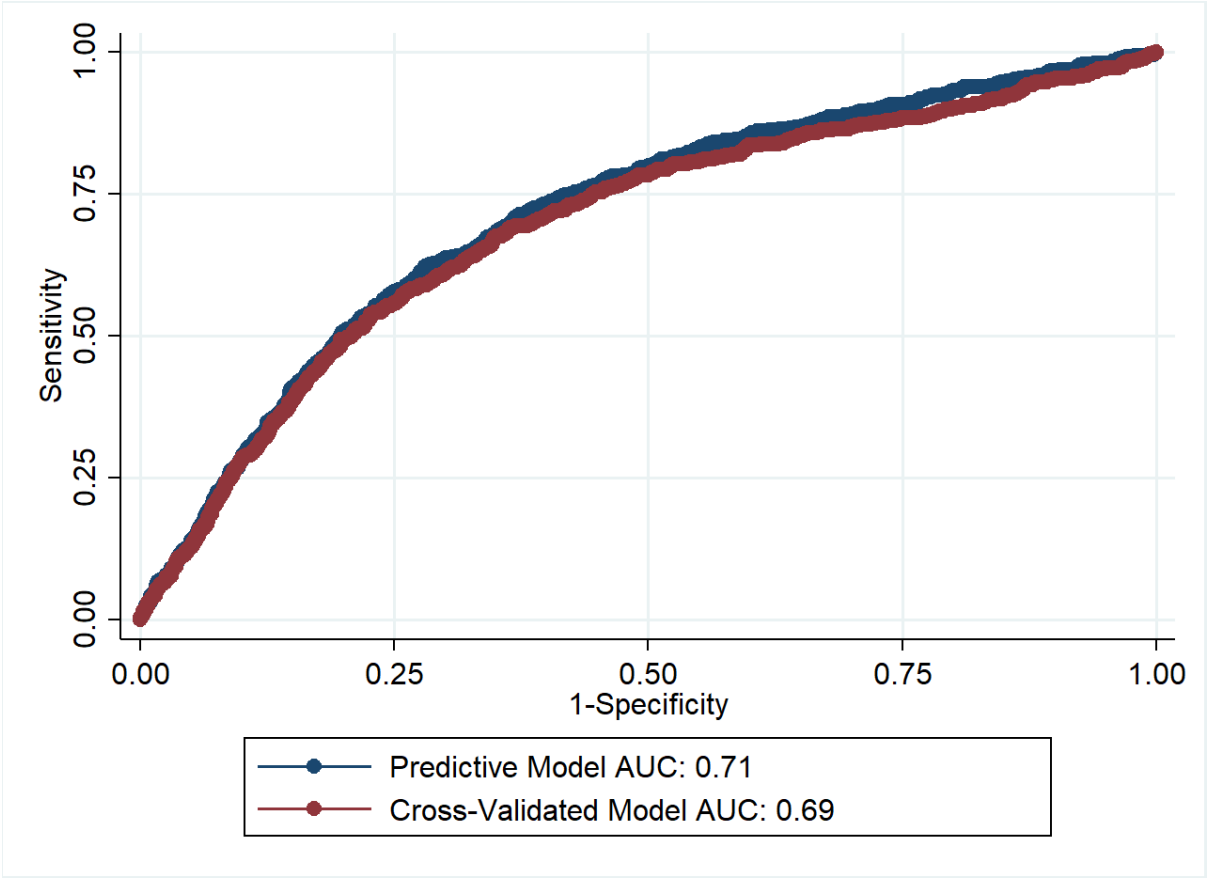

Figure 7-2: Comparison of predictive model and cross–validated model.

Table 7-5: Predictive model and cross–validation model confusion matrix using the optimal threshold of sensitivity and specificity.

Predicted Model			
True Outcome	**Predictive Outcome**		
	SANO	**No SANO**	**Total**
SANO	422	217	639
No SANO	1,611	3,188	4,799
Total	2,033	3,405	5,438
Cross Validation Model			
True Outcome	**Predicted Outcome**		
	SANO	**No SANO**	**Total**
SANO	414	225	639
No SANO	1,603	3,196	4,799
Total	2,017	3,421	5,438

SANO: Severe Adverse Neonatal Outcome

Table 7-6: Predictive model and cross–validation model diagnostic evaluation using the optimal threshold of sensitivity and specificity.

	Predictive Model	**Cross–Validated Model**
Sensitivity	66.0% (62.2 – 69.7)	64.8% (60.9 – 68.5)
Specificity	66.4% (65.1 – 67.8)	66.6% (65.2 – 67.9)
PPV	20.8% (19.0 – 22.6)	20.5% (18.8 – 22.4)
NPV	93.6% (92.8 – 94.4)	93.4% (92.5 – 94.2)
PLR	2.0 (1.8 – 2.1)	1.9 (1.8 – 2.1)
NLR	0.51 (0.46 – 0.57)	0.53 (0.48 – 0.59)
Correctly Classified	66.2%	66.4%
AUROC Curve	0.71 (0.69 – 0.73)	0.70 (0.68 – 0.72)

AUC: Area Under the Receiver Operating Characteristic Curve; PLR: Positive Likelihood Ratio; NLR: Negative Likelihood Ratio; PPV: Positive Predictive Value; NPV: Negative Predictive Value

7.6 Discussion

The results of this study demonstrate it is possible to predict with moderate accuracy, infants that are at risk of SANO at term using a combination of maternal, intrapartum and ultrasound variables. Cross–validation analysis suggests a high calibration of the model (Table 7.5, Table 7.6, Figure 7.2).

There is increasing demand for a test to predict adverse late pregnancy outcome and the EFW and CPR are often being used to guide clinical management (15, 50, 80, 145, 171). We have previously shown that both these variables identify separate cohorts of infants at risk of SANO and emphasize the need to incorporate both in risk stratification models (186). In this paper we extend our previous findings and use a variety of maternal, intrapartum and ultrasound derived variables to develop a model for the prediction of a composite of adverse outcomes.

More complex predictive models have recently been developed to identify fetuses at risk of neonatal care unit admission and operative delivery for intrapartum fetal compromise, albeit in SGA cohorts (75, 77). Evaluation of our model within high risk cohorts (SGA or low CPR) cohort saw an improvement in the PPV as well as the PLR but only a small increase in the AUROC. Our results demonstrate that the relationship between EFW as well as CPR and SANO is linear (illustrated in Figure 7.3) and suggests that using a threshold to categorise a higher risk cohort (e.g. EFW $<10^{th}$ centile) based on fetal weight will not only affect the accuracy of a model but also fail to identify fetuses that have an increased risk when their weights are close to but do not exceed the threshold (76).

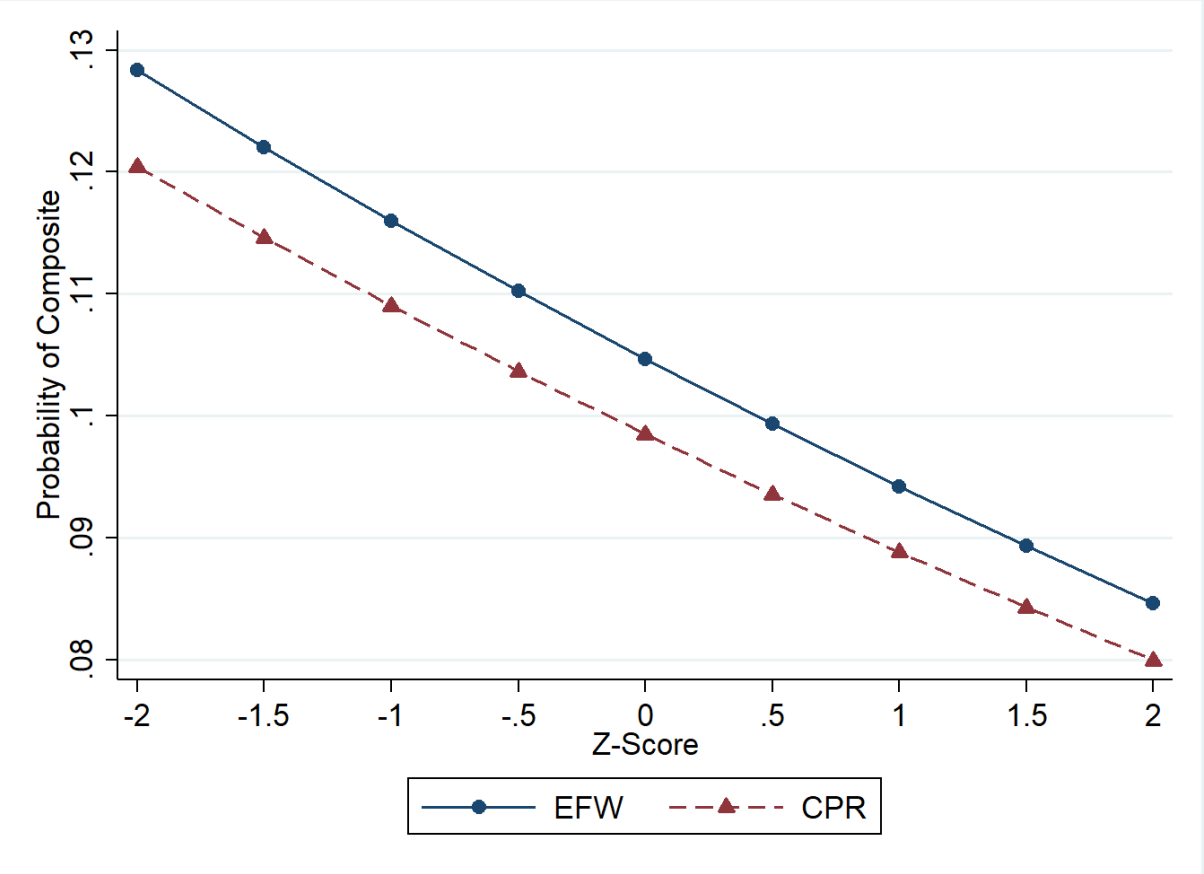

Figure 7-3: Adjusted probabilities of severe adverse neonatal outcome for estimated fetal weight and cerebroplacental ratio.

Indeed, there is good evidence that the incidence of adverse outcomes including perinatal death rises when birthweight is <20th centile for gestation (191-193). Using a predictive model that incorporates risk factors as continuous variables is more reflective of the true "real life" relationship with adverse outcomes. While creating predictive models in high risk cohorts using pre–determined cut–offs may provide superficially more impressive model diagnostics, they are arguably misleading and may provide false reassurance for individuals that fall outside, but are very close to the cut–off threshold (76).

The strengths of this study lie in the large study cohort and development of a regression model which was not subjected to overfitting. We also chose components of the composite outcome to reflect poor condition at birth and the association with hypoxic birth injury which are important clinically relevant outcomes. These outcomes are also correlated with both short–term morbidity such as hypoxic ischaemic encephalopathy as well as longer term complications including cerebral palsy. We also used a reasonably contemporary cohort of women so that perinatal outcomes should not have been significantly influenced by evolution in obstetric or neonatal practices. Nevertheless, there are several limitations that must be acknowledged. Although the

CPR was not reported, the EFW and UA PI were, which sometimes may have influenced management decisions. Furthermore, as routine late third trimester scans are not normally performed at our institution, by definition our study cohort cannot be truly considered an unselected or low risk population. Although the AUROC curve for our model was good the PLR was modest suggesting only a small increase in the likelihood of the outcome. When combined with a low pre–test probability of adverse outcomes at term the veracity and clinical utility of any model needs to interpreted with caution (194).

Clearly, any screening test has potential for harm from false positive or false negative results. During pregnancy, a positive screen result is often followed considerable maternal anxiety, increased obstetric intervention and early term birth. Indeed, there is evidence that children born at early term gestations not only have higher rates of neonatal complications (172, 195) but are also at risk for longer term adverse neurodevelopmental sequelae (196-198). The low rates of serious outcomes for term births constrains the development of any screening test for use in the general obstetric population and clinicians need to be cognizant of the limitations of these tests. It is possible however, that the addition of placental biomarkers may improve the performance of such models (20, 187). Despite the above–mentioned caveats, our model could be used to guide prenatal decision making and may help guide clinical practice.

Chapter 8: Discussion

8.1 Overview of key findings and implications

This thesis aimed to assess maternal and perinatal factors that are associated with adverse perinatal outcomes. It uses a pragmatic approach as it utilises routinely collected data, which accurately reflects real–world clinical situations. This thesis had the overarching aim of building appropriate robust statistical predictive models that are able to assist in identifying those fetuses most at risk. Each chapter builds on the background and knowledge that is related to adverse outcomes and explores the possibility of integrating ultrasound measures, in particular the EFW and the CPR, into predictive models. These parameters change in mean and variance over time and to account for these changes, a need arose to find suitable standardisation through the use and creation of accurate reference centiles. The reference centiles allowed the calculation of standardised *Z*–scores for use within the models. The predictive models maintained the continuous nature of the EFW and CPR variables and illustrated their linear association with the adverse outcomes. This is contrary to previous attempts at modelling adverse outcomes using dichotomised versions of these variables to create "high–risk" cohorts, but ignoring the erroneous implications of using such cut–offs.

8.2 Use of Routinely Collected Data: Birth Trends Between 2010 – 2016

This chapter explored the use of routinely collected data for research purposes. It also assessed the data integrity and generalisability of the MMH dataset. Today's society is more data driven than any time in the past. As hospitals and health care facilities increase their collection of patient data it offers the researcher a chance to access an abundance of data that has been collected under normal clinical situations. Not only is it pragmatic but is also avoids bias from studying highly selected groups in highly controlled environments and has the added benefit of the absence of the "Hawthorne effect". However, it is subject to other bias through measurement error, increased measurement variability and missing data. As routinely collecting data increases in hospitals and health care facilities, so will the resources that will be dedicated to the set–up, maintenance and education regarding collection of data which will help minimise those errors.

Assessment of the MMH data found there few differences in the maternal demographics and perinatal outcomes of the MMH cohort compared to the AIHW cohort. It concluded that the

MMH is representative of other major tertiary facilities within Australia and therefore the results drawn from the data is generalisable to other metropolitan hospitals. The similarities between the two cohorts also indicated that the data aggregations and manipulations were appropriate.

8.3 Is the fetal cerebroplacental ratio better that the estimated fetal weight in predicting adverse perinatal outcomes in a low risk cohort?

The premise for this chapter was that both a low CPR and low EFW can be the result of suboptimal placental function and both measures have been shown to be associated with adverse perinatal outcomes. While assessment of the EFW is part of clinical care, increasingly clinicians are incorporating the CPR into their routine care. The purpose of this chapter therefore, was to assess both measures individually and then in combination to evaluate whether they identify the same cohorts of adverse outcomes and if detectability is enhanced when used in combination.

This retrospective cohort study included all non–anomalous singleton fetuses that had ultrasound scans of the MCA PI and UA PI as well as the EFW measured between 36+0 and 38+6 weeks. After excluding major fetal congenital abnormalities, aneuploidy, multiple pregnancies, preterm births and any women who had diabetes or hypertension we were left with a low–risk term cohort. I was able to show that both the CPR and the EFW had associations with most of the same adverse outcomes and after adjusting for parity had similar odds ratios. The analysis of the sensitivity of the CPR $<10^{th}$ centile and EFW $<10^{th}$ centile, indicated that for both the outcomes of serious neonatal composite and the emergency caesarean for non-reassuring fetal status, there was substantial improvement when used in combination. Figures 3–1 and 3–2 clearly show that the use of both measures identify between 25% and 41% more fetuses that suffer adverse outcome than the use of the individual components. We found that a low CPR was associated with emergency caesarean for non–reassuring fetal status regardless of the EFW.

In conclusion, due to the EFW and the CPR being able to identify different cohorts of fetuses suffering the adverse outcomes, the use of both measures in any risk stratification model is preferred. Furthermore, the findings of a low CPR's association with emergency caesarean for non–reassuring fetal status regardless of EFW would suggest linear associations and negate the use of "high–risk" cohorts for risk stratification models based on cut-offs of the 10^{th} centile of either measure.

8.4 The magnitude of change in the fetal cerebroplacental ratio in the third trimester and the risk of adverse pregnancy outcome.

As the CPR is indicative of impaired placental function, I investigated whether the diagnostic utility of the CPR could be increased by measuring the magnitude of change that occurs between 30+0 weeks and 37+6 weeks gestation compared to a single measure late in pregnancy (between 35 – 37 weeks gestation).

This was a retrospective cohort of non–anomalous singleton fetuses with ultrasound scans for the MCA PI and the UA PI. I excluded any major congenital abnormality, aneuploidy and multiple pregnancy.

Due to the change in the mean and variance in CPR over the gestational period, there was a need to standardise each measure using *Z*–scores. I therefore created a separate cohort of normal pregnancies from which to calculate reference centiles. This cohort excluded any births other than spontaneous vaginal deliveries, preterm births, multiple pregnancies, major congenital abnormalities, aneuploidy, indeterminate fetal gender, perinatal death, admission to the NICU, hypoglycaemia, acidosis, respiratory distress, resuscitation low Apgar score at 5–min <7 and diabetes or hypertension. I then used a GAMLSS model to create the normal reference ranges from which the *Z*–scores for the study cohort could be calculated. There was also differing time periods between the scans for each fetus. To account for this, I standardised each delta *Z*–score (i.e. the *Z*–score of the second scan – the *Z*–score of the first scan) by dividing the delta *Z*–score by the number of gestational weeks between the scans to give the change per week.

I was able to show that a decreasing CPR *Z*–score was associated with emergency caesarean, emergency caesarean for non–reassuring fetal status, preterm delivery, BW <10th centile and hypoglycaemia. However, the area under the curves indicated that the change in CPR *Z*–score gave no improvement in detectability than a single scan taken between 35 – 37 weeks gestation. Furthermore, adjusting for the change in CPR *Z*–score as added no benefit to the area under the curve of the single scan taken between 35 – 37 weeks gestation.

In conclusion, while the change in CPR is associated with adverse perinatal outcomes, a single scan late in gestation is potentially a more useful indicator of adverse outcome.

8.5 Reference centiles for the middle cerebral artery and umbilical artery pulsatility index and cerebroplacental ratio from a low–risk population – a Generalised Additive Model for Location, shape and Scale (GAMLSS) approach.

A number of papers have been written by Altman, Royston and Cole, outlining the appropriate methodologies needed to create anthropometric charts (89, 97, 98, 100-104, 106, 107, 111, 115). Despite this, centiles for the MCA PI and UA PI as well as the CPR have often suffered from methodological flaws such as small sample size, suboptimal modelling and lack of reporting of model diagnostics or subsequent goodness–of–fit evaluation. According to Oros' systematic review on reference centiles for Doppler indices, Ebbings 2007 longitudinal reference ranges were methodologically the most robust that were published to date (93). However, when I applied Ebbings 10th centile to the Mater obstetric cohort, I found that it was reflective of 20% of our population (i.e. the 20th centile), indicating that Ebbings centiles were too high to be applied to our population.

I therefore set out to create reference centiles for the MCA PI, the UA PI and the CPR using the GAMLSS technique in a large sample of low–risk women. This method was chosen after a publication in 2006 by Borghi *et al* evaluated 30 different methodologies for the creation of growth curves and concluded that the GAMLSS method was the most appropriate for this purpose (99).

I used cross–sectional data and included all women aged between 18 – 40 years with a single non–anomalous term fetus. To create a low–risk population I excluded all women who used artificial reproductive technologies, had a BMI ≥35 kg/m^2, with diabetes mellitus, hypertension, respiratory, thyroid or heart disease or fetuses that had known FGR. All ultrasound scans were performed between 18+0 and 41+6 weeks gestation.

Fractional polynomial additive terms and BCT distributions were used for the calculation of the centiles for the MCA PI and the CPR on 4,473 and 4,473 fetuses respectively. Centiles for the UA PI were calculated on 6,008 fetuses using a cubic spline additive term with BCT distribution. Model diagnoses indicated appropriate fitting of the four parameters of distribution for each of the models. Appropriate fitting of the distribution in the tails was evidence by an absence of excessive skewness and kurtosis and with the detrended Owen's plot not exceeding the confidence intervals shows that the normalised residuals came from normal distributions for all models. Each model was found to be a reasonable fit for the data.

In conclusion I created accurate gestational centile reference ranges for the MCA PI, UA PI and CPR using statistically robust techniques and a biologically and clinically plausible low–risk cohort.

8.6 Development of cross–validated model for the prediction of emergency caesarean for intrapartum fetal compromise at term.

A previous study by Kalafat *et al* had attempted to create a predictive model for operative delivery for intrapartum fetal compromise in a SGA cohort, defined as an EFW <10th centile. Their erroneous methodology in dichotomising continuous variables is well established in statistics and clearly described in a 2006 publication by Altman and Royston (76). Kalafat *et al* even explore the linear associations that exist in the CPR and go on to explain the need for it to remain a continuous variable but insist on dichotomising the EFW (75). Our previous study showed that a low CPR was associated with emergency caesarean for non–reassuring fetal status regardless of the EFW (186). The aim of this study thus was to develop a predictive model for emergency caesarean for fetal distress at term using a combination of maternal and late pregnancy ultrasound parameters measured at ≥36 weeks gestation.

This was a cohort study of all singleton, non-anomalous births between January 2010 and April 2017, with ultrasound recordings of the MCA PI and UA PI, the CPR as well as the EFW. Standardisation of the Doppler indices was done using *Z*–scores against previously published references (177, 178). Mixed effects generalised linear models were used to generate univariable and multivariable models. Variables for the predictive model were selected using a backward elimination technique based on the Akaike information criterion. Validation of the model was performed using the K–fold cross validation technique.

The final model included ethnicity, nulliparity, induction of labour and the CPR and EFW *Z*–scores. The model returned an AUC of 0.77 (95% CI 0.74 – 0.80). Evaluation of the model in high–risk cohorts showed improvement in the positive likelihood ratio for fetuses with a low EFW and improvement in positive predictive value for fetuses with both a low CPR and low EFW. Overall there was little difference in the area under the curve for the higher–risk cohorts. Even after adjustment, a clear linear association was shown to exist for the variables of the EFW and the CPR and the outcome of emergency caesarean for non–reassuring fetal status.

In conclusion I created a model in a general population that combined the CPR, the EFW and several maternal factors that is able to identify with improved accuracy, term fetuses that develop intrapartum fetal compromise and require emergency caesarean for delivery. This improvement was obtained without using a high–risk cohort. Furthermore, I have provided evidence of the linear associations between emergency caesarean for non–reassuring fetal status and the Doppler indices of the EFW and the CPR.

8.7 Cross–validated prediction model for severe adverse neonatal outcomes in a term, non–anomalous, singleton cohort.

As a follow–up to the predictive model for emergency caesarean for non–reassuring fetal status I investigated a model for a severe adverse neonatal outcome. Considering conclusions observed from the paper investigating the EFW and CPR in low risk cohorts (186) and the linear trends detected in the previous predictive model, this model was also constructed from a general all–inclusive cohort using the continuous variables of the CPR and EFW. Previous model had been constructed with the outcomes of operative delivery for intrapartum fetal compromise and admission to the NICU but both within SGA cohorts (75, 77).

The same inclusion criteria and statistical methodology was used for model building as used in the previous chapter.

The final model consisted of ethnicity, SEIFA score, nulliparity, induction of labour, method of birth and the EFW and CPR *Z*–scores. This model calculated an AUC of 0.71 (95% CI 0.69 – 0.73). When applying this model to higher–risk cohorts, improvements were observed in the positive predictive value in the cohort of fetuses with an EFW $<10^{th}$ centile and fetuses with a low CPR and low EFW. There were no real improvements in AUC or positive likelihood ratios from the general cohort to the higher–risk cohorts. Again, after adjustment, there were clear linear associations between the composite outcome and the continuous variables of the CPR and the EFW.

In conclusion this model was able to predict severe adverse neonatal outcome with moderate accuracy. More importantly I was able to replicate the linear association between the Doppler indices and the outcome that was observed in the previous model. These models reflect what is observed in real–life scenarios. There is no distinct difference in the probability of outcome between the 10^{th} and 11^{th} centile of either the EFW or the CPR. Researchers often decide to use

predetermined cut–offs to build predictive models under the guise of being high–risk cohorts when this does not have true clinical representativeness. While this approach may produce superficially more impressive model diagnostics, it is misleading and provides false reassurance for individuals that fall outside, but are very close to the cut–off threshold (76).

8.8 Future directions for research.

While the use of the Doppler indices of the EFW and the CPR improve the predictability of the models developed for this thesis, their diagnostic characteristics are still relatively poor and not convincing enough that they could be employed in routine clinical practice. The reason for the poor diagnostic characteristics can be a result of the complexity of the disease as well as the accuracy of some of the predictor variables that we currently use. We often include ethnicity in models as there are known associations between some ethnicities and adverse outcomes. However, in today's multicultural societies, the biological differences that once defined ethnic groups has become blurred and there is a now a need to investigate the epigenetic characteristics rather than rely on self–reported ethnicity. Furthermore, variables such as ethnicity can be surrogates for other social disparities such as socio–economic status and other geographical related disparities.

There is also now evidence that placental biomarkers such as the placental growth factor may be useful for identifying vulnerable fetuses (187, 199). Work within our group has shown that in low risk term pregnancies, lower concentrations of maternal PLGF is associated with intrapartum fetal compromise as well as a composite outcome that comprised of abnormal cord gases and/or 5–minute Apgar <7 and/or admission to NICU (199). In a pilot study, the same team investigated the use of a combination of CPR and PLGF in predicting intrapartum fetal compromise and a composite neonatal outcome in low risk term pregnancies. They found that a model that combined both CPR and PLGF showed an improvement in diagnostic performance compared to the individual components for both intrapartum fetal compromise and for the composite neonatal outcome (187). Dunn and Kumar in another pilot study, showed that not only are PLGF levels are lower in pregnancies with intrapartum fetal compromise and composite neonatal outcomes but there is also a sharper decline in levels of PLGF in pregnancies complicated by intrapartum fetal compromise (200). In a systematic review by Sherrell *et al*, they concluded that low maternal PLGF levels have consistently been found to be associated with intrapartum fetal compromise as well as other adverse neonatal outcomes such as SGA,

NICU admission and stillbirth (201). With these findings future work needs to elucidate what role such biomarkers, in particular PLGF, may have in similar models.

8.9 Conclusion

The research presented in this thesis adds to our understanding of the impact maternal, intrapartum and ultrasound variables have on adverse perinatal outcomes. It highlights the need to use appropriate methodology for the creation of reference centiles and the use of variables that are measured on the continuous scale. I have been able to develop predictive models for emergency caesarean for non–reassuring fetal status and severe adverse neonatal outcome. While their area under the curves were relatively strong, they were lacking strength in the diagnostic accuracies of the positive likelihood ratios and positive predictive values. Opportunities for further work include evaluation the inclusion of placental biomarkers into risk stratification models for the identification of at–risk pregnancies.

References

1. AIHW. National core maternity indicators. Canberra, Australia: AIHW; 2013. Contract No.: Cat. no. PER 58. .
2. Gaylord M, Greer M, Botti J. Improving perinatal health: a novel approach to improve community and adult health. Journal of perinatology : official journal of the California Perinatal Association. 2008;28(2):91-6.
3. Figueras F, Gratacos E. Stage-based approach to the management of fetal growth restriction. Prenatal diagnosis. 2014;34(7):655-9.
4. Figueras F, Gratacos E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. Fetal diagnosis and therapy. 2014;36(2):86-98.
5. Baschat AA. Fetal growth restriction - from observation to intervention. Journal of perinatal medicine. 2010;38(3):239-46.
6. Muresan D, Rotar IC, Stamatian F. The usefulness of fetal Doppler evaluation in early versus late onset intrauterine growth restriction. Review of the literature. Medical ultrasonography. 2016;18(1):103-9.
7. Baschat AA. Neurodevelopment following fetal growth restriction and its relationship with antepartum parameters of placental dysfunction. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2011;37(5):501-14.
8. Baschat AA. Fetal responses to placental insufficiency: an update. BJOG : an international journal of obstetrics and gynaecology. 2004;111(10):1031-41.
9. Lausman A, McCarthy FP, Walker M, Kingdom J. Screening, diagnosis, and management of intrauterine growth restriction. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC. 2012;34(1):17-28.
10. Hernandez-Andrade E, Stampalija T, Figueras F. Cerebral blood flow studies in the diagnosis and management of intrauterine growth restriction. Current opinion in obstetrics & gynecology. 2013;25(2):138-44.
11. Akolekar R, Syngelaki A, Gallo DM, Poon LC, Nicolaides KH. Umbilical and fetal middle cerebral artery Doppler at 35-37 weeks' gestation in the prediction of adverse perinatal outcome. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2015;46(1):82-92.
12. Harrington K, Carpenter RG, Nguyen M, Campbell S. Changes observed in Doppler studies of the fetal circulation in pregnancies complicated by pre-eclampsia or the delivery of a small-for-gestational-age baby. I. Cross-sectional analysis. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 1995;6(1):19-28.
13. Hecher K, Spernol R, Stettner H, Szalay S. Potential for diagnosing imminent risk to appropriate- and small-for-gestational-age fetuses by Doppler sonographic examination of umbilical and cerebral arterial blood flow. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 1992;2(4):266-71.
14. Morales-Rosello J, Khalil A, Morlando M, Papageorghiou A, Bhide A, Thilaganathan B. Changes in fetal Doppler indices as a marker of failure to reach growth potential at term. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2014;43(3):303-10.
15. Prior T, Mullins E, Bennett P, Kumar S. Prediction of intrapartum fetal compromise using the cerebroumbilical ratio: a prospective observational study. Am J Obstet Gynecol. 2013;208(2):124 e1-6.
16. Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth restriction. Am J Obstet Gynecol. 2018;218(2s):S745-s61.
17. Marsal K. Obstetric management of intrauterine growth restriction. Best practice & research Clinical obstetrics & gynaecology. 2009;23(6):857-70.

18. Nardozza LM, Araujo Junior E, Barbosa MM, Caetano AC, Lee DJ, Moron AF. Fetal growth restriction: current knowledge to the general Obs/Gyn. Archives of gynecology and obstetrics. 2012;286(1):1-13.
19. Froen JF, Gardosi JO, Thurmann A, Francis A, Stray-Pedersen B. Restricted fetal growth in sudden intrauterine unexplained death. Acta obstetricia et gynecologica Scandinavica. 2004;83(9):801-7.
20. Gaccioli F, Aye I, Sovio U, Charnock-Jones DS, Smith GCS. Screening for fetal growth restriction using fetal biometry combined with maternal biomarkers. Am J Obstet Gynecol. 2018;218(2S):S725-S37.
21. Mifsud W, Sebire NJ. Placental pathology in early-onset and late-onset fetal growth restriction. Fetal diagnosis and therapy. 2014;36(2):117-28.
22. Baschat AA. Venous Doppler evaluation of the growth-restricted fetus. Clinics in perinatology. 2011;38(1):103-12, vi.
23. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2016;48(3):333-9.
24. Pijnenborg R, Vercruysse L, Hanssens M. The uterine spiral arteries in human pregnancy: facts and controversies. Placenta. 2006;27(9-10):939-58.
25. Turan OM, Turan S, Gungor S, Berg C, Moyano D, Gembruch U, et al. Progression of Doppler abnormalities in intrauterine growth restriction. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2008;32(2):160-7.
26. Lyall F. Priming and remodelling of human placental bed spiral arteries during pregnancy--a review. Placenta. 2005;26 Suppl A:S31-6.
27. Crispi F, Dominguez C, Llurba E, Martin-Gallan P, Cabero L, Gratacos E. Placental angiogenic growth factors and uterine artery Doppler findings for characterization of different subsets in preeclampsia and in isolated intrauterine growth restriction. Am J Obstet Gynecol. 2006;195(1):201-7.
28. Ness RB, Sibai BM. Shared and disparate components of the pathophysiologies of fetal growth restriction and preeclampsia. Am J Obstet Gynecol. 2006;195(1):40-9.
29. Khong SL, Kane SC, Brennecke SP, da Silva Costa F. First-trimester uterine artery Doppler analysis in the prediction of later pregnancy complications. Disease markers. 2015;2015:679730.
30. Odibo AO, Zhong Y, Longtine M, Tuuli M, Odibo L, Cahill AG, et al. First-trimester serum analytes, biophysical tests and the association with pathological morphometry in the placenta of pregnancies with preeclampsia and fetal growth restriction. Placenta. 2011;32(4):333-8.
31. Pilalis A, Souka AP, Antsaklis P, Daskalakis G, Papantoniou N, Mesogitis S, et al. Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler and PAPP-A at 11-14 weeks' gestation. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2007;29(2):135-40.
32. Abdel Moety GA, Almohamady M, Sherif NA, Raslana AN, Mohamed TF, El Moneam HM, et al. Could first-trimester assessment of placental functions predict preeclampsia and intrauterine growth restriction? A prospective cohort study. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2016;29(3):413-7.
33. Figueras F, Caradeux J, Crispi F, Eixarch E, Peguero A, Gratacos E. Diagnosis and surveillance of late-onset fetal growth restriction. Am J Obstet Gynecol. 2018;218(2s):S790-S802.e1.
34. Parra-Saavedra M, Crovetto F, Triunfo S, Savchev S, Peguero A, Nadal A, et al. Association of Doppler parameters with placental signs of underperfusion in late-onset small-for-gestational-age pregnancies. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2014;44(3):330-7.
35. Parra-Saavedra M, Crovetto F, Triunfo S, Savchev S, Peguero A, Nadal A, et al. Placental findings in late-onset SGA births without Doppler signs of placental insufficiency. Placenta. 2013;34(12):1136-41.
36. Bassan H, Stolar O, Geva R, Eshel R, Fattal-Valevski A, Leitner Y, et al. Intrauterine growth-restricted neonates born at term or preterm: how different? Pediatric neurology. 2011;44(2):122-30.

37. MacDonald TM, McCarthy EA, Walker SP. Shining light in dark corners: diagnosis and management of late-onset fetal growth restriction. The Australian & New Zealand journal of obstetrics & gynaecology. 2015;55(1):3-10.
38. Bjoro K, Jr., Myhre E. The role of chronic non-specific inflammatory lesions of the placenta in intra-uterine growth retardation. Acta pathologica, microbiologica, et immunologica Scandinavica Section A, Pathology. 1984;92(2):133-7.
39. Althabe O, Labarrere C. Chronic villitis of unknown aetiology and intrauterine growth-retarded infants of normal and low ponderal index. Placenta. 1985;6(4):369-73.
40. Prior T, Paramasivam G, Bennett P, Kumar S. Are fetuses that fail to achieve their growth potential at increased risk of intrapartum compromise? Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2015;46(4):460-4.
41. Prior T, Kumar S. Expert review--identification of intra-partum fetal compromise. European journal of obstetrics, gynecology, and reproductive biology. 2015;190:1-6.
42. Cruz-Martinez R, Figueras F. The role of Doppler and placental screening. Best practice & research Clinical obstetrics & gynaecology. 2009;23(6):845-55.
43. Vergani P, Roncaglia N, Ghidini A, Crippa I, Cameroni I, Orsenigo F, et al. Can adverse neonatal outcome be predicted in late preterm or term fetal growth restriction? Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2010;36(2):166-70.
44. Alfirevic Z, Stampalija T, Gyte GM. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. The Cochrane database of systematic reviews. 2013(11):CD007529.
45. Hershkovitz R, Kingdom JC, Geary M, Rodeck CH. Fetal cerebral blood flow redistribution in late gestation: identification of compromise in small fetuses with normal umbilical artery Doppler. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2000;15(3):209-12.
46. Farrell T, Chien PF, Gordon A. Intrapartum umbilical artery Doppler velocimetry as a predictor of adverse perinatal outcome: a systematic review. British journal of obstetrics and gynaecology. 1999;106(8):783-92.
47. Alfirevic Z, Stampalija T, Medley N. Fetal and umbilical Doppler ultrasound in normal pregnancy. The Cochrane database of systematic reviews. 2015(4):CD001450.
48. Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, et al. Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. Am J Obstet Gynecol. 2013;208(4):290 e1-6.
49. Morris RK, Say R, Robson SC, Kleijnen J, Khan KS. Systematic review and meta-analysis of middle cerebral artery Doppler to predict perinatal wellbeing. European journal of obstetrics, gynecology, and reproductive biology. 2012;165(2):141-55.
50. Cruz-Martinez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E. Fetal brain Doppler to predict cesarean delivery for nonreassuring fetal status in term small-for-gestational-age fetuses. Obstetrics and gynecology. 2011;117(3):618-26.
51. Leung TY, Fok WY, Chan LW, Law LW, Lau TK. Prediction of intrapartum Cesarean delivery for non-reassuring fetal status after a successful external cephalic version by a low pre-version pulsatility index of the fetal middle cerebral artery. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2006;27(4):416-9.
52. DeVore GR. The importance of the cerebroplacental ratio in the evaluation of fetal well-being in SGA and AGA fetuses. Am J Obstet Gynecol. 2015;213(1):5-15.
53. Khalil AA, Morales-Rosello J, Morlando M, Hannan H, Bhide A, Papageorghiou A, et al. Is fetal cerebroplacental ratio an independent predictor of intrapartum fetal compromise and neonatal unit admission? Am J Obstet Gynecol. 2015;213(1):54 e1- e10.
54. Khalil AA, Morales-Rosello J, Elsaddig M, Khan N, Papageorghiou A, Bhide A, et al. The association between fetal Doppler and admission to neonatal unit at term. Am J Obstet Gynecol. 2015;213(1):57 e1- e7.

55. Khalil A, Thilaganathan B. Role of uteroplacental and fetal Doppler in identifying fetal growth restriction at term. Best practice & research Clinical obstetrics & gynaecology. 2017;38:38-47.
56. Nassr AA, Abdelmagied AM, Shazly SA. Fetal cerebro-placental ratio and adverse perinatal outcome: systematic review and meta-analysis of the association and diagnostic performance. Journal of perinatal medicine. 2016;44(2):249-56.
57. Bahado-Singh RO, Kovanci E, Jeffres A, Oz U, Deren O, Copel J, et al. The Doppler cerebroplacental ratio and perinatal outcome in intrauterine growth restriction. Am J Obstet Gynecol. 1999;180(3 Pt 1):750-6.
58. Prior T, Mullins E, Bennett P, Kumar S. Prediction of fetal compromise in labor. Obstetrics and gynecology. 2014;123(6):1263-71.
59. Murata S, Nakata M, Sumie M, Sugino N. The Doppler cerebroplacental ratio predicts non-reassuring fetal status in intrauterine growth restricted fetuses at term. The journal of obstetrics and gynaecology research. 2011;37(10):1433-7.
60. Morales-Rosello J, Khalil A, Morlando M, Bhide A, Papageorghiou A, Thilaganathan B. Poor neonatal acid-base status in term fetuses with low cerebroplacental ratio. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2015;45(2):156-61.
61. Twomey S, Flatley C, Kumar S. The association between a low cerebro-umbilical ratio at 30-34 weeks gestation, increased intrapartum operative intervention and adverse perinatal outcomes. European journal of obstetrics, gynecology, and reproductive biology. 2016;203:89-93.
62. Regan J, Masters H, Warshak CR. Association between an abnormal cerebroplacental ratio and the development of severe pre-eclampsia. Journal of perinatology : official journal of the California Perinatal Association. 2015;35(5):322-7.
63. Makhseed M, Jirous J, Ahmed MA, Viswanathan DL. Middle cerebral artery to umbilical artery resistance index ratio in the prediction of neonatal outcome. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2000;71(2):119-25.
64. Bligh LN, Al Solai A, Greer RM, Kumar S. Diagnostic Performance of Cerebroplacental Ratio Thresholds at Term for Prediction of Low Birthweight and Adverse Intrapartum and Neonatal Outcomes in a Term, Low-Risk Population. Fetal diagnosis and therapy. 2018;43(3):191-8.
65. Odibo AO, Riddick C, Pare E, Stamilio DM, Macones GA. Cerebroplacental Doppler ratio and adverse perinatal outcomes in intrauterine growth restriction: evaluating the impact of using gestational age-specific reference values. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 2005;24(9):1223-8.
66. Ebbing C, Rasmussen S, Kiserud T. Middle cerebral artery blood flow velocities and pulsatility index and the cerebroplacental pulsatility ratio: longitudinal reference ranges and terms for serial measurements. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2007;30(3):287-96.
67. Sabdia S, Greer RM, Prior T, Kumar S. Predicting intrapartum fetal compromise using the fetal cerebro-umbilical ratio. Placenta. 2015;36(5):594-8.
68. Bakalis S, Akolekar R, Gallo DM, Poon LC, Nicolaides KH. Umbilical and fetal middle cerebral artery Doppler at 30-34 weeks' gestation in the prediction of adverse perinatal outcome. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2015;45(4):409-20.
69. Khalil A, Morales-Rosello J, Townsend R, Morlando M, Papageorghiou A, Bhide A, et al. Value of third-trimester cerebroplacental ratio and uterine artery Doppler indices as predictors of stillbirth and perinatal loss. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2016;47(1):74-80.
70. Morales-Rosello J, Khalil A. Fetal cerebroplacental ratio and adverse perinatal outcome. Journal of perinatal medicine. 2016;44(3):355.
71. Gibbons A, Flatley C, Kumar S. Cerebroplacental ratio in pregnancies complicated by gestational diabetes mellitus. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2017;50(2):200-6.

72. Baschat AA, Gembruch U. The cerebroplacental Doppler ratio revisited. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2003;21(2):124-7.
73. Figueras F, Meler E, Iraola A, Eixarch E, Coll O, Figueras J, et al. Customized birthweight standards for a Spanish population. European journal of obstetrics, gynecology, and reproductive biology. 2008;136(1):20-4.
74. Nassr AA, Abdelmagied AM, Shazly SA. Reply to: Fetal cerebroplacental ratio and adverse perinatal outcome. Journal of perinatal medicine. 2016;44(3):357.
75. Kalafat E, Morales-Rosello J, Thilaganathan B, Tahera F, Khalil A. Risk of operative delivery for intrapartum fetal compromise in small-for-gestational-age fetuses at term: an internally validated prediction model. Am J Obstet Gynecol. 2018;218(1):134 e1- e8.
76. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ. 2006;332(7549):1080.
77. Kalafat E, Morales-Rosello J, Thilaganathan B, Dhother J, Khalil A. Risk of neonatal care unit admission in small for gestational age fetuses at term: a prediction model and internal validation. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2018:1-8.
78. Conde-Agudelo A, Villar J, Kennedy SH, Papageorghiou AT. Predictive accuracy of cerebroplacental ratio for adverse perinatal and neurodevelopmental outcomes in suspected fetal growth restriction: systematic review and meta-analysis. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2018;52(4):430-41.
79. Miranda J, Triunfo S, Rodriguez-Lopez M, Sairanen M, Kouru H, Parra-Saavedra M, et al. Performance of third-trimester combined screening model for prediction of adverse perinatal outcome. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2017;50(3):353-60.
80. Morales-Rosello J, Khalil A, Fornes-Ferrer V, Perales-Marin A. Accuracy of the fetal cerebroplacental ratio for the detection of intrapartum compromise in nonsmall fetuses(). The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2018:1-11.
81. Acharya G, Wilsgaard T, Berntsen GK, Maltau JM, Kiserud T. Reference ranges for serial measurements of umbilical artery Doppler indices in the second half of pregnancy. Am J Obstet Gynecol. 2005;192(3):937-44.
82. Arduini D, Rizzo G. Normal values of Pulsatility Index from fetal vessels: a cross-sectional study on 1556 healthy fetuses. Journal of perinatal medicine. 1990;18(3):165-72.
83. Bahlmann F, Reinhard I, Krummenauer F, Neubert S, Macchiella D, Wellek S. Blood flow velocity waveforms of the fetal middle cerebral artery in a normal population: reference values from 18 weeks to 42 weeks of gestation. Journal of perinatal medicine. 2002;30(6):490-501.
84. Kurmanavicius J, Florio I, Wisser J, Hebisch G, Zimmermann R, Muller R, et al. Reference resistance indices of the umbilical, fetal middle cerebral and uterine arteries at 24-42 weeks of gestation. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 1997;10(2):112-20.
85. Kurmanavicius J, Streicher A, Wright EM, Wisser J, Muller R, Royston P, et al. Reference values of fetal peak systolic blood flow velocity in the middle cerebral artery at 19-40 weeks of gestation. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2001;17(1):50-3.
86. Palacio M, Figueras F, Zamora L, Jimenez JM, Puerto B, Coll O, et al. Reference ranges for umbilical and middle cerebral artery pulsatility index and cerebroplacental ratio in prolonged pregnancies. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2004;24(6):647-53.

87. Wellek S, Merz E. Age-related reference ranges for growth parameters. Methods of information in medicine. 1995;34(5):523-8.
88. Parra-Cordero M, Lees C, Missfelder-Lobos H, Seed P, Harris C. Fetal arterial and venous Doppler pulsatility index and time averaged velocity ranges. Prenatal diagnosis. 2007;27(13):1251-7.
89. Royston P. Calculation of unconditional and conditional reference intervals for foetal size and growth from longitudinal measurements. Statistics in medicine. 1995;14(13):1417-36.
90. Morales-Rosello J, Khalil A, Morlando M, Hervas-Marin D, Perales-Marin A. Doppler reference values of the fetal vertebral and middle cerebral arteries, at 19-41 weeks gestation. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2015;28(3):338-43.
91. Seffah JD, Swarray-Deen A. Fetal middle cerebral artery Doppler indices and clinical application at Korle Bu Teaching Hospital, Accra, Ghana. International Journal of Gynecology & Obstetrics. 2016;134(2):135-9.
92. Rigby RA, Stasinopoulos DM. Smooth centile curves for skew and kurtotic data modelled using the Box-Cox power exponential distribution. Statistics in medicine. 2004;23(19):3053-76.
93. Oros D, Ruiz-Martinez S, Staines-Urias E, Conde-Agudelo A, Villar J, Fabre E, et al. Reference ranges for Doppler indices of umbilical and middle cerebral arteries and cerebroplacental ratio: a systematic review. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2018.
94. Medina Castro N, Figueroa Diesel H, Guzman Huerta M, Hernandez Andrade E. [Normal reference values of the pulsatility index from the uterine and umbilical arteries during pregnancy]. Ginecologia y obstetricia de Mexico. 2006;74(10):509-15.
95. Medina Castro N, Figueroa Diesel H, Hernandez Andrade E. [Normal reference values of the pulsatility index and peak systolic velocity in the fetal middle cerebral artery during normal pregnancy]. Ginecologia y obstetricia de Mexico. 2006;74(7):376-82.
96. Ciobanu A, Wright A, Syngelaki A, Wright D, Akolekar R, Nicolaides KH. Fetal Medicine Foundation reference ranges for umbilical artery and middle cerebral artery pulsatility index and cerebroplacental ratio. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2018.
97. Altman DG, Chitty LS. Design and analysis of studies to derive charts of fetal size. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 1993;3(6):378-84.
98. Altman DG, Chitty LS. Charts of fetal size: 1. Methodology. British journal of obstetrics and gynaecology. 1994;101(1):29-34.
99. Borghi E, de Onis M, Garza C, Van den Broeck J, Frongillo EA, Grummer-Strawn L, et al. Construction of the World Health Organization child growth standards: selection of methods for attained growth curves. Statistics in medicine. 2006;25(2):247-65.
100. Cole TJ. Fitting Smoothed Centile Curves to Reference Data. Journal of the Royal Statistical Society Series A (Statistics in Society). 1988;151(3):385-418.
101. Cole TJ. The development of growth references and growth charts. Annals of human biology. 2012;39(5):382-94.
102. Royston P. Constructing time-specific reference ranges. Statistics in medicine. 1991;10(5):675-90.
103. Royston P, Altman DG. Design and analysis of longitudinal studies of fetal size. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 1995;6(5):307-12.
104. Royston P, Wright EM. How to construct 'normal ranges' for fetal variables. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 1998;11(1):30-8.
105. Wade AM, Ades AE. Age-related reference ranges: significance tests for models and confidence intervals for centiles. Statistics in medicine. 1994;13(22):2359-67.

106. Altman DG. Construction of age-related reference centiles using absolute residuals. Statistics in medicine. 1993;12(10):917-24.
107. Royston P, Wright EM. Goodness-of-fit statistics for age-specific reference intervals. Statistics in medicine. 2000;19(21):2943-62.
108. Wright EM, Royston P. Simplified estimation of age-specific reference intervals for skewed data. Statistics in medicine. 1997;16(24):2785-803.
109. Wright EM, Royston P. A Comparison of Statistical Methods for Age-related Reference Intervals. Journal of the Royal Statistical Society: Series A (Statistics in Society). 1997;160(1):47-69.
110. Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet. 2014;384(9946):857-68.
111. Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. Statistics in medicine. 1992;11(10):1305-19.
112. Hopkins KD, Weeks DL. Tests for Normality and Measures of Skewness and Kurtosis: Their Place in Research Reporting. Educational and Psychological Measurement. 2016;50(4):717-29.
113. Rigby RA, Stasinopoulos DM. Generalized additive models for location, scale and shape (with discussion). Journal of the Royal Statistical Society: Series C (Applied Statistics). 2005;54(3):507-54.
114. Papageorghiou AT, Kennedy SH, Salomon LJ, Altman DG, Ohuma EO, Stones W, et al. The INTERGROWTH-21(st) fetal growth standards: toward the global integration of pregnancy and pediatric care. Am J Obstet Gynecol. 2018;218(2s):S630-s40.
115. Ohuma EO, Altman DG. Design and other methodological considerations for the construction of human fetal and neonatal size and growth charts. Statistics in medicine. 2018.
116. Villar J, Dorgan J, Menendez R, Bolanos L, Pareja G, Kestler E. Perinatal data reliability in a large teaching obstetric unit. British journal of obstetrics and gynaecology. 1988;95(9):841-8.
117. Stasinopoulos DM, Rigby RA. Generalized Additive Models for Location Scale and Shape (GAMLSS) inR. Journal of Statistical Software. 2007;23(7):46.
118. Hemkens LG, Contopoulos-Ioannidis DG, Ioannidis JP. Routinely collected data and comparative effectiveness evidence: promises and limitations. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2016;188(8):E158-64.
119. Benchimol EI, Langan S, Guttmann A, Committee RS. Call to RECORD: the need for complete reporting of research using routinely collected health data. J Clin Epidemiol. 2013;66(7):703-5.
120. Black N. Why we need observational studies to evaluate the effectiveness of health care. BMJ. 1996;312(7040):1215-8.
121. Meinecke AK, Welsing P, Kafatos G, Burke D, Trelle S, Kubin M, et al. Series: Pragmatic trials and real world evidence: Paper 8. Data collection and management. J Clin Epidemiol. 2017;91:13-22.
122. Zuidgeest MGP, Goetz I, Groenwold RHH, Irving E, van Thiel G, Grobbee DE, et al. Series: Pragmatic trials and real world evidence: Paper 1. Introduction. J Clin Epidemiol. 2017;88:7-13.
123. Tugwell P, Knottnerus JA, Idzerda L. Has the time arrived for clinical epidemiologists to routinely use 'routinely collected data'? J Clin Epidemiol. 2013;66(7):699-701.
124. Ware JH, Hamel MB. Pragmatic trials--guides to better patient care? N Engl J Med. 2011;364(18):1685-7.
125. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet. 2005;365(9453):82-93.
126. Hemkens LG, Ewald H, Naudet F, Ladanie A, Shaw JG, Sajeev G, et al. Interpretation of epidemiologic studies very often lacked adequate consideration of confounding. J Clin Epidemiol. 2018;93:94-102.
127. Rothwell PM. Factors that can affect the external validity of randomised controlled trials. PLoS clinical trials. 2006;1(1):e9.
128. Welsing PM, Oude Rengerink K, Collier S, Eckert L, van Smeden M, Ciaglia A, et al. Series: Pragmatic trials and real world evidence: Paper 6. Outcome measures in the real world. J Clin Epidemiol. 2017;90:99-107.
129. McCarney R, Warner J, Iliffe S, van Haselen R, Griffin M, Fisher P. The Hawthorne Effect: a randomised, controlled trial. BMC Med Res Methodol. 2007;7(1):30.

130. Sedgwick P, Greenwood N. Understanding the Hawthorne effect. BMJ. 2015;351:h4672.
131. AIHW. Perinatal Data Visualisations: Australian Institute of Health and Welfare; 2018 [updated 02 August 2018. Cat. no: PER 98 [Available from: https://www.aihw.gov.au/reports/mothers-babies/perinatal-data-visualisations/contents/data-visualisations.
132. AIHW. Australia's mothers and babies, 2016 - in brief. Canberrra: AIHW; 2018.
133. Casey BM, McIntire DD, Leveno KJ. The continuing value of the Apgar score for the assessment of newborn infants. N Engl J Med. 2001;344(7):467-71.
134. Royston P. PTREND: Stata module for trend analysis for proportions. 2014.
135. Morales-Roselló J, Khalil A, Morlando M, Papageorghiou A, Bhide A, Thilaganathan B. Changes in fetal Doppler indices as a marker of failure to reach growth potential at term. Ultrasound Obstet Gynecol. 2014;43(3):303-10.
136. Prior T, Paramasivam G, Bennett P, Kumar S. Are fetuses that fail to achieve their growth potential at increased risk of intrapartum compromise? Ultrasound Obstet Gynecol. 2015;46(4):460-4.
137. Baschat AA, Gembruch U. The cerebroplacental Doppler ratio revisited. Ultrasound Obstet Gynecol. 2003;21(2):124-7.
138. Bahado-Singh RO, Kovanci E, Jeffres A, Oz U, Deren O, Copel J, et al. The Doppler cerebroplacental ratio and perinatal outcome in intrauterine growth restriction. Am J Obstet Gynecol. 1999;180(3):750-6.
139. Makhseed M, Jirous J, Ahmed M, Viswanathan D. Middle cerebral artery to umbilical artery resistance index ratio in the prediction of neonatal outcome. International Journal of Gynecology & Obstetrics. 2000;71(2):119-25.
140. Odibo AO, Riddick C, Pare E, Stamilio DM, Macones GA. Cerebroplacental Doppler ratio and adverse perinatal outcomes in intrauterine growth restriction evaluating the impact of using gestational age–specific reference values. J Ultrasound Med. 2005;24(9):1223-8.
141. Gramellini D, Folli MC, Raboni S, Vadora E, Merialdi A. Cerebral-umbilical Doppler ratio as a predictor of adverse perinatal outcome. Obstetrics and gynecology. 1992;79(3):416-20.
142. Arias F. Fetus-Placenta-Newborn: Accuracy of the middle-cerebral-to-umbilical-artery resistance index ratio in the prediction of neonatal outcome in patients at high risk for fetal and neonatal complications. Am J Obstet Gynecol. 1994;171(6):1541-5.
143. Devine PA, Bracero LA, Lysikiemcz A, Evans R, Womack S, Byrne DW. Middle cerebral to umbilical artery doppler ratio in post-date pregnancies. Obstet Gynecol. 1994;84(5):856-60.
144. Mendez-Figueroa H, Truong VT, Pedroza C, Chauhan SP. Morbidity and Mortality in Small-for-Gestational-Age Infants: A Secondary Analysis of Nine MFMU Network Studies. American journal of perinatology. 2017;34(4):323-32.
145. Flatley C, Greer RM, Kumar S. Magnitude of change in fetal cerebroplacental ratio in third trimester and risk of adverse pregnancy outcome. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2017;50(4):514-9.
146. Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. Radiology. 1991;181(1):129-33.
147. Khalil A, Morales-Rosello J, Khan N, Nath M, Agarwal P, Bhide A, et al. Is cerebroplacental ratio a marker of impaired fetal growth velocity and adverse pregnancy outcome? Am J Obstet Gynecol. 2017;216(6):606.e1-.e10.
148. Sirico A, Diemert A, Glosemeyer P, Hecher K. Prediction of adverse perinatal outcome by cerebroplacental ratio adjusted for estimated fetal weight. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2017.
149. MacLennan AH, Thompson SC, Gecz J. Cerebral palsy: causes, pathways, and the role of genetic variants. Am J Obstet Gynecol. 2015;213(6):779-88.
150. Alfirevic Z, Stampalija T, Medley N. Fetal and umbilical Doppler ultrasound in normal pregnancy. Cochrane Database Syst Rev. 2015;4:CD001450.
151. Bricker L, Medley N, Pratt JJ. Routine ultrasound in late pregnancy (after 24 weeks' gestation). The Cochrane database of systematic reviews. 2015(6):Cd001451.

152. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. Lancet. 2015;386(10008):2089-97.
153. Triunfo S, Crispi F, Gratacos E, Figueras F. Prediction of delivery of small for gestational age neonates and adverse perinatal outcomes by feto-placental Doppler at 37 weeks' gestation. Ultrasound Obstet Gynecol. 2016.
154. Morales-Rosello J, Khalil A, Alba-Redondo A, Martinez-Triguero L, Akhoundova F, Perales-Marin A, et al. Protein S100beta in Late-Pregnancy Fetuses with Low Birth Weight and Abnormal Cerebroplacental Ratio. Fetal diagnosis and therapy. 2017;41(1):15-22.
155. Cruz-Martinez R, Figueras F, Oros D, Padilla N, Meler E, Hernandez-Andrade E, et al. Cerebral blood perfusion and neurobehavioral performance in full-term small-for-gestational-age fetuses. Am J Obstet Gynecol. 2009;201(5):474.e1-7.
156. Meher S, Hernandez-Andrade E, Basheer SN, Lees C. Impact of cerebral redistribution on neurodevelopmental outcome in small-for-gestational-age or growth-restricted babies: a systematic review. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2015;46(4):398-404.
157. Mula R, Savchev S, Parra M, Arranz A, Botet F, Costas-Moragas C, et al. Increased fetal brain perfusion and neonatal neurobehavioral performance in normally grown fetuses. Fetal diagnosis and therapy. 2013;33(3):182-8.
158. Savchev S, Figueras F, Cruz-Martinez R, Illa M, Botet F, Gratacos E. Estimated weight centile as a predictor of perinatal outcome in small-for-gestational-age pregnancies with normal fetal and maternal Doppler indices. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2012;39(3):299-303.
159. Allam NE MT. Cerebro-Placental Doppler Indices Ratio and Perinatal Outcome among High Risk Pregnancy J Am Sci. 2015;11(6):170-4.
160. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. Bmj. 2014;348:g2301.
161. Monaghan C, Binder J, Thilaganathan B, Morales-Rosello J, Khalil A. Perinatal loss at term: role of uteroplacental and fetal Doppler assessment. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2018;52(1):72-7.
162. Tanner JM. Growth at adolescence : with a general consideration of the effects of heredity and environmental factors upon growth and maturation from birth to maturity. 2nd ed.. ed: Oxford : Blackwell Scientific Publications; 1962.
163. Stasinopoulos M RB, Akantziliotou C. Instructions on how to use the GAMLSS package in R second Edition; 2008 [cited 2018 2 Febuary]. Available from: http://www.gamlss.com/wp-content/uploads/2013/01/gamlss-manual.pdf.
164. Dunn PK, Smyth GK. Randomized quantile residuals. Journal of Computational and Graphical Statistics. 1996;5(3):236-44.
165. Owen AB. Nonparametric likelihood confidence bands for a distribution function. Journal of the American Statistical Association. 1995;90(430):516-21.
166. Indrayan A. Demystifying LMS and BCPE methods of centile estimation for growth and other health parameters. Indian pediatrics. 2014;51(1):37-43.
167. DeCarlo LT. On the meaning and use of kurtosis. Psychological methods. 1997;2(3):292.
168. Lee AC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. The Lancet Global health. 2013;1(1):e26-36.
169. Mendez-Figueroa H, Truong VT, Pedroza C, Khan AM, Chauhan SP. Small-for-gestational-age infants among uncomplicated pregnancies at term: a secondary analysis of 9 Maternal-Fetal Medicine Units Network studies. Am J Obstet Gynecol. 2016;215(5):628.e1-.e7.
170. McIntyre S, Taitz D, Keogh J, Goldsmith S, Badawi N, Blair E. A systematic review of risk factors for cerebral palsy in children born at term in developed countries. Developmental medicine and child neurology. 2013;55(6):499-508.

171. Dunn L, Sherrell H, Kumar S. Review: Systematic review of the utility of the fetal cerebroplacental ratio measured at term for the prediction of adverse perinatal outcome. Placenta. 2017;54:68-75.
172. Madden JV, Flatley CJ, Kumar S. Term small-for-gestational-age infants from low-risk women are at significantly greater risk of adverse neonatal outcomes. Am J Obstet Gynecol. 2018;218(5):525 e1- e9.
173. Low JA, Pickersgill H, Killen H, Derrick EJ. The prediction and prevention of intrapartum fetal asphyxia in term pregnancies. Am J Obstet Gynecol. 2001;184(4):724-30.
174. Hilder L ZZ, Parker M, Jahan S, Chambers GM. Australia's mothers and babies 2012. Perinatal statistics series no. 30. Australian Institute of Health and Welfare; 2014.
175. ABS. Building on SEIFA: Finer Levels of Socio-Economic Summary Measures Canberra: Australian Bureau of Statistics.; 2013. Contract No.: 1352.0.55.135.
176. Fagerland MW. t-tests, non-parametric tests, and large studies--a paradox of statistical practice? BMC Med Res Methodol. 2012;12(1):78.
177. Flatley C, Kumar S, Greer RM. Reference centiles for the middle cerebral artery and umbilical artery pulsatility index and cerebro-placental ratio from a low-risk population - a Generalised Additive Model for Location, Shape and Scale (GAMLSS) approach. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2018:1-8.
178. Stirnemann J, Villar J, Salomon LJ, Ohuma E, Ruyan P, Altman DG, et al. International estimated fetal weight standards of the INTERGROWTH-21(st) Project. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2017;49(4):478-86.
179. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? BMJ. 2009;338:b375.
180. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373-9.
181. Sauerbrei W, Royston P, Binder H. Selection of important variables and determination of functional form for continuous predictors in multivariable model building. Statistics in medicine. 2007;26(30):5512-28.
182. Akaike H. A new look at the statistical model identification. IEEE Transactions on Automatic Control. 1974;19(6):716-23.
183. Arlot S, Celisse A. A survey of cross-validation procedures for model selection. Statistics Surveys. 2010;4(0):40-79.
184. Steyerberg EW, Harrell FE, Jr., Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol. 2001;54(8):774-81.
185. Schuit E, Kwee A, Westerhuis ME, Van Dessel HJ, Graziosi GC, Van Lith JM, et al. A clinical prediction model to assess the risk of operative delivery. BJOG : an international journal of obstetrics and gynaecology. 2012;119(8):915-23.
186. Flatley C, Kumar S. Is the fetal cerebroplacental ratio better that the estimated fetal weight in predicting adverse perinatal outcomes in a low risk cohort? The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2018:1-7.
187. Bligh LN, Alsolai AA, Greer RM, Kumar S. Pre-labour screening for intrapartum fetal compromise in low risk pregnancies at term: cerebroplacental ratio and placental growth factor. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2017.
188. RCOG. Each Baby Counts: 2015 Full Report. London: Royal College of Obstetricians and Gynaecologists.; 2017.
189. Flenady V, Wojcieszek AM, Middleton P, Ellwood D, Erwich JJ, Coory M, et al. Stillbirths: recall to action in high-income countries. Lancet. 2016;387(10019):691-702.
190. Dall'Asta A, Ghi T, Rizzo G, Cancemi A, Aloisio F, Arduini D, et al. Early labor cerebroplacental ratio assessment in uncomplicated term pregnancies and prediction of adverse perinatal outcomes: a

prospective, multicentre study. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2018.
191. Yu J, Flatley C, Greer RM, Kumar S. Birth-weight centiles and the risk of serious adverse neonatal outcomes at term. Journal of perinatal medicine. 2017.
192. Dowdall D, Flatley C, Kumar S. Birth weight centiles, risk of intrapartum compromise, and adverse perinatal outcomes in term infants. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2017;30(17):2126-32.
193. Moraitis AA, Wood AM, Fleming M, Smith GC. Birth weight percentile and the risk of term perinatal death. Obstetrics and gynecology. 2014;124(2 Pt 1):274-83.
194. Kumar S, Figueras F, Ganzevoort W, Turner J, McCowan L. Using cerebroplacental ratio in non-SGA fetuses to predict adverse perinatal outcome: caution is required. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2018;52(4):427-9.
195. Seikku L, Gissler M, Andersson S, Rahkonen P, Stefanovic V, Tikkanen M, et al. Asphyxia, Neurologic Morbidity, and Perinatal Mortality in Early-Term and Postterm Birth. Pediatrics. 2016;137(6).
196. Dueker G, Chen J, Cowling C, Haskin B. Early developmental outcomes predicted by gestational age from 35 to 41weeks. Early Hum Dev. 2016;103:85-90.
197. Shapiro-Mendoza C, Kotelchuck M, Barfield W, Davin CA, Diop H, Silver M, et al. Enrollment in early intervention programs among infants born late preterm, early term, and term. Pediatrics. 2013;132(1):e61-9.
198. Spong CY, Mercer BM, D'Alton M, Kilpatrick S, Blackwell S, Saade G. Timing of indicated late-preterm and early-term birth. Obstetrics and gynecology. 2011;118(2 Pt 1):323-33.
199. Bligh LN, Greer RM, Kumar S. The relationship between maternal placental growth factor levels and intrapartum fetal compromise. Placenta. 2016;48:63-7.
200. Dunn L, Kumar S. Changes in intrapartum maternal placental growth factor levels in pregnancies complicated by fetal compromise at term. Placenta. 2018;74:9-13.
201. Sherrell H, Dunn L, Clifton V, Kumar S. Systematic review of maternal Placental Growth Factor levels in late pregnancy as a predictor of adverse intrapartum and perinatal outcomes. European journal of obstetrics, gynecology, and reproductive biology. 2018;225:26-34.

Appendix 1: Research Involving Human or Animal Subjects Mater Research Institute Human Research and Ethics Committee (EC00332) approval: HREC/14/MHS/37

Mater
Exceptional People. Exceptional Care.

8 June 2017

Professor Sailesh Kumar
Staff Specialist Maternal Fetal Medicine & Obstetrics Team
Mater Health & MRI-UQ
Level 1 Whitty Building
Raymond Terrace
South Brisbane Qld 4101

Dear Professor Kumar

Re: HREC Ref #: HREC/14/MHS/37
Project title: The relationship between antenatal fetal Doppler indices and obstetric and perinatal outcome

I refer to your correspondence dated 2 June 2017 requesting an extension to the above study.

I write to advise that on behalf of the Mater Misericordiae Ltd Human Research Ethics Committee (MML HREC) (EC00332), I reviewed and approved this request for an extension for a further 3 years and noted the accompanying annual progress report on 5 June 2017 and this will be noted by the Committee at its 18 July 2017 meeting.

The approval expiry date has been extended to **27 February 2020**. Please continue to provide annual progress reports until the study has been completed.

This letter constitutes ethical approval only. Please liaise with your Research Governance office in regard to any additional requirements. At Mater Health Services please contact the Research Governance Office on 07 3163 3769.

It should be noted that all requirements of the original approval still apply. Please continue to provide at least annual progress reports until the study has been completed.

Please accept our best wishes for the remainder of the study and should you have any queries, please do not hesitate to contact the Research Ethics Office on 3163 1585.

Yours sincerely

Dr Conor Brophy MBBS; MD; MBioethics; FRCP; AFRACMA
Chairperson
Mater Misericordiae Ltd Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), updated in 2015. The processes used by this HREC to review multi-centre research proposals have been certified by the National Health and Medical Research Council.

Mater Research HREC Office
Room 294 Level 2 Aubigny Place *Ph: 07 3163 1585 Fax: 07 3163 1588* *Email: research.ethics@mmri.mater.org.au*

Mater Misericordiae Health Services Brisbane Limited
ACN 096 708 922
Raymond Terrace,
South Brisbane,
Queensland 4101 Australia
Phone + 61 7 3163 8111
www.mater.org.au

F0621
11/07