Novel phenotype definition and management of Fetal Growth Restriction occurring late in pregnancy

Thesis presented for the degree of MD (Res) in the Faculty of Women's Health, University College London

Dr Rachel Laura Peasley

Signed Declaration

‘I, Rachel Laura Peasley confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.'

Abstract

Aims and Objectives: Define a new late fetal growth restriction (FGR) neonatal phenotype based on antenatal ultrasound (USS) parameters associated with placental insufficiency and adverse NNO. (Aim 1-Chapter 4) Assess the impact of antenatal USS parameters to risk stratify late FGR to allow a “low-risk” group expectant management to 41 weeks. (Aim 2-Chapter 5) Evaluate a new FGR risk stratification and management protocol versus a pre-clinic implementation cohort. (Aim 3-Chapter 6) Develop an outcome model of prediction.

Methods: Women were reviewed in the UCLH late FGR clinic and evaluated prospectively (February 2018 – September 2019). Late FGR USS diagnostic criteria included ≥32 weeks and EFW <10th centile, or EFW >10th centile with abdominal circumference (AC) drop ≥50 centiles, cerebroplacental ratio (CPR)<5th centile or umbilical artery pulsatility index (UmbA PI) >95th centile. Late FGR pregnancies were risk-stratified by USS (UtA Doppler, EFW centile, AC drop, CPR, UmbA Doppler), maternal biochemistry and comorbidities. Low-risk FGR were conservatively managed to 41 weeks and high-risk FGR pregnancies advised delivery at 37-38 weeks. Individual elements of adverse NNO were identified from literature review, core outcomes and a local expert Neonatologist. Association between antenatal USS parameters and adverse NNO was explored (Aim 1). Late FGR pregnancies managed before the “late fetal FGR clinic management protocol” were evaluated as a comparison group (Aim 2). A multiple parameter model for outcome prediction was developed using a time series analysis (Aim 3).

Results: There were 321 pregnancies in the late FGR clinic included in the study; 165 “high-risk” and 156 “low-risk” and 323 pregnancies in the pre-clinic cohort. Compared to the high-risk late FGR clinic and the “low-risk” pre-clinic cohorts; the “low-risk” late FGR clinic had significantly less overall adverse NNO 44.9 vs 57.6% OR 0.6 (0.4-0.9) p=0.04. No difference was found in severe adverse NNO or maternal outcome. In a time series analysis including fetuses managed according to clinician’s expertise and local guideline prior to the implementation of the new protocol, adverse NNO was lower in the “new” versus the “old” group (56.5 vs 63% OR 0.8 (0.5-1.3) p=0.319. The predictive model showed that the lowest risk of adverse NNO in low-risk pregnancies was with delivery at 39-40 weeks with increased risk after 41 weeks.

Conclusions: I defined a new neonatal phenotype of the baby affected by late FGR in both SGA and AGA fetuses and successfully implemented the UCLH late FGR clinic. I antenatally defined and showed high- and low-risk FGR pregnancies were associated with a higher and lower risk of adverse NNO. I showed that low-risk late FGR expectantly managed to full term had improvement in NNO with no increase in neonatal mortality or adverse maternal outcome. The impact of my protocol was confirmed in a time series analysis and I developed a model for prediction of outcome which showed that the lowest risk of adverse NNO was with delivery at 39-40 with increased risk after 41 weeks where risk of prematurity is low and the risk of pregnancy associated complications start to increase.

Impact Statement

Prior to my new late FGR management clinic at UCLH, late FGR was diagnosed on USS in SGA fetus or if there was suspected placental insufficiency due to (reduced growth velocity on biometry, reduced amniotic fluid, raised pulsatility index or abnormal umbilical artery Doppler waveform). However, there was no consensus on what parameter to use in addition to biometry in isolation. Once diagnosed late FGR pregnancies were reviewed by doctors with varying fetal medicine expertise. Follow up varied from 1-4 weeks and in line with national guidelines delivery was often organised at term or as soon as possible if diagnosed > 37 weeks. No additional third trimester USS parameters were used to diagnose late FGR or risk stratification employed to identify the optimal timing of surveillance and delivery.

My project including > 600 singleton late FGR pregnancies showed that by using additional third trimester USS parameters (UtA Doppler, EFW, fetal AC drop, CPR, UmbA Doppler), maternal biochemistry and maternal co-morbidities; I was able to identify a high and low-risk FGR group according to the perceived risk of placental insufficiency and optimise the timing of surveillance and delivery accordingly. I also showed that the high-risk FGR group were at significant increased risk of adverse NNO independent of final neonatal size. This has potentially identified a new definition of neonatal late FGR allowing these babies prompt identification and closer monitoring for potential late FGR complications and need for treatment.

In the new late FGR clinic I implemented the antenatal late FGR risk classification into clinical practice and showed in low-risk FGR babies delayed delivery up to 41 weeks potentially avoided intrapartum interventions with less neonatal morbidity in the immediate neonatal period and potential advantages for long term organ maturity and neurodevelopmental outcome. Compared to the pre-clinic cohort the low-risk late FGR pregnancy management pathway was associated with significant improvements in spontaneous labour, reduction in labour induction with heavier weights and older gestational ages at delivery.

I have received positive patient feedback that my new late FGR management clinic has been extremely useful for patients regarding diagnosis, management and potential adverse NNO. The late FGR clinic protocol was also more cost effective than pre-clinic management strategies due to a significant reduction in USS usage and labour induction, reduced NNU admission and duration and decrease in treatment costs. Overall, the late FGR clinic involved no additional costs.as staff and equipment were already in place,

By direct involvement in establishing the new UCLH late FGR management clinic I have improved local neonatal and maternal outcomes. At international conferences my data has been presented as an invited speaker. I have also had an accepted peer-reviewed international journal submission. I have received more than six requests to share guidelines and implement the protocol in other hospitals. The new RCOG green top guideline on SGA management has also cited my publication as an example of late FGR management at term.

UCL Research Paper Declaration Form: referencing the doctoral candidate's own published work(s)

Doctoral candidate's own published work:

R Peasley, L A Abrego Rangel, D Casagrandi, V Donadono , M Willinger, G Conti, Y Seminara, N Marlow, A L David, G Attilakos, P Pandya, A Zaikin, D Peebles, R Napolitano. Management of late-onset fetal growth restriction: pragmatic approach. *Ultrasound Obstet. Gynecol.* 62, 106–114 (2023).

Doctoral candidate's oral and electronic presentations:

Management of late-onset fetal growth restriction: An evidence based approach and outcome of late fetal growth retricted babies according to risk stratification in a novel evidence based fetal growth restriction clinic. Oral presentation at the 19th World Congress in Fetal Medicine in Crete, Greece (2022).

R Peasley, D Cassagrandi, G Conti, V Donadono, G Attilakos, P Pandya, D Peebles, R Napolitano. Conservative management of low-risk late fetal growth restriction: An evidence based management protocol. Online oral presentation ISUOG 31st World Congress on Ultrasound in Obstetrics and Gynecology (2021).

R Peasley, D Casagrandi, D Tortora, M Willinger, P Peebles, P Pandya, R Napolitano. Late Fetal Growth Restriction at term: should all babies be delivered before 40 weeks. Electronic poster presentation.ISUOG 29th World Congress on Ultrasound in Obstetrics and Gynecology (2019).

R Peasley, D Casagrandi, C Lia, I Tskimi, D Peebles, P Pandya, R Napolitano.Late Fetal Growth Restriction management: impact of an evidence based approach. Electronic poster presentation. ISUOG 29th World Congress on Ultrasound in Obstetrics and Gynecology (2019).

3. For multi-authored work, please give a statement of contribution covering all authors

I, Rachel Peasley was the primary author involved in this study, I selected the late FGR population according to inclusion/exclusion criteria and performed the patient clinical scans, reviews and management according to the late FGR clinic risk stratification and management protocol. I performed the preliminary analysis. Mr. Luis Rangel, UCL research fellow and Prof. Alexey Aikin; Professor of systems medicine in the Department of mathematics at UCL advised and performed the completed statistical analysis for the paper and developed in collaboration with me and Mr Napolitano the modelling with clinical input. Mr. David Casagrandi, Specialty doctor in the maternal fetal assessment unit (MFAU) and Ms. Vera Donadono and Ms. Marie Willinger, ultrasound clinical fellows at UCLH were also involved in running the late FGR management clinic and initial preliminary analysis.

Guiliana Conti and Ylenia Seminara both medical students from the University of Catania completed 6 months at UCLH and were involved in data collection and helped to run the late FGR management clinic. Prof. Neil Marlow; Professor in Neonatal medicine at UCLH advised on my perinatal data outcomes, study planning, data analysis and the manuscript writing. Prof. Anna David; Professor in Obstetrics and Maternal Fetal medicine and Director at the Elizabeth Garrett Anderson for Women's Health and Mr. George Attilakos; Consultant in Fetal Medicine and lead clinician for the MFAU, UCLH and Mr. Pranav Pandya; Director and clinical lead of the Fetal Medicine service at UCLH were all involved

in advising on study planning, data analysis and the final manuscript. Prof. Donald Peebles and Mr. Raffaele Napolitano, my primary and secondary MD (Res) supervisors were involved in implementing the late FGR clinic, study planning, data analysis and the manuscript writing.

4. In which chapter(s) of your thesis can this material be found?

Material from the paper can be found in **Chapters 4, 5, 6 and 7**.

e-Signatures confirming that the information above is accurate:

Candidate signature:

Date: 08/10/2024

Supervisor signature:

Date: 08/10/2024

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Table of contents Pages

Title page……..…….....1

Signed Declaration…….……...…….....2

Abstract……..…...…….....3

Impact statement……...…….....5

UCL Research Paper Declaration Form.....7

Acknowledgments…….....……...…….....10

Table of contents……..……..…...….12

List of Figures……..…...…..19

List of Tables……..…….....20

List of common abbreviations…….....….....23

Chapter 1: Introduction……..…….....27

1.1 Late fetal growth restriction…….....27

1.1.1 Definition of late FGR…….....27

1.1.2 Defining late versus early-onset FGR.....28

1.1.3 Doppler changes in late FGR.....30

1.1.4 Cerebroplacental ratio in late FGR.....31

1.1.5 Biophysical changes in late FGR.....31

1.2 Pathophysiology of late FGR…..32

1.2.1 Suboptimal trophoblastic infiltration of the uterine arteries….32

1.2.2 Maladaptation of the maternal cardiovascular system…….32

1.2.3 Associated changes in the uterine artery Doppler…….33

1.2.4 Placental ischaemia-reperfusion injury…….36

1.3 Antenatal ultrasound definition of late FGR.....37

1.3.1 Ultrasound definition of a small for gestational age fetus…….37

1.3.2 Ultrasound definition of a constitutionally small fetus…….37

1.3.3 Ultrasound definition of late fetal growth restriction…….38

1.3.4 The PORTO study…….39

1.3.5 Issues with the current late FGR ultrasound definition.....40

1.3.6 Using additional ultrasound parameters to detect late FGR.....41

1.3.7 Associated changes in the umbilical artery Doppler.....42

1.3.8 Fetal growth charts.....57

1.3.9 Customised versus population fetal growth charts.....57

1.4 Postnatal definition of FGR in the neonate……61

1.4.1 Defining a small for gestational age neonate…….61

1.4.2 Defining a constitutionally small neonate…….62

1.4.3 Defining a low birth weight neonate…….62

1.4.4 Defining late FGR in the neonate…….63

1.4.5 Issues with using size to define late FGR in the neonate…….65

1.4.6 Updated definition to diagnose late FGR in the neonate…….65

1.4.7 Proposed new definition for late FGR in the neonate…….67

1.5 Late FGR short and long term consequences.....69

1.5.1 Initial compensatory mechanisms…….69

1.5.2 Intermediate compensatory mechanisms…….69

1.5.3 Late compensatory mechanisms…….70

1.5.4 Fetal compensation and sonographic late FGR criteria…….70

1.5.5 Fetal decompensation…….71

1.5.6 The effects of labour on growth restricted fetus…….71

1.5.7 Intrapartum outcomes in growth restricted fetus..... 72

1.5.8 The effects of labour on late FGR neonatal phenotype…..…..…..72
1.5.9 Mild and severe adverse NNO in the late FGR clinic…….....73

1.6 Late FGR perinatal morbidity and mortality…….....…….....74
1.6.1 Intrauterine fetal death…….....74
1.6.2 FGR related risk factors associated with intrauterine death……....74
1.6.3 Acute and long term serious perinatal morbidity……..…....75
1.6.4 Adverse birth, labour, neonatal and maternal outcomes……..…....78
1.6.5 Neonatal phenotype in high and low-risk late FGR.....80

1.7 Antenatal management of late FGR .....……...…..81
1.7.1 Current management of term late FGR.....……..…....81
1.7.2 Onset of labour and mode of delivery in term late FGR…....81
1.7.3 Current issues with the management of term late FGR…….....90
1.7.4 Determining timing of delivery in term late FGR.....92
1.7.5 Studies on management in term late FGR.....96
1.7.6 Late FGR expectant delivery and improved NNO 100

1.8 Additional USS parameters in late FGR management...……..…..106
1.8.1 Multiparametric models to predict and manage late FGR…....…..106
1.8.2 A stage-based management protocol for late FGR…….....107
1.8.3 Multiparametric management models used in late SGA fetus.....109

Chapter 2: MD (Res) on late fetal growth restriction.....110

2.1 Introduction.....110

2.1.1 Background.....110
2.2.2 Aims of the MD (Res)…….... 112
2.3.3 Objectives and hypothesis of the MD (Res)…….....……..... 113

Chapter 3: Setting up the late FGR clinic…..…115

3.1 Introduction.....115

3.1.1 The new UCLH late FGR clinic…….…….115

3.1.2 Late FGR clinic aims and objectives.....116

3.1.3 Examples of pre-existing late FGR clinics…….....116

3.1.4 Models used to establish a new clinical service……...…..117

3.1.5 Guidance and issues in setting up a new clinic.....118

3.2 Methods.....……..…..120

3.2.1 Create a business plan.....120

3.2.2 Establish patient criteria and patient participation involvement.....122

3.2.3 Novel aspects of the ULCH late FGR clinic.....126

3.2.4 Novel management protocol used in the late FGR clinic.…..…126

3.2.5 Novel neonatal outcomes measured in the late FGR clinic.…....127

3.2.6 Methodology involved in running the late FGR clinic.…….....127

3.2.7 Screening in the late FGR clinic.....128

3.2.8 Risk stratification used in the late FGR clinic……..…….....130

3.2.9 Management protocol……..……131

3.3

Results.....……..……135

Chapter 4: Antenatal diagnosis, monitoring and management of late FGR and association with novel definition of FGR related adverse NNO.....136

4.1 Introduction……..…..136

4.1.1 Background……...136

4.2.2 Aims, objectives and hypotheses.....137

4.2 Methods……..……**138**

4.2.1 Study type……....138

4.2.2 Late FGR clinic study referral criteria…….…….....138

4.2.3 Late FGR clinic patient study selection……...…139
4.2.4 Late FGR clinic review……..…..…141
4.2.5 Management protocols used in the late FGR clinic……..…....144
4.2.6 Labour induction and augmentation……..……. 144
4.2.7 Gynaecological, medical and obstetric FGR risk factors…..……145
4.2.8 Birth, labour, maternal and neonatal outcome.....146
4.2.9 Statistical analysis……..…..…148

4.3 Results……..……149
4.3.1 Number of women in the study……..…….. ….149
4.3.2 Maternal baseline features…..……..…151
4.3.3 Late FGR clinic sonographic and biochemical parameters.....153
4.3.4 Onset of labour and mode of delivery…….....155
4.3.5 Adverse maternal outcome...……...157
4.3.6 Birth outcomes……..…161
4.3.7 Severe adverse NNO……..…...166
4.3.8 Overall adverse NNO.....166

4.4 Discussion…….....167
4.4.1 Main findings……167
4.4.2 Comparison with other studies……..……....168
4.4.3 Clinical implications……..……...171
4.4.4 Strengths and weaknesses…….....171
4.4.5 Conclusions……....173

Chapter 5: Evaluation of the late FGR clinic protocol.....174

5.1 Introduction……...174
5.1.1 Background……..174
5.1.2 Aims, objectives and hypotheses……..…..……175

5.2 Methods……..176
5.2.1 Pre-clinic study type…..……..…. 176
5.2.2 Pre-clinic study referral criteria.....176

5.2.3 Pre-clinic patient study selection…..…176
5.2.4 Clinical review in the pre-clinic cohort.....178
5.2.5 Management of late FGR in the pre-clinic cohort.....178
5.2.6 Timing and mode of delivery in the pre-clinic cohort.....178
5.2.7 Gynaecological, medical and obstetric risk factors for FGR…....179
5.2.8 Adverse birth, labour, neonatal and maternal outcomes…….....179
5.2.9 Statistical analysis……....179

5.3 Results……180
5.3.1 Number of women in the study……..……180
5.3.2 Maternal baseline features.....……184
5.3.3 Onset of labour and mode of delivery……..…188
5.3.4 Adverse maternal outcome……..…..192
5.3.5 Birth outcomes…….....…196
5.3.6 Severe adverse NNO……..…....203
5.3.7 Overall adverse NNO…….....…..…203

5.4 Discussion……..……...204
5.4.1 Main findings……...204
5.4.2 Comparison with other studies……..……....205
5.4.3 Clinical implications……...……208
5.4.4 Strengths and weaknesses……....…208
5.4.5 Conclusions……...……209

Chapter 6: Multiparametric model to predict adverse NNO …….....211

6.1 Introduction……...211
6.1.1 Background……..…211
6.1.2 Aims, objectives and hypotheses.....213

6.2 Methods……..……214
6.2.1 Risk stratifying the late FGR and the pre-clinic cohort.....214
6.2.2 Estimating the probability score of an adverse NNO by GA.....214

6.3 Results……..……..…..215
6.3.1 number of women in the study.....215
6.3.2 Maternal features in the old and new late FGR cohorts..... .218
6.3.3 Maternal and labour outcomes in old + new late FGR cohorts.....221
6.3.4 Birth details in the old + new late FGR cohorts.....224
6.3.5 Neonatal outcomes in the old and new late FGR cohorts.....227
6.3.6 Adverse NNO according to GA and risk stratification.....232

6.4 Discussion…….....233
6.4.1 Maternal + labour outcomes in risk stratified late FGR cohorts.....233
6.4.2 GA and BW in in risk stratified late FGR cohorts.....233
6.4.3 Severe + overall adverse NNO in risk stratified late FGR 234
6.4.4 Risk stratification and timing of delivery.....234
6.4.5 Comparison with other studies.....235
6.4.6 Current evidence and literature.....237

Chapter 7: Conclusions.....238

7.1 Introduction.....238
7.1.1 Background**…….....…238**
7.1.2 Late FGR outcome and association with antenatal definitions....241
7.1.3 Evaluation of the late FGR clinic versus the pre-clinic cohort.....242
7.1.4 Producing a multiparametric model to predict adverse NNO.....243
7.1.5 Future Aims..... 243

References…….....……....245

List of Figures Pages

Figure 1.1: Fetal deterioration and monitoring in late-onset FGR.....29

Figure 1.2: Normal uterine artery Doppler waveform…….....…34

Figure 1.3: Abnormal uterine artery Doppler waveform…….....…35

Figure 1.4: Normal umbilical artery Doppler waveform….....43

Figure 1.5: Abnormal umbilical artery Doppler waveform…….....44

Figure 1.6: Clinical features of neonates affected by late FGR.....77

Figure 1.7: Risks and benefits in delivery versus continuing the pregnancy.....95

Figure 1.8: Integrated stage based protocol for the management of FGR…....108

Figure 4.1: Late FGR clinic patient study selection flow chart…….....140

Figure 4.2: Gestational age at delivery in low versus high-risk FGR….....…159

Figure 4.3: Birth weight at delivery in low versus high-risk FGR ….....160

Figure 4.4: Mild adverse NNO in low versus high-risk late FGR clinic.….....163

Figure 4.5: Severe adverse NNO in low versus high-risk late FGR clinic…....164

Figure 5.1: Late FGR clinic and pre-clinic patient selection flow chart.….....178

Figure 6.1: Box plot per gestational age (weeks) and risk group.....231

Figure 6.2: Fitted Bayesian logistic regression.....232

List of Tables Pages

Table 1.1a: Short term adverse NNO associated with an abnormal CPR….....49

Table 1.1b: Long term adverse NNO associated with an abnormal CPR….....49

Table 1.2: Consensus agreed definitions for late-onset FGR.....60

Table 1.3: Definitions used to define FGR in the neonate.....64

Table 1.4: New consensus definition of FGR in the neonate.....66

Table 1.5: Short and long term neonatal morbidity in late FGR.....76

Table 1.6: Severity criteria of NAESS developed for use in neonates.....79

Table 1.7a: RCOG management of late FGR….....…82

Table 1.7b: ISUOG management of late FGR…….....83

Table 1.7c: SMFM management of late FGR…….....84

Table 1.7d: ACOG management of late FGR…….....…85

Table 1.7e: SOGC management of late FGR…….....86

Table 1.7f: FIGO management of late FGR…….....87

Table 1.7g: NFZMFMN management of late FGR…….....…88

Table 1.7h: CNGOF management of late FGR…….....89

Table 1.8a: Intrauterine fetal death in SGA fetus + advancing gestation.....93

Table 1.8b: Severe perinatal morbidity in SGA fetus + advancing gestation.....94

Table 1.9: Studies using screening models to predict SGA neonates.....105

Table 3.1: Late FGR management protocol EFW >10th centile…….....132

Table 3.2: Late FGR management protocol EFW 3rd to 10th centile….....133

Table 3.3: Late FGR management protocol EFW <3rd centile…….....134

Table 4.1: Maternal features in low and high-risk late FGR…….....150

Table 4.2: Parameters used in the late FGR clinic risk stratification.....152

Table 4.3: Labour onset and mode of delivery in low + high-risk late FGR.....154

Table 4.4: Mode of delivery and abnormal FHR in low + high-risk late FGR.....156

Table 4.5: Birth outcomes in low + high-risk late FGR…….....158

Table 4.6a: Neonatal outcome in low + high-risk late FGR…….....162

Table 4.6b: Neonatal outcome severity in low + high-risk late FGR……..…....165

Table 5.1a: Maternal features in the late FGR clinic + pre-clinic cohort.....182

Table 5.1b: Maternal features in the low-risk FGR clinic + pre-clinic cohort.....183

Table 5.1c: Maternal features in the high-risk FGR clinic + pre-clinic cohort..184

Table 5.2a: Labour onset +MOD in the late FGR clinic + pre-clinic cohort.....186

Table 5.2b: Labour onset +MOD in low-risk FGR clinic+ pre-clinic cohort.....187

Table 5.2c: Labour onset +MOD in high-risk FGR clinic+ pre-clinic cohort.....188

Table 5.3a: MOD + abn FHR in the late FGR clinic + pre-clinic cohort.....190

Table 5.3b: MOD + abn FHR in the low-risk FGR clinic + pre-clinic cohort.....191

Table 5.3c: MOD + abn FHR in the high-risk FGR clinic + pre-clinic cohort.....192

Table 5.4a: Birth outcomes in the late FGR and the pre-clinic cohort…….....194

Table 5.4b: Birth outcomes in the low-risk FGR clinic + pre-clinic cohort.....195

Table 5.4c: Birth outcomes in the high-risk FGR clinic + pre-clinic cohort.....196

Table 5.5a: NNO in the late FGR clinic and the pre-clinic cohort.....198

Table 5.5b: NNO in the low-risk FGR clinic and the pre-clinic cohort…….....199

Table 5.5c: NNO in the high-risk FGR clinic and the pre-clinic cohort…....……200

Table 5.6a: NNO severity in the late FGR clinic and pre-clinic cohort…….....201

Table 5.6b: NNO severity in the low-risk FGR clinic and pre-clinic cohort.....202

Table 5.6c: NNO severity in the high-risk FGR clinic and pre-clinic cohort.....203

Table 6.1a: Maternal features: Old vs new low-risk FGR cohort….....217

Table 6.1b: Maternal features: Old vs new high-risk FGR cohort….....…...218

Table 6.2a: Maternal+labour outcome:Old vs new low-risk late FGR cohort....220

Table 6.2b: Maternal+labour outcome:Old vs new high-risk late FGR cohort...221

Table 6.3a: Birth details: Old vs New low-risk late FGR cohort……...…...223

Table 6.3b: Birth details: Old vs New high-risk late FGR cohort…….....224

Table 6.4a: Neonatal outcomes: Old vs new low-risk FGR cohorts…....….226

Table 6.4b: Neonatal outcomes: Old vs new high-risk FGR cohorts….....227

Table 6.5: Summary statistics 1…..……229

Table 6.6: Summary statistics 2…….....…….230

List of common abbreviations

AC	Abdominal circumference
ACOG	American college of Obstetricians
AFI	Amniotic fluid index
AGA	Appropriately grown for gestational age
AoI	Aortic isthmic
APO	Adverse perinatal outcome
APH	Antepartum haemorrhage
AREDF	Absent reversed end diastolic flow
A T.I.M.E	A torah infertility medium of exchange
BP	Blood pressure
BPP	Biophysical profile
BW	Birth weight
CAO	Combined adverse outcome
CAPO	Composite adverse perinatal outcome
cCTG	Computerised CTG
CNGOF	French College of Gynecologists and Obstetrician
COSGROVE	Core outcome set for prevention and treatment of FGR: developing Endpoints
COSNEON	Core Outcome Set and minimum reporting set for intervention studies in growth restriction in the NEwbOrN
CPR	Cerebroplacental ratio
CRL	Crown rump length
CS	Caesarean section
CTG	Cardiotocography
DESiGN	Detection of SGA neonate
DIC	Disseminated intravascular coagulation

DIGITAT	Disproportionate Intrauterine Growth Intervention Trial At Term
DV	Ductus Venosus
EDF	End diastolic flow
EFW	Estimated fetal weight
FGR	Fetal growth restriction
FHR	Fetal heart rate
FIGO	International Federation of Gynecology and Obstetrics
FL	Femur length
FMU	Fetal medicine unit
GA	Gestational age
GAP	Growth assessment protocol
GDM	Gestational diabetes mellitus
GRIT	Growth restriction intervention trial
GROW	Gestation related optimal weight
GV	Growth velocity
HC	Head circumference
HIE	Hypoxic ischaemic encephalopathy
INC NAESS	International neonatal consortium neonatal adverse event severity scale
IOL	Induction of labour
ISUOG	International Society of Ultrasound in Obstetrics and Gynecology
IUFD	Intrauterine fetal death
IUGR	Intrauterine growth restriction
LBW	Low birth weight
+ LR	Positive likelihood ratio
MBRRACE-UK	Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK
MCA	Middle cerebral artery
MOD	Mode of delivery
MoM	Multiples of the median
NHS	National Health Service

NICE	National institute of clinical excellence
NICU	Neonatal intensive care unit
NND	Neonatal death
NNO	Neonatal outcome
NNU	Neonatal unit
NZMFMN	New Zealand Maternal Fetal Medicine Network
O_2	Oxygen
PAPP-A	Pregnancy associated plasma protein
PET	Preeclampsia
PI	Pulsatility Index
PIH	Pregnancy induced hypertension
POP	Pregnancy Outcome Population
PORTO	Prospective Observational Trial to Optimize Pediatric Health in Intrauterine growth restriction
PPI	Patient and public involvement
RCOG	Royal college of Obstetricians and Gynaecologists
RCT	Randomised Controlled Trial
RI	Resistance index
SANDS	The Stillbirth and Neonatal Death
S/D	Systolic/diastolic ratio
SDVP	Single deepest vertical pocket
SEN	Special educational needs
sFlt-1 to PlGF	Soluble fms-like tyrosine kinase to Placental growth factor
SGA	Small for gestational age
SMFM	The Society for Maternal Fetal Medicine
SOGC	The Society of Obstetricians and Gynaecologists of Canada
SOL	Spontaneous onset of labour
SPSS	Statistical package for the social sciences
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TB	Trophoblastic
TRUFFLE	Trial of Randomized Umbilical and Fetal Flow in Europe

UCLH	University College London Hospitals
UmbA	Umbilical artery
USU	Ultrasound scan unit
USS	Ultrasound scan
UtA	Uterine artery
WHO	World Health Organization
Vs	Versus

Chapter 1: Introduction

1.1 Late fetal growth restriction

1.1.1 Definition of late fetal growth restriction

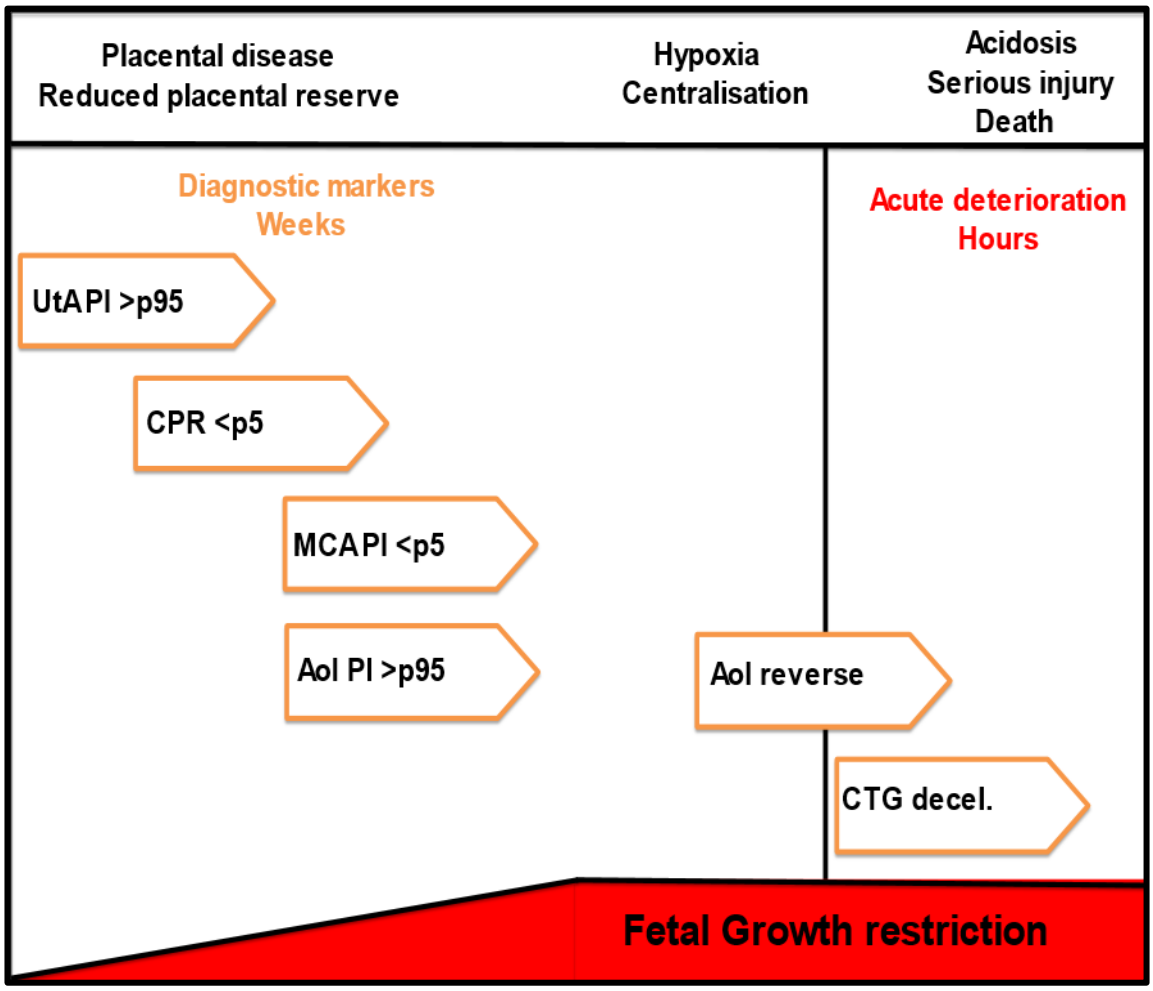
A healthy fetus, pregnant mother and intrauterine environment normally results in an appropriately sized healthy newborn[1]. Pathological late FGR, due to placental insufficiency occurs in up to 15% of pregnancies[2] when a fetus fails to reach their full growth potential ≥ 32 weeks[3,4,5]. Significant neonatal morbidity and mortality include intrauterine fetal death (IUFD) (1.9%), fetal compromise and emergency caesarean section (8.1%), neonatal death (NND) (0.1%), hypoxic ischaemic injury (HIE) (0.4%) and adverse neurodevelopment [6,7,8].

FGR is often diagnosed in SGA fetus due to an EFW <10th centile on fetal growth chart[9,10,11,12,13]. FGR and SGA are not synonymous terms[10]. Majority of SGA fetus (50-70%) are constitutionally small and appropriate size for maternal habitus with low risk of adverse NNO[10]. FGR also affects appropriately sized for gestational age (AGA) fetus as shown by placental insufficiency sonographic markers and adverse NNO[14,15,16,17,18]. Management normally involves iatrogenic term delivery potentially causing late preterm neonatal morbidity in some low-risk late FGR pregnancies [10,19,20,21].

1.1.2 Defining late versus early-onset FGR

FGR is defined as early or late onset according to whether diagnosed < or ≥32 weeks[3,4,5]. Within these two distinctive FGR subtypes and associated placental phenotypes, there are specific variations in prevalence, the pattern of placental disease, the natural history of fetal Doppler deterioration, perinatal prognosis and association with maternal preeclampsia (PET) see **Figure 1.1**[3,20,22].

Figure 1.1: Fetal deterioration and monitoring in late-onset FGR (modified from Figueras and Gratacós, 2014)[22]



UtA PI >p95; uterine artery pulsatility index above the 95th centile, CPR <p5; cerebroplacental ratio below the 5th centile, MCA PI <p5; middle cerebral artery pulsatility index below the 5th centile, AoI PI >p95; aortic isthmic pulsatility index above the 95th centile, AoI reverse; reversed diastolic blood flow in the aortic isthmic, CTG decel; decelerations on cardiotocography.

1.1.3 Doppler changes in late FGR

In the Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) study, the risk of poor neurodevelopmental outcome in babies delivered after 32 weeks' gestation remained static until term[23]. This may be due to the pathophysiology of late FGR not being fully understood which can adversely affect late FGR diagnosis near term[24]. Fetus near term also have reduced tolerance to hypoxaemia as > 90% of fetal growth occurs during the 2nd half of pregnancy and this rapid growth has high metabolic demands on fetal tissues[25]. In the presence of hypoxaemia, aerobic fetal metabolic functions continue in the presence of sufficient fetal oxygen reserves. However, once oxygen (O_2) reserves are depleted, fetal hypoxemia and tissue hypoxia result in anaerobic metabolism, with lactic acidosis and ultimately fetal tissue death[25].

Fetuses with sufficient oxygen reserves can compensate for interference in oxygen supply and continue oxidative metabolism, but fetus with minimal oxygen supply will not tolerate mild O_2 deficiency without significant tissue hypoxia and potential death in utero[25]. Therefore, once diagnosed, close monitoring of late-onset FGR is required as in early-onset FGR[3]. In late FGR due to the presence of milder placental disease and reduced impact on cardiovascular function compared with early onset FGR, the umbilical artery (UmbA) Doppler and fetal Ductus Venous (DV) Doppler- correlating with cardiovascular function, are frequently normal and can fail to identify adverse NNO in late-onset FGR[3,22].

1.1.4 Cerebroplacental ratio in late FGR

Late-onset FGR is associated with vasodilation of the fetal middle cerebral artery (MCA) known as the “brain sparing effect” and in late FGR the MCA PI Doppler to the UmbA pulsatility index (PI) Doppler ratio (the cerebroplacental ratio (CPR)) is important for surveillance[22]. The CPR is effective in identifying changes between the cerebral and placental blood flows compared to isolated Doppler parameters and as shown in **Figure 1.1** can be an early diagnostic marker in late FGR, weeks before the presence of fetal acidosis. Several studies on low fetal CPR and late FGR prediction have also shown increased risk of IUFD, fetal compromise and operative delivery and abnormal neurodevelopment [6,26,27,28,29].

1.1.5 Biophysical changes in late FGR

Biophysical (BPP) abnormalities associated with late FGR include changes to fetal breathing rate, reduction in amniotic fluid volume and loss of fetal heart rate (FHR) reactivity on conventional CTG[6]. However, in fetuses with late-FGR, the BPP may only become abnormal shortly before an impending IUFD. In one study in 90% of IUFD cases there was evidence of cerebral vasodilation, but the BPP was normal. In late FGR most hypoxic fetus often compensate and maintain normal parameters and therefore BPP has poor predictive value to determine surveillance frequency and outcome prediction as the reduced fetal movements assessed in BPP is mainly associated with preterminal hypoxia [6].

1.2 Pathophysiology of late FGR

1.2.1 Suboptimal trophoblastic infiltration of the uterine arteries

Late FGR is known to be associated with impaired extravillous trophoblastic (TB) cell infiltration and abnormal remodelling of the maternal spiral uterine arteries (UtA's) in early pregnancy[30]. In physiologically normal pregnancies adequate UtA artery remodelling allows conversion to a high blood flow vessel under low resistance, with adequate maternal blood flow delivery to the fetus[31]. In FGR, maternal uterine arteries retain their normal tone causing high resistance to maternal blood flow, with uneven perfusion of the villous tree and insufficient time for both maternal and fetal nutrient and waste exchange[32,33].

1.1.2 Maladaptation of the maternal cardiovascular system

Professor Thilaganathan in 2016 proposed that maladaptation of the maternal cardiovascular system, such as an inadequate increase in plasma volume, cardiac output and reduction in total peripheral resistance due to maternal prehypertension can contribute to placental dysfunction in late FGR[34]. Increase in maternal blood pressure (BP) even within normal range is associated with an SGA infants[35]. Normotensive women with SGA infants have also been shown to have evidence of ventricular remodelling and impaired diastolic function and placental blood flow[36,37]. Isolated placental histological findings often seen in SGA versus (vs) AGA infants are associated with poor placental perfusion[38].

1.2.3 Associated changes in the uterine artery Doppler

In late FGR pregnancies suboptimal remodelling of the maternal UtA vessels and corresponding increase in vessel resistance is associated with an abnormal UtA Doppler waveform on ultrasound (USS). In **Figure 1.2** in (A), (B) and (C) there is a high diastolic blood flow volume indicating normal maternal UtA TB invasion and normal UtA Doppler appearance in the 1st, 2nd and 3rd trimester. In **Figure 1.3** there is an increase in the PI and persistent early diastolic notch indicating increased resistance within the maternal uterine arteries[39].

Figure 1.2: Normal uterine artery Doppler waveform (adapted from Bruin et al, 2021)[39]

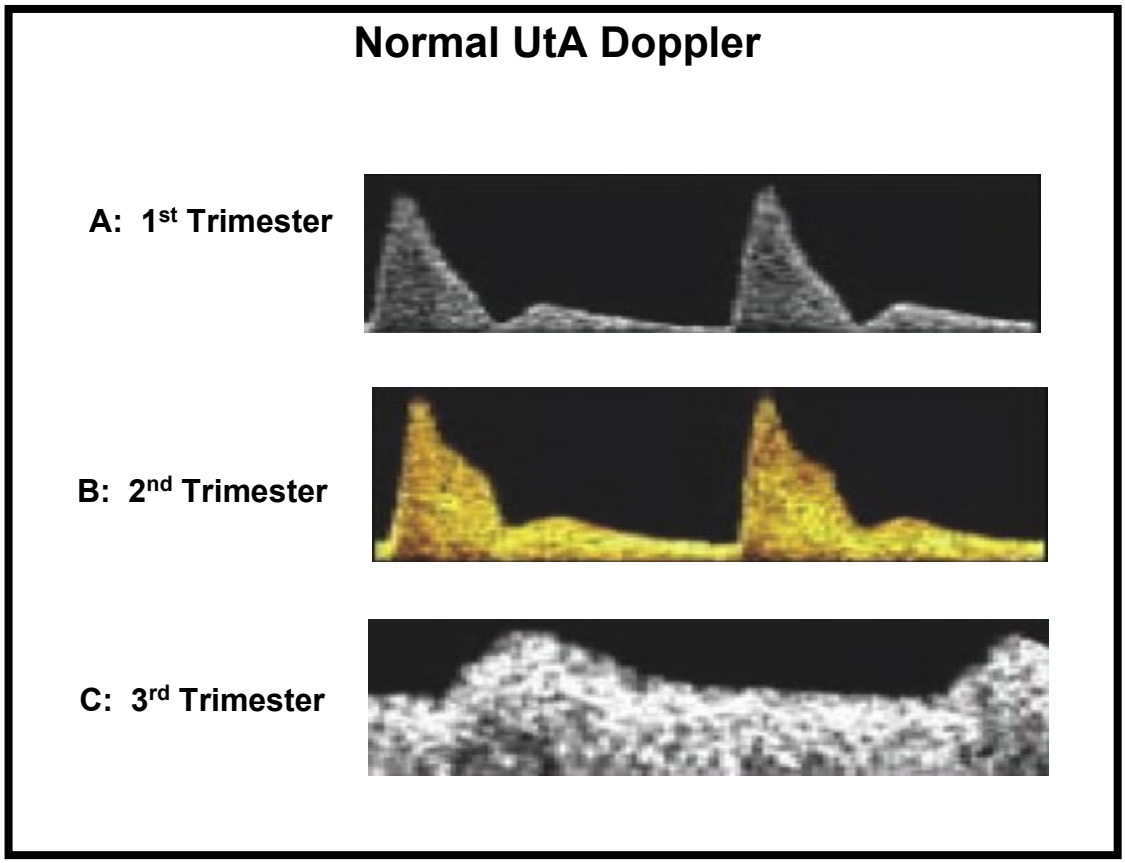
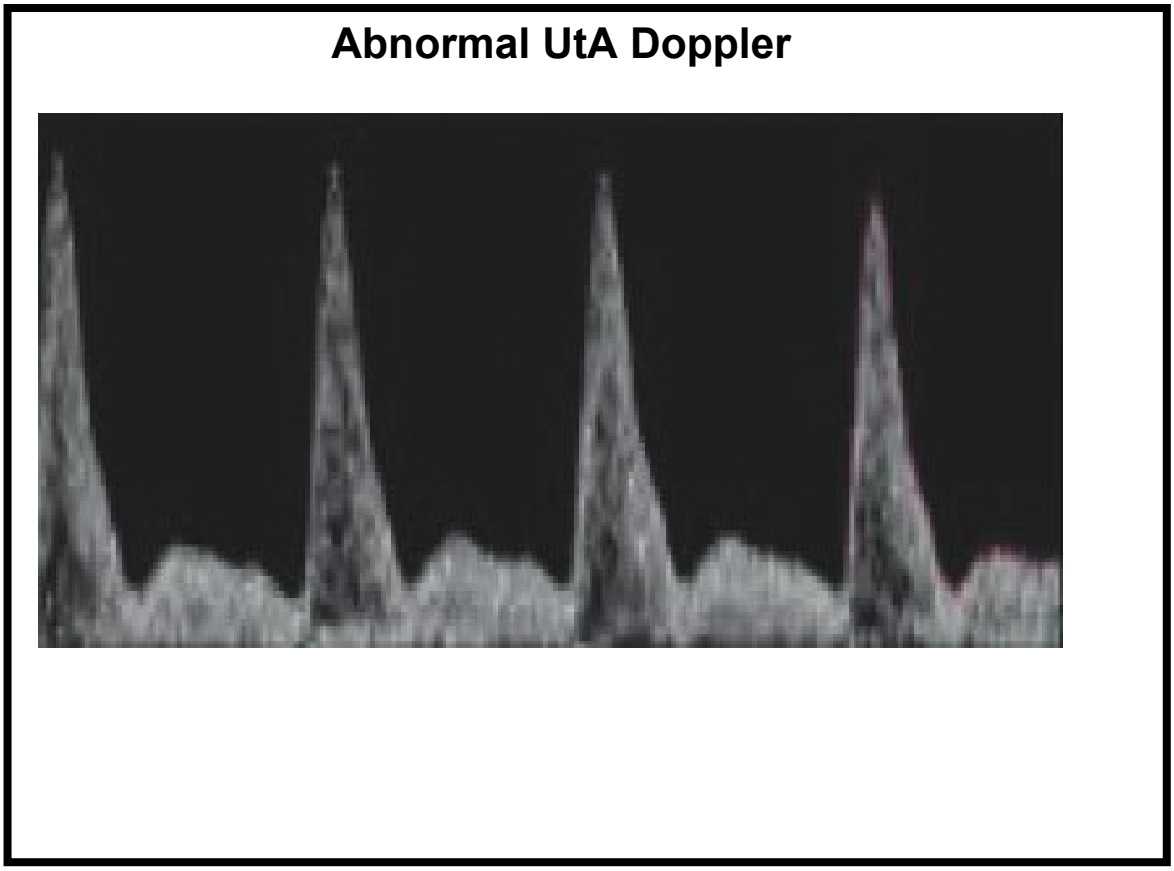


Figure 1.3: Abnormal uterine artery Doppler waveform (adapted from Bruin et al, 2021)[39]



1.2.4 Placental ischaemia-reperfusion injury

In late FGR pregnancies the maternal uterine spiral arteries retain the ability to constrict, resulting in inadequate and uncontrolled blood flow into the placental intervillous spaces causing hypoxia, inflammation and ischaemia-reperfusion injury, with long term mechanical damage to the placenta[40]. Abnormal UtA vessel remodelling can also pre-dispose the maternal spiral arteries to atherosclerotic changes, foam cell accumulation and narrowing of the vessel lumen and reduced placental blood flow[33]. The resultant placental changes can be seen at gross and microscopic placental pathology and by affecting placental villi and villi vessel development can have serious adverse effects on fetal growth[41,42].

1.3.1 Antenatal ultrasound definition of late FGR

1.3.1 Ultrasound definition of a small for gestational age fetus

Small for gestational age is a large umbrella term and commonly includes constitutionally small fetus, incorrectly dated pregnancies as well as growth restricted fetus[43,44,45,46]. Several size threshold definitions have been used including EFW <3rd, 5th, 15th, 10th or 25th centile or abdominal circumference (AC) <3rd, 5th or 10th centile[43,44,47]. EFW <10th centile is the most commonly used definition for late FGR as adverse NNO increases at this size threshold. Studies indicate EFW <3rd centile may be more accurate at determining true late FGR vs constitutionally small fetus although this small size threshold can also inadvertently miss some true late FGR babies[9,10,47]. Those cut off are arbitrary but chosen also to allow comparison with previous literature and balance the risk of false positives versus false negatives.

1.3.2 Ultrasound definition of a constitutionally small fetus

A constitutionally small fetus normally has EFW <10th centile on USS for gestational age and in accordance with a standard reference fetal growth chart. The fetus often has normal fetal anatomy and no other sonographic evidence of placental insufficiency. The pregnant mother commonly has no co-morbidities associated with FGR and the fetus is appropriate size for the pregnant women's size and ethnicity and is normally at low risk of adverse perinatal outcome[10].

1.3.3 Ultrasound definition of late fetal growth restriction

FGR is often diagnosed in SGA fetus, as small size is believed to be due to underlying placental insufficiency and abnormal fetal growth[9]. Using a smaller size to define FGR is more likely to identify pathologically small fetus with studies showing an EFW <3rd centile most strongly associated with adverse NNO[47]. FGR can also be diagnosed in SGA or AGA fetus in the presence of placental insufficiency markers on USS including unexplained oligohydramnios, reduced or static growth velocity or an abnormal UmbA Doppler[48,49].

EFW or AC below 10th centile

EFW or a fetal AC <10th centile for gestational age on a reference fetal growth chart is often used to diagnose FGR[9,10] as low birth weight (LBW) neonates are at increased risk of adverse NNO[43] and EFW and or AC threshold <10th centile are believed to be most accurate in identifying FGR neonates at increased risk of morbidity and mortality[50,51]. Measuring AC can be technically challenging but reflects liver size and subcutaneous fat stores and directly relates to the fetal nutritional state[52]. Although EFW has potential inherent error with each variable used I believe it more in line with current standards to define a SGA neonate and therefore more accurate than using an isolated fetal AC measurement[51].

Identifying FGR in the SGA fetus

Additional sonographic markers have been used in SGA fetus to differentiate constitutionally small fetus from pathologically small fetus due to FGR. These sonographic parameters are believed to be associated with uteroplacental insufficiency and include the presence of severe SGA (EFW <3rd centile), unexplained oligohydramnios, abnormal UmbA Doppler and signs of slow fetal growth as indicated by small fetal biometry, growth velocity <10th centile, static or slowing of growth on serial measurements[49, 53, 54].

1.3.4 The PORTO study

The Prospective Observational Trial to Optimize Pediatric Health in intrauterine growth restriction (IUGR) (PORTO) study investigated several sonographic markers in SGA to differentiate constitutionally small from IUGR small fetus with adverse risk of perinatal morbidity and mortality. Several FGR definitions were investigated including EFW or AC <5th, 3rd,10th centile, the presence or absence of oligohydramnios and a normal or abnormal UmbA Doppler (defined as a PI >95th centile, or an absent or reverse end diastolic flow (EDF)). The study concluded that an abnormal UmbA Doppler and severe SGA were the two main sonographic markers with a significantly adverse NNO. Oligohydramnios was only associated with adverse NNO in the presence of a severe SGA fetus[47].

1.3.5 Issues with the current late FGR ultrasound definition

Which size threshold to use

There is considerable overlap in the size definitions used for FGR and SGA however these definitions are not strictly interchangeable[10]. It is difficult to identify the optimal size threshold to define FGR, too high a threshold inadvertently results in more constitutionally small fetus incorrectly diagnosed as FGR with risk of unnecessary intervention and complications associated with an iatrogenic term delivery. FGR is strongly associated with a smaller size thresholds; but too small a threshold can also increase the rate of falsely negative FGR cases[47].

Using EFW alone has a low predictive value in diagnosing late FGR

Large prospective cohort studies have shown 3rd trimester ultrasound can increase detection rate of SGA fetus in unselected women, however an RCT has also shown routine late pregnancy ultrasound in low-risk populations does not confer benefit on mother or baby with no difference in perinatal mortality, preterm birth <37 weeks, CS or IOL[55]. In “high-risk” pregnancies it can however be useful to identify some FGR cases with serial measurements best to assess for FGR within small as well as AGA fetus[10,56,57,].

Furthermore, using an EFW <10th centile identifies 50-70% of small fetus who are in fact constitutionally small with a normal postnatal outcome[10,58] . Also, in late vs early FGR due to the associated mild placental pathology present not all FGR babies are small and fetal Doppler and amniotic fluid can be normal. Late FGR is strongly associated with IUFD, yet 2/3^{rds} of term IUFD are within the normal size range[59]. In addition abnormal UmbA Doppler related to placental insufficiency is associated with adverse NNO in AGA as well as SGA fetus[57]. I propose additional parameters to improve late FGR diagnosis in SGA and AGA fetus[14,15,16,17,18,60].

1.3.6 Using additional ultrasound parameters to detect late FGR

Identification and surveillance of late FGR in the SGA and AGA populations is difficult due to the lack of studies on perinatal identification and management protocols. It is important to identify additional USS markers for fetal well-being in high- risk pregnancies; EFW has a poor diagnostic and predictive value for FGR and fetal wellbeing[55]. In late FGR antenatal diagnosis I suggest should use additional specific sonographic factors associated with placental insufficiency and adverse NNO including an abnormal UmbA Doppler, low CPR, a reduction in AC growth velocity and abnormal uterine artery Doppler. These sonographic parameters potentially have a low predictive value in detecting FGR in low-risk pregnancies; but in SGA and AGA pregnancies at risk, could improve FGR detection, surveillance and management[61,62,63].

1.3.7 Associated changes in the umbilical artery Doppler

The fetal circulatory blood flow is markedly affected by placental blood flow resistance, fetal oxygenation, fetal organ autoregulation and vessel reactivity. Increased resistance in the maternal spiral uterine arteries and reduced uterine perfusion causes changes in the placental villi structure including abnormal branching and progressive vascular occlusion of the placental tertiary villi. Increased resistance to placental blood flow produces a distinctive pattern in the fetal UmbA Doppler waveform[64]. Normal and abnormal fetal UmbA Doppler waveforms are reported in **Figures 1.4 and 1.5**[65]. The fetal hypoxaemia and acidaemia risk correlates to the severity of the UmbA Doppler abnormalities[64].

Figure 1.4: Normal umbilical artery Doppler waveform (adapted from Kennedy et al, 2019)[65]

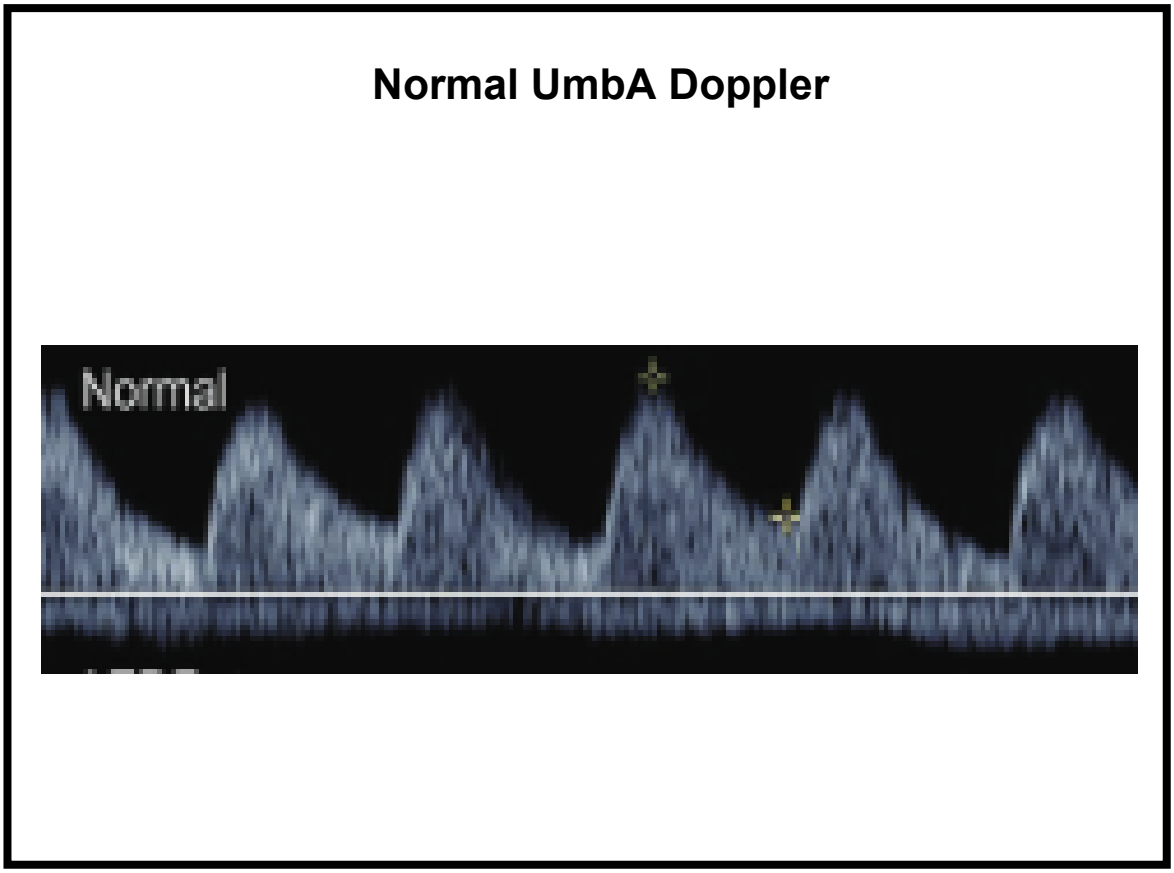
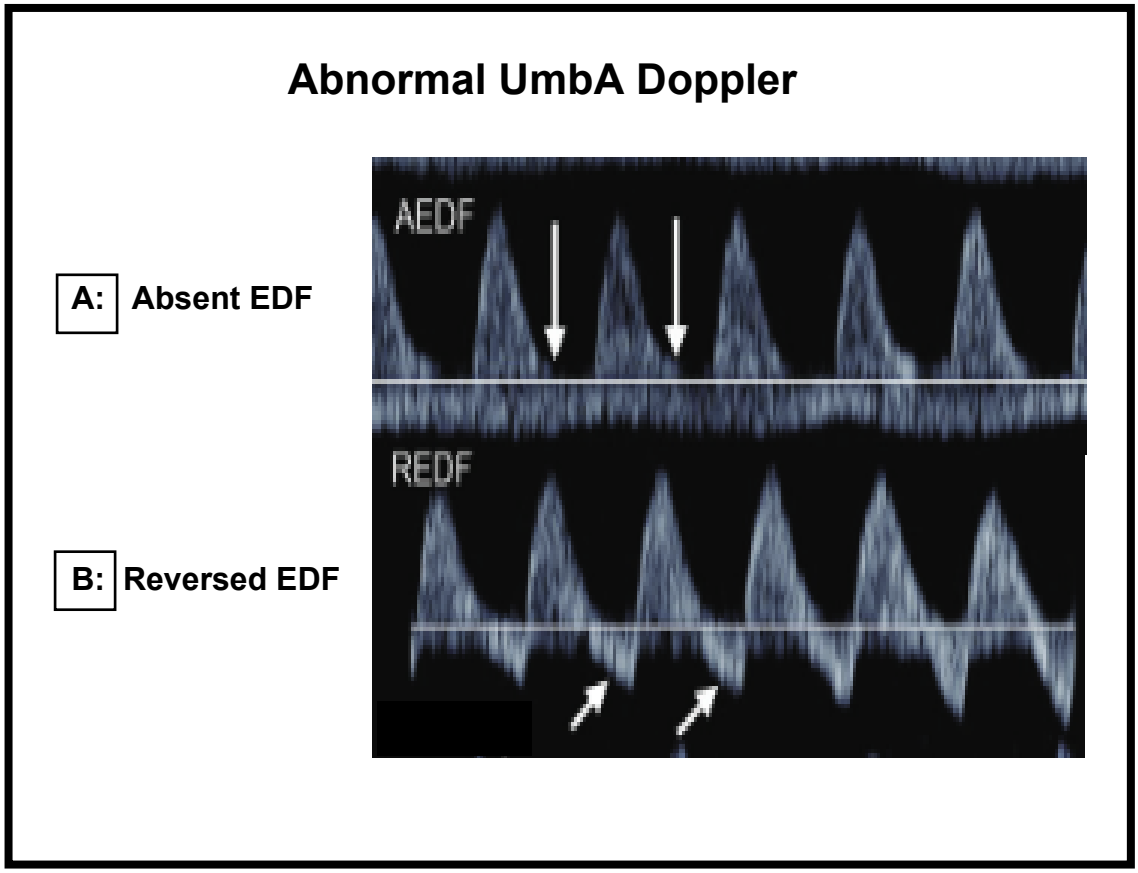


Figure 1.5: Abnormal umbilical artery Doppler waveform (adapted from Kennedy et al, 2019)[65]



Initially there is increased resistance to blood flow and a reduction in the fetal UmbA EDF due to abnormal structure within some of the placental villi vessels. In (A) there is absent EDF which can be associated with a 30% reduction in the normal placental villi vessel structure. With extensive (50-70%) loss of the normal placental villi vessel structure fetal UmbA EDF may be absent or reversed (B).

UmbA Doppler to detect SGA and FGR neonates in low-risk pregnancies

Studies have shown that an abnormal UmbA Doppler in low-risk AGA fetus can increased risk of a SGA or LBW neonate and adverse NNO including NNU admission and the need for CS[66,67,68,69,70]. Several systematic reviews however have shown that overall UmbA Doppler alone has a low predictive value for adverse NNO in low-risk pregnancies with no statistical differences seen in antenatal hospitalisation, obstetric outcome, abnormal intrapartum FHR, IUFD, perinatal morbidity or mortality[61]. It is currently not advisable to use UmbA Doppler for FGR detection in low-risk pregnancies due to limited knowledge on long term childhood neurodevelopmental and maternal psychological effects[61].

UmbA Doppler to detect SGA and FGR neonates in high-risk pregnancies

Systematic review by Morris et al. in 2011 showed UmbA Doppler was effective in detecting SGA and AGA pregnancies at risk of severe neonatal morbidity and mortality. This study assessing 104 studies (19,191 fetus) showed that in a high-risk population UmbA Doppler was accurate at identifying SGA fetus with a positive likelihood ratio (+LR) of 3.76 (95% CI 2.96-4.76), fetal or neonatal compromise with a +LR of 3.41 (95% CI 2.68-4.34), IUFD with a +LR of 4.37 (95% CI 0.88-21.88) and acidosis with a +LR of 2.75 (95% CI 1.48- 5.11). Overall, in a high-risk population, fetal UmbA Doppler was shown to effectively predict the risk of fetal compromise and mortality in SGA and AGA fetus at risk of FGR[60].

The cerebroplacental ratio (CPR)

Fetal cerebral circulation is controlled by autoregulation and influenced by metabolic, neural and chemical factors: hypercapnia, hypoxaemia and acidaemia[72]. In response to hypoxia the fetal cerebral circulation vasodilates and preferentially allows cardiac output to the fetal brain at the expense of other organs; a phenomenon described by Wladimiroff in 1986 as the “brain sparing effect”[73]. Underlying placental pathology increases placental resistance and reduces diastolic flow in the UmbA whilst in chronic hypoxia increases diastolic flow to the fetal brain[74]. The CPR was described by Arbeille in 1987 and is calculated from the MCA and UmbA Doppler PI ratio[75].

Low cerebroplacental ratio (CPR)

Changes in fetal cerebral blood flows due to chronic hypoxia causing fetal cerebral vasodilation, increases the diastolic flow in the MCA with decrease in the MCA Doppler indices including the systolic/diastolic ratio (S/D), the resistance index (RI) and the PI. These same Doppler indices increase in the UmbA due to increased resistance within the placental circulation. The S/D ratio, RI and PI can all been used to calculate the CPR, however more recent studies use PI and so this is the current favoured parameter. FGR associated changes in blood flow can create an abnormally low CPR due to three main Doppler changes including UmbA and MCA PI in the upper and normal range, UmbA PI normal but MCA PI reducing or an abnormally high UmbA PI and an abnormally low MCA PI[76].

CPR to detect SGA and FGR

FGR associated chronic hypoxia causes cerebral redistribution in late FGR independent of fetal size and as such can produce a low MCA Doppler and an even more pronounced abnormally low CPR. In late FGR as described by several authors including Khalil et al. in 2018 the UmbA Doppler can remain normal; therefore CPR could be used to more accurately identify placental insufficiency and late FGR in both “at risk” SGA and AGA pregnancies[74].

CPR to detect SGA and FGR neonates in low-risk pregnancies

Studies have shown that CPR combined with EFW in the 2nd and 3rd trimester vs EFW alone in low-risk populations may only mildly improve the detection of a late SGA fetus or FGR according with various definitions: (1) birth weight (BW) <3rd or 10th centile (2) EFW <10th or 3rd centile (3) BW <3rd centile or BW <10th centile in addition to EFW <10th customised centile, CPR<5th centile or an UmbA -PI ≥95th centile)[77,78]. These FGR definitions are however size limited. Systematic review and cost-effectiveness analysis by Gordon et al. in 2021 however showed that CPR was similar to UmbA Doppler in prediction, whereas severe oligohydramnios was only weakly predictive for a SGA neonate and neonatal morbidity. There was however heterogeneity between the studies, the abnormal CPR threshold values and also the clinicians were unblinded to the CPR results[71].

CPR to detect FGR neonates in "at risk" SGA pregnancies

Flood et al. in 2014 showed in 881 SGA pregnancies with suspected FGR, a low CPR (<1) performed at 33 weeks mean gestation vs a normal CPR had an 18% increased risk of adverse perinatal outcome (APO). In this study an abnormally low CPR was also present in the 3 perinatal mortality cases[79]. Several studies including systematic reviews by Nassr et al. in 2016 and Ali et al. in 2021 have also shown that an abnormally low CPR may be effective at detecting FGR in the late SGA population due to identifying increased risk of adverse intrapartum and NNO such as: IUFD, perinatal death, BW<10th centile, low Apgar score, neonatal acidosis, NICU admission, operative delivery due to intrapartum compromise and long term neurocognitive impairment (see **Table 1.1a and 1.1b**)[80,81,82].

Systematic review by Conde-Agudelo, in 2018 involving 22 studies and 4301 women, also showed that an abnormally low CPR was effective at predicting a SGA neonate and perinatal death but was less effective at predicting composite adverse perinatal outcome (CAPO) such as CS for non-reassuring fetal status, low Apgar score, NICU admission, neonatal acidosis and neonatal morbidity[83]. Predicting adverse NNO with CPR was however comparable to UmbA and MCA Doppler inferring CPR could be used to potentially risk stratify SGA fetus to optimise management such as surveillance and optimal timing of delivery[74].

Table 1.1a: Short term adverse NNO associated with an abnormal CPR (adapted from Khalil et al., 2018) [74]

Adverse NNO	**Likelihood ratio**
CS for presumed fetal compromise	LR: 2.3, 95% CI: 2.0–2.6
Low Apgar score <7 at 5 minute	LR: 1.9, 95% CI: 1.5–2.4
Neonatal acidosis	LR: 1.6, 95% CI: 1.3–2.0
Ventilation support	LR: 1.5, 95% CI: 1.2–1.7
NICU admission	LR: 2.2, 95% CI: 1.9–2.5
Perinatal death	LR: 3.9, 95% CI: 3.4–4.5
Neonatal brain lesions	LR: 1.1, 95% CI: 0.8–1.4
Composite adverse perinatal outcome	LR: 2.5, 95% CI: 2.3–2.8

Table 1.1b: Long term adverse NNO associated with an abnormal CPR (adapted from Khalil et al., 2018) [74]

Long term adverse NNO
Abnormal CPR (<1) was associated with significantly poorer neurological outcome at 2 years in all score variables measured on Ages and Stages Questionnaire and the Bayley Scales of Infant and Toddler Development; indicating increased risk of delayed childhood development. E.g. communication score in FGR with abnormal CPR vs normal CPR was significantly lower; mean 46 +/- 17 standard deviation vs 51 +/- 15, P <0.01[84].
Abnormal CPR (<5th centile) was associated with long term (6-8 years) poorer neurological outcome: significantly lower cognitive functioning, verbal comprehension, perceptual reasoning, working memory, processing speed indices, full scale IQ, broad reading, written language and mathematic scores. E.g. broad reading score in FGR and abnormal CPR vs normal CPR was reduced; mean 89.87+/-15.44 standard deviation vs 101.34 +/-11.34, p=0.13[85].

CPR to detect FGR neonates in "at risk" AGA pregnancies

Studies show that an abnormally low CPR can identify an "at risk" AGA group with risk of suboptimal fetal growth, LBW and adverse NNO[15,16,86,]. Khalil et al. in 2008 assessed several studies on low CPR; most studies showed increased risk of operative delivery for presumed intrapartum compromise. The three most common associations with low CPR in AGA babies were an increased risk of fetal compromise, low BW and earlier gestational age at delivery. However adverse NNO including NICU admission and low UmbA pH was inconsistently associated with a low CPR in AGA compared to SGA babies, the authors inferred the higher predictive value of CPR for adverse perinatal outcomes in SGA fetus may be due to reduced oxygen reserves and resistance to metabolic stress vs AGA fetus[74].

A systematic review by Dunn et al. in 2017 summarised 21 studies and assessed CPR in both SGA and AGA pregnancies and also showed that an abnormally low CPR at term (37+0 to 42 weeks) can accurately predict adverse perinatal outcomes independent of fetal size, including the risk of a SGA or FGR neonate at delivery, CS for presumed fetal compromise and NICU admission. Low CPR was also significantly associated with an abnormal FHR pattern, meconium-stained liquor, low Apgar score <7 at 5 minutes, neonatal acidosis and CAPO scores[15]. Although studies have shown CPR has reduced predictive value for adverse NNO after 34 weeks, this contradicts the study by Dunn et al. when CPR at term was comparable or more predictive than preterm CPR values[15].

Drop in abdominal circumference growth velocity (AC GV) to detect FGR

In FGR due to chronic hypoxia or nutrient deprivation, as shown in studies in sheep, there is redistribution of fetal cardiac output to maximise O_2 and nutrient supply to the organs vital for fetal survival. These include the fetal brain, heart and the adrenal glands and is known as the "brain sparing effect" [87,88]. In the short term this allows these fetal organs to be less affected by FGR compared to other organs such as the fetal skeletal muscles, gastrointestinal tract and the kidneys, which are less important for immediate survival[88]. Redistribution of fetal O_2 and nutrients however induces changes to fetal body proportions producing a disproportionately large fetal head, thin limbs and a small abdomen[89].

A smaller AC in FGR is due to redistribution of O_2 and nutrients reducing fetal liver size and the abdominal subcutaneous fat.[89]. Some studies show that a small fetal AC may be the single most accurate marker for SGA fetus, FGR or FGR related morbidity, with a very small AC< 5th centile most associated with FGR associated biochemical markers including hypoxia and acidaemia[90,91,92,93,94]. A single small AC value is at increased risk of error and if used to diagnose FGR may inadvertently identify a constitutionally small fetus. Slowing in serial AC measurements are more accurate than a single value and due to association with adverse NNO could identify FGR in SGA and AGA pregnancies[56,57].

Drop in AC GV to detect SGA and FGR neonates in low-risk pregnancies

As FGR is a progressively worsening condition, using longitudinal growth compared to cross-sectional measurements is believed to be more appropriate at detecting FGR and as such a panel of experts agreed that slow growth should be used in the definition for late FGR[95]. Several studies have shown however that longitudinal growth assessment has a low predictive value in low-risk pregnancies for identifying a SGA or FGR neonates[96]. Study by Hutcheon et al. in 2010, which assessed conditional growth from 32 weeks to birth compared to a cross-sectional growth assessment at 32 weeks in 9239 unselected pregnancies showed that conditional growth assessment did not improve identification of adverse NNO in low-risk pregnancies[97].

Study by Caraduex et al., in 2018 which investigated 2696 women also showed that longitudinal serial assessment of fetal growth according to either the fetal AC growth velocity or conditional centiles from the second to the third trimester had a low predictive performance to identify SGA and late FGR in a low-risk population with no evidence of chromosomal or structural abnormalities, infection or preeclampsia or FGR <32 weeks[98]. Ciobanu et al in 2019 also showed that in a low-risk population (14,497 pregnancies) that the predictive performance of the EFW Z-score taken between 35+0 to 36+6 weeks to detect a SGA neonate or adverse NNO did not improve with the addition of an estimated growth velocity based on fetal AC or EFW value taken between 32 and 36 weeks gestation[99].

Drop in AC GV to detect SGA and FGR neonates in high-risk pregnancies

Several studies have shown however that in SGA or high-risk pregnancies with a pathologically slow EFW growth trajectories or a small conditional EFW growth centiles < 5th centile there is an increased risk of adverse NNO including operative delivery for presumed fetal compromise, NICU admission and a non-significant increase in acidotic UmbA pH[100,101,102].Chang et al. in 1994 also showed in 104 suspected SGA fetus that 3rd trimester fetal growth based on AC and EFW measurements was superior to predelivery estimates of fetal size alone at predicting adverse NNO[103]. The Pregnancy Outcome Population (POP) study by Sovio et al. in 2015, which assessed 3977 women; also showed in 562 SGA fetus, that AC growth velocity <10th centile was associated with a significantly increased risk of adverse NNO including a 4 times increase in neonatal morbidity, an 18 times increase in SGA neonates with morbidity (RR 17·6, 95% CI 9·2–34·0, P<0.0001) and a 40 times increase in a SGA infant with serious APO (RR 39·8, 95% CI 3·6–436·6, P<0.007)[104].

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Drop in AC GV to detect FGR in "at risk" AGA pregnancies

In AGA pregnancies a statistically defined decrease in growth velocity (GV) could potentially identify an AGA group at risk of FGR, with associated increase in adverse NNO. MacDonald et al, in 2017 showed in 308 nulliparous women a drop in AC or EFW GV > 30 centiles between 28 and 36 weeks was associated with an increased risk of placental insufficiency indicators including a low CPR, a low MCA PI, neonatal acidosis and a low body fat percentage[56]. Kennedy et al, in 2020 also showed reduction in AC or EFW GV in 305 low-risk women between 20 to 36 weeks in AGA fetus was also associated with the same placental insufficiency indicators, as well as a placental weight <10th centile[57]. A specific decrease in EFW or AC GV of > 30 centiles from 20 to 36 weeks was shown to increase by 2-3 fold the parameters associated with placental insufficiency[57].

Hendrix et al. in 2019 also compared 569 AGA fetus with suboptimal fetal growth and 365 AGA fetus with normal growth and showed that neonates with a composite adverse NNO and NICU admission had a significantly lower growth velocity in mm/week in the following 3 biometric parameters: (AC 10.57 vs 10.94, p=0.034; head circumference (HC) 10.28 vs 10.59, p=0.003 and BPD 2.97 vs 3.04, p=0.043), compared to neonates with normal outcomes. AGA neonates with a lower BW than expected (according to the fetal AC recorded at 20 weeks) also had significantly more composite adverse NNO 8.5% vs 5.0% (p = 0.047), NICU admission 9.6% vs 3.8% (p < .0001) and hospital stays 44.4% vs 35.6% (p =0.006) compared to neonates with a BW which met expectations[17].

Abnormal third trimester uterine artery (UtA) Doppler

High-resistance to blood flow in the maternal UtA is associated with FGR and PET[105]. In low and high-risk pregnancies 2nd and 3rd vs 1st trimester UtA Doppler have an increased predictive ability to detect FGR pregnancies [106,107,108]. In early-FGR high-resistance to blood flow in the UtA's in the 1st and 2nd trimester is due to inadequate trophoblastic invasion[109]. In late FGR 3rd trimester UtA Doppler assessment allows opportunity to assess for defective TB invasion in early pregnancy, as well as other pathological mechanisms such as failure of the TB function, suboptimal maternal haemodynamic adaptation, placental insults in the late 2nd or 3rd trimester and the effects of maternal vascular co-morbidities[107].

UtA Doppler to detect SGA/FGR neonates in low-risk pregnancies

Studies have shown that 1st, 2nd and 3rd trimester UtA Doppler have limited ability and low predictive value to detect SGA and FGR in low-risk pregnancies[110,111,112,113,114]. Assessment of 3rd trimester UtA Doppler in the study by Rial-Crestelo, in 2019 showed addition of 3rd trimester UtA Doppler and CPR to the fetal EFW and maternal characteristics in an unselected population was shown to only mildly improve the detection of SGA and did not change the predictive performance for FGR[63]. Study by Triunfo et al, in 2016 in AGA fetus at a routine 32-36 weeks scan also showed 3rd trimester UtA Doppler was not accurate in predicting SGA neonates at birth[114].

UtA Doppler to detect SGA/FGR neonates in SGA pregnancies

Similar to the CPR, the UtA PI can also be abnormal in the presence of a normal UmbA Doppler and due to increased adverse NNO in SGA fetus, an abnormal UtA Doppler can potentially predict FGR. A systemic review in 2020 showed in 7552 SGA fetus or SGA infants, an abnormal 3rd trimester UtA Doppler was associated with a 2-3 fold increased risk of adverse NNO. The UtA Doppler predictive value was moderately effective and had similar ability to current parameters in differentiating constitutionally SGA from small FGR fetus as well as predicting perinatal death. The authors concluded abnormal UtA Doppler and adverse NNO prediction was similar to current late FGR predictive parameters but advised not using in isolation due to its limited predictive ability[18].

1.3.8 Fetal growth charts

Fetal growth charts can be based on population or customised centiles, individual or conditional measurements. Conditional fetal growth chart centiles produce an individualised fetal range based on previous fetal growth measurements, resulting in ranges that are narrower and shifted from reference range centiles for the entire population.[115,116]. Addition of conditional growth centiles to size centiles has been shown in some studies to improve prediction of adverse perinatal outcomes in fetuses < 10th centile[116]. However this approaches require serial ultrasounds which are not always available and non-conditional based references therefore remain in wide use. In contrast non-conditional fetal growth charts monitor the rate of weight gain (i.e. whether changes in weight gain over time are below or above those compared to the reference population) under the assumption that normality corresponds to growth within the same centile[116].

1.3.9 Customised versus population fetal growth charts

Non conditional fetal growth charts include customised and population based fetal weight centiles. Large observational studies show customised fetal and neonatal growth charts, based on maternal demographics and previous pregnancy outcome, may be more accurate at identifying fetus and neonates with late FGR vs population based fetal growth charts[117,118]. The Detection of SGA Neonate (DESiGN) trial a cluster randomised controlled trial (RCT) compared SGA detection and several maternal and fetal outcomes using customised vs population based EFW centiles[119].

The DESiGN Trial

Customised EFW centiles have advantages and disadvantages, customised centiles may be more accurate at differentiating pathological from constitutional small fetus as they are based on a pregnant mother's demographics including weight, height, ethnicity and parity[118, 120]. They are however still size limited in definition. Overall customised vs population based EFW may be more potentially advantageous at determining late FGR and has other positive features such as identifying women with previous SGA babies at risk of this reoccurring and requiring additional antenatal USS surveillance for at an risk fetus. However, the current parameters used for customisation do not reflect true biological and clinically meaningful differences and might carry the risk of normalise abnormal babies and increase the false positive rate.

The DESiGN trial was a large and well-constructed study comparing several maternal and NNO. The results however showed no impact in using customisation on antenatal detection of SGA and no difference in maternal or NNO vs standard care. The authors concluded that these results may be due to the wide variation in the Growth Assessment Protocol (GAP) implementation used [119,121]. It is likely that in the future multiparametric competing risk models generated by AI could better identify FGR babies according with individual characteristics, rather than the current customisation process.

The Delphi consensus to define USS parameters for FGR

Due to current controversy and variations in antenatal FGR sonographic definitions, a Delphi consensus using an international panel of experts in the field of FGR was performed to optimise the definition for FGR. There was agreement on late FGR definitions and the threshold values which are summarised in **Table 1.2** and adapted from Gordijin et al in 2016[95]. This new definition for late FGR incorporates third trimester UmbA Doppler, CPR and AC GV with the aim to diagnose FGR more accurately in the SGA and AGA populations.

Table 1.2: Consensus agreed definitions for late-onset FGR (adapted from Gordijin et al)[95]

Late FGR
GA ≥ 32 weeks in the absence of congenital abnormalities
AC/EFW <3rd centile
Or at least two out of the three:
1.AC/EFW <10th centile
2.AC/EFW crossing centiles > 2 centiles on population based centiles
3. CPR <5th or UmbA -PI>95th

GA; gestational age, AC; abdominal circumference, EFW; estimated fetal weight, UmbA; umbilical artery, CPR; cerebroplacental ratio, PI; pulsatility index.

1.4 Postnatal definition of late FGR in the neonate

1.4.1 Defining a small for gestational age neonate

Historically gestational age dependent BW centiles based on population birth weight charts from Lubchenco in 1963 have been used to identify SGA neonates. BW <10th centile was commonly used to define a SGA neonate, due to the increased mortality in this cohort, compared with gestational age matched AGA neonates[50]. In 1995 the World Health Organisation (WHO) defined SGA neonates if the BW was <10th centile, according to a gender specific reference population or if the BW was < 2.5kg and gestational age unknown[122].

More recently a multi-disciplinary consensus meeting of experts in obstetrics, perinatology, neonatology, paediatrics, epidemiology and pharmacology in 2007 updated the neonatal definition of SGA as a BW or length > 2 standard deviation (SD) below the mean (<2.3rd centile)[123]. These measurements were chosen as they identify the majority of infants where further growth assessment may be required in case children required growth hormone treatment[123]. Definitions for a SGA neonate also includes head circumference (HC) <2.3rd or BW <3rd centile. However, the above definitions do not include in full the parameters used to diagnose the neonate or the child affected by wasting and stunting[124].

1.4.2 Defining a constitutionally small neonate

A constitutionally small neonate is normally suspected if antenatally the EFW <10th centile but there are no other sonographic parameters associated with placental insufficiency. USS normally shows forward fetal growth velocity, normal Dopplers and amniotic fluid[10]. Diagnosis is often confirmed on examination postdelivery. Constitutionally small neonates frequently have BW <10th centile due to inherent factors due to maternal weight, height, ethnicity, parity, with no evidence of fetal or maternal pathology underlying the small neonatal size[1,50].

1.4.3 Defining a low birth weight neonate

The WHO defines LBW as a BW < 2.5kg, a very LBW as BW < 1.5kg and an extremely LBW as BW <1kg independent of gestational age[122]. This classification allows international comparison of neonatal health and allows early surveillance, detection and treatment of complications associated with potential prematurity and FGR[125]. LBW however is an all-encompassing definition and although there is overlap between LBW, SGA and FGR, these conditions are not strictly equivalent. LBW includes premature babies who are AGA whereas only one 1/3rd of LBW neonates are also SGA at term[126,127,128].

1.4.4 Defining late FGR in the neonate

Historically the terms LBW, SGA and FGR have been used interchangeably to diagnose FGR in the neonate[129]. Late FGR in the neonate may also be suspected if evidence of in utero malnutrition or dehydration on clinical examination, or less often in the presence of severe adverse NNO including HIE or neonatal death. However as described FGR, SGA and LBW are not synonymous and severe FGR related complications such as HIE and neonatal death are more commonly associated with early rather than late-onset FGR [130,131,132]. There is currently no gold standard and variation in the parameters used to define FGR in the neonate (see **Table 1.3:** definitions used to define FGR in the neonate).

Table 1.3: Definitions used to define FGR in the neonate

Authors	Definition
The World Health Organisation, Report of a WHO expert committee 1995[122]	BW <10th centile for gender and GA or <2.5Kg if GA not known
Hay, 2004[133]	BW, Length, HC <10th centile or Ponderal index less than normal
A consensus statement of the international societies of pediatric endocrinology and the growth hormone research society **Clayton et al, 2007**[123]	BW or length <2 SD below mean or around 2nd centile
Mayer et al 2013[134]	BW <3rd, 5th or 10th centile
Sharma et al, 2016[89]	Clinical features of malnutrition and intrauterine FGR irrespective of BW according to: - Clinical examination - Anthropometry - Ponderal index - CAN score - Cephalization index - Mid-arm circumference - Mid-arm/head circumference ratio
Chew et al, 2023[135]	BW <10th centile and appears emaciated with reduced muscle mass and subcutaneous fat +/- disproportionally large HC +/- thin face +/- shrunken umbilical cord +/- wide cranial suture +/- large fontanelle +/- Ponderal index <10th centile

WHO; world health organisation, BW; birth weight, GA; gestational age, HC; head circumference, SD; standard deviations, FGR; fetal growth restriction, CAN; clinical assessment of nutrition.

1.4.5 Issues with using size to define late FGR in the neonate

One size does not fit all

Although there is significant overlap in the size thresholds used to define SGA, LBW and FGR in the neonate, these terms are not interchangeable[10]. SGA and similarly LBW are umbrella terms comprising of neonates who represent the lower normal range, who have reached their full growth potential in a healthy in utero environment, as well as neonates who are not achieving their full growth potential due to FGR[133]. Using a smaller, more restrictive size definition for FGR can increase the detection of pathologically small neonates but can inadvertently miss growth restricted fetus above the size threshold used for diagnosis[47]..

1.4.6 Updated definition to diagnose late FGR in the neonate

A new definition for FGR in the neonate was produced by a Delphi consensus to improve detection of neonates with FGR and increased risk of adverse NNO and included parameters in addition to fetal size (see **Table 1.4** adapted from Beune in 2018)[136]. However, this FGR definition can inadvertently diagnose constitutionally small neonates as FGR and may not detect FGR in appropriately sized for gestational age neonates. Neonates with FGR are also at increased risk of acute morbidity and additional adverse neonatal outcome measures may be more accurate at diagnosing underlying FGR independent of neonatal size[89,125].

Table 1.4: New consensus definition of FGR in the neonate (adapted from Beune et al, 2018)[136]

Consensus definition of FGR in the neonate
Birth weight <3rd centile on population based or customised growth charts
Or at least 3 out of 5 of the following:
Birth weight <10th centile on population or customised growth chart
Head circumference <10th centile
Length <10th centile
Prenatal diagnosis of FGR
Maternal morbidity associated with FGR (hypertension or preeclampsia)

1.4.7 Proposed new definition for late FGR in the neonate

Using neonatal outcome measures to define neonatal FGR

Neonates with underlying FGR due to the utero adaptations associated with a chronically nutrient deplete environment as well as constitutionally SGA fetus related to late preterm delivery are at increased risk of adverse NNO measures. I identified from local meetings with my neonatal colleagues that neonates were requiring NNU admission within normal size range but with morbidity associated with suspected underlying late FGR and it was discussed whether I could improve local current sonographic and neonatal diagnosis of late FGR. By liaising with my neonatal colleagues I therefore proposed that a novel phenotype for FGR in the neonate could include the presence of acute mild neonatal morbidity including hypoglycemia, hypothermia, jaundice, feeding difficulties, a low Apgar score, neonatal unit (NNU) admission and hospital readmission as well as severe neonatal morbidity including sepsis, cerebral, respiratory or circulatory morbidity, IUFD or neonatal death. I wanted to explore the hypothesis that these adverse NNO measure could improve FGR diagnosis in neonates at delivery independent of neonatal size as well as determine whether my novel late FGR diagnostic sonographic and management pathways including delayed delivery in the low-risk vs the high-risk group could improve late FGR diagnosis and reduce late preterm complications[89,125].

Potential to improve FGR antenatal definition

I planned to develop a composite adverse NNO outcome involving the adverse NNO measures mentioned, to produce a more accurate FGR diagnosis antenatally and to test my theory of delayed delivery in the low-risk FGR group. 2nd and 3rd trimester USS parameters, maternal and biochemical factors were used to identify FGR pregnancies and to risk stratify into high and low-risk groups for placental insufficiency. The high-risk FGR group were suspected to have more severe underlying placental insufficiency, whilst the low-risk FGR group were expected to have milder underlying placental insufficiency or constitutional smallness. If the antenatal defining parameters for FGR were accurate I would expect more adverse NNO measures in the high vs low-risk antenatal FGR group.

1.5 Late FGR short and long term consequences

1.5.1 Initial compensatory mechanisms

In FGR there is reduced uteroplacental blood flow and transfer of O_2 and nutrients including amino acids and glucose to the fetus, this reduces fetal insulin production and secretion[137]. This leads to a hypoxic and nutrient deplete environment which is inadequate for optimal fetal aerobic metabolism and growth. Consequentially the fetus undertakes several compensatory and adaptive mechanisms, including enhanced erythropoiesis to increase the fetal red blood cell O_2 carrying capacity[138,139,140] as well as fetal liver gluconeogenesis to maintain the fetal and placenta O_2 and glucose requirements[141].

1.5.2 Intermediate compensatory mechanisms

As the pregnancy advances however the limited fetal hepatic glycogen stores can become exhausted resulting in the fetus and placenta becoming nutrient deplete. The resultant fetal hypoglycaemia often further impairs function of the active placental transport system and the ability to maintain fetal oxidative metabolism. The fetus often mobilises alternative energy sources such as amino acids resulting in a cascade of metabolic responses and adaptations[64]. Gluconeogenic amino acids from the fetal muscle stores are also catabolised to glucose, which reduces the essential amino acids available for fetal growth and development[142].

1.5.3 Late compensatory mechanisms

As anaerobic metabolism and lactic acid accumulation continues, fetal acid–base balance is maintained as long as fetal acid production is buffered by fetal plasma bicarbonate and haemoglobin and removed by fetal organs[64]. In advanced malnutrition, lactate is metabolised by the fetal liver; the fetal brain and myocardium can also change their main energy source to lactate allowing lactate removal[143,144]. Fetal blood flow also redistributes to the fetal heart, brain and adrenal glands but at the expense of the musculoskeletal system, kidneys and the gastrointestinal tract, resulting in thin limbs, reduced urine output, renal impairment, feeding intolerance and necrotising enterocolitis [64,145,146,147,148,149].

1.5.4 Fetal compensation and sonographic late FGR criteria

I based my sonographic definitions for late FGR on the FGR compensatory mechanisms described as well as on several studies showing how placental insufficiency can produce a small fetus, reduction in fetal growth velocity or can be associated with abnormal maternal and fetal Doppler. The specific USS Citeria used to define my high-risk late FGR group included sonographic evidence of severe fetal SGA[47], an UmbA PI >95th centile[47] or an EFW <10th centile[9,10,43] with a low CPR <5th centile[150] or an AC drop across ≥ 50 centiles [151].

1.5.5 Fetal decompensation

If the fetal compensatory mechanisms to the hypoxic and nutrient deplete environment described succeed, then fetal growth and survival is possible. However with deteriorating placental function, if these compensatory mechanisms start failing, to maintain physiological fetal organ function then the fetus will start to decompensate[64]. This can be associated with severe metabolic complications including fetal hypoxaemia, hyperlactaemia, hypoaminoacidaemia, hypercapnia and triglyceridaemia. The resulting fetal acidaemia can cause fetal cardiac dysfunction and effect normal physiological responses, which can result in end fetal organ damage and IUFD[137,152,153].

1.5.6 The effects of labour on growth restricted fetus

Placental insufficiency causes depleted nutrient energy stores in the fetal liver and the subcutaneous tissue in growth restricted fetus, therefore these fetus have reduced tolerance to additional labour induced hypoxic stress compared to AGA fetus[154]. Labour induced hypoxia rapidly consumes the limited energy reserves available in the growth restricted fetus, in order to produce energy these fetuses must often switch from aerobic to anaerobic metabolism which produces a fetal metabolic acidosis[3]. This associated intrapartum metabolic acidosis and fetal acidaemia is a major cause of perinatal morbidity and mortality[148].

1.5.7 Intrapartum outcomes in growth restricted fetus

Fetal acidaemia can affect the fetal central nervous system and cardiovascular system and result in acute fetal compromise causing an abnormal fetal heart rate pattern on cardiotocography (CTG) requiring expedited operative delivery via emergency CS or instrumental assisted vaginal delivery[155,156,157]. Underlying fetal compromise in FGR pregnancies can also cause a low Apgar score[158], a low UmbA pH[159] or a need for neonatal resuscitation at delivery[160]. If not promptly delivered acute on chronic intrapartum hypoxia or an FGR-related sentinel event such as a placental abruption can cause acute fetal asphyxia or fetal death[89].

1.5.8 The effects of labour on late FGR neonatal phenotype

The MD (Res) primary aim was to identify a novel neonatal late FGR definition using adverse NNO measures rather than isolated small size at delivery. I based these adverse NNO measures on known perinatal morbidity known to be associated with the physiological changes in fetal organs associated with the chronically deplete nutrient and oxygen environment associated with late FGR as well as the stressful effects of labour in growth restricted fetus. I hypothesised that my high-risk late FGR group would have increased risk of adverse labour outcomes and NNO due to these pregnancies having more severe placental disease, greater in-utero fetal adaptive changes, lower energy reserves and less resilience to intrapartum hypoxic stress compared to the low-risk late FGR group.

1.5.9 Mild and severe adverse NNO in the late FGR clinic

The adverse maternal outcome measures included operative delivery (emergency CS or instrumental assisted vaginal delivery) for abnormal CTG indicating intrapartum fetal compromise. Mild adverse NNO including hypoglycaemia, hypothermia, jaundice requiring treatment, infection, difficulties establishing breast feeding, low Apgar score < 7 at 1 minute, NNU admission and hospital readmission for FGR related complications. Severe adverse NNO included IUFD, severe cardiac, cerebral or respiratory morbidity, low Apgar score < 7 at 5 minutes, severe metabolic acidosis or sepsis or neonatal death.

The adverse NNO measures described above are increased in late iatrogenic prematurity as well as in late FGR with in-utero compromise. I would therefore expect my “high-risk” FGR group to have increased risk of adverse NNO measures due to chronic hypoxia exposure as well as an earlier iatrogenic term delivery. In contrast I would expect my “low-risk” FGR group to have reduced risk of adverse NNO measures due to not having such a severe degree of chronic hypoxia exposure, including some constitutionally small pregnancies as well as delayed delivery in this group reducing the risks associated with late prematurity.

1.6 Late FGR perinatal morbidity and mortality

1.6.1 Intrauterine fetal death

Gardosi in 2004 investigated multiple risk factors associated with IUFD and FGR was the strongest risk factor (in 52% of all cases)[161]. Gardosi reported that IUFD has a background rate of 4.2 per 1000 births but FGR increases this rate to 9.7 per 1000 births[162]. FGR can cause serious perinatal morbidity and sudden or late IUFD, mortality in FGR at term has been shown to be 5-10 times higher than in babies which are AGA[12,148,163,164]. This is related to FGR related chronic hypoxia and fetal decompensation, intrapartum induced acute on chronic hypoxia, a sentinel event, or an underlying maternal or pregnancy condition such as PET[148].

1.6.2 FGR related risk factors associated with intrauterine death

The Euro-Peristat project showed the UK compared to other high resource countries had higher IUFD rates[165]. Studies comparing 10 European regions showed IUFD was associated with suboptimal care and in 10% of cases failed detection[166]. In 2017 the Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK) enquiry into term, singleton, intrapartum IUFD and intrapartum related NND also identified that perinatal deaths could be reduced with improved FGR detection and management; detection allows optimally timed delivery which can significantly reduce adverse NNO[167,168,169,170,171]. Saving babies lives version 3, 2023 aims to improve detection and management and reduce the risks due to late FGR[172].

1.6.3 Acute and long term serious perinatal morbidity

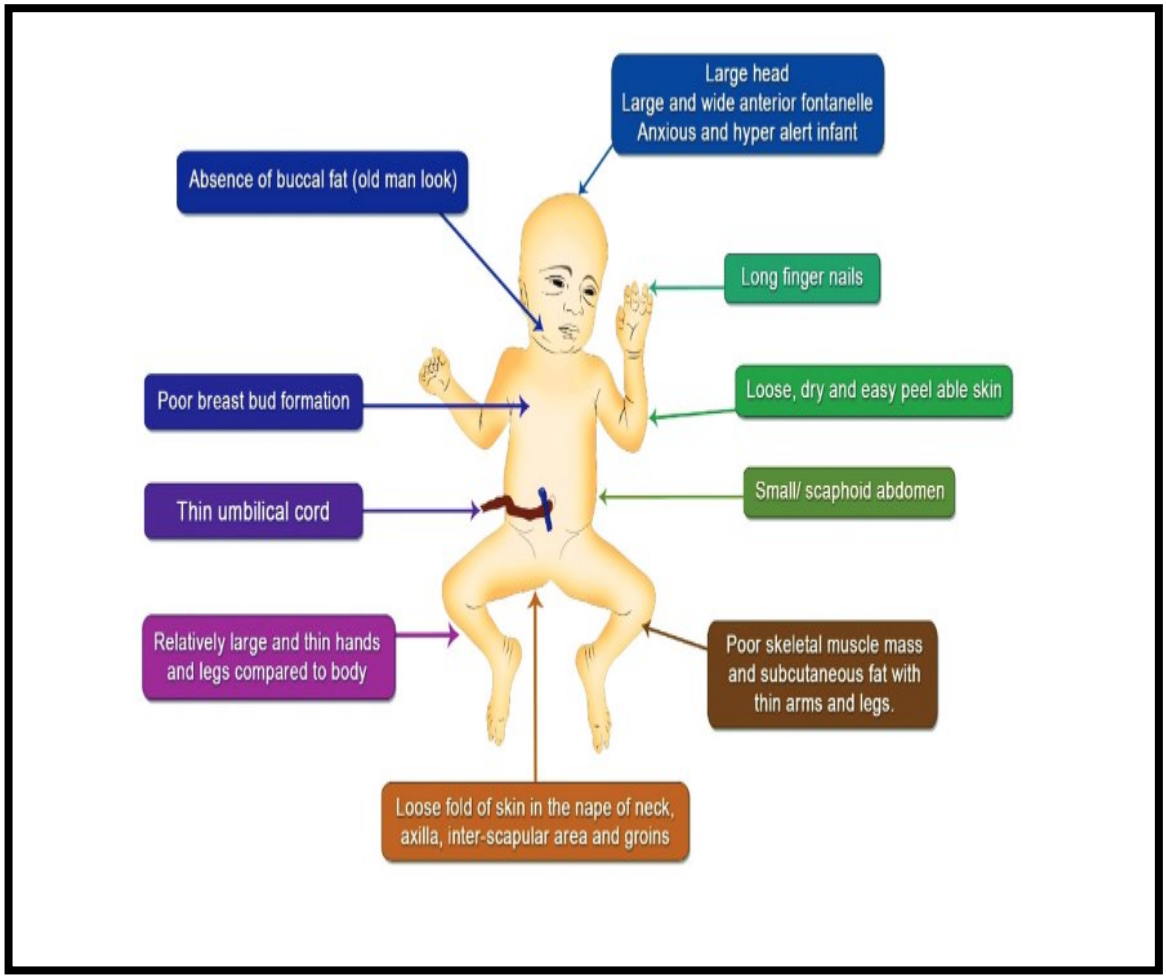
Placental insufficiency, chronic hypoxia, poor nutrition and oxygenation in late FGR causes abnormal organ development and remodelling with significant perinatal morbidity and mortality see **Table 1.5** and **Figure 1.6**[101,125,173]. These complications are partly due to iatrogenic late preterm delivery to avoid IUFD, however FGR is an independent risk factor[174]. Late FGR is associated with serious hypoxic events; Mendez-Figueroa et al, 2016 showed in 5416 term SGA babies (BW <10th centile) NND was 1.1 in 1000 births (OR 2.56 95% CI 1.83-3.57 vs AGA babies)[175]. Chauhan et al, 2017 also showed in 4983 non-anomalous singleton SGA fetus (BW <10th) 5-minute Apgar score <5 (0.4%), HIE (0.5%), seizures (0.1%) and NND (0.1%). Hypoxic composite neonatal morbidity was increased in SGA (1.1%) vs AGA babies (0.7%) RR 1.44; 95% CI 1.07-19.3)[7].

There are also severe long term effects associated with late FGR which I was unable to assess in the time frame of my late FGR study population. In a case control study involving 493 babies delivered ≥ 35 weeks; late FGR (BW < 2 standard deviations) was associated with cerebral palsy OR 4.81 95% CI 2.7-8.5)[176]. Meta-analysis analysing 7861 term SGA babies has also showed SGA-born infants had 0.32 SD poorer standardised neurodevelopmental scores (95%CI, 0.25-0.38)[177]. Long term effects in a recent study (n = 1,100,980) adjusted for parental educational levels showed that term SGA babies were also associated with poorer school performance (grades <10th centile) and less likely to graduate from compulsory school level. In severe SGA poor school performance OR was1.85 (95% CI 1.65-2.07) > 3SD below expected BW level[178].

Table 1.5: Short and long term neonatal morbidity in late FGR adapted from Longo et al, 2013[173], Sharma et al, 2016[89], Malhorata et al, 2019[179]

Neonatal adverse effects	**Pathogenesis:**
Hypoglycaemia	Low glycogen stores in liver + muscle Reduced gluconeogenesis
Hyperglycaemia	Reduction in insulin production from pancreatic beta cells
Hypothermia	Relatively large surface area to small body size Reduced body/fat subcutaneous layer
Polycythaemia	Increase in erythropoiesis
Jaundice	Hyperbilirubinaemia due to increase in erythropoiesis
Hypocalcaemia	Immature parathyroid gland Reduction in placenta derived calcium
Meconium aspiration	Increased production due to chronic hypoxia and aspiration due to intrapartum fetal compromise
Feeding difficulties Renal dysfunction Immunodeficiency Sepsis	Redistributed blood flow from non-vital to vital organs causes • Poor perfusion of peripheral organs • Adverse organ development • Organ immaturity • Ischaemic injury to fetal tissues
Metabolic acidosis	Chronic hypoxia causes increase in anaerobic metabolism and lactic acid production
Cerebral adverse effects: Hypoxic ischaemic encephalopathy Intraventricular haemorrhage Neonatal seizures	Chronic hypoxic environment causes: • more vulnerable to superimposed hypoxia with quicker decompensation
Effects to other major organs including cardiovascular and respiratory systems	Chronic hypoxic and nutrient deplete environment: • Fetal and organ adaptations • Organ remodelling • Stillbirth • Long term comorbidities

Figure 1.6: Clinical features of neonates affected by late FGR reprinted from Sharma et al, 2016[89]



1.6.4 Adverse birth, labour, neonatal and maternal outcomes

An adverse outcome can be defined as “an unintended and unwanted event or state occurring during or following medical care that is so harmful to a patient’s health that adjustment of treatment is required or permanent damage can result”[180]. I identified adverse labour, neonatal and maternal outcomes for FGR using the core outcome set for prevention and treatment of FGR: developing Endpoints: the COSGROVE study and the Core Outcome Set and minimum reporting set for intervention studies in growth restriction in the NEwbOrN: the COSNEON study and by consulting with local experts in neonatology[160,181].

My primary study outcome was overall adverse NNO due to either a mild or severe adverse NNO and my secondary outcomes were adverse maternal outcome, mild and severe adverse NNO. Adverse NNO was categorised as mild or severe according to the international neonatal consortium neonatal adverse event severity scale (INC NAESS)[182]. The NAESS age-appropriate behaviour refers to oral feeding, voluntary movements and activity, crying pattern, social interactions and pain perception. Physiological processes relate to oxygenation, ventilation, tissue perfusion, metabolic stability and organ functioning. Minor changes involve brief, local, non- invasive or symptomatic treatments whilst major care changes include surgery or long- term treatment. My mild and severe adverse NNO’s corresponded to NAESS grades 1-2 and 3-5 (**Table 1.6**)[182].

Table 1.6: Severity criteria of NAESS developed for use in neonates adapted from Salaets et al[182]

Grade	Severity	Symptoms	Treatment
1	MILD	Asymptomatic or mild	No change in baseline care or monitoring
2	MODERATE	Minor changes to baseline age-appropriate behaviour or non-life threatening changes in physiological processes	Requires minor changes in baseline care or monitoring
3	SEVERE	Major changes to baseline age-appropriate behaviour or non-life threatening changes in physiological processes	Requires major changes in baseline care or monitoring
4	LIFE-THREATENING	Life-threatening changes to baseline age-appropriate behaviour or non-life threatening changes in physiological processes	Requires urgent major changes in baseline care or monitoring
5	DEATH	Death due to adverse event	

1.6.5 Neonatal phenotype in high and low-risk late FGR

I proposed that the more severe placental insufficiency associated with my “high-risk” late FGR group identified according to sonographic parameters based on FGR associated in utero adaptive changes are more likely to have a neonatal phenotype associated with a severely placental nutrient deplete environment and have increased risk of adverse NNO measures. In comparison I proposed that my “low-risk” late FGR group comprising babies based on sonographic features associated with less severe placental insufficiency or constitutionally small and managed with delayed delivery would be less likely to be strongly associated with the neonatal phenotypes seen in late prematurity or severe placental insufficiency and therefore would have reduced adverse NNO measures

1.7 Antenatal management of late FGR

1.7.1 Current management of term late FGR

There is no known treatment to improve abnormal fetal growth[183,184,185]. Management in term FGR involves close surveillance of the fetus and assessment for prelabour acidaemia and clinical deterioration to avoid end organ damage and IUFD. In late versus early-onset FGR, management normally involves iatrogenic term delivery with international variation in the exact parameters, pathways and the timing of surveillance and delivery[3,9,10,12,13,186,] (see tables 1.7a-g).

1.1.3 1.7.2 Onset of labour and mode of delivery in term late FGR

SGA fetus compared to AGA fetus have an increased risk of abnormal FHR abnormalities requiring emergency intrapartum CS; 3-9% in SGA fetus with normal UmbA Doppler to 13-26% in SGA fetus with abnormal UmbA Doppler (increased PI with positive EDF)[187]. In term SGA fetus with normal UmbA Doppler, or abnormal UmbA Doppler with positive EDF, induction of labour (IOL) can be offered, with continuous FHR monitoring from uterine contraction onset, due to risk of fetal compromise and emergency CS[10]. In SGA fetus with AREDF in the UmbA Doppler, due to risk of emergency CS for suspected intrapartum fetal compromise in 75-96% of cases elective CS is routinely advised[10,188].

Table 1.7a: RCOG management of late FGR

	Monitoring	**Timing of delivery**
RCOG, 2014[10]	UmbA Doppler+/- MCA Doppler, CTG, Amniotic fluid, BPP	UmbA Doppler +/- MCA Doppler or growth
	SGA (EFW<10th centile) + UmbA Doppler normal: UmbA Doppler every 14 days	**Offer delivery by 37 week**
	UmbA PI or RI >2 SD: UmbA Doppler x 2 weekly	**Delivery by 37 week**
	AREDV in UmbA Doppler: UmbA Doppler daily.	**Delivery between 32-34 week**
	Abnormal DV Doppler +/or abnormal cCTG ≥ 24 week+ EFW >500g del.	**Delivery <32 week**
	AREDV Doppler	**Consider delivery at 30-32 week. Delivery by 32 week**
	MCA PI<5th centile	**Delivery by 37 week**
	Static growth over 3 week:	**Delivery from 34 week**

RCOG; Royal college of Obstetricians and Gynaecologists, UmbA; Umbilical artery; MCA, Middle cerebral Artery; CTG; Cardiotocography; BPP, Biophysical profile; SGA; Small for gestational age, EFW; Estimated fetal weight, PI; Pulsatility index; RI; Resistance index, SD; standard deviation, AREDV, Absent or reversed end diastolic velocity; DV, Ductus venosus; cCTG, computerised cardiotocography.

Table 1.7b: ISUOG management of late FGR

	Monitoring	**Timing of delivery**
ISUOG, 2020[3]	Biometry, UmbA Doppler +/- MCA Doppler + cCTG	UmbA Doppler + cCTG
	In late SGA: Fortnightly assessment of biometry and weekly assessment of UmbA - PI, MCA-PI, CPR and UCR	**Delivery by 39 weeks**
	UmbA -PI >95th centile	**Delivery at 36-37 week**
	AREDF Doppler in UmbA: UmbA Doppler every 2-3/7	**Delivery between 32-34 week**
	UmbA -REDF/cCTG <3.5	**Delivery ≥ 32 week**
	UmbA -AEDF/cCTG < 4.5	**Delivery ≥ 34 week**
	Cerebral redistribution or Additional FGR features	**Delivery at 38-39 week**
	AC/EFW <3rd centile	**Delivery 38-39 week**
	Spontaneous unprovoked decelerations, BPP <4 or maternal indication	**Delivery if ≥ 36 week**

ISUOG; International Society of Ultrasound in Obstetrics and Gynecology, UmbA; Umbilical artery, cCTG; computerised cardiotocography, MCA; Middle cerebral artery; PI; Pulsatility index, AREDV; Absent or reversed end diastolic velocity; UmbA; Umbilical artery, AC; Abdominal circumference, EFW; Estimated fetal Weight, BPP; Biophysical Profile.

Table 1.7c: SMFM management of late FGR

	Monitoring	**Timing of delivery**
SMFM, 2020[13]	Primarily UmbA Doppler and CTG	UmbA Doppler + CTG
	UmbA Doppler normal and EFW ≥3rd - 9th : UmbA Doppler 1-2/52 for 1-2/52 if stable UmbA Doppler 2-4/52, CTG 1/52 + EFW 3-4/52	**Delivery at 38-39 week**
	UmbA Doppler normal and EFW <3rd : UmbA Doppler x 1/52 + EFW 2/52	**Delivery at 37 week**
	UmbA Doppler S/D, PI, RI >95th centile: UmbA Doppler 1/52+ EFW 2/52	**Delivery at 37 week**
	Absent EDF UmbA Doppler: UmbA Doppler 2-3x per week, CTG 2x week if outpatient + EFW 2/52	**Delivery at 33-34 week**
	Reversed EDF UmbA Doppler: CTG 1-2x day + EFW 2/52	**Delivery at 30-32 week**

SMFM; The Society for Maternal Fetal Medicine, UmbA; Umbilical artery, CTG; Cardiotocography, EFW; Estimated fetal weight, S/D; systolic velocity/diastolic velocity, PI; Pulsatility index, RI; Resistance index, EDF; End diastolic flow.

Table 1.7d: ACOG management of late FGR

	Monitoring	**Timing of delivery**
ACOG, 2020[9]	Serial USS every 3-4/52 for growth+ UmbA doppler +/- CTG + BPP **Isolated FGR** **In FGR with additional risk factors for adverse outcome (oligohydramnios, abnormal Doppler, maternal risk factors or comorbidities)**	 **Delivery 38- 39 week** **Delivery 34- 37 week**

ACOG; The American College of Obstetricians and Gynecologists, UmbA; Umbilical artery; CTG; Cardiotocography, BPP, Biophysical profile.

Table 1.7e: SOGC management of late FGR

	Monitoring	**Timing of delivery**
SOGC, 2013[186]	BPP and UmbA Doppler weekly and growth 2 weekly	
	SGA (AC or EFW<10th) + no other issues	**Delivery at 38-40 week**
	SGA and growth plateau/stops + <34 weeks increase surveillance to 2 to 3 x per week. If abnormal UmbA Doppler check MCA + DV Doppler	
	< 34 week + If abnormal UmbA, MCA, and DV Doppler studies and abnormal NST.	**Advise Delivery**
	< 34 week + abnormal (A/R EDF) in Doppler + normal BPP and NST). BPP and UmbA Doppler 2 to 3 times each week; if BPP or UmbA Doppler worsen or MCA/DV are abnormal.	**Advise Delivery**
	• If > 34 weeks+ normal AFV and DVP, BPP, and Doppler studies: continue weekly surveillance	**Delivery >37 weeks**
	– If >34 weeks + abnormal amniotic fluid BPP +/- Doppler	**Consider delivery**

SOGC; The Society of Obstetricians and Gynaecologists of Canada, BPP; Biophysical profile, SGA; Small for gestational age, AC; Abdominal circumference, EFW; Estimated fetal weight, MCA; Middle cerebral artery, DV; Ductus venosus, NST; Non stress test, A/R EDF; Absent/reverse end diastolic flow, AFV; Amniotic fluid volume, DVP; Deepest vertical pocket.

Table 1.7f: FIGO management of late FGR

	Monitoring	Timing of delivery
FIGO, 2021[12]	**SGA (EFW 3rd to 9th) + normal fluid and Doppler: UmbA + MCA Doppler 1-2x week, Growth fortnightly+ ≥ 37 weeks consider BPP/NST 1-2x week**	**IOL at 37-39 week**
	Uncomplicated FGR <3rd centile + normal Doppler and amniotic fluid: UmbA +MCA Doppler 1-2x week, growth fortnightly + ≥ 37 weeks BPP/NST 1-2x week	**IOL at 36-38 week**
	FGR + mild abnormalities: **- Early Doppler change** • **UmbA PI>95th centile** • **MCA PI<5th centile** • **CPR<5th centile** • **UtA PI >95th centile** **- Oligohydramnios** **- Suboptimal growth** **- Suspected PET** **: UmbA +MCA+DV Doppler 1-2x week, growth fortnightly + ≥ 37 weeks BPP/NST 1-2x week**	**IOL at 34-37 week**
	FGR + AREDF UmbA Doppler: **UmbA AEDF or cCTG <3.5** **UmbA REDF or cCTG <4.5**	**Delivery 30-32 week by CS** **Delivery 30-32 week by CS**

FIGO; The International Federation of Gynecology and Obstetrics, SGA; Small for gestational age, EFW; Estimated fetal weight, UmbA ; Umbilical artery; MCA, Middle cerebral Artery, BPP; Biophysical profile, NST; Non stress test, FGR; Fetal growth restriction, CPR; Cerebral placental ratio, UtA PI; Uterine artery pulsatility index, PET; Preeclampsia, DV; Ductus venosus, AREDF; Absent reverse end diastolic flow, cCTG; computerised cardiotocography, IOL; Induction of labour.

Table 1.7g: NZMFMN management of late FGR

	Monitoring	Timing of delivery
NZMFMN, 2014[189,190]	**SGA (EFW<10th centile) + normal UmbA, MCA, CPR, UtA Doppler: Clinical review 1/52, Growth, UmbA, MCA, CPR every 2-3/52**	**Delivery by 40 week**
	SGA (EFW<5th centile) + normal UmbA, MCA, CPR, UtA Doppler: Clinical review + CTG 2x week, Growth 2-3/52 UmbA, MCA, Liquor vol 1-2xweek	**Delivery by 38 week**
	SGA + abnormal UmbA Doppler:	
	Reduced diastolic flow	**Delivery at > 37 weeks**
	Absent EDF	**Delivery at ≥ 34 weeks**
	Reversed EDF	**Delivery at ≥ 32 weeks**

NZMFMN; New Zealand Maternal Fetal Medicine Network, SGA; Small for gestational age, EFW; Estimated fetal weight, UmbA; Umbilical artery; MCA, Middle cerebral Artery; CTG; Cardiotocography, EDF; End diastolic flow.

Table 1.7h: CNGOF management of late FGR

	Monitoring	**Timing of delivery**
CNGOF, 2015[191]	FGR (EFW<10th centile) or EFW near 10th centile + signs abnormal growth +/- abnormal UtA +/- abnormal UmbA Doppler	
	SGA/FGR + normal UmbA Doppler: biometry +UmbA Doppler every 3 weeks	**Delivery > 37 weeks**
	SGA/FGR + DV PI >95th centile or abnormal FHR	**Delivery < 32 weeks**
	SGA + abnormal UmbA Doppler:	
	Positive EDF +PI >95th centile: Surveillance 3 X week: CTG + UmbA + MCA Doppler	**Delivery at > 37 weeks**
	Absent EDF	**Delivery at ≥ 34 weeks**
	Reversed EDF	**Delivery at ≥ 34 weeks**

CNGOF; French College of Gynecologists and Obstetrician; FGR; Fetal growth restriction, EFW; Estimated fetal weight, UtA; Uterine artery, UmbA; Umbilical artery, SGA; Small for gestational age, DV PI; Ductus venosus pulsatility index, FHR; Fetal heart rate, CTG;Computerised tomography, EDF; End diastolic flow.

1.7.3 Current issues with the management of term late FGR

1. Management, surveillance and timing of delivery is size dependent

In late FGR The main challenges are detection and optimal timing of delivery[3]. Current management of late FGR mainly concentrates on managing SGA fetus, however as previously discussed a large proportion of SGA fetus are in fact constitutionally small and healthy, at low risk of adverse NNO and not requiring late preterm iatrogenic delivery[10,58]. In addition this size definition for management inadvertently misses a large proportion of AGA pregnancies with potential FGR at increased risk of IUFD and adverse NNO[162]. Late FGR management should include SGA fetus and AGA fetus "at risk" of FGR.

2. UmbA Doppler as surveillance in late FGR

In early-onset FGR the UmbA Doppler normally has a clear temporal pattern with increase in the UmbA vessel PI lasting 2-6 weeks, followed by absent EDF for 2-4 weeks and reverse EDF around 1 week prior to fetal death. In late FGR however UmbA Doppler has no clear temporal pattern and may remain normal or not progress beyond increased resistance just prior to fetal death see Figure 1.1[52]. Additional surveillance in SGA and AGA fetus "at risk" of late FGR is required.

3. No clear guidance on optimising the timing of delivery in late FGR

In SGA fetus with normal dopplers, there is no clear standard international guidance on optimal time for delivery and whether or not to use risk stratification to optimise the timing of delivery. Additional maternal and fetal parameters can be useful to risk stratify SGA and AGA fetus “at risk” of late FGR to optimise the timing of delivery and vice versa potentially delay delivery and avoid early iatrogenic delivery in constitutionally small or low-risk late FGR pregnancies. Early term delivery is often advised to prevent adverse perinatal outcome and IUFD associated with placental insufficiency and dysfunction in isolated late FGR.

4. Term delivery and late preterm/term neonatal morbidity

There are however higher rates of perinatal mortality and serious perinatal morbidity associated with early term delivery **see tables 1.8a and 1.8b.** Most perinatal morbidity is mild and transient however late preterm and early term deliveries have been shown to be associated with long term respiratory[192,193] cardiovascular[194], metabolic and endocrine[195], haematological[196], neurodevelopmental abnormalities[197] and childhood mortality[198]. In addition late preterm and early term deliveries can have a financial impact, it is important to avoid unnecessary early deliveries[199]. Overall, it is important to organise early term delivery in late FGR only when the benefits of delivery outweigh the potential serious perinatal morbidity and mortality associated with early term delivery[9].

1.7.4 Determining timing of delivery in term late FGR

Studies have shown that IUFD does increase and serious perinatal morbidity remains present with advancing gestation in suspected late FGR see **Table 1.8a** and **1.8b.** Severe SGA appear to be most at risk[200,201,202,203]. Induced labour at 37 weeks has been shown to reduce risk of IUFD in late FGR[204]. However, most studies are retrospective, mainly focus on birth weight rather than EFW or other antenatal parameters, with no specific monitoring or delivery protocol and have not necessarily corrected for confounding variables. As shown in **Figure 1.7** there are also potential fetal and maternal benefits with delayed delivery. However due to concerns that higher rates of perinatal morbidity and mortality are seen in term FGR and studies suggest that term FGR babies have reduced tolerance to hypoxia exposure, USS monitoring parameters can be unreliable as well as risk of acute placental dysfunction and fetal deterioration[22, 205] these anxieties leads many clinicians to advise iatrogenic term delivery in late FGR[10].

Table 1.8a: Intrauterine fetal death in SGA fetus and advancing gestation

Gestational age (Weeks)	**36**	**37**	**38**	**39**	**40**	**41**
IUFD risk per 10,000 ongoing pregnancies						
Damhuis et al, 2023[200] - EFW ≤ 10th - N = 684938	6.5	4.5	6.0	11.0	15.0	47.0
Pilliod et al, 2019[201] - EFW < 10th - N = 1,641.000	91.0	10.2	12.8	10.9	20.7	-
Hong et al, 2023[202] - EFW < 10th - N = 813,077	-	7.2	13.0	18.5	68.7	-
Trudell et al, 2013[203] - EFW < 10th - N = 57,195	-	21	11	26	60	-

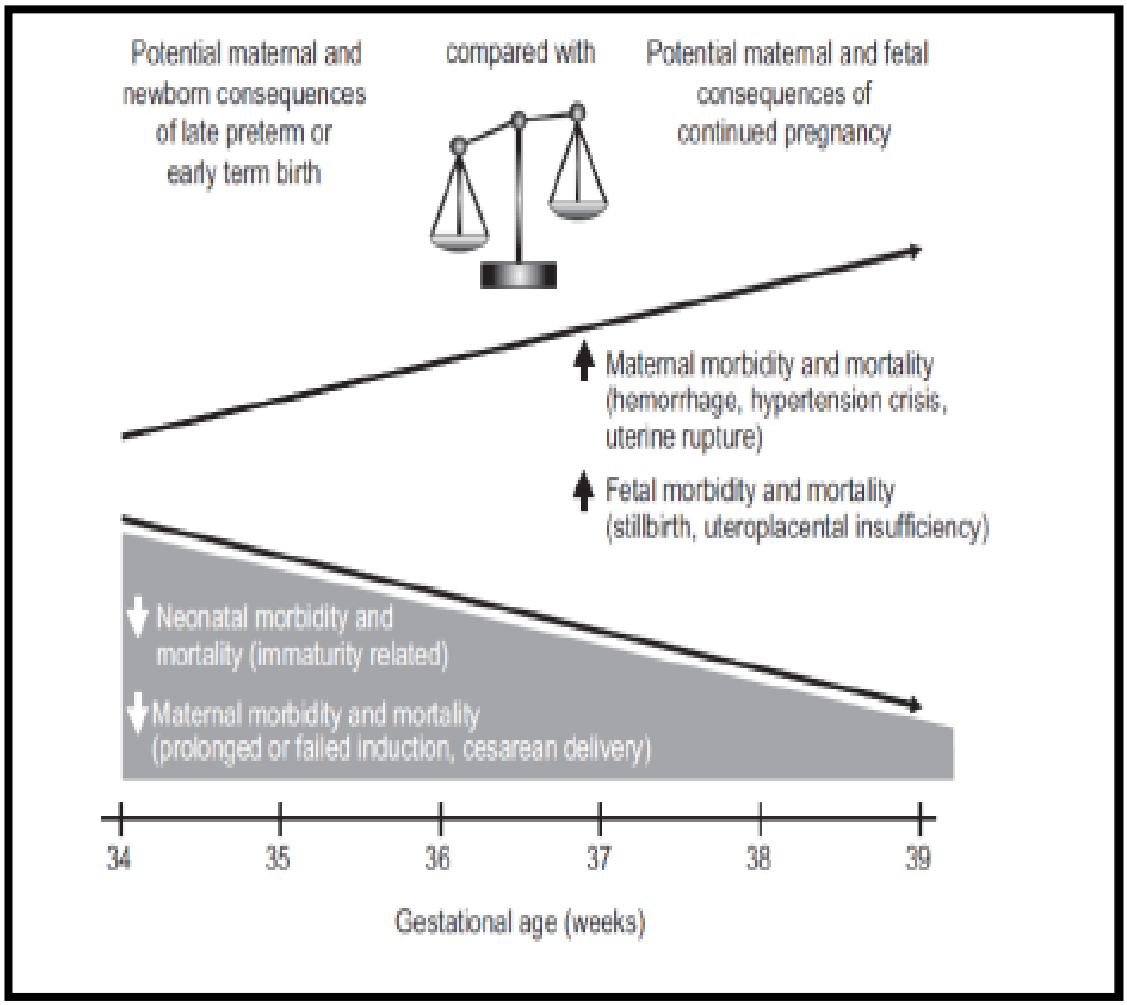
SGA; small for gestational age, EFW; estimated fetal weight.

Table 1.8b: Severe perinatal morbidity in SGA fetus and advancing gestation

Gestational age (Weeks)	**36**	**37**	**38**	**39**	**40**	**41**
Severe perinatal morbidity (perinatal mortality or HIE) in n						
Damhuis et al, 2023[200] - N =684938	168	184	251	300	329	280
Severe perinatal morbidity (NICU admission, severe acidosis, significant resuscitation at delivery, Apgar score <4 at 5 mins)per 10,000 pregnancies in n						
Hong et al, 2023[202] - EFW <10th - N =813,077	-	603.5	391.6	287.5	359.1	-
Severe perinatal morbidity (NICU admission, RDS, MAS, LOS ≥ 5 days) per 10,000 pregnancies in n						
Trudell et al, 2013[203] - EFW <10th - N =57,195	-	142	100.5	162	254	-

SGA; small for gestational age, EFW; estimated fetal weight, NICU; Neonatal intensive care unit, RDS; respiratory distress syndrome, MAS; meconium aspiration syndrome, LOS; length of stay.

Figure 1.7: Risks and benefits in delivery versus continuing the pregnancy. Reprinted from Spong et al, 2011[206]



1.7.5 Studies on management in term late FGR

Expectant management in isolated term FGR pregnancies

The TRUFFLE group reported outcomes of a multicentre cohort of > 800 babies at risk of late preterm FGR (32+0 to 36+6 weeks). Pregnancies had suspected FGR when either EFW or fetal AC <10th centile, an abnormal UmbA Doppler or a drop in AC GV > 40 centiles. Combined adverse outcome (CAO) was present in 11% of the suspected late FGR infants and 53% of adverse outcomes occurred in infants delivered > 37 weeks. There were however no recommended thresholds for delivery and FGR management was not risk stratified and so these results may reflect a lack of FGR characterisation, with “high-risk” FGR not delivered earlier and “low-risk” FGR potentially delivered too early[29].

Cochrane review in 2015; identified only 2 studies comparing delivery with expectant management in term fetuses at risk of in utero compromise or late FGR and both showed no difference in outcome. The review included studies on term FGR pregnancies and pregnancies with isolated oligohydramnios at 41 weeks gestation and included 546 participants, 269 in the early delivery group and 277 in the expectantly managed group. All trials were of reasonable quality, with a low risk of bias, however overall there was no difference in perinatal mortality, significant neonatal or maternal morbidity or neurodevelopmental disability between the early vs the expectantly managed delivery group[207,208.]

The Disproportionate Intrauterine Growth Intervention Trial At Term (DIGITAT) study by Boers et al in 2010 randomly allocated women between 36+0 to 41+0 weeks with suspected FGR to immediate IOL with 48 hours (N = 321) or expectant management until spontaneous labour, unless earlier delivery was clinically indicated (N= 329). FGR was suspected in the presence of an EFW or fetal AC < 10th centile, or reduction in the third trimester GV. The IOL group delivered on average 9.9 days earlier and were 130g lighter. There was no significant difference 6.1% vs 5.3% in composite adverse NNO (perinatal death, low Apgar score, neonatal acidosis or NICU admission) and no difference in CS rate (13.7 vs 14%) in the immediate vs the expectant delivery group[209].

In the immediate IOL group, more neonates were admitted to intermediate-level care, although this was reduced in IOL performed > 38 weeks. In the expectant monitoring group with conservative management up to 41 weeks, there were more neonates with BW < 3rd percentile and a greater proportion of women with PET[209]. There were however no stillbirths or perinatal deaths in either group, there was composite adverse NNO 17(5.3%) in the induction group and 20 (6.1%) in the expectantly monitored group with difference −0.8%, 95% CI −4.3% to 2.8%). Overall there was no differences between the two groups in any of the components of the composite adverse neonatal outcome[209]. At two year follow up in the expectantly monitored group apart from infants with BW < 2.3rd centile, there was no significant difference in neurodevelopmental, behavioural outcome or adverse NNO compared with the immediate IOL group[210].

SGA babies after 37 weeks: impact study of risk stratification protocol

In study by Veglia et al in 2018[211], SGA fetus were stratified as "low" or "high-risk" babies, with different pathways for USS surveillance and delivery timing according to the risk of placental insufficiency. Risk stratification was determined by the EFW, the fetal and maternal Doppler values and the presence of maternal pregnancy induced hypertension (PIH). High-risk babies were identified in the presence of any of the following: an EFW <3rd centile, CPR <5th, Mean UtA PI Doppler at the anomaly USS >95th centile, pregnancy associated plasma protein A (PAPP-A) <0.4 multiples of the median (MoM) in the 1st trimester or maternal PIH (defined as BP ≥ 140/90). In the absence of these parameters SGA fetus were identified as "low-risk" babies. "High-risk" SGA babies delivered at 37+0 weeks and "low-risk" SGA babies had expectant management to 41 weeks[211].

Results from this risk stratified and management protocol driven SGA group was compared with a cohort of SGA babies managed using pre-protocol strategies. There was 1 IUFD in the protocol and pre-protocol groups. In the protocol group however, babies were significantly older and heavier at delivery, had more vaginal deliveries, less intrapartum intervention or delivery complications and reduced adverse NNO. This study showed in appropriately stratified "low-risk" SGA babies, delayed delivery >37 weeks can be associated with improvement in perinatal, labour and maternal outcomes compared to term delivery, whilst high-risk babies were still delivered at a timely gestation[211].

Ten-year experience of protocol-based management SGA fetuses: perinatal outcome in late pregnancy cases diagnosed after 32weeks

Study by Meler et al in 2020[212] reported on their 10 year experience of their protocol based management of 1100 late onset SGA fetus (defined as EFW < 10th centile > 32 weeks). According to a multiparameter USS risk stratification model, late SGA fetus were identified as a "FGR" group (N= 578) in the presence of an EFW <3rd centile combined with either a UtA-PI ≥95th centile or a CPR <5th centile and a "low-risk SGA" group in the absence of these additional USS parameters. The FGR group delivered at 37+0 weeks whilst the low-risk SGA group had expectant management up to 40 weeks unless delivery indicated.

There were no neonatal deaths in any of the pregnancies delivered >37 weeks. The risk of CAO defined as neonatal death, metabolic acidosis, endotracheal intubation or NICU admission was increased in the FGR vs the low-risk SGA group. The authors concluded that protocol based risk stratification with different management pathways for monitoring and timing of delivery in late SGA fetus allowed identification and delivery of the high-risk FGR group in a timely manner, whilst expectant management of the appropriately stratified low-risk group was associated with a safe perinatal outcome[212]. These studies on expectant management and NNO in risk stratified low-risk pregnancies as well as studies below showing improved NNO with expectant management support my late FGR management protocol with delivery allowed up to 41 weeks in low-risk late FGR.

1.7.6 Late FGR expectant delivery and improved NNO

Delayed delivery and improvement in academic milestones

Term iatrogenic delivery is not commonly associated with pulmonary immaturity, but there are still adverse fetal and maternal outcomes[213,214]. Studies show children born before 40 weeks are at risk of affecting academic milestones and having special educational needs (SEN)[19,20,]. Retrospective study by Selvaratnam et al, in 2021 which assessed 705,937 infants over 10 years and compared the developmental outcomes in 693 infants with severe SGA (BW <3rd centile), suspected to have FGR antenatally and iatrogenic early delivery, with 435 infants with severe SGA not identified antenatally showed that gestational age at delivery was significantly reduced in known severe SGA fetus[21].

This group also had significant increase in poor developmental outcome at school entry (16.2% vs 12.7%; absolute difference 3.5% 95% CI (0.5%-6.5%) and aOR 1.36 95% CI (1.07-1.74) and poor educational outcomes in grades 3, 5 and 7. In the 1227 infants suspected to have FGR but in fact had normal growth (BW>10th centile), although these infants were also delivered significantly earlier (38 vs 39.1 weeks), compared to the 679 infants with normal growth and no suspected FGR, there was no significant difference in developmental or educational outcomes[21]. This supports evidence for my management decision involving delayed delivery in my low-risk late FGR clinic group.

Delayed delivery and reduction in SEN

MacKay et al in 2010 showed, in a population based retrospective study of 407,503 school aged children, risk of SEN followed a J-shaped curve and steadily declined with increasing gestational age until 40-41 weeks, with risk increasing again > 42 weeks. There was also evidence of significant SEN in children born at 39 weeks (OR 1.09, 95% CI 1.04–1.14, p<0.001). This study provides evidence that deliveries when suitable should wait until 40 weeks, as delivery even 1 week before had a significantly increased risk of SEN compared to babies delivered 1 week later[19]. Gale-grant et al, 2021 showed infants born 37-38 weeks had slower neurodevelopment compared to full term infants delivered (40-41 weeks) inferring that gestational age at delivery could have a direct effect on brain function[19].

.**Delayed delivery and reduction in adverse NNO**

Recent systematic review by Li et al, in 2020 assessed the adverse NNO associated with expedited IOL vs expectant management in FGR and involved 8 articles and 6,706 women. The authors concluded that there was no statistically significant difference in adverse NNO between expedited or delayed delivery when FGR is suspected in late preterm and full term infants. The expedited compared to the expectantly management group however had increased adverse NNO (hypoglycaemia and respiratory comorbidity). This study shows delayed delivery in expectantly managed FGR can be associated with improved NNO[215].

Potential to improve FGR antenatal management

In my late FGR clinic I planned to risk-stratify FGR pregnancies to determine optimal pathways for surveillance and delivery, the high-risk FGR group were still advised delivery in a timely manner at 37-38 weeks whilst the low-risk group were allowed expectant management up to 41 weeks. Using the adverse NNO outcomes described above to identify neonates with suspected FGR independent to neonatal size, if the USS, maternal and biochemical factors used to identify, and risk stratify FGR antenatally was accurate and the management pathways correct, in addition to avoiding early iatrogenic delivery in the low-risk FGR group; I would expect less adverse NNO in the low vs the high-risk FGR group.

Potential confounding factors

I assessed for potential confounding factors/sensitivity concerns with the parameters used to risk stratify the low and high-risk group of my late FGR clinic which formed the patient population for my MD (Res) see **3.2.8 Risk stratification used in the late FGR clinic**. There is a risk that low-risk SGA fetus with normal 1st trimester PAPP-A and 2nd trimester uterine artery Doppler could have increased risk of genetic/chromosomal conditions. In my low-risk FGR patient population there were only 2 SGA fetus with either chromosomal or genetic conditions one in the high-risk and one in the low-risk group. These were both identified antenatally, diagnosed on invasive testing and excluded from my study see **Figure 4.1: Late FGR clinic patient study selection flow chart**

There is also a risk that the "high-risk late FGR group which were advised earlier delivery at 37-38 weeks and who delivered earlier than the low-risk group FGR group allowed expectant management up to 41 weeks could be at increased risk of adverse NNO due to gestation related iatrogenic late preterm complications. In order to address this questions I assessed adverse NNO in low and high-risk late FGR groups and compared these adverse NNO at different gestational time points <36 weeks and >40 weeks (see **Chapter 6: Multiparameteric model to predict adverse NNO** this showed that high-risk late FGR were at increased adverse NNO at all gestational ages from 32 to 42 weeks.

Using multiparametric models to predict SGA and FGR neonates

Third trimester EFW used in isolation has several limitations for diagnosing FGR and adverse NNO in SGA and AGA populations[55]. 1st and 2nd trimester parameter screening in isolation for late FGR also however appear to have limited value. Studies have shown that combining evidence-based 3rd trimester USS parameters known to be associated with placental insufficiency such as abnormal UmbA Doppler, CPR and UtA Doppler and drop in AC GV could increase the ability to detect FGR in SGA and AGA pregnancies at risk of FGR[104].

Triunfo et al in 2017 used a multiparametric model in 946 low-risk pregnancies at 37 weeks by combining EFW with multiple Doppler measurements including the UtA-PI, CPR and the umbilical vein blood flow. Although this did not improve the prediction of SGA and FGR (defined by BW <10th centile and BW <3rd centile) compared to EFW alone; it did improve the prediction of APO compared to using these parameters in isolation. This included the presence of a non-reassuring fetal status requiring CS, a low Apgar score or a metabolic acidosis at birth[77]. This multiparametric model was however limited to low-risk pregnancies and the FGR definition limited by size. Other studies using multiparametric models to predict see **table 1.9** and manage SGA and FGR in low and high-risk pregnancies have been associated with improvement in labour outcome and NNO[211,212,216].

Table 1.9: Studies using screening models to predict SGA neonates

Study	Aim	Screening	Results
Bakalis et al, 2014[217]	To assess the value of fetal biometry at 30-34 weeks in the absence of PET to predict SGA neonates	Screening included: - Maternal characteristics - Obstetric history - EFW z-score at 30-34 weeks	Screening identified: 79%, 87% and 92% of the SGA neonates that delivered < 5 weeks following assessment, with a birth weight < 10^{th}, < 5^{th} and <3^{rd} percentiles, respectively with a 10% false-positive rate.
Tan et al, 2018[218]	To examine the effect of 1^{st} trimester screening for PET on the prediction of delivering a SGA neonate	Screening for PET included: - maternal factors - MAP - Ut A PI - Serum PIGF	Screening for PET identified 64 (19.3%), 100 (45.8%) 28 (56.3%) SGA fetus delivered ≥ 37, <37, <32 week gestation
Papastefanou et al, 2021[219]	To assess ability of maternal factors, biophysical and biochemical markers at 11 – 13 weeks' gestation to predict delivering a SGA neonate	Screening included: - maternal factors - PAPP-A - PIGF - Ut A PI - Mean arterial BP	Screening identified 6299 (11.8%) 1210 (33.9%) 274 (46.8%) of all SGA neonate with birth weight<10^{th} centile delivered ≥37,<37 and<32 weeks' gestation

PET; preeclampsia, SGA; small for gestational age, MAP; mean arterial pressure, Ut A PI; Uterine artery pulsatility index, PIGF; Placental growth factor, PAPP-A; plasma associated protein A, BP; blood pressure.

1.8 Additional USS parameters in late FGR management

1.8.1 Multiparametric models to predict and manage late FGR

The current management strategy in suspected late FGR and a viable fetus is iatrogenic delivery of the fetus, however as discussed this strategy is not always the best option. The next clinical challenge is to identify in which fetus expectant management could be a safe and improved option. In this respect a combination of tests with good "ruling in" capacity could be used to improve diagnosis of "high-risk" FGR, as well as a set of tests with good "ruling out capacity" to identify "low-risk" FGR, which may include constitutionally small fetus as well as growth restricted SGA and AGA fetus with only mild placental insufficiency.

Miranda et al, in 2017 used a multiparameter screening model involving maternal characteristics and biochemistry and fetal/maternal Doppler (UtA-PI, UmbA-PI, MCA-PI and CPR), in 1590 low-risk women, at 32 to 36+6 weeks, to assess detection of SGA and FGR at delivery compared to using customised (c)EFW alone. FGR cases were delivered at 37–38 weeks, SGA cases delivered at 40 weeks and the remaining pregnancies had expectant management, with elective delivery offered at 41 weeks. SGA at delivery was defined as BW <10th customised centile and FGR at delivery was defined as BW <3rd centile or BW <10th centile combined with antenatal cEFW <10th centile, or an abnormally low CPR or UtA-PI ≥95th centile. In a low-risk cohort this multiparametric screening only mildly improved SGA and FGR infants detection compared to cEFW alone[216]

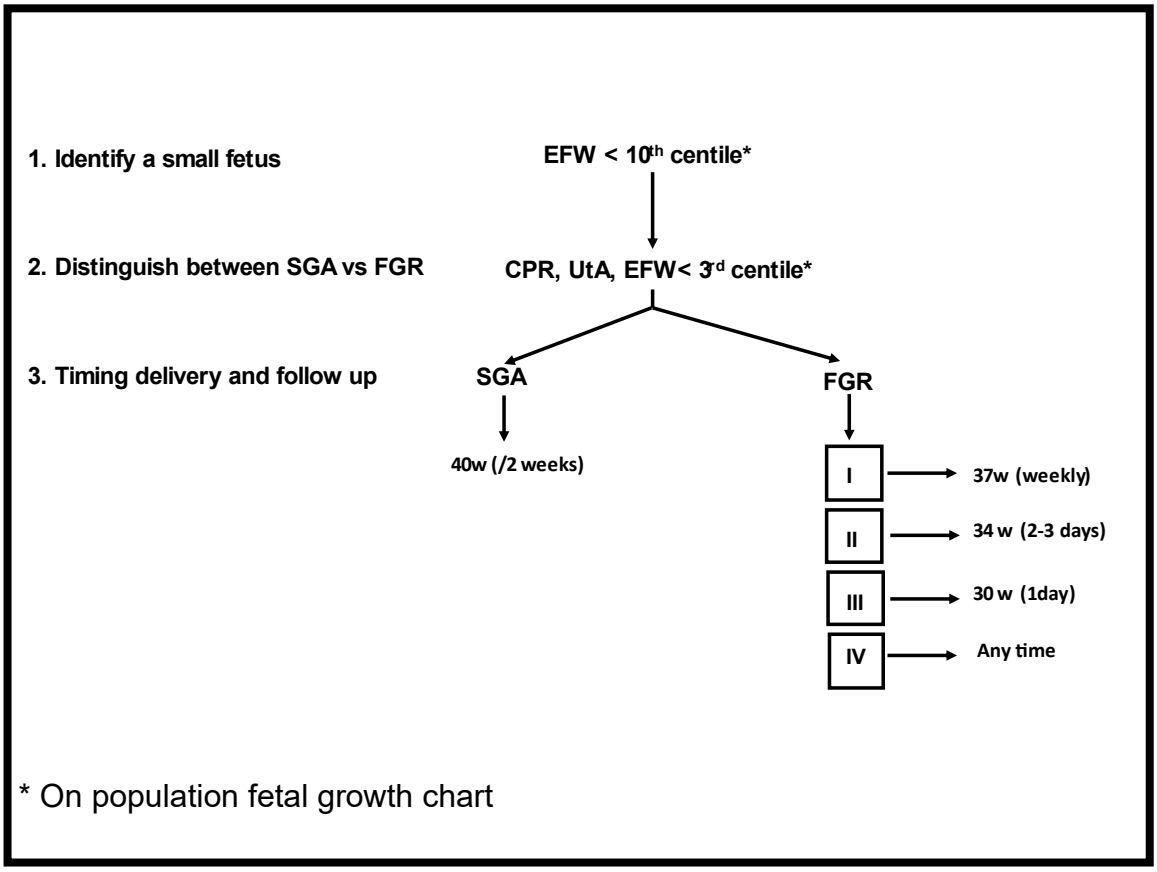
1.8.2 A stage based management protocol for late FGR

Figueras et al, in 2017 proposed an updated management protocol, due to the paucity of evidence, clear recommendations and variation in clinical practice regarding the exact surveillance strategy and timing of delivery in SGA and FGR pregnancies. The proposed multiparameter risk stratified management model advised differentiating SGA and FGR pregnancies according to the EFW, CPR and UtA Doppler. A SGA fetus was defined in the presence of an isolated small fetus (EFW 4-10th centile) with a normal CPR and UtA Doppler. Management was fortnightly USS surveillance and delivery at 40 weeks[220].

In contrast FGR was defined in the presence of a very small fetus (EFW <3rd centile) or an abnormal CPR or UtA Doppler. In FGR the presence of additional parameters: UmbA, ductus venosus (DV) and Aortic isthmus (AoI) Doppler and computerised CTG (cCTG) were proposed to determine the severity of the FGR from stage 1 (severe fetal smallness or mild placental insufficiency) to stage 4 (high risk of fetal acidosis and fetal death) with each stage assigned different strategies for surveillance and timing of delivery (see **Figure 1.8**)[220]**.**

Figure 1.8: Integrated stage based protocol for the management of FGR

(adapted from Figueras et al 2017)[220]



Stage II FGR (severe placental insufficiency). This stage is associated with UmbA AEDV+/- reverse AoI. Advice monitoring is normally twice a week. Delivery is recommended > 34 weeks. Elective CS is normally advised as risk of emergency CS with labour induction is >50%.

Stage III FGR (advanced fetal deterioration with low suspicion of fetal acidosis). This stage is associated with UmbA REDF or a DV PI >95th centile. Advice monitoring every 24-48 hours. This stage has a high risk of IUFD and poor neurological outcomes. As signs associated with a high risk of IUFD within days are not yet present advice delaying elective delivery due to reduce the risks of premature delivery. Elective CS normally recommended > 30 weeks.

Stage IV FGR (high suspicion of fetal acidosis and high risk fetal death). This stage is associated with spontaneous FHR decelerations, reduced short term variability (<3ms) in the cCTG, or reverse atrial flow in the DV Doppler. Monitoring advised every 12-24 hours until delivery and delivery > 26 weeks by CS, in a tertiary centre with steroid and magnesium sulphate administration for lung maturation and prophylaxis of cerebral palsy.

1.8.3 Multiparametric management models used in late SGA fetus

Multiparametric models used by Veglia et al in 2018[211] and Meler et al in 2020[212] as described earlier were used to detect and manage “high” and “low”-risk SGA babies with expectant management in the “low” risk SGA group up to 41 and 40 weeks respectively; adverse NNO and labour outcomes in these groups were compared with a pre-protocol group managed according to pre-protocol strategies. There was significant improvement in labour outcomes and less adverse NNO in the low-risk groups compared to the pre-protocol group[211].

These studies suggests that when all clinical criteria are normal, expectant management beyond 37 weeks may be safe. Assuming independence, the negative likelihood ratios and the capacity to rule out disease using several tests can be potentially combined to calculate the risk of adverse NNO in the presence of normal test results. In systematic review by Martinez-Portilla et al. the authors showed using a baseline 28% for adverse NNO in suspected SGA fetus, a normal UtA Doppler assessment reduces the risk of adverse outcome to 19.4% whilst the presence of a normal CPR would reduce the risk of adverse NNO to 18.2%. When both the UtA and CPR Doppler are normal, assuming independence, the risk of adverse NNO is multiplied by the negative LR of both tests, reducing the risk of adverse NNO in SGA fetus from 28% to 13%[18].

Chapter 2: MD (Res) on late fetal growth restriction

2.1 Introduction

2.1.1 Background

Current challenges in late FGR diagnosis and management

There are many ongoing challenges in the antenatal and postnatal diagnosis and antenatal management of late FGR this includes current late FGR diagnosis and management mainly being based on fetal and neonatal size which inadvertently diagnoses late FGR in constitutionally small fetus and misses late FGR diagnosis in some AGA fetus both potentially resulting in serious maternal and fetal complications. In addition, late FGR are currently advised term delivery with no risk stratification to optimise timing of surveillance and delivery.

Current studies aiming to improve late FGR diagnosis and management

Several studies have aimed to improve diagnosis of late FGR in SGA and AGA fetus by using additional USS parameter associated with placental insufficiency. In addition studies assessing management of late FGR have shown that delayed delivery in late FGR does not appear to significantly increase serious short and long term NNO with more recent studies in SGA fetus which risk-stratified according to using USS parameters, maternal medical history, physiological and biochemical markers, with delayed delivery in low-risk FGR groups was associated with improvement in neonatal and maternal outcomes.

Further improvements needed in late FGR diagnosis and management

Further studies are needed to assess using additional USS parameters to diagnose late FGR in AGA fetus without obvious maternal risk factors for FGR. In addition, further studies are required to assess the effect of risk stratification to optimise management (surveillance and timing of delivery) in AGA fetus with suspected late FGR as well as SGA fetus. In my study I aimed to improve diagnosis of late FGR in AGA as well as SGA fetus by assessing for additional USS parameters in this cohort associated with placental insufficiency. I also used risk stratification in AGA as well as SGA fetus with suspected late FGR to assess whether delayed delivery in the “low-risk” late FGR group was potentially associated with reduction in adverse NNO and assessed for this by comparing with a high-risk late FGR group as well as a pre-clinic cohort. Overall an RCT would be required to assess if risk stratified low-risk FGR pregnancies can safely have delayed delivery with no significant increase in adverse NNO and IUFD.

2.2.2 Aims of the MD (Res)

The main aims of the MD (Res) were:

1. Define a new late fetal growth restriction (FGR) neonatal definition in SGA and AGA fetus based on adverse neonatal outcome (NNO) markers and antenatal ultrasound (USS) parameters known to be associated with late FGR associated placental insufficiency. Assess USS parameters associated with placental insufficiency in SGA and AGA fetus at risk stratifying low and high-risk late FGR groups according to placental insufficiency with delayed delivery (up to 41 weeks) in low-risk pregnancies whilst high-risk FGR were still advised delivered at 37-38 weeks; with the aim to reduce adverse maternal and perinatal morbidity associated with iatrogenic term delivery in low-risk late FGR.

2. Evaluate the new risk stratification UCLH late FGR clinic management protocol by comparing adverse labour, maternal and NNO outcomes in the late FGR clinic cohort compared to a pre-clinic cohort.

3. Develop a multiparameter late FGR predictive model of adverse NNO by identifying high-risk late FGR in the presence of additional USS parameters associated with placental insufficiency and comparing risk of adverse NNO at different gestational ages

2.2.3 Objectives and hypothesis of the MD (Res)

I hypothesised that the group of fetuses referred to my late FGR clinic based on small EFW will be heterogenous and include fetuses where deteriorating placental function leading to reduced growth velocity and significant effects on fetal development and metabolism and early delivery required to prevent in utero demise. By contrast, the cohort will also include fetuses where placental function might be optimal and the small fetal size reflects normal growth for that fetus.

I also hypothesised that it would be possible to define these two groups antenatally based on known risk factors, markers of placental function as well as fetal haemodynamics and growth. I would anticipate therefore that the “high-risk” group would be more likely to have an adverse neonatal outcome than the “low-risk” group. Finally, these parameters can then be used to inform decisions about delivery timing with low-risk fetuses delivered at later gestations without an increase in hypoxia related adverse outcomes.

Aim 1: Identify new USS parameters diagnostic of FGR based on phenotype

I predicted that if the additional USS parameters used accurately identified late FGR associated with placental insufficiency then there would be increased adverse NNO markers in the high-risk vs the low-risk late FGR clinic cohort.

Aim 2: To implement and evaluate new management protocols for FGR

I predicted that if the late FGR clinic management protocol had appropriately risk stratified the late FGR cohort then the low-risk group in particular would have improved adverse NNO compared to a pre-clinic cohort. This will mainly affect constitutional small fetuses and late FGR with mild placental disease.

Aim 3: Develop a multiparameter late FGR predictive model of adverse NNO

I predicted that if the parameters used had appropriately risk stratified the late FGR pregnancies then the high-risk group would have increased adverse NNO at any gestational age vs the low-risk late FGR pregnancies due to more severe placental disease.

Chapter 3: Setting up the late FGR clinic

3.1 Introduction

3.1.1 The new UCLH Late FGR clinic

More than 6000 women give birth at University College London Hospitals NHS Foundation Trust (UCLH) every year. I was keen to improve patient care and outcomes and it was following discussion with my neonatal colleagues that I was informed that there were many babies being delivered iatrogenically at term due to suspected FGR and having suspected late preterm complications and needing NNU admission and prolonged stay and vice versa other babies not being identified as FGR antenatally with birth weight size within normal range but behaving physiologically like an FGR neonate. In response to this I was keen to identify FGR more accurately in SGA as well as AGA fetus. Therefore in 2018 in the Ultrasound Screening Unit (USU) and Fetal Medicine Unit (FMU) at UCLH I set up a new late FGR clinic and implemented a service improvement project on late FGR management with the aim to improve perinatal and maternal morbidity.

3.1.2 Late FGR clinic aims and objectives

The main aims and objectives of the clinic was to identify and manage late FGR according to new specific late FGR risk stratification and management protocols to identify a low and high-risk late FGR group with separate pathways for surveillance and timing of delivery (see **3.2.8 Risk stratification used in the late FGR clinic and 3.2.9 Management protocol**). Risk stratification and management protocols were based on maternal biochemical parameters and FGR risk factors as well as additional 2nd and 3rd trimester USS parameters.

3.1.3 Examples of pre-existing late FGR clinics

Examples of pre-existing late FGR clinics have been described in studies by Veglia et al in 2018[211] and Meler et al in 2020[212] see **2.6.3 Multiparametric management models used in late SGA fetus.** Both these studies used several parameters (maternal biochemistry and risk factors and fetal sonography) and risk stratification within a dedicated late FGR clinic with the aim to optimise the surveillance and timing of delivery in low and high-risk late FGR pregnancies.

3.1.4 Models used to establish a new clinical service

Several models have been published on how to implement and establish a new clinical service and these were used in the implementation of the late FGR clinic at UCLH[221,222] . The 'McKinsey 7S model' created by Robert Waterman and Tom Peters devised in the 1970's is a highly effective framework which can allow change in any organisation. The core elements of the McKinsey 7S model involves ensuring that all the necessary and appropriate resources for change are in place including a suitable strategy, structure, systems, shared values, skills, staff and style. Comparing the current and ideal state of these areas in an organisation can help produce an action plan for effective change.

The National health service (NHS) England in 2012 published the 'Change Model Guide' an effective framework for sustainable change in clinical practice; key important areas in this guide include the presence of a shared purpose, spread and adoption, improvement tools, project and performance management, measurement, system drivers, motivation and mobilisation and leadership by all. NHS England in 2018 also provided further guidance for commissioners and providers on how to implement service change in the document 'planning, assuring and delivering service change for patients with preparation and planning, evidence base, leadership and the clinical involvement of patients and the public highlighted as important key areas.

3.1.5 Guidance and issues in setting up a new clinic

Several guides have also been published on the practical aspects involved in setting up specialist obstetrics and gynaecology clinics and were used when setting up the new late FGR clinic at UCLH[222,223]. These guides highlighted the importance of a suitable location, appropriate staff training, resources and capital, an accurate cost analysis and the steps and negotiations needed to set up a new clinical service. These guides also discussed the difficulties with setting up a new clinical service, how these issues were overcome and clinic data showing the clinical and financial advantages associated with specialised clinics.

Specific issues I encountered when setting up the late FGR clinic at ULCH were associated with training, accuracy and reproducibility. Both myself and the other senior doctor running the late FGR clinic were Obstetrics and Gynaecology trainees (ST6 and ST7 level) and not pure sonographers; both competent and had performed several RCOG OSAT assessments in fetal growth and wellbeing, 1st trimester dating and anomaly ultrasound scans. At the time the once weekly late FGR clinic was implemented both myself and the other trainee had started and completed a 2 year fellowship in ultrasound scan and fetal medicine. Both of us had also completed relevant FMF online courses, attended relevant Fetal medicine conference as well as theoretical and clinical ultrasound scan courses.

To overcome the issues with accuracy and reproducibility of biometry measurements both myself and the other trainee always scanned patients with both of us in the room, one scanning and the other checking the images for cross section accuracy giving feedback on cross section accuracy as required. I also carried out a reproducibility assessment in which both of us trainees measured biometry on the same patient at different gestations from 32 to 41 weeks, taking 2 measurements in the same patient for biometry, amniotic fluid and Dopplers. There was no significant difference ($p>0.04$) between the measurements taken.

The two main guides considered when setting up the new late FGR clinic at UCLH included 2008 Richard Hatchett published Nurse-led clinics: 10 essential steps to setting up a service. This included: (1) build a business case (2) define aims and objectives (3) establish patient criteria (4) plan your publicity (5) select a location, (6) gain support from colleagues (7) plan professional development (8) consider medicine management (9) plan audit and evaluation and (10) facilitate ongoing improvement[224]. The BMJ in 2019 also published practical steps on setting up a new clinical service which included conception, preparation, a business case, a pilot study and audit[225]. I have explained in **3.2 methods** how these two guides were used to set up and implement the UCLH Late FGR clinic.

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3.2 Methods

3.2.1 Create a business case

I first created a business case which explained my late FGR clinic vision from conception to delivery of the clinical service and I presented this to the Trust to convince those in charge of finances and service provision that my new clinical service would be in my patient's and the trust's financial interests. My 'business case for the late FGR clinic' involved a summary statement, background, service description, benefits analysis, project planning, pilot study and audit.

- **Summary statement:** UCLH will implement a new late FGR clinic in February 2018. Observational studies have shown that specialised obstetric clinics can improve neonatal and maternal outcome.

- **Background:** I summarised the services already in place at UCLH and the necessity of the new late FGR clinic. Prior to initiating the late FGR clinic there was no dedicated service or clear management guidance in place for FGR pregnancies. Women were reviewed in a variety of clinical settings and by doctors varying in seniority and fetal medicine expertise. This caused discrepancy in late FGR management.

- **Description of the service:** This included a short summary of the new late FGR clinic: “Women diagnosed with late FGR according to the new UCLH FGR screening and management pathways will have review with USS, BP and urinalysis every 1-4 weeks until delivery”

- **Benefits analysis:** The economic cost of the new late FGR clinic was assessed and was identified to have minimal economic impact, with no additional cost needed for equipment, staff employment or staff training.

- **Project planning:** An appropriate timeline was produced for the late FGR clinic implementation steps and a start date organised for the 26.02.2018

- **Pilot study and audit:** Following approval of the business case for the late FGR clinic, a pilot study was performed with the appropriate staff and equipment and late FGR clinic management protocol involving 30 women with suspected late FGR. Adverse labour, maternal and neonatal outcomes were collected, independently audited and presented to the business plan board with the aim to set up a long term late FGR clinic.

3.2.2 Establish patient criteria and patient participation involvement

Patient criteria

Additional 3rd trimester USS parameters associated with placental insufficiency and based on the updated definitions by Gordijn et al in 2016 were introduced into the USU department at UCLH to diagnose late FGR in SGA and AGA fetus with suspected late FGR pregnancies referred to the UCLH late FGR clinic see **3.2.7 Screening in the late FGR clinic**.

Patient participation involvement

Teaching and training on the referral pathways and the management protocols used in the late FGR clinic was presented at Departmental and Audit meetings by the author of this thesis who also managed the UCLH late FGR clinic. A local patient participation group (PPI) was also set up to obtain public feedback and to improve the clinic structure and protocols which included patient associations aimed at improving maternity care such as The Stillbirth and Neonatal Death (SANDS) charity and A torah infertility medium of exchange (A T.I.M.E). Representatives reviewed the protocol and patient information leaflets.

Step 5. Select a location

There was a suitable structure and support from the clinical, administration and information technology teams already in place for several specialised USS clinics to function simultaneously, this allowed the new late FGR clinic to work efficiently in the current system. The late FGR clinic already had suitable equipment (Voluson E8 USS machine, a Dinamap v100 BP machine and siemens multistix 10 SG urinalysis strips) as well as appropriately trained staff.

Step 6. Gain support from colleagues

PPI meetings and consultations between the health care professionals running the late FGR clinic and experts in fetal medicine and neonatology, obstetricians and midwives showed that that the clinic principles, structure and aims were enthusiastically supported. The proposed changes were also importantly in line with the aims and principles of UCLH which includes providing top quality patient care, excellent education and world class research.

Step 7. Plan professional development

The late FGR clinic was consultant led with two senior Obstetric doctors (≥ST6) level and a midwife all competent in performing USS for fetal growth and fetal well-being in line with international standards and quality control. These Specialists graduated in the Training Programme in the UCLH Obstetric Ultrasound and Fetal Medicine [226], which has since evolved into the MSc programme in Obstetric Ultrasound and Fetal Medicine **https://www.ucl.ac.uk/womens-health/msc-obstetric-ultrasound-and-fetal-medicine**. Healthcare professionals involved in running the late FGR clinic kept up to date with current advances in the management of late FGR and attended local, national and international fetal medicine courses and presented results at maternity frame networks including the London Maternity Network.

Step 8. Consider medicine management

The senior obstetric doctors involved in running the late FGR clinic had access to prescribing medications for co-existent or new-onset medical and obstetric conditions as required for the pregnant patients reviewed in the late FGR clinic.

Step 9. Plan audit and evaluation

It was planned to audit neonatal, maternal and labour outcomes in the late FGR clinic and to compare with late FGR diagnosed and managed according to pre-clinic strategies. The late FGR clinic results have since been presented at UCLH audit meetings and to my dedicated patient public involvement (PPI) groups by the author of this MD (RES) with the aim to further improve my clinical service.

Step 10. Facilitate ongoing improvement

I planned to regularly audit labour, maternal and neonatal outcomes from the late FGR clinic at least once per year and to continue presenting at local audit and risk management meetings as well as the local late FGR clinic PPI group to allow further and ongoing improvements in the late FGR clinic.

3.2.3 Novel aspects of the UCLH late FGR clinic

In contrast to the late SGA management clinics described by Veglia et al in 2018[211] and Meler et al in 2020[212] the UCLH late FGR clinic detected and managed women from an earlier gestation (≥ 32 weeks vs ≥ 36 weeks). It also diagnosed, risk-stratified and managed late FGR in AGA as well as SGA fetus by using USS parameters associated with placental insufficiency in addition to fetal size. It also used adverse NNO measures to identify a new neonatal definition for FGR independent of birthweight. This included mild neonatal morbidity (hypoglycaemia, hypothermia, jaundice, feeding difficulties, a low Apgar score, NNU and hospital readmission) as well as severe neonatal morbidity (sepsis, cerebral, respiratory or circulatory morbidity, IUFD or NND).

3.2.4 Novel management protocol used in the late FGR clinic

In the late FGR clinic pregnancies were risk stratified according to the presence of maternal risk factors for FGR, 1st trimester PAPP-A level and the presence or absence of 3rd trimester USS parameters associated with placental insufficiency (**see 3.2.8 Risk stratification used in the late FGR clinic**). High-risk FGR pregnancies had USS surveillance every 1-2 weeks and were advised delivered at 37-38 weeks, whilst low-risk FGR pregnancies had USS surveillance every 2-4 weeks and allowed expectant management up to 41 weeks.

3.2.5 Novel neonatal outcome measured in the late FGR clinic

The novel NNO measures used to define FGR in neonates independent of neonatal small size were based on the fetal changes associated with placental insufficiency and chronic hypoxia with the aim to identify a new definition for FGR neonates independent of neonatal size (see **4.2.8 Birth, labour, maternal and neonatal outcomes in the late FGR clinic).**

3.2.6 Methodology involved in running the late FGR Clinic

The author had the role of lead clinical fellow and was involved in running the late FGR clinic. This role also involved being a champion for introducing the customised fetal growth charts at UCLH and providing large group teaching on how to use customised growth charts, as well as local training in the new departmental late FGR USS screening parameters and the USS referral criteria to the late FGR clinic. The author also produced departmental protocols on the new USS screening parameters and pathways, use of customised fetal growth charts and the late FGR management clinic.

3.2.7 Screening in the late FGR clinic

At the time of implementation of the late FGR clinic a new pathway for screening was introduced. In addition to NICE criteria for third trimester screening scans, universal Doppler at the time of the anomaly scan was introduced. Also AC drop and CPR less than the 5th centile were formally introduced as screening for referral to the late FGR clinic, in addition to EFW or AC <10th centile. These screening parameters were chosen due to their known association with late FGR and association with adverse NNO in SGA and AGA fetus[9,10,32,43,37,150,151]. Further explanation for my criteria used to screen for late FGR in my clinic are discussed in **1.3.6 Using additional ultrasound parameters to detect late FGR** and **1.5.4 Fetal compensation and sonographic late FGR criteria**

UCLH late FGR clinic inclusion criteria

1- Gestational age ≥ 32 weeks gestational age according to a 1st trimester Crown Rump Length (CRL)[227,228] 2nd trimester head circumference[229] or in assisted conception by date of embryo transfer[230].

2- Any of the following USS parameters:
   a. EFW< 10th centile on customised fetal growth chart[231 ,232]
   b. CPR < 5th centile[233]
   c. Drop in AC or EFW growth velocity ≥ 50 centiles compared with a 2nd trimester USS[95,151]
   d. UmbA Doppler >95th centile[234]

UCLH late FGR clinic exclusion criteria

1- Gestational age ≤ 32 weeks and/or pregnancies dated in the third trimester
2- Multiple pregnancy
3- Known fetal structural anomaly (ante- or postpartum)
4- Known fetal chromosomal or genetic abnormality (ante- or postpartum)

3.2.8 Risk stratification used in the late FGR clinic

Low-risk late FGR fetuses were classified if any of the criteria below were present:

1- EFW between 3rd and 10th centile plus any of the criteria below:
   a. Normal 1st trimester PAPP-A (>0.4 MoM)
   b. Normal 2nd or 3rd trimester UtA PI
   c. Normal CPR (>5th centile)
   d. No AC drop across ≥50 centiles

2- EFW >10th centile with drop across fetal EFW/AC centile ≥50 centiles compared to 2nd trimester USS or an abnormal CPR (<5th centile)

High-risk late FGR included fetuses with:

1- EFW < 3rd centile[47]
2- EFW between 3rd and 10th centile plus any of the criteria below:
   a. Maternal comorbidity associated with late FGR[10]
   b. Low PAPP-A in the first trimester (<0.4 MoM)[235]
   c. Increased 2nd trimester combined sum UtA PI (>2.5) or mean UtA PI >95th centile at ≥32 weeks[18]
   d. CPR <5th centile[150]
   e. AC drop across ≥50 centiles[95,151]
3- Any size fetus with an UmbA PI >95th centile[47]

3.2.9 Management protocol

The late FGR clinic management protocol used 3rd trimester USS parameters associated with placental insufficiency (EFW <10th centile, UmbA Doppler >95th centile, abnormal EDF, CPR, <5th centile or AC GV ≥50th centile) to diagnose, risk-stratify and manage late FGR pregnancies to determine the optimal frequency of USS surveillance and the timing of delivery according to the perceived risk of placental insufficiency (see **Tables 3.1- 3.3**).

Table 3.1: Late FGR management protocol EFW >10th centile

EFW	UmbA centile	AC Drop	CPR	GA	Follow up	Monitoring	Timing of delivery
EFW > 10th Centile	< 95th	No AC drop	>5th		No follow up		
			< 5th		2 weeks	EFW + Doppler fortnightly	40-41 weeks
		AC drop	>5th		1 week	EFW + Doppler fortnightly	40-41 weeks
			< 5th		1 week	EFW + Doppler fortnightly	38-39 weeks
	> 95th				1 week	EFW + Doppler fortnightly	37-38 weeks

EFW; estimated fetal weight, AC; abdominal circumference, CPR; cerebroplacental ratio, GA; gestational age, PAPP-A; pregnancy associated plasma protein-A, UtA-PI; uterine artery pulsatility index, UmbA PI; umbilical artery pulsatility index.

Table 3.2: Late FGR management protocol EFW 3rd to 10th centile

EFW	UmbA centile	AC Drop	CPR	GA	Follow up	Monitoring	Timing of delivery
EFW 3rd-10th centile	< 95th	No AC drop	>5th		2 weeks	EFW + Doppler fortnightly	40-41 weeks
			>5th		2 weeks	EFW + Doppler fortnightly	37-38 weeks if UtA PI > 95th
			< 5th		1 week	EFW + Doppler fortnightly	37-38 weeks
		AC drop	>5th		1 week	EFW + Doppler fortnightly	39-40 weeks
			< 5th		1 week	EFW + Doppler fortnightly	37-38 weeks
	> 95th			< 36w	1 week	EFW + Doppler fortnightly	36-37 weeks
				> 36w	same day	Doppler every 3 days	36-37 weeks

EFW; estimated fetal weight, AC; abdominal circumference, CPR; cerebroplacental ratio, GA; gestational age, PAPP-A; pregnancy associated plasma protein-A, UtA-PI; uterine artery pulsatility index, UmbA PI; umbilical artery pulsatility index.

Table 3.3: Late FGR management protocol EFW < 3rd centile

EFW	UmbA centile	AC Drop	CPR	GA	Follow up	Monitoring	Timing of delivery
EFW < 3rd centile	< 95th	No AC drop	>5th		1 week	EFW + Doppler fortnightly	37-38 weeks
		AC drop			1 week	EFW + Doppler fortnightly	37 weeks
	> 95th			< 36w	1 week	EFW + Doppler fortnightly	36-37 weeks
				> 36w	same day	Doppler every 3 days	36-37 weeks

EFW; estimated fetal weight, AC; abdominal circumference, CPR; cerebroplacental ratio, GA; gestational age, PAPP-A; pregnancy associated plasma protein-A, UtA-PI; uterine artery pulsatility index, UmbA PI; umbilical artery pulsatility index.

3.3 Results

For results of the labour, maternal and neonatal outcomes of the late FGR clinic in the low and high-risk FGR groups see **4.3 Results** and for results of the late FGR clinic and sub risk groups versus the pre-clinic cohort see **5.3 Results**

Chapter 4: Antenatal diagnosis, monitoring and management of late FGR and association with novel definition of FGR related adverse neonatal outcome measures

4.1 Introduction

4.1.1 Background

FGR in the neonate is often diagnosed on weight (BW < 10th centile or BW < 2.5kg at term)[122]. Newer diagnosis for FGR diagnosis in the neonate includes the presence of ≥ 3: BW, HC or Length <10th centile; prenatal diagnosis of FGR or maternal morbidity associated with FGR[136]. Low neonatal weight inaccurately misdiagnoses constitutionally small neonates as FGR whilst missing FGR in AGA neonates. As most SGA neonates are constitutionally small there is less association with USS parameters associated with placental insufficiency which is more commonly seen in FGR neonates at increased risk of adverse NNO such as hypoglycaemia, hypothermia, and jaundice independent of neonatal size.

4.1.2 Aims, objectives and hypotheses:

The first aim of the MD (Res) was:

- Define antenatal USS parameters known to be associated with late FGR with the new late fetal growth restriction (FGR) neonatal definition of phenotype. Assess USS parameters associated with placental insufficiency in SGA and AGA fetus at risk stratifying low and high-risk late FGR groups according to placental insufficiency with delayed delivery (up to 41 weeks) in low-risk pregnancies whilst high-risk FGR were still advised delivered at 37-38 weeks; with the aim to reduce adverse maternal and perinatal morbidity due to term delivery in low-risk late FGR.

4.2 Methods

4.2.1 Study type

This was a prospective cohort study involving 321 pregnancies with evidence of late FGR on USS according to the inclusion criteria used in the late FGR clinic (see **Figure 4.1: Late FGR clinic patient study selection flow chart) and 4.2.2 Late FGR clinic study referral criteria.** Late FGR pregnancies were reviewed in the UCLH late FGR clinic between 26.02.2018 to 27.09.2019. Study design, analysis and reporting was according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations[236].

4.2.2 Late FGR clinic study referral criteria

This included all women with an USS performed ≥ 32 weeks gestation, with a singleton, non-anomalous pregnancy and either:

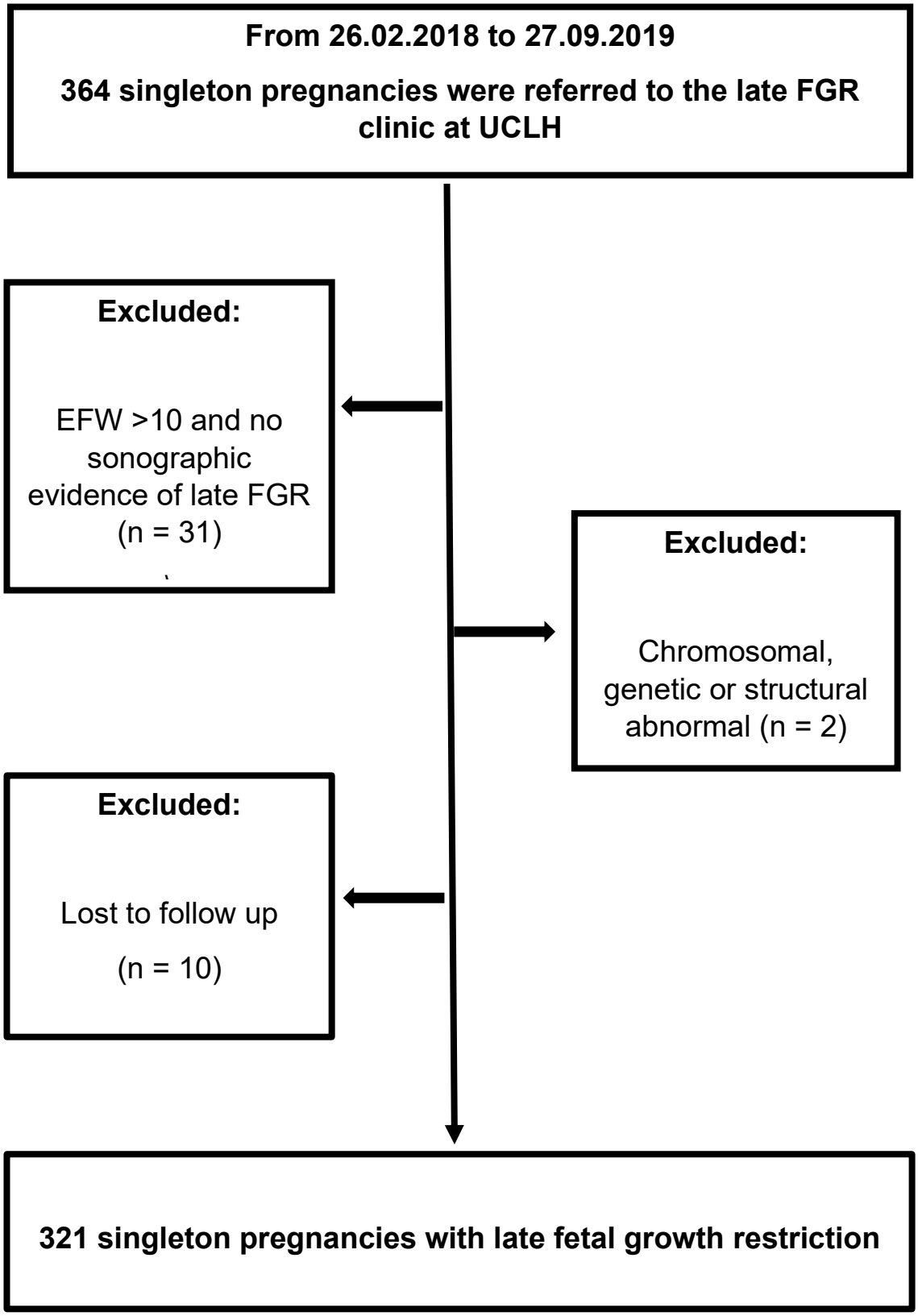
1) EFW ≤ 10th centile on a customised or population fetal growth chart[231,232]

2) EFW > 10th centile on these same fetal growth chart with either:
    a. an increased UmbA Doppler PI > 95th centile[47]
    b. a low CPR < 5th centile150
    c. a reduction in the fetal AC ≥ 50 centiles compared to a second or a third trimester USS[95,151].

4.2.3 Late FGR clinic patient study selection

Between 26.02.2018 to 27.09.2019; 364 singleton pregnancies ≥32 weeks gestation, accurately dated were referred to the late FGR clinic at UCLH. I excluded from my final data analysis pregnancies with no evidence of growth abnormalities (n = 31); pregnancies with structural, chromosomal or genetic abnormalities diagnosed ante- or postpartum (n = 2) and pregnancies with outcome data missing (n =10) see **Figure 4.1: Late FGR clinic patient study selection flow chart and 4.2.2 Late FGR clinic study referral criteria.** There were 321 pregnancies in the final analysis.

Figure 4.1: Late FGR clinic patient study selection flow chart



4.2.4 Late FGR clinic review

The late FGR consultant led clinic was managed by two senior obstetric doctors and a midwife competent in growth and Doppler scanning and trained in a dedicated 2-year programme in obstetric USS and fetal medicine. USS examinations were performed according to local, national and international guidelines[237,238,239,240,241]. The author of this MD was one of the senior doctors managing the late FGR clinic, this involved performing fortnightly USS to measure fetal size and weekly USS to measure fetal UmbA and MCA Doppler and amniotic fluid. During each clinic review the women's BP was measured with an automatic V100 DINAMAP sphygmomanometer and urinalysis performed using SIEMENS Labstix® reagent strips to assess for evidence of PIH or PET[242].

Biometric measurements

Fetal biometry, Doppler and amniotic fluid was measured according to local and international standards and guidance[,238,239,240,241,243,244]. The fetal HC was measured in a symmetrical plane, containing the cavum septum pellucidum and thalamus. The fetal AC was measured in a symmetrical plane, involving the stomach bubble and the portal sinus. The femur length (FL) was measured with both ends visible and < 45^{o} to the horizontal. Biometric measurements were recorded with callipers at right angle for the HC and AC, an outer to outer position for the HC, AC and FL; with magnified images occupying > ½ screen.

Fetal UmbA and MCA Doppler measurements

The fetal UmbA and MCA Doppler were assessed at every fetal growth USS, Routine maternal UtA Doppler was assessed at the anomaly USS and if abnormal were repeated during the 3rd trimester. The UmbA Doppler was assessed in both UmbA arteries, with colour flow mapping to identify free loops of cord and the pulsed-wave Doppler gate placed within each vessel. The MCA Doppler was identified in an axial fetal brain section, including the thalami and sphenoid bone wing and colour flow mapping used to identify the circle of Willis and proximal MCA with the pulsed-wave Doppler gate within the proximal third of the MCA.

Maternal UtA Doppler measurements

Transabdominal UtA Doppler was performed over the maternal lower lateral abdominal quadrants, with colour flow mapping to identify the point 1cm below where the UtA crosses the external iliac artery. If the UtA branched before intersecting the external iliac artery, the UtA was assessed before the bifurcation. For all Doppler measurements, the image was magnified, the angle between the USS beam and the blood flow direction kept close to zero, the Doppler scale and the sweep speed reduced to magnify the velocity recording on the screen and to allow 3-9 consecutive wave. Doppler was assessed during fetal quiescence and with light transducer pressure. Fetal growth and Doppler measurements were repeated by a 2nd operator in the late FGR clinic in 50 women to calculate the reproducibility of my fetal biometry and Doppler measurements[226,245.]

Amniotic fluid measurement

During each USS performed in the late FGR clinic amniotic fluid was assessed by measuring either the single deepest vertical pool (SDVP) or the amniotic fluid index (AFI). Fetal biometry (HC, AC and FL), Doppler and amniotic fluid measurements were recorded on population based fetal charts. The EFW in grams was calculated using the Hadlock 4 formula using the fetal HC, BPD, AC and FL measurements and was plotted and assessed on a customised fetal growth chart to calculate the EFW centile[246].

Customised fetal growth chart

Customised fetal growth charts were reproduced in the late FGR clinic as required using the Grow Related Optimal Weight (GROW) software (accessible at **https://ukasw.growservice.org/App/Account/Login**. Customised fetal growth charts adjusted for maternal height, weight, ethnicity and previous pregnancy birth weights and was used simultaneously with the GAP package. The author of this MD was one of the champions involved in the local training and implementation of the GAP package and use of customised fetal growth charts.

4.2.5 Management protocols used in the late FGR clinic

In the Late FGR clinic pregnancies were risk stratified as low or high-risk FGR groups according to the risk of placental insufficiency see **3.2.8 Risk stratification used in the late FGR clinic** . Low-risk FGR pregnancies had USS surveillance every 2 weeks and expectant management up to 41 weeks, whilst the high-risk FGR pregnancies had USS surveillance every 1-2 weeks and delivery advised between 37-38 weeks (see **Tables 3.1, 3.2, 3.3**). Following each late FGR clinic review pregnancies continued with either low or high-risk FGR group management according to the USS results. If there were obstetric indications requiring delivery this was expedited as clinically indicated. Final risk-group status was based on last late FGR clinic review before delivery.

4.2.6 Labour induction and augmentation

Timing and mode of delivery (MOD) was determined by the late FGR clinic management protocol, the couples wishes and if no contraindications for vaginal delivery. Labour was induced by promoting cervical ripening by administering either prostaglandin E2 vaginal gel (2mg) for a maximum of 2 doses 6 hours apart or slow-release prostaglandin E2 vaginal pessary (10mg). If onset of labour did not occur within 12-24 hours, oxytocin augmentation was initiated after artificial rupture of membranes. Operative delivery for abnormal FHR followed National Institute of Clinical Excellence (NICE) CTG indications[247].

4.2.7 Gynaecological, medical and obstetric FGR risk factors

Each woman reviewed in the late FGR clinic, had their past and current gynaecological, obstetric and medical history reviewed on the UCLH electronic USS database ViewPoint 6 to assess for risk factors associated with FGR to compare these factors in the low and high-risk FGR groups and are discussed below. Maternal medical comorbidities associated with late FGR was the only maternal risk factors used within the late FGR risk stratification protocol.

Gynaecological risk factors

Gynaecological risk factors for FGR included the presence of multiple fibroids (>3), a single fibroid (>5cm), uterine anomalies (bicornuate, unicornuate, didelphus, or septated uterus) and previous surgery for a uterine anomaly.

Obstetric risk factors

Past obstetric risk factors included previous SGA or FGR baby or placental abruption. Current obstetric risk factors included PET (diagnosed according to current international criteria for BP and proteinuria)., PIH, gestational diabetes mellitus (GDM) and unexplained antepartum haemorrhage (APH). Some women in the low-risk group had past and current obstetric factors as this did not determine risk status, most of these women had only mild features and spontaneous delivery prior to iatrogenic delivery or developed raised BP intrapartum or postdelivery. The only maternal risk factor deciding risk status was maternal medical comorbidities associated with late FGR (see below).

Medical risk factors

Medical co-morbidities associated with FGR included chronic HTN, diabetes, ulcerative colitis, Crohn's disease, coeliac disease, sickle cell disease, HIV, rheumatoid arthritis, nephrectomy, chronic renal disease, sleeve gastrectomy, protein S deficiency, homozygous factor 5 Leiden thrombophilia, antiphospholipid syndrome, complex or cyanotic cardiac conditions and scleroderma.

4.2.8 Birth, labour, maternal and neonatal outcomes

Birth, labour, adverse maternal outcomes, mild and severe adverse NNO were collected for all women managed in the late FGR clinic. Birth weight centiles were calculated with customised birth weight centiles[248]. The late FGR management clinic was approved by local hospital clinical governance and implemented as part of routine service and so requirement for ethical approval and individual patient consent was waived. Labour outcomes included the onset of labour (spontaneous or induced) and the MOD (vaginal delivery, vaginal assisted instrumental delivery and elective or emergency CS).

Adverse maternal outcomes

Adverse maternal outcome was defined as need for operative delivery in labour, (instrumental assisted vaginal delivery or emergency CS) for abnormal FHR and suspected fetal compromise according to NICE CTG guidelines, 2014[249]

Mild adverse neonatal outcome

Mild adverse NNO included any of the following neonatal outcome measures present at delivery: hypoglycaemia (serum glucose < 2.5mmol/L), hypothermia (temperature < 36.5C), jaundice requiring phototherapy treatment or exchange transfusion according to NICE bilirubin threshold treatment graphs, suspected infection (defined as ≤ 48 hours antibiotics combined with negative microbiology cultures), difficulties in establishing breast feeding, Apgar score < 7 at 1 minute, NNU admission or hospital readmission for FGR related hypoglycaemia, jaundice, hypothermia, poor oral intake or weight loss ≥10%.

Severe adverse neonatal outcome

Severe adverse NNO included IUFD or NND, advanced cardiac or respiratory neonatal resuscitation with inotropes or mechanical ventilation, an Apgar score < 7 at 5 minutes, severe metabolic acidosis (defined as cord blood pH < 7.0 and base deficit > 12mmol/L), sepsis (defined as clinical sepsis and positive blood cultures, necrotising enterocolitis or meningitis) or severe cerebral, respiratory or circulatory morbidity. Severe cerebral morbidity included intracerebral haemorrhage or intraventricular haemorrhage grade 3 or 4, HIE, seizures or brain cooling therapy. Severe respiratory morbidity included respiratory distress syndrome, persistent pulmonary hypertension, respiratory support > 1-week, meconium aspiration or BPD. Severe circulatory morbidity included hypotensive, ductus arteriosus treatment and disseminated intravascular coagulation (DIC).

Overall adverse neonatal outcome

Any baby with either mild or severe adverse NNO were identified as having overall adverse NNO

1.1.4 4.2.9 Statistical analysis

Statistical package for the social sciences (SPSS) and R were used for data analysis. Data was normally distributed if skewness and kurtosis z scores were between -1.96 to +1.96, Shapiro-Wilk test for normality p-value was > 0.05 and if the histograms, normal Q-Q plots and box plots showed symmetrical distribution. Parametric data was presented using means and standard deviation and the independent sample t-test compared means. The Mann-Whitney U test was used for non-parametric data. Categorical data was presented as N (%). To test for association and significance the Pearson's chi-square test was used with the fisher's exact test used if the expected cell count was < 5. Multiple logistic regression analysis adjusted for significant differences in the two FGR groups.

Power calculation

From previous pilot and observational data, to identify a significant difference in adverse NNO of more than 15% between the low- and high-risk FGR groups, a minimum of 152 women per group was required (alpha 0.05 and power 80%).

4.3 Results

4.3.1 Number of women in the study

Between February 2018 and September 2019, 364 women were referred to the late FGR clinic at UCLH. According to my exclusion criteria see **Figure 4.1**; there were 321 pregnancies in the final analysis. There were 156 pregnancies (48.6%) in the low-risk group and 165 pregnancies (51.4%) in the high-risk group.

Table 4.1: Maternal features in low and high-risk late FGR

Maternal features	Low-Risk N = 156	High-Risk N = 165	p-value
Age (years)	33 (29-36)	33 (30-36)	0.596*
BMI (kg/m2)	22.8 (20.4-25.6)	23.6 (20.8-27.5)	0.131*
Nulliparous	71 (45.5)	80 (48.5)	0.594
Current smoker	8 (5.1)	13 (7.9)	0.319
Recreational drug user	1 (0.6)	6 (3.6)	0.122**
Medical comorbidity	10 (6.4)	12 (7.3)	0.760
Past obstetric history	34 (21.8)	37 (22.4)	0.892
Gynaecological history	5 (3.2)	14 (8.5)	0.045
Current obstetric history	13 (8.3)	33 (20.0)	0.003
Preeclampsia	1 (0.6)	12 (7.3)	0.003
Gestational diabetes mellitus	11 (7.1)	13 (7.9)	0.779
EFW <10th population chart	86 (55.1)	90 (54.5)	0.964
EFW <10th customised chart	73 (46.8)	109 (66.1)	<0.001
CPR <5th centile	6 (3.8)	11 (6.7)	0.255
AC Drop ≥ 50 centiles	16 (10.3)	13 (7.9)	0.459

Values reported as median (interquartile range, IQR 25th to 75th centile) or absolute values (%). BMI; body mass index, EFW; estimated fetal weight, CPR; cerebroplacental ratio, AC; abdominal circumference. To test for significance either the Pearson's Chi-squared test, the Mann- Whitney U test (*) or the Fishers exact test (**) were used.

4.3.2 Maternal baseline features

The two groups were comparable over a range of demographic variables but varied on underlying gynaecological and obstetric risk factors which were adjusted for during data comparison. Low-risk women were significantly less likely to have an underlying gynaecological risk factor for FGR n=5 (3.2%) vs n=14 (8.5%) p=0.045 or a current obstetric risk factor for FGR n=13 (8.3%) vs n= 33 (20%), p=0.03, especially PET n=1 (0.6%) vs n=12 (7.3%), p= 0.03 see **Table 4.1** . As expected more women had an EFW ≤10th customised centile in the high-risk group. In line with previous reproducibility studies the mean (95% CI) was between 0 (1.6) and 5.9 (21.2) mm and between 0.04 (0.73) and 0.06 (0.95) for the fetal biometry and the CPR values respectively.

Table 4.2: Sonographic and biochemical parameters used in the late FGR clinic risk stratification

Risk classification/characteristics	n (%)
Low-risk FGR fetuses	156 (49)
EFW centile 3rd – 10th and Normal PAPP-A and normal UtA-PI	140 (90)
EFW centile >10th and AC drop	15 (10)
EFW centile >10th and CPR <5th	1 (<1)
High-risk FGR fetuses	165 (51)
EFW centile <3rd	90 (55)
EFW centile 3rd - 10th and PAPP-A <0.4 MoM or increased 2nd or 3rd trimester UtA-PI	69 (42)
EFW centile 3rd - 10th and AC drop or CPR <5th	4 (2)
EFW centile 3rd - 10th and UmbA -PI >95th	2 (1)

Data is documented as n (%). EFW; estimated fetal weight, AC; abdominal circumference, CPR; cerebroplacental ratio, PAPP-A; pregnancy associated plasma protein-A, UtA-PI; uterine artery pulsatility index (abnormal if sum PI >2.5 in the second trimester or mean PI >95th centile in the third trimester), UmbA; umbilical artery.

4.3.3 Late FGR clinic sonographic and biochemical parameters

Majority of the low-risk late FGR clinic; 140 fetus (90%) were categorised as SGA (EFW 3rd to 10th centile) with normal PAPP-A and UtA Doppler; 15 fetus (10%) had an EFW >10th centile with a significant AC drop ≥ 50% and only 1 fetus (1%) had an EFW >10th centile and an abnormal CPR. In contrast in the high-risk late FGR clinic 90 fetus (55%) had severe SGA (EFW >3rd centile); a smaller proportion; 69 fetus (42%) were SGA with low PAPP-A or abnormal UtA Doppler and only 4 fetus (2%) were SGA (EFW 3rd to 10th centile) with a significant AC drop or CPR <5th and only 2 fetus (1%) were SGA (EFW 3rd to 10th centile) with abnormal UmbA Doppler (**see Table 4.2**)

Table 4.3: Onset of Labour onset and MOD in low and high-risk late FGR

Outcome	Low-risk N= 156 n (%)	High-risk N=165 n (%)	OR (95% CI)	p-value	aOR (95%CI)	p-value
Spontaneous onset of labour	75 (48.1)	43 (26.1)	2.6 (1.6-4.2)	<0.001	2.4 (1.5-3.9)	<0.001
Induction of labour	61 (39.1)	84 (50.9)	0.6 (0.4-1.0)	0.034	0.6 (0.4-1.0)	0.065
Spontaneous onset of labour and unassisted vaginal delivery	49 (31.4)	32 (19.4)	1.9 (1.1-3.2)	0.013	1.7 (1.0-3.0)	0.033
Unassisted vaginal delivery	80 (51.3)	72 (43.6)	1.4 (0.9-2.1)	0.170	1.3 (0.8-2.0)	0.235
Instrumental assisted vaginal delivery	27 (17.3)	22 (13.3)	1.4 (0.7-2.5)	0.322	1.4 (0.7-2.5)	0.341
Emergency caesarean section CAT 1 -3	34 (21.8)	50 (30.3)	0.72 (0.5-1.1)	0.083	0.6 (0.4-1.0)	0.059
Elective caesarean section CAT 4	15 (9.6)	21 (12.7)	0.7 (0.4-1.5)	0.377	0.8 (0.4-1.7)	0.575

Data is documented as n (%). OR; odds ratio, 95% CI; 95% confidence interval, aOR; adjusted odds ratio. The Pearson's Chi-squared test assessed for significance. Multiple logistic regression adjusted for gynaecology and current obstetric history.

4.3.4 Onset of labour and mode of delivery

Low- compared with high-risk women were more likely to achieve a spontaneous labour 48 vs 26%, aOR: 2.4 (95% confidence interval (CI): 1.5-3.9), p<0.001. The low-risk women were also more likely to have a spontaneous labour followed by an unassisted vaginal delivery compared to the high-risk group 31 vs 19% aOR: 1.7 (95% CI: 1.0-3.0), p =0.033. There were no other significant differences in mode of delivery between the low and high-risk late FGR groups see **Table 4.3**.

Table 4.4: Mode of delivery and abnormal FHR in low and high-risk late FGR

Outcome	Low-risk N = 156 n (%)	High-risk N = 165 n (%)	OR (95% CI)	p-value	aOR (95% CI)	p-value
vaginal delivery + episiotomy due to abnormal FHR monitoring	3 (1.9)	6 (3.6)	0.4 (0.1-1.8)	0.309**	0.4 (0.1-1.7)	0.212
Instrumental delivery for abnormal FHR monitoring	9 (5.8)	12 (7.3)	0.8 (0.3-1.9)	0.589	0.8 (0.3-1.9)	0.566
Emergency caesarean section for abnormal FHR monitoring	19 (12.2)	28 (17.0)	1.0 (0.4-2.4)	0.991	0.6 (0.3-1.2)	0.173
Adverse maternal outcome	28 (17.9)	40 (24.2)	0.7 (0.4-1.2)	0.142	0.7 (0.4-1.2)	0.142

Data is documented as n (%). OR; odds ratio, 95% CI; 95% confidence interval, aOR; adjusted odds ratio. FHR; fetal heart rate. Either the Pearson's Chi-squared test or the Fishers exact test (**) was used to assess for significance. Multiple logistic regression adjusted for gynaecology and current obstetric history.

4.3.5 Adverse maternal outcome

There was no significant difference in adverse maternal outcome: 18 vs 24%, aOR: 0.7 (95% CI:0.4-1.2), p=0.142, there were similar numbers in both the low and high-risk FGR group requiring an instrumental assisted vaginal delivery or emergency CS for abnormal fetal heart rate monitoring (**see Table 4.4**).

1.1.5 **Table 4.5:** Birth outcomes in low and high-risk late FGR

Outcome	Low-risk N = 156	High-risk N =165	p-value
BW (g)	2840 (2663-3054)	2558 (2266-2735)	<0.001
GA at delivery (weeks + days)	39+5 (38+5-40+2)	38+2 (37+5-39+0)	<0.001
BW ≤ 10th population centile	100 (64.1)	128 (77.6)	<0.001
BW <3rd population centile	13 (8.3)	59 (35.8)	<0.001
BW customised centile	9.1 (5-16)	4.6 (1-10)	<0.001
BW ≤ 10th customised centile	87 (55.8)	129 (78.2)	<0.010
BW <3rd customised centile	19 (12.2)	71(43.0)	<0.001
Length of stay in NNU (days)	3 (1-7)	3 (2-8)	0.929
5-min Apgar Score <7	1 (0.6)	1 (0.6)	1.000
Arterial pH	7.26 (7.21-7.30)	7.27 (7.22-7.32)	0.523
UmbA pH < 7.1	1 (0.6)	1 (0.6)	1.000

Values reported as mean (SD) in normally distributed data and median (interquartile range 25th-75th percentile) in non-normally distributed data or absolute values (%). BW; birth weight, GA; gestational age, NNU; neonatal unit.

1.1.6 **Figure 4.2:** Gestational age at delivery in low versus high-risk FGR

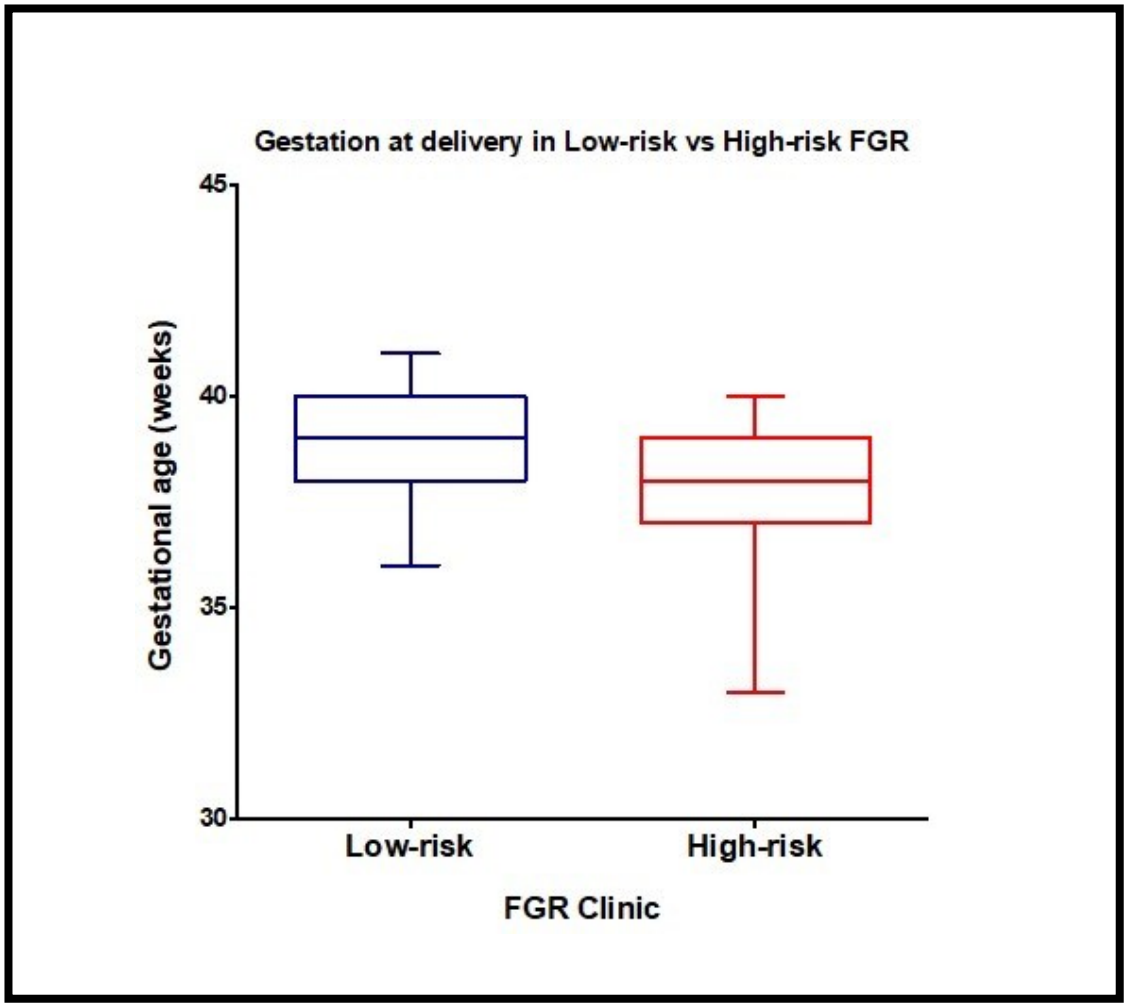
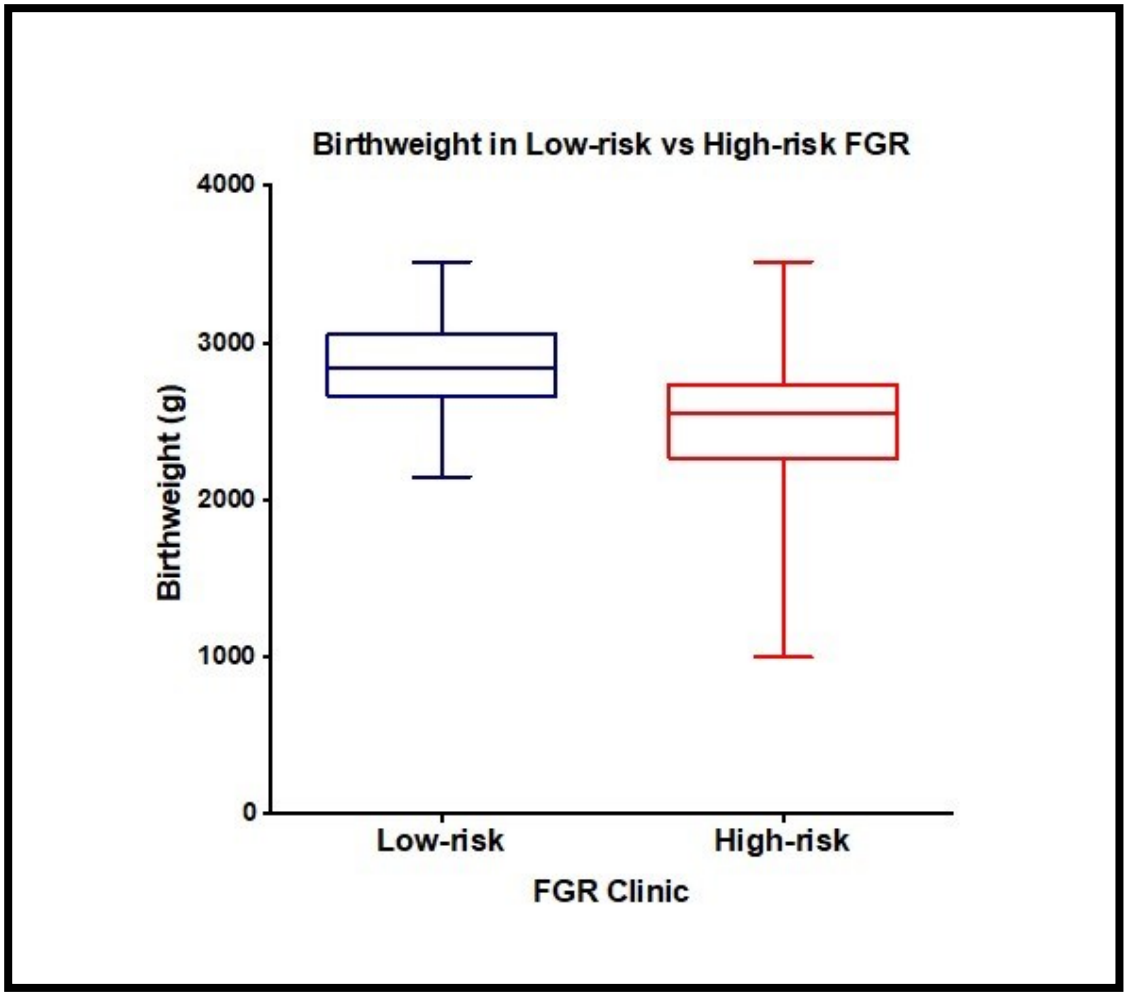


Figure 4.3: Birth weight at delivery in low versus high-risk FGR



4.3.6 Birth outcomes

Low-risk neonates weighed 300 grams heavier than the high-risk FGR group (median 2840 vs 2558 grams, p<0.001) and delivered 10 days later (39w+5d vs 38w+2d; p<0.001). There was no significant difference in condition at birth (Apgar score or pH), with only 1 infant in each group delivered by emergency caesarean section with an UmbA pH <7.1. There were no IUFD or NND in either group. BW <3rd centile was 8 and 36% in the low and high-risk groups respectively (**Table 4.5 and Figures 4.2 and 4.3)**.

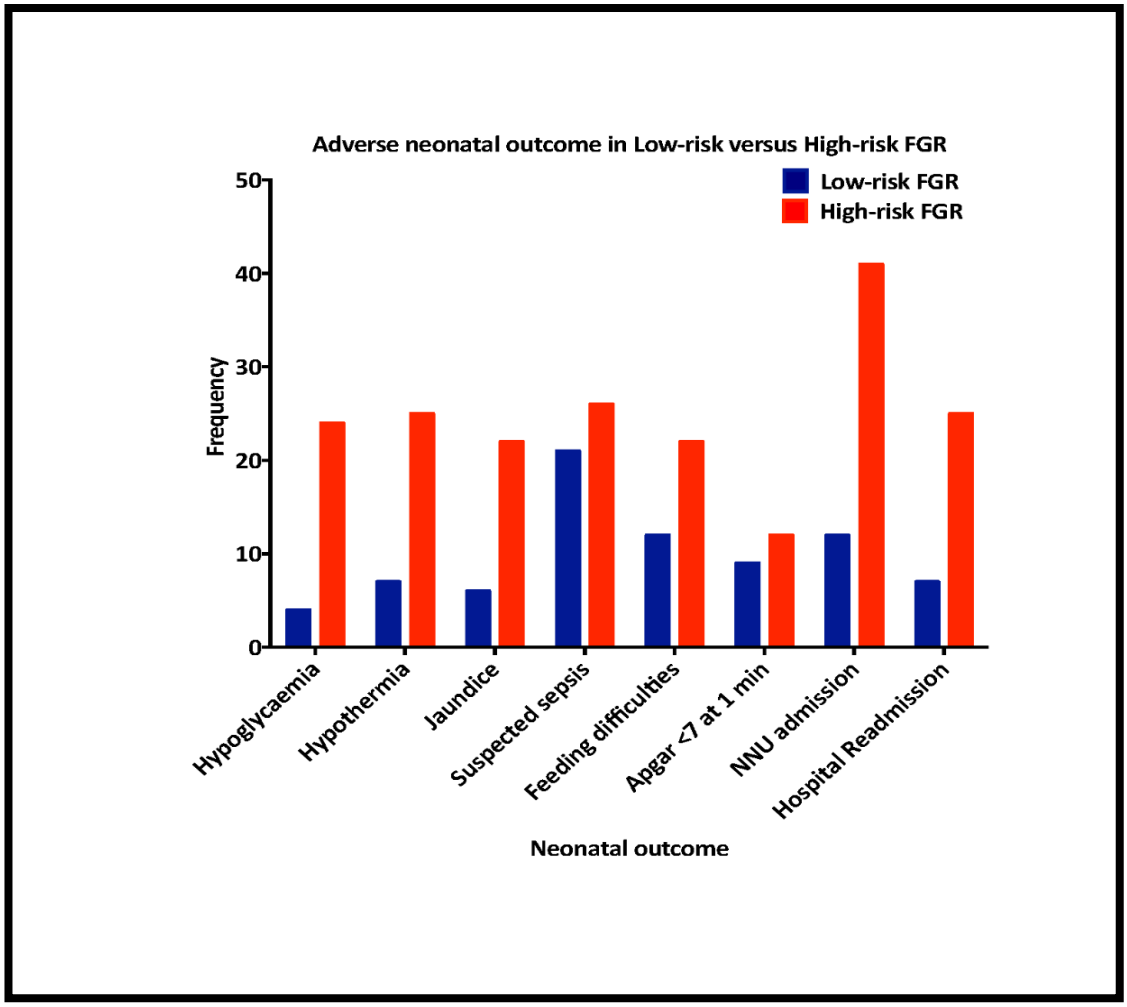
Fourteen women delivered < 36 weeks (14%), this was mainly iatrogenic delivery due to PET or spontaneous preterm labour (1 in the low and 13 in the high-risk FGR groups). In the low-risk group women delivered <40 weeks in 15% of cases due to maternal preference, SOL or due to elective CS at 39 weeks. In the high-risk group 34% of women delivered >38 weeks due to either declining intervention, meeting high-risk criteria after 37 weeks or due to elective CS already booked at 39 weeks.

Table 4.6a: NNO in low and high-risk late FGR

Outcome	Low-risk N = 156 n (%)	High-risk N = 165 n (%)	OR (95%CI)	p-value	aOR (95% CI)	p-value
GA ³ 39 weeks	110 (70.5)	42 (25.5)	7.0 (4.3-11.4)	<0.001	6.7 (4.1-11.1)	<0.001
GA ³ 40 weeks	68 (43.6)	6 (3.6)	20.5 (8.5-49.1)	<0.001	19.9 (8.3-48.2)	<0.001
GA ³ 41 weeks	12 (7.7)	0 (0.0)	1.1 (1.0-1.1)	<0.001		
Hypothermia	7 (4.5)	25 (15.2)	0.3 (0.1-0.6)	0.001	0.3 (0.1-0.7)	0.005
Hypoglycaemia	4 (2.6)	24 (14.5)	0.1 (0.0-0.5)	<0.001	0.2 (0.1-0.5)	0.002
Jaundice needing treatment	6 (3.8)	22 (13.3)	0.3 (0.1-0.7)	0.003	0.3 (0.1-0.7)	0.008
NNU admission	12 (7.7)	41 (24.8)	0.2 (0.1-0.5)	<0.001	0.3 (0.1-0.5)	<0.001
NNU ≥ 3 days and < 5 days	5 (3.2)	14 (8.5)	0.3 (0.1-1.0)	0.033	0.3 (0.1-0.9)	0.040
NNU ≥ 5 days	5 (3.2)	19 (11.5)	0.2 (0.1-0.7)	0.004	0.2 (0.1-0.7)	0.008
Assisted ventilation	2 (1.3)	5 (3.0)	0.4 (0.1-2.2)	0.449**	0.4 (0.1-2.3)	0.330
Sepsis	3 (1.9)	5 (3.0)	0.6 (0.1-2.7)	0.724	0.7 (0.2-3.2)	0.678
Severe cerebral morbidity	1 (0.6)	2 (1.2)	0.5 (0.0-5.9)	1.000**	0.5 (0.0-5.6)	0.567
Severe respiratory morbidity	6 (3.8)	10 (6.1)	0.4 (0.1-1.3)	0.128	0.5 (0.0-5.6)	0.567
Severe circulatory morbidity	1 (0.6)	2 (1.2)	0.5 (0.0-5.8)	1.000	0.4 (0.1-1.4)	0.175

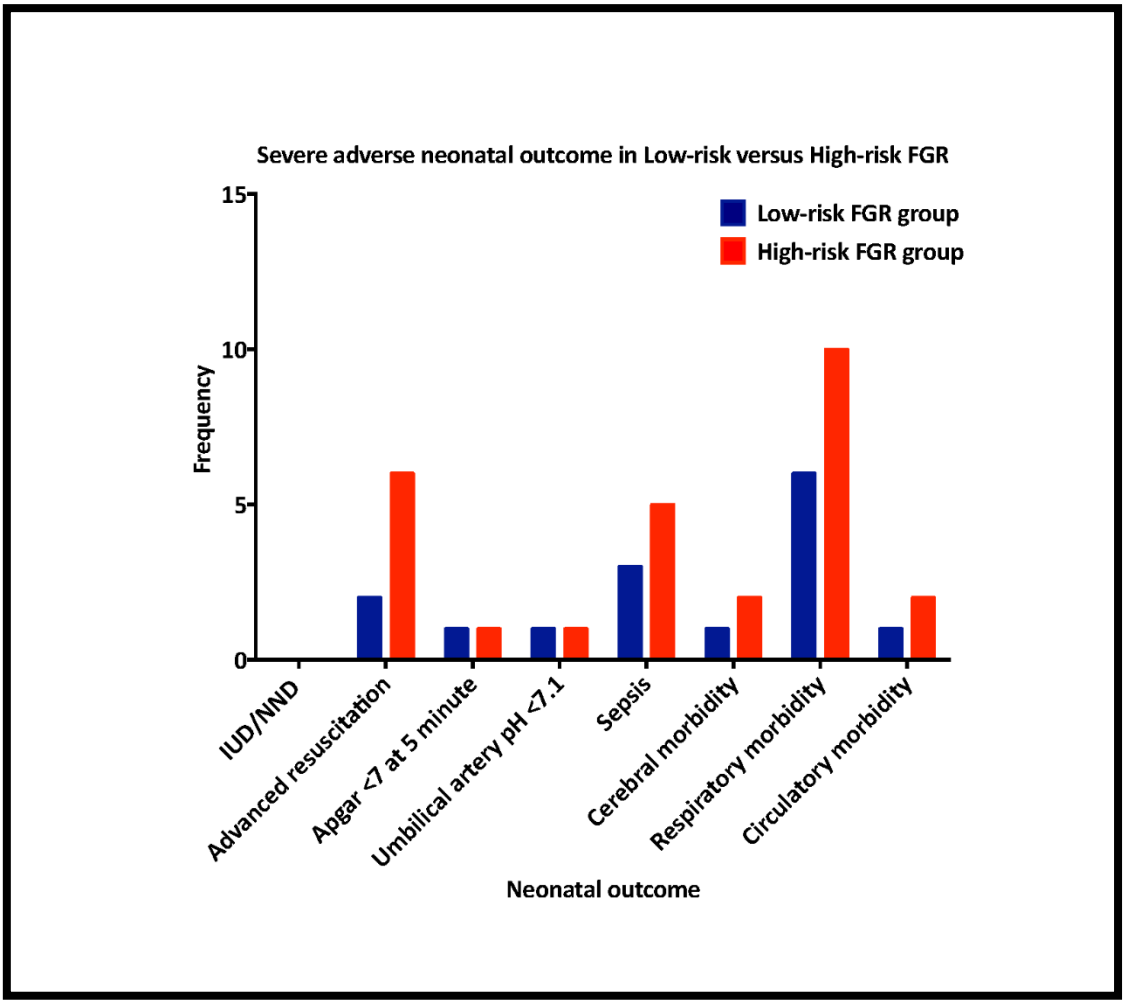
Data is recorded as n (%). OR; odds ratio, aOR; adjusted odds ratio for gynaecological and current obstetric history, NNU; neonatal unit, GA; gestational age, NNO; neonatal outcome. Either the Pearson's Chi-squared test or the Fishers exact test (**) was used.

Figure 4.4: Mild adverse NNO in low versus high-risk late FGR clinic



Frequency reported in %; NNU, neonatal unit

Figure 4.5: Severe adverse NNO in low versus high-risk late FGR



Frequency reported in %; IUD, intrauterine death; NND, neonatal death

Table 4.6b: NNO severity in low and high-risk late FGR

Outcome	Low-risk N=156	High-risk N=165	OR (95% CI)	p-value	aOR (95% CI)	p-value
Severe Adverse NNO	6 (3.8)	14 (8.5)	0.4 (0.2-1.2)	0.094	0.5 (0.2-1.3)	0.153
Overall Adverse NNO	70 (44.9)	95 (57.6)	0.6 (0.4-0.9)	0.023	0.6 (0.4-0.9)	0.022

Data was presented as n (%). OR, Odds ratio; 95% CI: 95% confidence interval; aOR: adjusted odds ratio. To test for significance the Pearson's Chi-squared test was used. Multiple logistic regression adjusted for gynaecology factors and obstetric morbidity associated with FGR.

4.3.7 Severe adverse NNO

There was a downward trend in severe adverse NNO in the low-risk compared to the high-risk late FGR clinic there was however no significant difference in severe adverse NNO between these two cohorts see **Table 4.6a and Figure 4.5**.

4.3.8 Overall adverse NNO

In the low vs the high-risk late FGR clinic cohorts there was a significant differences in the overall adverse NNO 44.9 vs 57.6%) aOR 0.6 (95% CI 0.4-0.9), p=0.022. There was however no significant differences in severe adverse NNO in the low vs the high-risk group: 3.8 vs 8.5%, aOR: 0.5 (95% CI 0.2-1.3), p=0.153 respectively see **Table 4.6b**).

4.4 Discussion

4.4.1 Main findings

My study used a multiparametric model to risk stratify late FGR pregnancies into low and high-risk late FGR groups for placental insufficiency (see **3.2.8 risk stratification used in the late FGR clinic)** and allowed identification of a high-risk group at increased risk of adverse NNO. The sonographic parameters used to diagnose late FGR in the late FGR clinic similar to other studies showed strong association between these parameter thresholds and adverse NNO believed to be due to placental insufficiency and late FGR[43,47,150,151.] This indicates that the antenatal USS and postnatal neonatal outcome measures appropriately identified FGR neonates using parameters not just based on size alone. Risk stratification of late FGR pregnancies according to placental impairment allowed conservative management in low-risk women up to 41 weeks with reduction in early iatrogenic delivery and intervention and improvement in labour and NNO.

4.4.2 Comparison with other studies

Multiparametric models to manage late FGR

My findings support results of other non-randomised studies. Retrospective studies by Veglia et al. in 2018 and Meler et al. 2020 used a similar USS management protocol reporting on management of late SGA babies from 37 and 32 weeks respectively[211,212]. In comparison my study is prospective, includes fetus with EFW >10th centile and involves additional adverse neonatal outcome measures. Compared to Meler et al. 2020 study severe adverse NNO was comparable in the Low- (2.8% vs 3.8% in my study) and high-risk groups (6.5% vs 8.5% in my study)[212]. In my study there were less low-risk babies with BW <3rd centile, this may be due to my study including fetus with EFW >10th centile with AC drop or CPR<5th centile (15 and 1 respectively).It may be difficult however to make conclusive inferences about the high-risk group being lighter than the low-risk group as according to the late FGR Management protocol the high-risk late FGR group were delivered significantly earlier than the low-risk late FGR group.

The importance of late FGR characterisation

The TRUFFLE group reported the outcome of > 800 babies with late preterm FGR managed in tertiary centres. The aim of this feasibility study was to identity the best predictors of outcome to be tested in a randomised trial investigating the optimal timing of delivery of babies with late preterm FGR between 32 and 37 weeks. Their population is comparable to my late FGR population, however NNO is affected by the treatment effect of local policies, high-risk cases referred to tertiary centres (this is evidenced by very different contribution of cases from each centre), and the fact that there was no homogeneous protocol among centres. Severe adverse NNO (11%) was higher than in my study (3.8-8.5%). This could be due to a lack of characterisation of FGR and unnecessary iatrogenic prematurity as only 53% of babies delivered >37 weeks[250]. In addition, in comparison to the DIGITAT study which also lacked characterisation of late FGR I achieved a difference in GA and BW between early and later delivered babies of 10 days on and 282 grams. In the DIGITAT trial the difference in the two groups was also 10 days with smaller weight (150 grams)[209].

Optimal timing of delivery

It is possible that delayed delivery in the high-risk group could lead to a better outcome by reducing the impact of prematurity. Alternatively, a delivery prior to the due date of the low-risk group could lead to a better outcome by shortening the effect of chronic placental insufficiency. The ACOG FGR management is potentially more superior than other international guides on surveillance and timing of delivery uses risk stratification with delivery at 38-39 weeks in isolated FGR and earlier delivery with risk factors for an adverse NNO[9.] Identification of the optimal timing of delivery in late preterm FGR will require a randomised clinical trial which is currently on-going[251]. The population undergoing immediate delivery or expectant management includes fetuses with FGR (EFW<10th local population centile OR with a AC/EFW drop of >50 local population centiles, together with severe cerebral redistribution (umbilicocerebral ratio> 1.0 or 0.8 at >32 or 34 weeks respectively). It is however unlikely, that the results of the Truffle 2 RCT will answer the question on when to deliver babies after 37 weeks. From my cohort I showed that out of all late FGR babies, despite meeting the same criteria for diagnosis on biometry, only a minority of my high-risk fetuses will have severe cerebral redistribution and meet the recruitment criteria in Truffle 2[251].

4.4.3 Clinical implications

Using a novel combination of USS, maternal risk factors for FGR and PAPP-A; I was able to antenatally detect and manage FGR pregnancies at high- and low-risk of placental insufficiency. Evidence of increased adverse NNO measures in the high-risk FGR group means these NNO's could be used to diagnose growth restricted neonates independent of final neonatal size. In addition, identification of a low-risk FGR group allowed expectant management safely in this group up to 41 weeks with associated improvement in labour and adverse NNO measures.

4.4.4 Strengths and weaknesses

The main strength of my study was the cohort of late FGR pregnancies accurately dated, with no chromosomal, genetic or structural issues and labour outcomes. This provided sufficient data for analysis and to draw conclusions regarding maternal and NNO. There are limitations to my study, I included fetus with EFW >10^{th} centile and an abnormal CPR, at low risk of placental insufficiency, however, these accounted only for a few cases. Clinicians were not blinded to the USS results and there was not full adherence to the protocol; some women delivered >38 weeks in the high-risk group and <39 weeks in the low-risk group, this occurred in the minority of cases and reflects a real life scenario. High-risk women booked for elective caesarean section did not have elective CS moved to 38 weeks according to patient or clinician preference due to increased risk of transient tachypnoea of the newborn.

Despite my study being a non-randomised study there is a ‘treatment effect’ bias. Clinicians were not blinded to the results of the scan and the indications for delivery influenced the labour management. This however can also be seen as a strength as conducting a blind trial would not be ethical and indeed impossible to conduct and accept from pregnant mothers and clinicians’ perspective. My study reflects a pragmatic real clinical scenario where additional information of scan results can positively influence clinical outcome. The study was not powered to assess differences in severe adverse NNO, for this the TRUFFLE 2 trial is on-going, however this study does not involve risk stratification and as there are no delivery indications for babies >37 weeks it is unlikely to answer the question[251].

4.4.5 Conclusions

Using evidence-based third trimester USS parameters allowed risk stratification of FGR groups into low and high-risk FGR groups for placental insufficiency and overall identified a high-risk FGR group with increase in adverse NNO measures. This showed that antenatal parameter and risk stratification were appropriate in identifying a neonatal late FGR phenotype independent of final size. Risk stratification allowed separate management pathways for surveillance and delivery; allowing the low-risk FGR group delayed delivery up to 41 weeks with short term and potential long-term advantages whilst the high-risk FGR group was still advised delivered in a timely manner between 37 and 38 weeks.

Neonates expectantly managed in the low-risk FGR group due to a reduction in early iatrogenic delivery and intervention were also delivered at a significantly later gestation and were heaver at birth, with less adverse NNO vs the high-risk group. An older gestational age (GA) and BW may also be associated with improvement in long-term organ and neurodevelopment. My study demonstrated that late FGR babies can be classified as high- or low-risk of placental insufficiency and women classified as low-risk could potentially be managed conservatively with delayed delivery > 40 weeks. A randomised trial is needed to verify this hypothesis and to investigate different timings of delivery in each group.

Chapter 5: Evaluation of the late FGR clinic protocol

5.1 Introduction

5.1.1 Background

In Chapter 4 I described introducing new late FGR screening into UCLH USU department, to diagnose suspected late FGR pregnancies streamlined into the late FGR clinic, with surveillance and timing of delivery according to a low or high-risk late FGR management pathway. Risk stratification was based on fetal size, maternal biochemistry, maternal comorbidity risk factors for late FGR combined with 3rd trimester sonographic parameters including (uterine artery, CPR and UA Doppler). Overall there was significantly less adverse NNO in the low-risk late FGR group allowed expectant management up to 41 weeks compared with the high-risk late FGR group advised delivery at 37-38 weeks.

In chapter 5 I shall describe how I made comparisons in order to implement and evaluate the late FGR clinic between the maternal demographics, labour, maternal and neonatal outcomes in my late FGR clinic compared with a pre-clinic cohort of late FGR babies which were diagnosed and managed according to pre-clinic management strategies (**see 5.1.2. Aims, objectives and hypotheses**). I identified this pre-clinic cohort using a Viewpoint search and collected electronic labour, maternal and NNO compared within the pre-clinic cohort. I suspected if risk stratification accurate and correct there would be less adverse NNO in the low-risk late FGR clinic cohort compared to the pre-clinic cohort.

5.1.2 Aims, objectives and hypotheses:

The second main aim of the MD (Res) was:

- To implement and evaluate the impact of a new management protocols for late FGR

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5.2 Methods

5.2.1 Pre-clinic study type

I also investigated and made comparisons between the late FGR clinic and a historical cohort of 323 women with sonographic evidence of late FGR (according to pre-clinic definitions: EFW<10th centile, EFW or AC GV drop or increased umbilical artery resistance) and recruited prior to implementation of the new clinical management policy (01.05.2017 to 31.01.2018). Women in the "old" cohort were managed according to local guideline on management of SGA fetus at UCLH and were recruited retrospectively and consecutively to provide a comparison group similar in number to the "new" late FGR Clinic cohort. Some of the criteria for delivery was similar however not reported in a comprehensive structured protocol as I implemented.

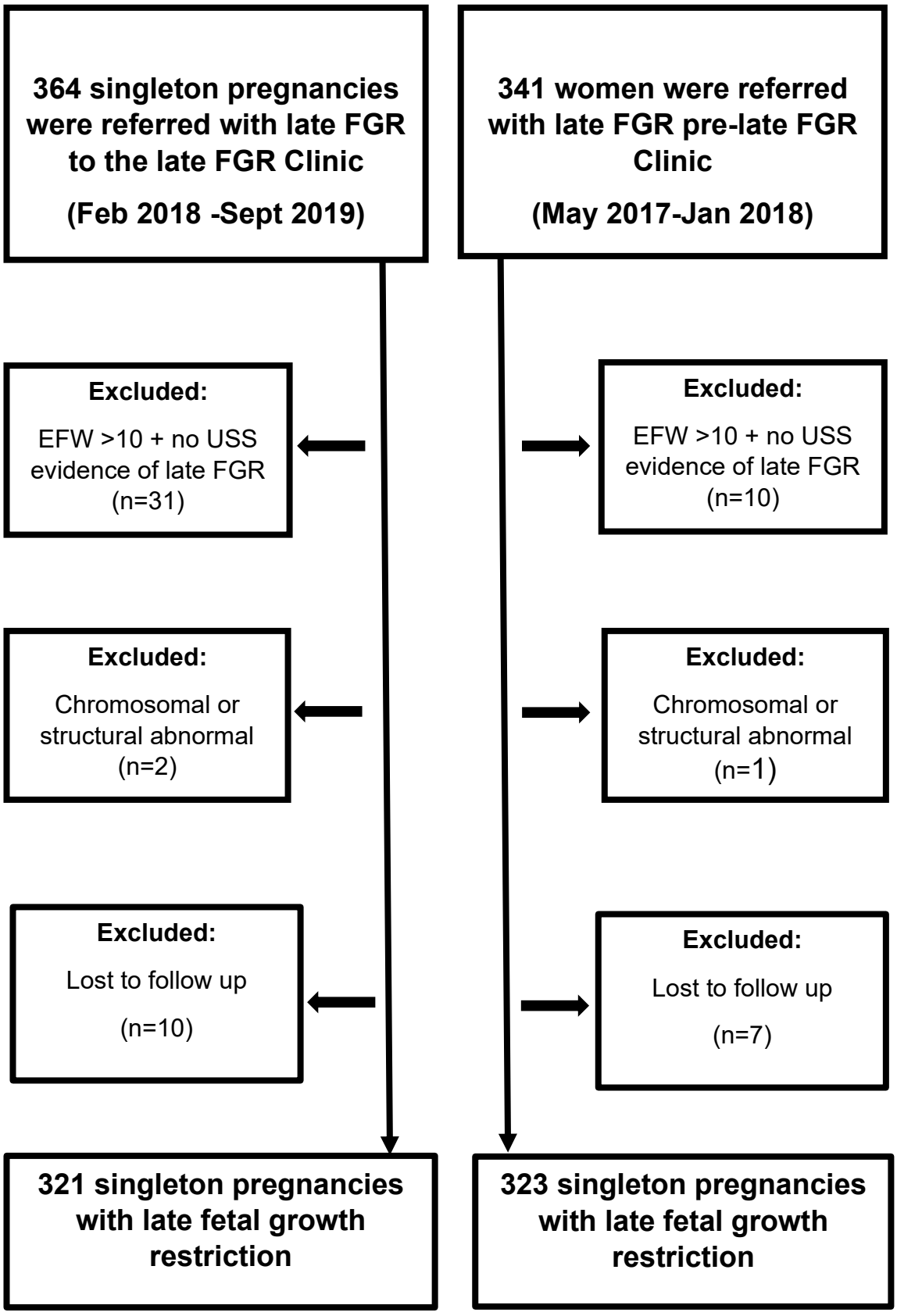
5.2.2 Pre-clinic study referral criteria

In the pre-clinic cohort, women were included if they met the same referral criteria as discussed in **4.2.2 Late FGR clinic study referral criteria.**

5.2.3 Pre-clinic patient study selection

Inclusion and exclusion criteria for the pre-clinic cohort were the same as the late FGR clinic and described in **4.2.3 late FGR clinic patient study selection.**

Figure 5.1: Late FGR and pre-clinic patient selection flow chart



5.2.4 Clinical review in the pre-clinic cohort

In the pre- clinic cohort women with suspected late FGR had USS performed by sonographers or doctors in the main USU department, MFAU or the FMU with further management plans according to local guideline on management of SGA fetus at UCLH.

5.2.5 Management of late FGR in the pre-clinic cohort

The management plans in the pre-clinic cohort varied in USS surveillance from every 1- 4 weeks with delivery advised in most cases at term (37-38) weeks or as soon as possible in FGR cases diagnosed > 37 weeks. Women in the old cohort were classified retrospectively as low- or high-risk according to risk stratification see **3.2.8 risk stratification used in the late FGR clinic**. Management was according to local as well as International RCOG and NICE guidelines but without a defined protocol.

5.2.6 Timing and mode of delivery in the pre-clinic cohort

In the pre-clinic cohort timing and mode of delivery was determined by the doctor reviewing the couple, the local UCLH guideline on management of SGA fetus, the couples wishes and in line with any contraindications for vaginal delivery. In the pre- clinic cohort IOL involved prostaglandin E2 vaginal gel (1-2mg); oxytocin augmentation and operative delivery indications the same as the late FGR Clinic.

5.2.7 Gynaecological, medical and obstetric risk factors for FGR

As in the late FGR Clinic, the electronic database Viewpoint 6 was reviewed for gynaecological, obstetric and medical risk factors associated with FGR; as described in **4.2.7 Gynaecological, medical and obstetric FGR risk factors.**

5.2.8 Adverse birth, labour, neonatal and maternal outcomes

As in the late FGR clinic labour, maternal and NNO were collected for each women managed in the pre-clinic cohort as described in **4.2.8 Birth, labour, maternal and neonatal outcomes.**

5.2.9 Statistical analysis

Outcome data from the pre-clinic cohort was analysed the same as the late FGR clinic outcomes; a detailed description is provided in **4.2.9 Statistical analysis**. Secondary analysis was performed to comparing outcomes of the late FGR Clinic with the pre-clinic cohort using the same biochemical, USS parameters and maternal risk factors used to risk stratify the pre-clinic cohort into low and high-risk groups to allow direct comparison with the pre-clinic cohort late FGR groups.

5.3 Results

5.3.1 Number of women in the study

At UCLH 364 women were managed in the late FGR clinic (02.2018 to 09.2019) and 341 women (05.2017 to 01.2018) managed according to pre-clinic strategies. In both cohorts after excluding fetus with a structural, genetic or chromosomal abnormality (N=3), fetus with no sonographic evidence of FGR (N=41) and those with no follow up data (N=17), there were then 644 pregnancies in the final data analysis. This included 321 pregnancies in the late FGR clinic and 323 pregnancies in the pre-clinic cohort (see **Figure 5.1**).

Table 5.1a Maternal features in the late FGR clinic and pre-clinic cohort

Maternal features	**Late FGR clinic N = 321**	**Pre-clinic N = 323**	**p-value**
Age (years)	33 (29-36)	33 (30-36)	0.831*
BMI (kg/m2)	23.2 (20.6-26.1)	22.4 (20.3-25.1)	0.043*
Nulliparous	151 (47.0)	186 (57.6)	0.006
Current smoker	21 (6.5)	21 (6.5)	0.983
Recreational drug user	7 (2.2)	4 (1.2)	0.356
Medical comorbidity	22 (6.9)	15 (4.6)	0.228
Past obstetric history	71 (22.1)	42 (13.0)	0.002
Gynaecological history	19 (5.9)	21 (4.6)	0.469
Current obstetric history	46 (14.3)	43 (13.3)	0.708
EFW < 10th population chart	176 (54.8)	215 (66.6)	0.002
EFW < 10thcustomised chart	182 (56.7)	249 (77.1)	<0.001
CPR < 5th centile	17 (5.3)	22 (6.8)	0.978
AC Drop ≥ 50 centiles	29 (9.0)	15 (4.6)	0.027

Data is recorded as median (interquartile range 25th to 75th percentile) or absolute values n (%). BMI; body mass index, EFW; estimated fetal weight, CPR; cerebroplacental ratio, AC; abdominal circumference. To test for significance either the Pearson's Chi-squared test was used, or the Mann- Whitney U test (*) or the Fishers exact test (**).

Table 5.1b Maternal features in the low-risk late FGR clinic and pre-clinic cohort

Maternal features	**Low-risk late FGR clinic N = 156**	**Pre-clinic N = 323**	**p-value**
Age (years)	33 (29-36)	33 (30-36)	0.633*
BMI (kg/m2)	22.9 (20.4-25.6)	22.4 (20.3-25.1)	0.407*
Nulliparous	71 (45.5)	186 (57.6)	0.012
Current smoker	8 (5.1)	21 (6.5)	0.555
Recreational drug user	1 (0.6)	4 (1.2)	1.000**
Medical comorbidity	10 (6.4)	15 (4.6)	0.415
Past obstetric history	34 (21.8)	42 (13.0)	0.014
Gynaecological history	5 (3.2)	15 (4.6)	0.461
Current obstetric history	13 (8.3)	43 (13.3)	0.112
EFW < 10th population chart	86 (55.1)	215 (66.6)	0.019
EFW < 10thcustomised chart	73 (46.8)	249 (77.1)	<0.010
CPR < 5th centile	6 (3.8)	22 (6.8)	0.200
AC Drop ≥ 50 centiles	16 (10.3)	15 (4.6)	0.018

Data is recorded as median (interquartile range 25th to 75th percentile) or absolute values n (%). BMI; body mass index, EFW; estimated fetal weight, CPR; cerebroplacental ratio, AC; abdominal circumference. To test for significance either the Pearson's Chi-squared test was used, or the Mann- Whitney U test (*) or the Fishers exact test (**).

Table 5.1c: Maternal features in the high-risk Late FGR clinic + pre-clinic cohort

Maternal features	**High-risk late FGR clinic N = 156**	**Pre-clinic N = 323**	**p-value**
Age (years)	33 (30-36)	33 (30-36)	0.906*
BMI (kg/m2)	23.6 (20.8-27.5)	22.4 (20.3-25.1)	0.014*
Nulliparous	80 (48.5)	186 (57.6)	0.052
Current smoker	13 (7.9)	21 (6.5)	0.572
Recreational drug user	6 (3.6)	4 (1.2)	0.077
Medical comorbidity	12 (7.3)	15 (4.6)	0.230
Past obstetric history	37 (22.4)	42 (13.0)	0.008
Gynaecological history	14 (8.5)	15 (4.6)	0.009
Current obstetric history	33 (20.0)	43 (13.3)	0.054
EFW < 10th population chart	90 (54.5)	215 (66.6)	0.009
EFW < 10thcustomised chart	109 (66.1)	249 (77.1)	0.009
CPR < 5th centile	11 (6.7)	22 (6.8)	0.966
AC Drop ≥ 50 centiles	13 (7.9)	15 (4.6)	0.146

Data is recorded as median (interquartile range 25th to 75th percentile) or absolute values n (%). BMI; body mass index, EFW; estimated fetal weight, CPR; cerebroplacental ratio, AC; abdominal circumference. To test for significance either the Pearson's Chi-squared test was used, or the Mann- Whitney U test (*) or the Fishers exact test (**).

5.3.2 Maternal baseline features

Women in the late FGR clinic had a significantly heavier BMI, were less likely to be nulliparous and had more past obstetric risk factors for FGR vs the pre- clinic cohort. The low-risk late FGR clinic group had significantly less nulliparous women and significantly more past obstetric risk factors for FGR, whilst the high -risk late FGR clinic group had a significantly heavier BMI and significantly more past obstetric and gynaecological risk factors for FGR. These differences may be due to data being collected prospectively in the late FGR clinic and the use of additional USS parameters used as referral criteria to the late FGR clinic. Outcomes were analysed by correcting for these variables (**Tables 5.1a-c**).

Table 5.2a Onset of labour and MOD in in the late FGR clinic and the pre-clinic cohort.

Outcome	Late FGR clinic N = 321	Pre-clinic N = 323	OR (95% CI)	p-value	aOR (95% CI)	p-value
Spontaneous onset of labour	118 (36.7)	85 (26.3)	1.6 (1.2-2.3)	0.004	1.6 (1.2-2.3)	0.005
Induction of labour	145 (45.1)	172 (53.2)	0.6 (0.4-0.9)	0.006	0.6 (0.4-1.0)	0.012
Spontaneous onset of labour and unassisted vaginal delivery	81 (25.2)	68 (21.1)	1.2 (0.9-1.8)	0.208	1.2 (0.8-1.8)	0.308
Unassisted vaginal delivery	152 (47.4)	143 (44.3)	1.1 (0.8-1.5)	0.433	1.1 (0.8-1.5)	0.663
Instrumental assisted vaginal delivery	49 (15.3)	46 (14.2)	1.1 (0.7-1.7)	0.714	1.3 (0.8-2.0)	0.309
Emergency caesarean section	84 (26.2)	93 (28.8)	0.9 (0.6-1.2)	0.456	0.9 (0.6-1.3)	0.614
Elective caesarean section	36 (11.2)	41 (12.7)	0.9 (0.5-1.4)	0.563	0.8 (0.5-1.3)	0.348

Data is documented as n (%). OR; odds ratio, 95% CI; 95% confidence interval, aOR; adjusted odds ratio. To test for significance, the Pearson's Chi-squared test was used. **Multiple logistic regression was used to adjust for maternal BMI, nulliparity and history of obstetric risk factors for FGR.**

Table 5.2b Onset of labour and MOD in the low-risk late FGR clinic and the pre-clinic cohort

Outcome	Low-risk late FGR clinic N = 156	Pre-clinic N = 323	OR (95% CI)	p-value	aOR (95% CI)	p-value
Spontaneous onset of labour	75 (48.1)	85 (26.3)	2.6 (1.7-3.9)	<0.001	2.6 (1.7-3.8)	<0.001
Induction of labour	61 (39.1)	172 (53.2)	0.6 (0.4-0.9)	0.006	0.6 (0.4-0.9)	0.012
Spontaneous onset of labour and unassisted vaginal delivery	49 (31.4)	68 (21.1)	1.7 (1.1-2.6)	0.013	1.6 (1.0-2.5)	0.034
Unassisted vaginal delivery	80 (51.3)	143 (44.3)	1.3 (0.9-1.9)	0.150	1.2 (0.8-1.8)	0.311
Instrumental assisted vaginal delivery	27 (17.3)	46 (14.2)	1.3 (0.8-2.1)	0.382	1.6 (0.9-2.8)	0.091
Emergency caesarean section	34 (21.8)	93 (28.8)	0.7 (0.4-1.1)	0.104	0.7 (0.5-1.2)	0.179
Elective caesarean section	15 (9.6)	41 (12.7)	0.7 (0.4-1.4)	0.326	0.6 (0.3-1.2)	0.143

Data is documented as n (%). OR; odds ratio, 95% CI; 95% confidence interval, aOR; adjusted odds ratio. To test for significance, the Pearson's Chi-squared test was used. **Multiple logistic regression was used to adjust for nulliparity and past obstetric risk factors for FGR.**

Table 5.2c Onset of labour and MOD in the high-risk late FGR clinic and the pre-clinic cohort

Outcome	High-risk late FGR clinic N = 165	Pre-clinic N = 323	OR (95% CI)	p-value	aOR (95% CI)	p-value
Spontaneous onset of labour	43 (26.0)	85 (26.3)	1.0 (0.6-1.5)	0.952	1.0 (0.7-1.6)	0.358
Induction of labour	84 (50.9)	172 (53.2)	0.9 (0.6-1.3)	0.624	0.9 (0.6-1.3)	0.650
Spontaneous onset of labour and unassisted vaginal delivery	32 (19.4)	68 (21.1)	0.9 (0.6-1.4)	0.668	0.9 (0.6-1.5)	0.754
Unassisted vaginal delivery	72 (43.6)	143 (44.3)	1.0 (0.7-1.4)	0.893	1.0 (0.7-1.5)	0.938
Instrumental assisted vaginal delivery	22 (13.3)	46 (14.2)	0.9 (0.5-1.6)	0.784	1.0 (0.6-1.8)	0.994
Emergency caesarean section	50 (30.3)	93 (28.8)	1.1 (0.7-1.6)	0.729	1.1 (0.7-1.7)	0.706
Elective caesarean section	21 (12.7)	41 (12.7)	1.0 (0.6-1.8)	0.992	0.9 (0.5-1.6)	0.669

Data is documented as n (%). OR; odds ratio, 95% CI; 95% confidence interval, aOR; adjusted odds ratio. To test for significance, the Pearson's Chi-squared test was used. **Multiple logistic regression was used to adjust for maternal BMI, history of gynaecological and obstetric risk factors for FGR.**

5.3.3 Onset of labour and mode of delivery

The late FGR clinic cohort due in particular to the low-risk late FGR clinic group were significantly more likely to have a spontaneous onset of labour (SOL) compared to the pre-clinic cohort; 36.7% vs 26.3%, aOR 1.6 (95% CI 1.2-2.3), p=0.005 and 48.1% vs 26.3%, aOR 2.6 (95% CI 1.7-3.8), p <0.001. The late FGR clinic and low-risk late FGR group were also significantly less likely to require IOL compared to the pre-clinic cohort 45.1% vs 53.2%, aOR 0.6 (95% CI 0.4-1.0), P=0.012 and 39.1% vs 53.2%, aOR 0.6 (95% CI 0.4-0.9), P=0.012. There were no significant differences in SOL and IOL between the high-risk late FGR clinic and the pre-clinic cohort (see **Tables 5.2a-c**).

The low-risk late FGR clinic cohort were also significantly more likely to have a SOL followed by an unassisted vaginal delivery compared to the pre-clinic cohort 31.4% vs 21.1%, aOR 1.6 (95% CI 1.0-2.5), P=0.034. Although there was a trend towards more unassisted vaginal deliveries and less emergency CS in the low-risk late FGR clinic compared to the pre-clinic cohort; there was overall no significant difference in MOD between the late FGR clinic or the low and high-risk late FGR clinic cohorts and the pre-clinic cohort (see **Tables 5.2a-c**).

Table 5.3a Mode of delivery and abnormal FHR changes in the late FGR clinic and the pre-clinic cohort

Outcome	Late FGR Clinic N = 321	Pre-clinic N = 323	OR (95% CI)	p-value	aOR (95% CI)	p-value
Vaginal delivery + episiotomy for abnormal FHR monitoring	9 (5.9)	28 (19.5)	0.3 (0.1-0.7)	0.001	0.3 (0.1-0.7)	0.003
Instrumental assisted vaginal delivery for abnormal FHR monitoring	26 (53)	30 (65.2)	0.8 (0.5-1.5)	0.543	0.9 (0.5-1.6)	0.801
Emergency caesarean section for abnormal FHR monitoring	47 (56)	54 (58)	0.9 (0.6-1.3)	0.469	0.9 (0.6-1.4)	0.672
Adverse Maternal Outcome	68 (21.2)	84 (26)	0.8 (0.6-1.1)	0.137	0.8 (0.6-1.2)	0.314

Data is documented as n (%). OR; odds ratio, 95% CI; 95% confidence interval, aOR; adjusted odds ratio, FHR; fetal heart rate. To test for significance, the Pearson's Chi-squared test was used. **Multiple logistic regression was used to adjust for maternal BMI, nulliparity and history of obstetric risk factors for FGR.**

Table 5.3b Mode of delivery and abnormal FHR changes in the low-risk late FGR clinic and the pre-clinic cohort

Outcome	Low-risk late FGR Clinic N = 156	Pre-clinic N = 323	OR (95% CI)	p-value	aOR (95% CI)	p-value
Vaginal delivery + episiotomy for abnormal FHR monitoring	3 (3.8)	28 (19.5)	0.2 (0.1-0.7)	0.005	0.2 (0.1-0.7)	0.014
Instrumental assisted vaginal delivery for abnormal FHR monitoring	9 (5.8)	30 (65.2)	0.6 (0.3-1.3)	0.175	0.7 (0.3-1.4)	0.286
Emergency caesarean section for abnormal FHR monitoring	19 (12.2)	54 (58)	0.7 (0.4-1.2)	0.195	0.8 (0.4-1.3)	0.323
Adverse Maternal Outcome	28 (17.9)	84 (26)	0.7 (0.5-1.0)	0.051	0.7 (0.4-1.1)	0.143

Data is documented as n (%). OR; odds ratio, 95% CI; 95% confidence interval, aOR; adjusted odds ratio, FHR; fetal heart rate. To test for significance, the Pearson's Chi-squared test was used. **Multiple logistic regression was used to adjust for nulliparity and past obstetric risk factors for FGR**

Table 5.3c Mode of delivery and abnormal FHR changes in the high-risk late FGR clinic and the pre-clinic cohort

Outcome	High-risk late FGR Clinic N = 165	Pre-clinic N = 323	OR (95% CI)	p-value	aOR (95% CI)	p-value
Vaginal delivery + episiotomy for abnormal FHR monitoring	6 (8.3)	28 (19.5)	0.4 (0.2-1.0)	0.039	0.4 (0.2-1.1)	0.071
Instrumental assisted vaginal delivery for abnormal FHR monitoring	12 (7.3)	30 (65.2)	0.8 (0.4-1.5)	0.418	0.8 (0.4-1.6)	0.496
Emergency caesarean section for abnormal FHR monitoring	28 (17.0)	54 (58)	1.0 (0.6-1.7)	0.944	1.0 (0.6-1.7)	0.870
Adverse Maternal Outcome	40 (24.2)	84 (26)	0.9 (0.7-1.3)	0.645	0.9 (0.6-1.5)	0.856

Data is documented as n (%). OR; odds ratio, 95% CI; 95% confidence interval, aOR; adjusted odds ratio, FHR; fetal heart rate. To test for significance, the Pearson's Chi-squared test was used. **Multiple logistic regression was used to adjust for maternal BMI, history of gynaecological and past obstetric risk factors for FGR.**

5.3.4 Adverse maternal outcome

In the late FGR clinic and in particular the low-risk late FGR clinic there were significantly less vaginal deliveries with episiotomy preformed due to evidence of abnormal FHR monitoring prior to delivery compared to the pre-clinic cohort; 5.9% vs 19.5% aOR 0.3 (95% CI 0.1-0.7), p=0.003 and 3.8% vs 19.5% aOR 0.2 (95% CI 0.1-0.7), p=0.014. There was also a non-significant downward trend in instrumental assisted vaginal delivery and emergency CS performed for abnormal FHR monitoring as well as overall adverse maternal outcome in the late FGR clinic and the low-risk late FGR clinic cohort vs the pre-clinic cohort.

The reductions in unassisted vaginal deliveries with abnormal FHR monitoring at delivery and the downward trend in instrumental assisted vaginal delivery and emergency CS performed for abnormal FHR monitoring and adverse maternal outcome were particularly apparent in the low-risk FGR clinic cohort vs the pre-clinic cohort. This suggests that the low-risk FGR babies coped better intrapartum compared to the pre-clinic cohort. There were no significant differences in abnormal FHR during unassisted vaginal delivery, instrumental assisted vaginal delivery, emergency CS and adverse maternal outcome in the high-risk late FGR clinic vs the pre-clinic cohort (see **Tables 5.3a-c**).

Table 5.4a Birth outcomes in the late FGR clinic and the pre-clinic cohort

Outcome	Late FGR clinic N = 321	Pre-clinic N = 323	p-value
BW (g)	2690 (2452-2952)	2670 (2380-2954)	0.420*
GA at delivery (weeks)	39+0 (37+6-40+1)	38+6 (38+1-39+6)	0.305*
BW ≤ 10th population centile	228 (71)	211 (65.3)	0.120
BW ≤ 3rd population centile	72 (22.4)	73 (22.6)	0.595
BW customised centile	6.8 (2.6-13.1)	7 (2.2-17.3)	0.556
BW ≤ 10th customised centile	216 (67.3%)	193 (59.8%)	0.047
BW ≤ 3rd customised centile	90 (28.1%)	110 (34.1%)	0.104
Length of stay in NNU (days)	3 (2-7)	4 (2-6)	0.785
5 min Apgar score <7	1 (0.3	3 (0.9)	0.624**
Arterial pH	7. 27 (7.22-7.31)	7.25 (7.20-7.29)	0.029*
Arterial pH <7.1	2 (0.6)	5 (1.5%)	0.450**

Data is recorded as median (25th-75th centile). GA; gestational age, NNU; neonatal unit. To test for significance according to appropriateness, either the Pearson's Chi-squared test was used, or the Mann- Whitney U test (*) or the Fishers exact test (**).

Table 5.4b: Birth outcomes in the low-risk late FGR clinic + the pre clinic cohort

Outcome	Low-risk late FGR Clinic N = 156	Pre-clinic N = 323	p-value
BW (g)	2840 (2662-3053)	2670 (2380-2954)	<0.001*
GA at delivery (weeks)	39+5 (38+5-40+2)	39+0 (37+6-40+1)	<0.001*
BW ≤ 10th population centile	100 (64.1)	211 (65.3)	0.755
BW ≤ 3rd population centile	13 (8.3)	73 (22.6)	<0.001
BW customised centile	9.1 (5-16)	7 (2.2-17.3)	0.014
BW ≤ 10th customised centile	87 (55.8)	193 (59.8%)	0.376
BW ≤ 3rd customised centile	19 (12.2)	110 (34.1%)	<0.001
Length of stay in NNU (days)	3 (1-7)	4 (2-6)	0.683
5 min Apgar score <7	1 (0.6)	3 (0.9)	1.000**
UmbA pH	7.26 (7.21-7.30)	7.25 (7.20-7.29)	0.143
UmbA pH <7.1	1 (0.6)	5 (1.5%)	0.667**

Data is recorded as median (25th-75th centile). GA; gestational age, NNU; neonatal unit. UmbA; umbilical artery. To test for significance either the Pearson's Chi-squared test was used, or the Mann- Whitney U test (*) or the Fishers exact test (**).

Table 5.4c: Birth outcomes in the high-risk late FGR clinic+ the pre-clinic cohort

Outcome	High-risk late FGR Clinic N = 165	Pre-clinic N = 323	p-value
BW (g)	2558 (2266-2735)	2670 (2380- 2954)	<0.001*
GA at delivery (weeks)	38+2 (37+5-39+0)	39+0 (37+6-40+1)	<0.001*
BW ≤ 10th population centile	128 (77.6)	211 (65.3)	0.005
BW ≤ 3rd population centile	59 (35.8)	73 (22.6)	0.002
BW customised centile	4.6 (1-10)	7 (2.2-17.3)	<0.010
BW ≤ 10th customised centile	129 (78.2)	193 (59.8%)	<0.001
BW ≤ 3rd customised centile	71(43.0)	110 (34.1%)	0.052
Length of stay in NNU (days)	3 (2-8)	4 (2-6)	0.905
5 min Apgar score <7	0 (0)	3 (0.9)	0.544**
UmbA pH	7.27 (7.22-7.32)	7.25 (7.20-7.29)	0.039*
UmbA pH <7.1	1 (0.6)	5 (1.5%)	0.668**

Data is recorded as median (25th-75th centile). GA; gestational age, NNU; neonatal unit. UmbA; umbilical artery. To test for significance either the Pearson's Chi-squared test was used, or the Mann- Whitney U test (*) or the Fishers exact test (**).

5.3.5 Birth outcomes

Although there were no significant differences in gestational age and birth weight at delivery between the late FGR clinic and the pre-clinic cohort; in a subgroup analysis comparison the low-risk late FGR clinic cohort delivered significantly later and neonates were significantly heavier at birth compared to the pre-clinic cohort median gestation 39w+5d (IQR 38+5 - 40+2) vs 39w+0d (IQR 37+6 - 40+1) weeks, p <0.001 and median BW 2840gr (IQR 2662 -3053) vs 2670gr (IQR 2380-2954), p<0.001. There was no significant differences in the Apgar or the UmbA pH inferring there was no difference in fetal compromise between the late FGR clinic cohorts and the pre-clinic cohort (see **Table 5.4a-c).**

Table 5.5a NNO in the late FGR clinic and the pre-clinic cohort

Outcome	Late FGR clinic N = 321	Pre-clinic N = 323	OR (95%CI)	p-value	aOR (95% CI)	p-value
GA ³ 39 weeks	151 (46.0)	171 (52.9)	0.8 (0.6-1.1)	0.134	0.9 (0.6-1.1)	0.225
GA ³ 40 weeks	77 (24.0)	91 (28.2)	0.8 (0.6-1.1)	0.226	0.9 (0.6-1.2)	0.413
GA ³ 41 weeks	12 (3.7)	47 (14.6)	0.2 (0.1-0.4)	<0.001	0.2 (0.1-0.5)	<0.001
Hypothermia	32 (10)	31 (9.6)	1.0 (0.6-1.8)	0.874	1.1 (0.6-1.9)	0.744
Hypoglycaemia	28 (8.7)	28 (8.7)	1.0 (0.6-1.7)	0.981	1.0 (0.6-1.8)	0.866
Jaundice needing Tx	28 (8.7)	32 (10.0)	0.9 (0.5-1.5)	0.605	0.9 (0.5-1.5)	0.605
NNU admission	53 (16.5)	52 (16.0)	1.0 (0.7-1.5)	0.929	1.0 (0.7-1.5)	0.990
NNU ≥ 3 days	18 (5.6)	18 (5.6)	1.0 (0.5-1.8)	0.850	1.0 (0.5-2.1)	0.907
NNU ≥ 5 days	24 (7.5)	27 (8.4)	0.9 (0.5-1.6)	0.687	0.9 (0.5-1.6)	0.631
Intubation and ventilation	7 (2.2)	7 (2.2)	1.0 (0.3-2.9)	0.991	1.0 (0.3-2.8)	0.952
Advanced resuscitation	8 (2.5)	12 (3.7)	0.7 (0.3-1.6)	0.364	0.6 (0.2-1.5)	0.294
IUFD/NND	0 (0.0)	1 (0.3)	1.0 (0.9-1.0)	0.318		
Sepsis	8 (2.5)	10 (3.1)	0.8 (0.3-2.1)	0.642	1.0 (0.4-2.7)	0.995
Severe cerebral morbidity	3 (0.9)	2 (0.6)	1.5 (0.3-9.0)	0.686**	1.4 (0.3-9.0)	0.706
Severe respiratory morbidity	14 (4.4)	17 (5.3)	0.8 (0.4-1.7)	0.568	0.8 (0.4-1.6)	0.453
Severe circulatory morbidity	3 (0.9)	3 (0.9)	1.0 (0.2-5.0)	1.000**	0.9 (0.2-4.7)	0.915

Data is recorded as n (%). OR; odds ratio, aOR; adjusted odds ratio, NNU; neonatal unit, IUFD; intrauterine fetal death, NND; neonatal death. To test for significance according to appropriateness, either the Pearson's Chi-squared test was used, or the Fishers exact test (**).**Multiple logistic regression was used to adjust for maternal BMI, nulliparity and past obstetric history.**

Table 5.5b NNO in the low-risk late FGR clinic and the pre-clinic cohort

Outcome	Low-risk late FGR clinic N = 156	Pre-clinic N = 323	OR (95%CI)	p-value	aOR (95% CI)	p-value
GA ³ 39 weeks	109 (69.9)	171 (52.9)	2.1 (1.4-3.1)	<0.001	2.3 (1.5-3.4)	<0.001
GA ³ 40 weeks	71 (45.5)	91 (28.2)	2.1 (1.4-3.2)	<0.001	2.4 (1.6-3.6)	<0.001
GA ³ 41 weeks	12 (7.7)	47 (14.6)	0.5 (0.3-1.0)	0.033	0.5 (0.3-1.0)	0.057
Hypothermia	7 (4.5)	31 (9.6)	0.4 (0.2-1.0)	0.052	0.4 (0.2-1.0)	0.056
Hypoglycaemia	4 (2.6)	28 (8.7)	0.3 (0.1-0.8)	0.012	0.3 (0.1-0.9)	0.029
Jaundice needing Tx	6 (3.8)	32 (10.0)	0.4 (0.1-0.9)	0.021	0.4 (0.1-1.0)	0.031
NNU admission	12 (7.7)	52 (16.0)	0.4 (0.2-0.8)	0.010	0.4 (0.2-0.9)	0.016
NNU ≥ 3 days	5 (3.2)	18 (5.6)	0.6 (0.2-1.5)	0.256	0.6 (0.2-1.6)	0.283
NNU ≥ 5 days	5 (3.2)	27 (8.4)	0.4 (0.1-1.0)	0.033	0.4 (0.1-1.0)	0.037
Intubation and ventilation	2 (1.3)	7 (2.2)	0.6 (0.1-2.9)	0.504	1.0 (0.1-3.0)	0.525
Advanced resuscitation	2 (1.3)	12 (3.7)	0.3 (0.1-1.5)	0.160**	0.4 (0.1-1.6)	0.178
IUFD/NND	0 (0.0)	1 (0.3)	1.0 (1.0-1.0)	1.000**		
Sepsis	3 (1.9)	10 (3.1)	0.6 (0.2-2.3)	0.561**	0.8 (0.2-2.8)	0.683
Severe cerebral morbidity	1 (0.6)	2 (0.6)	1.0 (0.1-11.5)	1.000**	1.0 (0.1-11.3)	0.985
Severe respiratory morbidity	4 (2.6)	17 (5.3)	0.5 (0.2-1.4)	0.171	0.5 (0.1-1.4)	0.159
Severe circulatory morbidity	1 (0.6)	3 (0.9)	0.7 (0.1-6.6)	1.000**	0.7 (0.1-6.9)	0.747

Data is recorded as n (%). OR; odds ratio, aOR; adjusted odds ratio, NNU; neonatal unit, IUFD; intrauterine fetal death, NND; neonatal death To test for significance according to appropriateness, either the Pearson's Chi-squared test was used, or the Fishers exact test (**). **Multiple logistic regression was used to adjust for nulliparity and past obstetric risk factors for FGR.**

Table 5.5c NNO in the high-risk late FGR clinic and the pre-clinic cohort

Outcome	High-risk late FGR clinic N = 156	Pre-clinic N =323	OR (95%CI)	p-value	aOR (95% CI)	p-value
GA ³ 39 weeks	42 (25.5)	171 (53.1)	0.5 (0.4-0.6)	0.000	0.3 (0.2-0.5)	0.000
GA ³ 40 weeks	6 (3.6)	91 (28.3)	0.1 (0.1-0.3)	0.000	0.1 (0.0-0.2)	0.000
GA ³ 41 weeks	0 (0.0)	47 (14.6)	0.9 (0.8-0.9)	0.000		
Hypothermia	25 (15.2)	31 (9.6)	1.6 (1.0-2.6)	0.069	1.7 (1.0-3.1)	0.067
Hypoglycaemia	24 (14.5)	28 (8.7)	1.7 (1.0-2.8)	0.047	1.8 (1.0-3.3)	0.046
Jaundice needing Tx	22 (13.3)	32 (9.9)	1.3 (0.8-2.2)	0.254	1.3 (0.7-2.4)	0.377
NNU admission	41 (24.8)	52 (16.0)	1.5 (1.1-2.2)	0.023	1.7 (1.0-2.7)	0.032
NNU ≥ 3 days	14 (8.5)	18 (5.6)	1.5 (0.8-3.0)	0.219	1.4 (0.6-2.9)	0.423
NNU ≥ 5 days	19 (12)	27 (8.6)	1.4 (0.8-2.4)	0.241	1.3 (0.7-2.5)	0.382
Intubation and ventilation	5 (3.0)	7 (2.2)	1.4 (0.5-4.3)	0.550**	1.3 (0.4-4.3)	0.645
Advanced resuscitation	6 (3.6)	12 (3.7)	1.0 (0.4-2.5)	0.955	0.9 (0.3-2.4)	0.781
IUFD/NND	0 (0)	1 (0.3)	1.0 (1.0-1.0)	1.000**		
Sepsis	5 (3)	10 (3.1)	1.0 (0.3-2.8)	0.968	1.0 (0.6-1.7)	0.980
Severe cerebral morbidity	2 (1.2)	2 (0.6)	2.0 (0.3-13.7)	0.607**	1.9 (0.3-14.1)	0.521
Severe respiratory morbidity	10 (6.1)	17 (5.3)	1.1 (0.5-2.4)	0.746	1.1 (0.5-2.5)	0.854
Severe circulatory morbidity	2 (1.2)	3 (0.9)	1.3 (0.2-7.7)	1.000**	1.2 (0.2-7.4)	0.841

Data is recorded as n (%). OR; odds ratio, aOR; adjusted odds ratio, NNU; neonatal unit, IUFD; intrauterine fetal death, NND; neonatal death To test for significance according to appropriateness, either the Pearson's Chi-squared test was used, or the Fishers exact test (**). **Multiple logistic regression was used to adjust for nulliparity and past obstetric risk factors for FGR**

Table 5.6a NNO severity in the late FGR clinic and the pre-clinic cohort

Outcome	Late FGR clinic N = 321	Pre-clinic N = 323	OR (95% CI)	p-value	aOR (95% CI)	p-value
Severe Adverse NNO	20 (6.2)	29 (9.0)	0.7 (0.4-1.2)	0.185	0.4 (0.2-1.0)	0.053
Overall Adverse NNO	165 (51.4)	194 (60.1)	0.9 (0.7-1.0)	0.027	0.7 (0.5-1.0)	0.037

Data was presented as n (%). OR, Odds ratio; 95% CI, 95% confidence interval; aOR, adjusted odds ratio. NNO; neonatal outcome. The Pearson's Chi-squared test was used to test for significant difference ($p < 0.05$).**Multiple logistic regression was used to adjust for maternal BMI, nulliparity and history of obstetric risk factors for FGR.**

Table 5.6b NNO severity in the low-risk late FGR clinic and the pre-clinic cohort

Outcome	Low-risk late FGR clinic N = 156	Pre-clinic N = 323	OR (95% CI)	p-value	aOR (95% CI)	p-value
Severe Adverse NNO	6 (3.8)	29 (9.0)	0.4 (0.2-1.0)	0.042	0.4 (0.2-1.0)	0.062
Overall Adverse NNO	70 (44.9)	194 (60.1)	0.7 (0.6-1.0)	0.020	0.6 (0.4-0.8)	0.040

Data was presented as n (%). OR, Odds ratio; 95% CI, 95% confidence interval; aOR, adjusted odds ratio. NNO; neonatal outcome. The Pearson's Chi-squared test was used to test for significant difference ($p < 0.05$).**Multiple logistic regression was used to adjust for nulliparity and past obstetric risk factors for FGR.**

Table 5.6c NNO severity in the high-risk late FGR clinic and the pre-clinic cohort

Outcome	High-risk late FGR clinic N = 165	Pre-clinic N = 323	OR (95% CI)	p-value	aOR (95% CI)	p-value
Severe Adverse NNO	14 (8.5)	29 (9.0)	0.9 (0.5-1.8)	0.848	0.9 (0.4-1.7)	0.631
Overall Adverse NNO	95 (57.6)	194 (70)	1.0 (0.8-1.1)	0.597	0.9 (0.6-1.3)	0.467

Data was presented as n (%). OR, Odds ratio; 95% CI, 95% confidence interval; aOR, adjusted odds ratio. NNO; neonatal outcome. The Pearson's Chi-squared test was used to test for significant difference ($p < 0.05$). **Multiple logistic regression was used to adjust for nulliparity and past obstetric risk factors for FGR.**

5.3.6 Severe adverse NNO

Although there was a downward trend in severe adverse NNO in the low-risk late FGR clinic cohort and the pre-clinic cohort; there was overall no significant difference in severe adverse NNO between the late FGR clinic and the low and high-risk FGR clinic cohorts and the pre-clinic cohort see (**Tables 5.6a-c**).

5.3.7 Overall adverse NNO

There were no significant differences in overall adverse NNO in the late FGR clinic and the pre-clinic cohort. In comparison there was a significant reduction between the overall adverse NNO in the low-risk late FGR clinic vs the pre-clinic cohort 45 vs 60% aOR 0.6 95% CI 0.4-0.8 P=0.04 . Specifically in the low-risk late FGR clinic there were significantly less babies with hypoglycaemia: 2.6 v 8.7%, aOR 0.3 (95% CI 0.1-0.9), p= 0.029; jaundice needing treatment: 3.8 vs 10%, aOR 0.4 (95% CI 0.1-1.0), p= 0.031; NNU admission: 7.7 vs 16%, aOR 0.4 (95% CI 0.2-0.9), p= 0.016 and NNU admission ≥ 5 days: 3.2 vs 8.4%, aOR 0.4 (95% CI 0.1-1.0), p= 0.037 (**Tables 5.5a-c**).

5.4 Discussion

5.4.1 Main findings

My study showed evaluation of the new late FGR clinic which used risk stratification to determine surveillance and timing of delivery had significant improvement in adverse NNO in the low-risk late FGR group vs the pre-clinic cohort. There was one IUFD in the pre-clinic cohort and no IUFD in the late FGR clinic. Risk stratification allowed the low-risk late FGR clinic group to avoid early iatrogenic delivery, with increase in GA and BW and potential long term benefits for organ maturation and neurodevelopment. Delayed delivery in the low-risk late FGR clinic group also allowed significant increase in SOL and vaginal delivery vs the pre-clinic group (31.4 vs 21.1%, aOR 1.6 (95% CI 1.0-2.5), p=0.034.

In the low-risk late FGR clinic group, there was a significant reduction in vaginal deliveries associated with suspected intrapartum fetal compromise due to an abnormal FHR pattern on CTG 3.9 vs 19.5%, aOR 0.2 (95%CI 0.1-0.7), p=0.014, vs the pre-clinic cohort. This suggests that risk stratification in the late FGR clinic was accurate at identifying a low-risk late FGR clinic cohort able to cope with intrapartum stress and vaginal delivery. This may also explain why the low-risk late FGR clinic compared to the pre-clinic cohort had significantly less overall adverse NNO, with significant reduction in neonatal hypothermia, hypoglycaemia, jaundice and NNU admission, even after adjusting for GA and BW at delivery.

5.4.2 Comparison with other studies

Timing of delivery

International guidelines vary in recommending timing of delivery in FGR and there are few studies assessing the management of late preterm or term FGR pregnancies. The growth restriction intervention trial (GRIT)[252] and TRUFFLE trials[251] recruited a minority of late preterm fetuses (210 and 147 respectively). In the GRIT study there was no difference in delayed vs immediate delivery, but there was no detailed classification antenatally with delivery timing in the delayed group left to individual clinician. The TRUFFLE 1 trial is not comparable with my study as my cohort were not randomised to delivery according to CTG, or DV changes, majority had normal UmbA Doppler and were delivered > 37 weeks. In TRUFFLE 1 although there were no stillbirths > 32 weeks; 12% of babies delivered >34 weeks had adverse NNO supporting need for risk stratification[252].

A Cochrane meta-analysis did not report any benefit in delivering near term babies with sign of compromise compared with waiting until the due date. Two randomised trials were selected[285]. The DIGITAT trial was the main study comparing IOL at 36 weeks vs conservative management in SGA fetus. There was no difference in the NNO and no IUFD reported in women managed conservatively after 38 weeks[209]. The differences in GA and BW between the two groups were minimal (<150 grammes, compared with the 300 grammes differences in my high and low-risk FGR clinic cohorts) and most of the babies had normal UmbA Doppler, which differed from my study where I adopted a multiparameter Doppler evaluation[253].

Conservative management > 37 weeks may reduce adverse NNO

As described in **2.6.3 Multiparametric management models used in late SGA fetus** which discusses the management protocol and results of studies by Veglia et al in 2018[211] and Meler et al in 2020[212] which both involved multiparametric and risk stratification based late SGA management clinics; delayed delivery in appropriately assessed low-risk late SGA pregnancies was associated with significant improvement in labour, neonatal and maternal outcomes. Similar to my study conservative management of the low-risk SGA group was associated with less intervention and significant improvement in adverse labour, neonatal and maternal outcomes, as discussed below in comparison my study was prospective, included FGR pregnancies with EFW >10th centile and used abnormal NNO measures[212,213].

Overall the reduction in adverse NNO in my low-risk FGR clinic group vs the high-risk group was lower than that seen in the low-risk vs the high-risk group in studies by Veglia et al, 2018[211] who showed neonatal composite adverse outcome (NCAO) in their low and high-risk group was 4 (4.5%) vs 9 (13%) and Meler et al, 2020[212] who showed combined adverse outcome in low vs high-risk group was 15 (2.8%) vs 32 (6.5%). Greater reduction in adverse NNO in my late FGR clinic versus these 2 studies could be due to the fact there were several differences between mine and these 2 studies. My study assessed 321 late FGR babies whilst Veglia et al[211] assessed fewer late FGR babies (N=281) and Meler et al[212] had a more late FGR babies in their study (N=1197). In addition both studies also used different risk stratification and adverse NNO measures.

Similar to my study high risk stratification by Veglia included EFW <3rd centile, low PAPP-A and Doppler measurements (CPR <5th) but it also included PIH to classify high-risk late FGR. In addition, their delivery protocol was strict and differed from my protocol with high-risk pregnancies (EFW <3rd centile) delivered exactly at 37+0 weeks, whilst low-risk fetus in the absence of these features but EFW 3-5th were delivered by 40+0 and EFW 5-10th delivered by 41+0 weeks. In addition their NCAO defined as the presence of at least one of the following: intrauterine or neonatal death; Apgar score < 7 at 5 min; cord arterial pH < 7.10; hypoglycemia (blood glucose < 2.5 mmol/L) and need for ventilation or cooling[211]. There was also similar risk stratification used between my study and Meler et al, 2020[212] with management protocol similar for the high-risk group with IOL advised at 37 but low-risk FGR group induced earlier at 40+0 weeks. There were also similarities in the adverse NNO assessed although my study looked at more adverse NNO measures compared to studies by Veglia et al[211] and Meler et al[212].

5.4.3 Clinical implications

My study showed that evidence-based 3rd trimester USS parameters can be used to risk stratify pregnancies within a dedicated late FGR clinic, allowing a more conservative approach in low-risk late FGR pregnancies with delayed delivery up to 41 weeks. This allowed a significant number of women to spontaneously labour with improvement in labour, maternal and NNO. Low-risk FGR babies were significantly older and heavier compared to the pre-clinic cohort with potential advantages for fetal organ maturation and neurodevelopment; in contrast the high-risk late FGR clinic group were advised delivery at 37-38 weeks.

5.4.4 Strengths and weaknesses

The strengths in the late FGR clinic and the pre-clinic cohorts include the study size (> 600 suspected late FGR pregnancies), similar maternal demographics, the quality of FGR babies and the outcome data. Limitations are that the pre-clinic cohort was a retrospective cohort, slightly different inclusion criteria were used to diagnose FGR as well as the sample sizes not being powered to explore severe adverse NNO in the late FGR clinic vs the pre-clinic cohort.

5.4.5 Conclusions

There were significant improvement in the labour outcomes in the low-risk late FGR cohort with a significant increase in women having a spontaneous vaginal delivery and significantly less women having an induction of labour compared with the pre-clinic cohort. In addition, in the low-risk late FGR clinic group vs the pre-clinic cohort there were less women having a vaginal delivery with evidence of suspected fetal compromise due to an abnormal FHR pattern on CTG as well as significantly less adverse NNO. This could be due to the lack of risk stratification in the pre-clinic cohort indicating that the pre-clinic cohort could have also benefited from risk stratification and an earlier or later delivery.

There was however no significant differences in the maternal outcomes (need for operative delivery due to suspected fetal compromise) between the late FGR clinic subgroups and the pre-clinic cohort potentially due to the small numbers assessed and the potential for any late FGR pregnancies being at risk of underlying placental insufficiency and at risk of potential intrapartum fetal compromise. There was also no difference in outcomes between the high-risk late FGR clinic cohort and the pre-clinic cohort potentially due to the fact both cohort were often delivered at a similar gestation at 37-38 weeks with potential late preterm complications.

The low-risk late FGR clinic group due to expectant management up to 41 weeks also had a significantly older gestational age and birth weight at delivery compared to the pre-clinic cohort. This could have potential long-term organ and neuro developmental advantages for these low-risk FGR fetuses. Overall, there appeared to be significant improvement in labour outcomes and reduction in adverse NNO in the low-risk late FGR cohort versus the pre-clinic cohort although a randomised trial would be needed to verify the ability of my multiparametric model to screen, risk stratify and manage late FGR pregnancies.

Chapter 6 Multiparametric model to predict adverse NNO

6.1 Introduction

6.1.1 Background

In Chapter 4 I compared labour, maternal and neonatal outcomes between the low and high-risk late FGR groups in a dedicated late FGR clinic and identified there was significantly less adverse NNO in the low versus the high-risk late FGR group. I demonstrated that, using a novel definition of neonatal phenotype of late FGR, the antenatal classification of low- and high-risk cases were appropriately identified. In Chapter 5 I evaluated the newly implemented late FGR clinic by comparing labour, maternal and neonatal outcomes in the late FGR clinic vs a pre-clinic cohort and identified there was significant improvement in the low-risk late FGR group versus the pre-clinic cohort. The pre-clinic cohort was managed according with individual clinician's expertise using NICE/RCOG/Internal UCLH guidelines according. I demonstrated that a protocolised management protocol can improve outcome. In Chapter 6 I was keen to assess whether the findings were due to induced prematurity or true biological differences due to placental insufficiency. As one of the issue in investigating NNO in late FGR is that the neonatal phenotype of a late FGR baby is similar to the one a premature normally grown individual. To answer this question I performed modelling to explore what would have happened if fetuses were not delivered at the advised gestations.

As the neonatal outcomes of late prematurity substantially overlap with the phenotype of a neonate affected by late FGR, there are two possible ways to answer this question. The most appropriate method would be to perform a interventional trial exploring the optimal timing of delivery in late FGR, with sufficient gestational age at delivery discrepancy in the two trial groups and a parallel trial group. Women could be classified as low- and high-risk and randomised to be delivered at 37 vs 38 weeks (high-) and at 37 vs 40 weeks (low-risk). This will answer the question around the impact of late prematurity versus potential placental insufficiency worsening in the defined group categories.

In the absence of a randomised interventional trial as described above see 6.1.2 Aims, objectives and hypotheses, I instead performed a sensitivity analysis with a predictive model of what would happen if low and high-risk women were delivered earlier or later respective to my cohort. I therefore developed a further multiparametric model to predict adverse NNO in high and low-risk pregnancies delivered from 34 to 42 weeks using actual and simulated data from the late FGR clinic and the pre-clinic cohort.

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6.1.2 Aims, objectives and hypotheses:

The third aim of the MD (Res) was:

- Develop a multiparameter late FGR predictive model of adverse NNO by identifying high-risk late FGR in the presence of additional USS parameters associated with placental insufficiency and comparing risk of adverse NNO at different gestational ages.

6.2 Methods

6.2.1 Risk stratifying the late FGR and the pre-clinic cohort

The pre-clinic late FGR clinic cohort was risk stratified as high or low-risk FGR groups according to the risk stratification models used in the late FGR clinic **see 3.2.8 Risk stratification used in the Late FGR clinic.**

6.2.2 Estimating the probability score of an adverse NNO by gestational age

Using a model-based approach I estimated the probability score of an adverse NNO at different gestational ages. Using a scale from 0 to 1 which indicated 0 and 100% chance of developing an adverse NNO, I fitted a Bayesian logistic regression using data from the new late FGR clinic[254,255]. Gestational age (in weeks) was used as a continuous variable and high and low-risk FGR pregnancies represented by a dichotomous variable. A non-linear relationship with the GA was captured by adding a quadratic term. This model was used to illustrate the estimated risk conferred to low- and high-risk FGR groups at different stages of the pregnancy. To estimate the probability of adverse NNO < 36 weeks and > 40 weeks I fitted a model using observed data from the new late FGR cohort and applied the model to the pre- clinic cohort using simulated data (as high-risk women were delivered later and low-risk were delivered earlier in the pre-clinic cohort) see **Tables 6.5, 6.6** and **Figure 6.1**.

6.3 Results

~~1.4~~1.2 6.3.1 Number of women in the study

There were then 644 pregnancies in the final data analysis. This included 321 pregnancies in the late FGR clinic and 323 pregnancies in the pre-clinic cohort (see **5.3.1 Number of women in the study)**

Table 6.1a: Maternal features: Old vs new low-risk late FGR cohort

Maternal characteristics	**New cohort N = 156**	**Old cohort N = 187**	**p-value**
Age (years)	33 (29-36)	33 (30-36)	0.852
BMI (kg/m2)	22.8 (20.4-25.6)	22.1(19.8-24.4)	0.239
Nulliparous	71 (45.5)	109 (58.3)	0.016
Current smoker	8 (5.1)	11 (5.9)	0.762
Recreational drug user	1 (0.6)	3 (1.6)	0.410
Medical comorbidity	10 (6.4)	9 (4.8)	0.521
Past obstetric history	34 (21.8)	18 (9.6)	0.002
Gynaecological history	5 (3.2)	9 (4.8)	0.455
Current obstetric history	13 (8.3)	20 (10.7)	0.461
Preeclampsia	1 (0.6)	3 (1.6)	0.410
Gestational diabetes mellitus	11 (7.1)	15 (8.0)	0.737
EFW < 10th population chart	86 (55.1)	128 (68.4)	0.011
EFW < 10th customised chart	73 (46.8)	124 (66.3)	<0.001
CPR <5th centile	6 (3.8)	9 (4.8)	0.664
AC Drop ≥50 centiles	16 (10.3)	12 (6.4)	0.436

Values reported as median (interquartile range 25th to 75th percentile) or absolute values (%). BMI; body mass index, EFW; estimated fetal weight, CPR; cerebroplacental ratio, AC; abdominal circumference.

Table 6.1b: Maternal features: Old vs new high-risk FGR cohort

Maternal characteristics	**New cohort N = 165**	**Old cohort N = 136**	**p-value**
Age (years)	33 (29-36)	33 (30-36)	0.849
BMI (kg/m2)	23.60 (20.8-27.5)	22.7 (20-25.4)	0.144
Nulliparous	80 (48.5)	77 (56.6)	0.161
Current smoker	13 (7.9)	10 (7.4)	0.866
Recreational drug user	6 (3.6)	1 (0.7)	0.098
Medical comorbidity	12 (7.3)	6 (4.4)	0.299
Past obstetric history	37 (22.4)	24 (17.6)	0.306
Gynecological history	14 (8.5)	6 (4.4)	0.159
Current obstetric history	33 (20.0)	23 (16.9)	0.495
Preeclampsia	12 (7.3)	5 (3.7)	0.180
Gestational diabetes mellitus	13 (7.9)	10 (7.4)	0.866
EFW <10th population chart	90 (54.5)	87 (63.9)	0.112
EFW <10th customised chart	109 (66.1)	125 (91.9)	<0.001
EFW <3rd population or customised chart	80 (48.5)	101 (74.3)	<0.001
CPR < 5th centile	11 (6.7)	13 (9.6)	0.366
AC Drop ≥50 centiles	13 (7.9)	3 (2.2)	0.029

Values reported as median (interquartile range 25th to 75th percentile) or absolute values (%). BMI; body mass index, EFW; estimated fetal weight, CPR; cerebroplacental ratio, AC; abdominal circumference.

6.3.2 Maternal features in the old and new late FGR cohorts

In the “old” versus the “new” low-risk late FGR cohorts; women were significantly more likely to be nulliparous n=109 (58.3%) vs 71 (45.5%) p=0.016 and to have an EFW <10th centile on both customised and population fetal growth charts. In addition, women in the new versus the old low-risk group were significantly less likely to have a past obstetric risk factors associated with an increased risk of FGR 21.8% (n=34) vs 9.6% (n=18), p=0.02 (**see table 6.1a**). In the old versus the new high-risk late FGR clinic cohort the women were also significantly more likely to have an EFW <10th centile on both customised fetal growth charts and to have a fetal AC drop >50 centiles **(Tables 6.1b).** Neonatal, labour and maternal outcomes were adjusted for these differences accordingly.

Table 6.2a: Maternal and labour outcome: Old vs new low-risk late FGR cohort

Outcome	New cohort N = 156	Old cohort N = 187	OR (95% CI)	p-value	aOR (95% CI)	p-value
Spontaneous onset of labor	75 (48.1)	58 (31.0)	2.06 (1.3-3.2)	0.001	2.09 (1.3-3.2)	0.001
Induction of labor	61 (39.1)	76 (40.6)	0.9 (0.6-1.4)	0.772	1.0 (0.6-1.5)	0.981
Spontaneous onset of labor and unassisted vaginal delivery	49 (31.4)	48 (25.7)	1.3 (0.8-2.1)	0.24	1.2 (0.8-2)	0.381
Unassisted vaginal delivery	80 (51.3)	83 (44.4)	1.3 (0.9-2.0)	0.203	1.2 (0.8-1.9)	0.380
Instrumental delivery for abnormal fetal heart monitoring	9 (5.8)	18 (9.6)	0.6 (0.2-1.3)	0.173	0.6 (0.3-1.4)	0.271
Emergency caesarean section for abnormal fetal heart monitoring	19 (12.2)	32 (17.1)	0.7 (0.4-1.2)	0.203	0.7 (0.4-1.4)	0.368
Elective caesarean section	15 (9.6)	36 (19.3)	0.4 (0.2-0.8)	0.014	0.4 (0.2-0.8)	0.007
Adverse maternal outcome	28 (17.9)	50 (26.7)	0.6 (0.3-1.0)	0.05	0.6 (0.4-1.1)	0.127

OR; odds ratio, 95% CI; 95% confidence interval, aOR; adjusted odds ratio for nulliparity and maternal past obstetric history.

Table 6.2b: Maternal and labour outcome: Old vs new high-risk late FGR cohort

Outcome	New cohort N = 165	Old cohort N = 136	OR (95% CI)	p-value
Spontaneous onset of labor	43 (26.1)	27 (19.9)	1.4 (0.8-2.5)	0.206
Induction of labor	84 (50.9)	67 (49.3)	1.1 (0.7-1.7)	0.776
Spontaneous onset of labor and unassisted vaginal delivery	32 (19.4)	20 (14.7)	1.4 (0.8-2.6)	0.286
Unassisted vaginal delivery	72 (43.6)	60 (44.1)	1.0 (0.6-1.5)	0.933
Instrumental delivery for abnormal fetal heart monitoring	12 (7.3)	12 (8.8)	0.8 (0.3-1.8)	0.595
Emergency caesarean section for abnormal fetal heart monitoring	28 (17.0)	22 (16.2)	1.0 (0.6-1.9)	0.854
Elective caesarean section	21 (12.7)	24 (17.6)	0.7 (0.4-1.3)	0.235
Adverse maternal outcome	40 (24.2)	35 (25.7)	0.9 (0.5-1.6)	0.766

OR; odds ratio, 95% CI; 95% confidence interval.

6.3.3 Maternal and labour outcome in the old and new late FGR cohorts

Women in the new versus the old low-risk cohorts were significantly more likely to have a spontaneous onset of labour aOR 2.09 95% CI (1.3-3.2), P= 0.001. There were however no other significant differences between these two groups and there was no significant differences in the maternal and labour outcomes in the old and the new high-risk cohorts **see Tables 6.2a and 6.2b.**

Table 6.3a: Birth details: Old vs New low-risk late FGR cohort

Outcome	**New cohort N = 156**	**Old cohort N = 187**	**p-value**
Birth weight (g)	2840 (2663-3054)	2800 (2570-3030)	0.167
Birth gestation (weeks^{+days})	39^{+5} (38^{+5}-40^{+2})	39^{+1} (38^{+1}-40^{+1})	0.023
Birth weight ≤10^{th} population centile	100 (64.1)	126 (67.4)	0.525
Birth weight <3^{rd} population centile	13 (8.3)	33 (17.6)	0.012
Birth weight ≤10^{th} customised centile	87 (55.8)	76 (40.6)	0.005
Birth weight <3^{rd} customised centile	19 (12.2)	16 (8.6)	0.262
Days admitted to neonatal unit	3 (1-7)	4 (2-6)	0.703
5 min Apgar Score <7	1 (0.6)	0 (0)	0.276

Values reported as mean in normally distributed and median in non-normally distributed (interquartile range 25^{th}-75^{th} percentile) or absolute values (%). GA; gestational age, NNU; neonatal unit.

Table 6.3b: Birth details: Old vs New high-risk late FGR cohort

Outcome	**New cohort N = 165**	**Old cohort N = 136**	**p-value**
Birth weight (g)	2558 (2266-2735)	2430 (2155-2705)	0.162
Birth gestation (weeks^{+days})	38^{+2} (37^{+5}-39^{+0})	38^{+5} (37^{+4}-39^{+6})	0.020
Birth weight ≤10th population centile	128 (77.6)	85 (62.5)	0.016
Birth weight <3rd population centile	59 (35.8)	40 (29.4)	0.245
Birth weight ≤10th customized centile	129 (78.2)	117 (86.0)	0.080
Birth weight <3rd customised centile	71 (43.0)	94 (69.1)	<0.001
Days admitted to neonatal unit	3 (2-8)	3 (2-4)	0.943
5 min Apgar Score <7	0 (0)	3 (2.2)	0.056

Values reported as mean in normally distributed and median in non-normally distributed (interquartile range 25th-75th percentile) or absolute values (%). GA; gestational age, NNU; neonatal unit.

6.3.4 Birth details in the old and new late FGR cohorts

Babies in the new versus the old low-risk group were delivered significantly later 39+5 vs 39+1 week and were significantly less likely to have an EFW <10th centile antenatally on customised or population fetal growth chart. In contrast in the new versus the old high-risk group women were delivered significantly earlier vs the old high-risk group; however, there were significantly more babies with birth weight <3rd centile in the old high-risk group **see Tables 6.3a and 6.3b.**

Table 6.4a: Neonatal outcomes: Old vs new low-risk FGR cohorts

Outcome	New cohort N= 156	Old cohort N= 187	OR (95%CI)	p-value	aOR (95% CI)	p-value
GA³39 weeks	110 (70.5)	109 (58.3)	1.7 (1.1-2.6)	0.023	1.8 (1.2-2.9)	0.010
GA³40 weeks	68 (43.6)	57 (30.5)	1.7 (1.1-2.7)	0.014	1.9 (1.2-2.9)	0.006
GA³41 weeks	12 (7.7)	30 (16.0)	0.4 (0.2-0.8)	0.021	0.4 (0.2-0.9)	0.033
Hypothermia	7 (4.5)	14 (7.5)	0.58 (0.2-1.5)	0.253	0.6 (0.2-1.6)	0.328
Hypoglycemia	4 (2.6)	8 (4.3)	0.6 (0.2-2)	0.395	0.6 (0.2-2)	0.410
Jaundice needing treatment	6 (3.8)	15 (8.0)	0.5 (0.2-1.2)	0.116	0.5 (0.2-1.2)	0.139
NNU admission	12 (7.7)	19 (10.2)	0.7 (0.4-1.5)	0.402	0.8 (0.4-1.7)	0.546
NNU ≥ 3 days	5 (3.2)	10 (5.3)	0.6 (0.2-1.7)	0.339	0.6 (0.2-1.8)	0.382
NNU ≥ 5 days	5 (3.2)	16 (8.6)	0.3 (0.1-1.0)	0.045	0.3 (0.1-0.9)	0.039
Assisted ventilation	2 (1.3)	9 (4.8)	0.6 (0.2-2.0)	0.457	0.6 (0.2-2.0)	0.452
Sepsis	3 (1.9)	5 (2.7)	0.7 (0.2-2.9)	0.465	0.9 (0.2-3.8)	0.873
Severe cerebral morbidity	1 (0.6)	0 (0.5)				
Severe respiratory morbidity	6 (3.8)	10 (5.3)	0.7 (0.2-2.0)	0.493	0.6 (0.2-1.7)	0.373
Severe circulatory morbidity	1 (0.6)	1 (0.5)	1.2 (0.1-19.4)	0.904	0.9 (0.1-14.7)	0.949
Severe Adverse NNO	6 (3.8)	16 (8.6)	0.4 (0.2-1.2)	0.084	0.4 (0.2-1.2)	0.100
Overall Adverse NNO	70 (44.9)	108 (57.8)	0.6 (0.4-0.9)	0.018	0.6 (0.4-0.9)	0.026

Data is recorded as n (%). OR; odds ratio, aOR; adjusted odds ratio for nulliparity and maternal past obstetric history, GA; gestational age, NNO; neonatal outcome, NNU; neonatal unit.

Table 6.4b: Neonatal outcomes: Old vs new high-risk FGR cohorts

Outcome	New cohort N = 165	Old cohort N = 136	OR (95%CI)	p-value
GA > 39 weeks	42 (25.5)	62 (46)	0.4 (0.2-0.7)	<0.001
GA > 40 weeks	6 (3.6)	34 (25)	0.1 (0.0-0.3)	<0.001
GA > 41 weeks	0 (0.0)	17 (12)		
Hypothermia	25 (15.2)	17 (12)	1.25 (0.6-2.4)	0.509
Hypoglycemia	24 (14.5)	20 (15)	1.0 (0.5-1.8)	0.969
Jaundice needing treatment	22 (13.3)	17 (12)	1.0 (0.5-2.1)	0.830
NNU admission	41 (24.8)	33 (24)	1.0 (0.6-1.7)	0.907
NNU ≥ 3 days	14 (8.5)	8 (6)	1.5 (0.6-3.6)	0.390
NNU ≥ 5 days	19 (11.5)	11 (8)	1.5 (0.7-3.3)	0.297
Assisted ventilation	5 (3.0)	8 (6)	0.9 (0.3-2.5)	0.873
Sepsis	5 (3.0)	5 (3.7)	0.8 (0.2-2.8)	0.759
Severe cerebral morbidity	2 (1.2)	2 (1)	0.8 (0.1-5.9)	0.846
Severe respiratory morbidity	10 (6)	7 (5)	1.2 (0.4-3.1)	0.756
Severe circulatory morbidity	2 (1.2)	2 (1)	0.8 (0.1-5.9)	0.846
Severe Adverse NNO	14 (8.5)	13 (10)	0.9 (0.4-1.9)	0.758
Overall Adverse NNO	95 (56.5)	86 (63)	0.8 (0.5-1.3)	0.319

Data is recorded as n (%). OR; odds ratio, GA; gestational age, NNO; neonatal outcome, NNU; neonatal unit.

6.3.5 Neonatal outcomes in the old and new late FGR cohorts

In the new versus the old low-risk FGR group babies were significantly more likely to be delivered after 39, 40 and 41 weeks gestational age. The old versus the new low-risk group were significantly more likely to spend >5 days in NNU and were significantly more likely to have more overall adverse NNO aOR 0.6 95% CI (0.4-0.9), p=0.026 In the new versus the old high-risk group babies were significantly less likely to be delivered after 39 weeks; but there were no other significant differences between these two groups **see Tables 6.4a and 6.4b.**

Table 6.5 Summary statistics 1: for the $\boldsymbol{\beta}$ estimates for the Bayesian logistic regression for low and high-risk FGR groups

Term	Mean (SD)	Median (IQR)	CrI 95%
High/Low-risk group	0.206 (0.269)	0.207 (0.361)	(-0.324, 0.732)
Gestational Age (weeks)	-18.24 (6.177)	-17.983 (8.363)	(-31.017, -6.902)
Squared Gestational Age (weeks^2)	0.23 (0.079)	0.227 (0.107)	(0.0847, 0.394)
Intercept	360.707 (120.459)	355.62 (163.088)	(139.901, 610.084)

Data is presented as SD; Standard deviation, IQR; Interquartile range and CrI 95%; 95% credible interval

In the table shown above, the corresponding estimated mean of the odds ratio (95% credible intervals) for the risk group was 1.229 (0.723 to 2.079). This shows there is a 95% probability that the odds-ratio lies within such a range. This suggests that in terms of percent change, in average the odds for the high-risk group was 22.9% higher than the odds for low-risk group in developing an adverse neonatal outcome, whilst leaving all the other variables fixed. Although the interpretation of the odds-ratio must be taken with care, as it can be lower than 1 according to the credible interval.

Table 6.6 Summary statistics 2: for the mean, SD, IQR and the CrI 95% at different gestational ages for the low and the high-risk FGR groups

Gestational age (weeks)	Mean (SD)	Median (IQR)	CrI 95%
34	0.001 (0.004)	0.000 (0.001)	(-0.001, 0.011)
35	0.005 (0.011)	0.002 (0.006)	(-0.006, 0.033)
36	0.017 (0.025)	0.011 (0.026)	(-0.021, 0.081)
37	0.039 (0.050)	0.036 (0.066)	(-0.052, 0.146)
38	0.051 (0.066)	0.051 (0.089)	(-0.078, 0.179)
39	0.050 (0.065)	0.050 (0.088)	(-0.079, 0.176)
40	0.050 (0.065)	0.050 (0.088)	(-0.077, 0.178)
41	0.049 (0.064)	0.050 (0.087)	(-0.078, 0.172)
42	0.035 (0.050)	0.035 (0.061)	(-0.071, 0.133)

Data is presented as SD; Standard deviation, IQR; Interquartile range and CrI 95%; 95% credible interval.

Figure 6.1: Boxplot per gestational age (weeks) and risk group

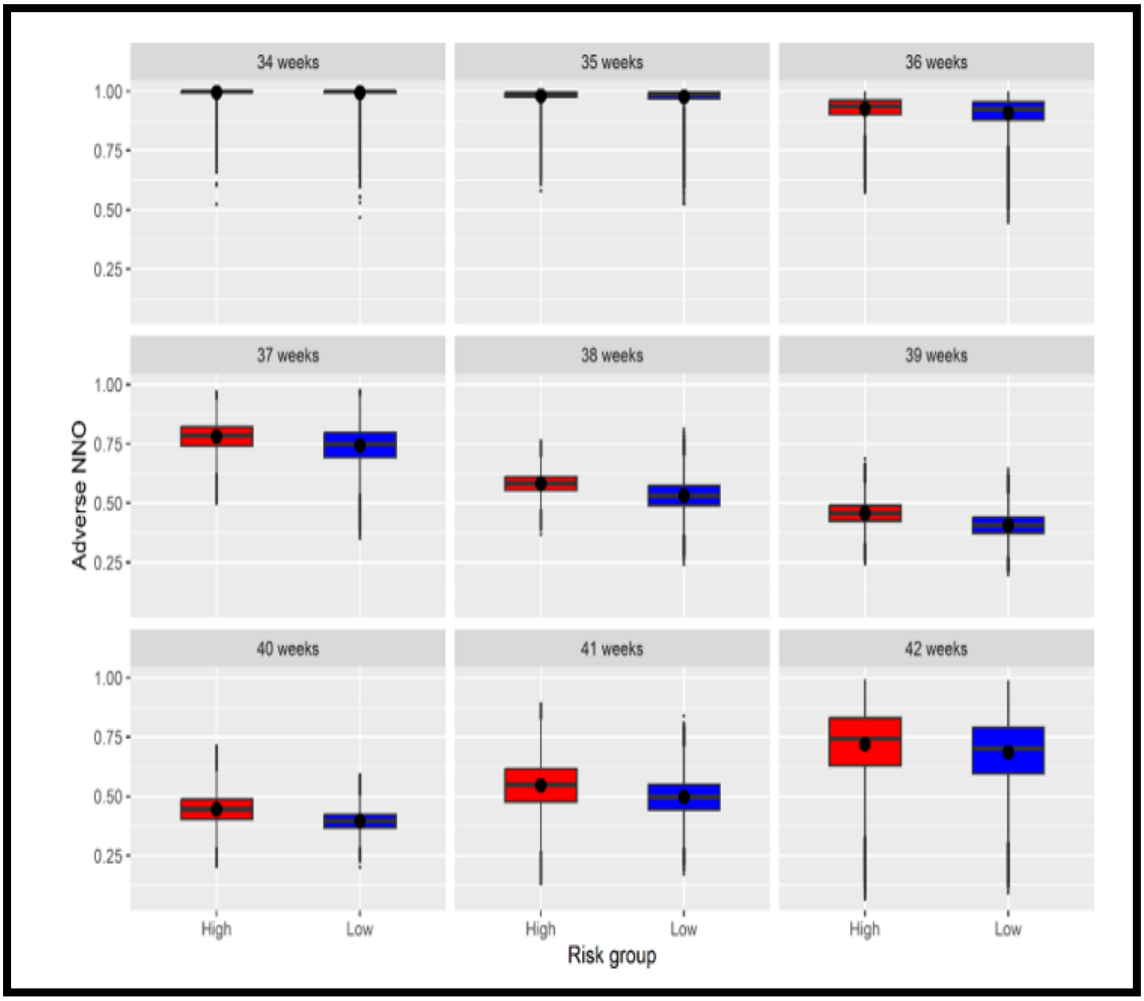
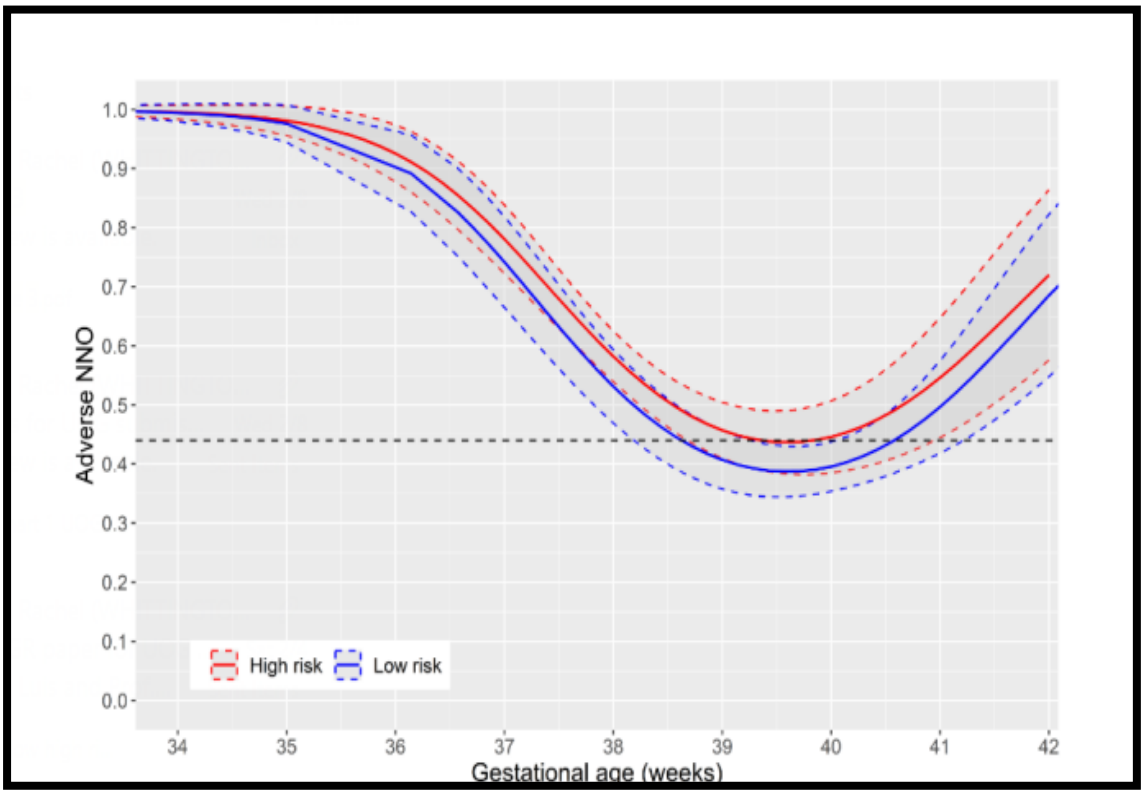


Figure 6.2: Fitted Bayesian logistic regression. This was used to indicate the estimated probability of an adverse NNO in high and low-risk women as a function of the gestational age. Estimations are applied to the late FGR clinic and pre clinic cohorts and simulated data. The bands (dashed blue and red lines for low- and high-risk respectively) represent the standard deviation around the predictive posterior probability. Probability of adverse NNO scale goes from 0 to 1 to represent 0 or 100% chances of adverse NNO respectively (Y axes) with advancing GA (X axes). Nadir of average lowest probability of abnormal NNO in the high-risk group is highlighted (horizontal dashed black line).



6.3.6 Adverse NNO according to GA and risk stratification

Using the methods described I developed a predictive model to explore probabilities of adverse NNO related to delivery between 34 to 42 weeks see **Table 6.5** and **Table 6.6** and **Figure 6.1**. The risk of adverse NNO was highest prior to 37 weeks of gestation, reached a nadir at 39-40 weeks and increased again after 41 weeks of gestation (**Figure 6.2**). At any gestation, low-risk FGR pregnancies appear to have on average a lower risk of adverse NNO and high-risk FGR pregnancies a higher risk of adverse NNO however this did not reach statistical significance (average OR: 1.229; standard deviations: 0.723, 2.079).

Despite the overlap of standard deviations, the average probability nadir of adverse NNO appears to be 39 weeks in the high-risk group which was equivalent to the probability risk at 38 and at 40 weeks of gestation for the low-risk group. This would suggest that the low-risk FGR group suffers a more disproportionate impact of late prematurity rather than exposure to chronic placental insufficiency, whereas only by waiting for delivery > 40 weeks can the probability score start to match that of the high-risk FGR group score.

6.4 Discussion

6.4.1 Maternal and labour outcome in risk stratified late FGR cohorts

Women in the new low-risk late FGR cohort vs the old pre clinic cohort were significantly more likely to have a SOL. There were however no significant differences in induction or labour rate, spontaneous onset of labour followed by vaginal delivery or significant difference in mode of delivery due to suspected FGR related fetal compromise in either the new or old low and high-risk groups. Increase in SOL within the new low-risk late FGR group was likely due to following the policy of delayed delivery within this group.

6.4.2 Gestational age and birth weight in risk stratified late FGR cohorts

The mean gestational age at delivery was significantly later in the new low-risk late FGR clinic vs the old low-risk pre-clinic cohort: 39+5 vs 39+1 weeks, p=0.023. BW <3rd population centile was also significantly lower in the new low-risk group 8 vs 17%, p=0.012. Difference in BW could be due to the new low-risk late FGR group being prospectively risk stratified and delivered later compared to the Old low-risk late FGR group which was risk stratified retrospectively. In contrast the high-risk group mean gestational age at delivery was earlier in the new vs old protocol 38+2 vs 38+5, p=0.02; this could be due to several of the FGR cases in the Old cohort were identified later in the now historic ULCH postdates clinic at 40-41 weeks. There was no significant difference in BW <3rd population centile in the new or old high-risk group as median gestational age was close to term.

6.4.3 severe and overall adverse NNO in risk stratified late FGR

Although there was a downward trend in severe adverse NNO in the new vs the old low-risk cohort there was overall no significant difference. There was however significantly less overall adverse NNO in the new vs the old low-risk late FGR cohorts 45% vs 58%, p=0.026. This was potentially due to appropriate risk stratification of this low-risk group prospectively which according to the late FGR clinic protocol allowed delayed delivery and reduced intervention in this group. Due to similar timing of delivery around term for the new and old high-risk groups with similar risk of early iatrogenic intervention and late preterm complications superimposed on placental insufficiency there was no significant difference in adverse NNO between these groups 56% vs 63%, p=0.319.

6.4.4 Risk stratification and timing of delivery

Overall, my multiparametric model showed that at any gestational age the low-risk late FGR pregnancies were at reduced risk of adverse NNO. The nadirs in adverse NNO in the low-risk group at 38 and 40 weeks were equivalent to the probability risk at 39 weeks in the high-risk group. This showed that the low-risk group were disproportionately affected by late prematurity rather than placental insufficiency and only when delivered >40 weeks in particular >41 weeks did the probability score start to reach that seen in the high-risk group. This supports my theory that “low-risk “late FGR pregnancies can be allowed delayed delivery to avoid the risks associated with late prematurity with improvement in NNO.

6.4.5 Comparison with other studies

There is only one RCT the DIGITAT study which has assessed the timing of delivery in preterm and early term late FGR babies. However, there was no risk stratification model used. Instead 650 pregnancies with suspected late FGR were randomised to IOL within 48 hours or expectant management until delivery was clinically indicated. Results showed no significant difference in short term neonatal or maternal outcomes[209] and there was also no difference at 2 years in developmental and behavioural outcomes. There was however a significant increase in maternal PET and neonatal BW<3rd centile reinforcing the importance of close fetal and maternal surveillance in the expectantly managed group[210] and overall advised not prolonging late FGR pregnancies > 38 weeks[211].

Studies on late FGR timing of delivery according to risk stratification have been performed by Veglia et al[211], Meler et al[212], Figueras et al[256] and Peasley et[253] al have shown improvement in labour, maternal and short term NNO in the low-risk late FGR groups. Initial studies by Veglia et al[211] and Meler et al[212] were retrospective however more recent studies by Figueras et al[256] and Peasley et al[253] have been prospective studies. Study by Peasley et al[253] was based on the study and results reported in this MD thesis dissertation. Sample sizes in these two prospective studies were n = 509 and n = 321 respectively.

In my study similar to studies by Veglia et al[211] and Meler et al[212] I used EFW <3rd and CPR <5th to classify high-risk late FGR pregnancies. In comparison Figueras et al[256] used MCA PI and CPR Doppler in their classification. In addition where as in my study 2nd or 3rd trimester UtA PI Doppler was used to classify high-risk late FGR, Meler et al[212] used 3rd trimester UtA Doppler >95th centile; whereas Veglia et al[211] used 2nd trimester UtA Doppler >95th centile. In other studies UtA Doppler was not used in the risk stratification or was excluded at the point of recruitment[256]. However apart from study by Peasley et al[253] which used AC drop >50 centiles in AGA and SGA fetus other studies focussed in managing SGA fetus; which may explain the heavier BW centiles in my cohort.

In my study 8.8% of patient were re-classified as high-risk after an initial low-risk classification. This is similar to a reclassification of 9.1% in the Meler et al study[212]. This highlights the importance of close fetal surveillance in the low-risk late FGR cohort especially when approaching late preterm and term gestation due to the potential for new onset in utero compromise at advancing gestations. In my study there were 55% with an EFW <3rd centile compared to 72% in the Meler et al study[212]. This can in part be explained due to the use of different fetal growth charts. In my study I used customised fetal growth charts, whereas Meler et al. used only Spanish customised fetal growth charts[212].

Although there were differences in the risk stratification parameters, study analysis, the presence of AGA fetus and the fetal growth charts used overall all the studies showed that delayed delivery in the low-risk late FGR groups was associated with heavier birth weight at delivery as well as the presence of reduced adverse NNO in the low vs the high-risk late FGR cohorts[212,211,256,253]. In my study similar to other studies, I identified a significant reduction in specific adverse NNO including hypoglycaemia, jaundice needing treatment, admission to NNU. I also assessed several additional neonatal outcomes and unlike other studies were able to combine neonatal parameters and showed a significant difference in overall “adverse NNO” in the low vs the high-risk late FGR group.

6.4.6 Current evidence and literature

There are however gaps remaining in the current literature regarding the optimal timing of delivery in late FGR. There is a lack of prospective trials which are powered for perinatal mortality as well as a lack of trials assessing long term maternal and NNO. Future studies should include RCT as well as trials assessing long term outcomes including developmental milestones at school age and characterisation of antenatal findings. Current management guidance on timing of delivery in late FGR pregnancies are based on the relatively small risk of stillbirth and in utero compromise at term which is not entirely evidence based; late term delivery can also have potential short and long term adverse NNO, financial implications and increased risk of special educational needs.

Chapter 7: Conclusions

7.1 Introduction

7.1.1 Background

In Chapter 1: I discussed the limitations associated with current antenatal and postnatal definition of late FGR in SGA and AGA fetus and the current limitations with antenatal management and timing of delivery in late FGR once diagnosed. I concluded that additional adverse NNO measures could be used to diagnose postnatal late FGR as well as using 3rd trimester USS parameters associated with placental insufficiency and adverse NNO (including CPR <5th, AC Drop >50 centiles and UA Doppler >95th centile in addition to EFW to diagnose late FGR.

In Chapter 2: I discussed the main aims, objectives and hypotheses of my MD which included to define a new late FGR neonatal definition in SGA and AGA fetus using adverse NNO markers and additional 3rd trimester antenatal USS parameters. I performed this by: (1) Evaluating the new implemented dedicated late FGR clinic management protocol which used risk stratification to determine timing of delivery by comparing labour, maternal and neonatal outcome with a pre-clinic cohort (see Chapter 4) (2) comparing in a time series analysis implementation impact of the new management protocol (see Chapter 5)(3) developing a multiparameter late FGR predictive model of adverse NNO identified using the same USS parameters to report on risk of adverse NNO at different gestational ages (see Chapter 6).

In Chapter 3: I discussed the processes used and employed to set up and implement the new dedicated UCLH Late FGR clinic. I also described the risk stratification used which combined maternal PAPP-A, Maternal comorbidities associated with late FGR and the same 3rd trimester USS described in chapter 1 and 2 to determine a high -risk late FGR cohort advised delivery at 37-38 weeks and a low-risk late FGR cohort allowed expectant management up to 41 weeks.

In Chapter 4: I assessed my late FGR clinic risk stratification and management protocol by comparing the labour, maternal and neonatal outcomes between the low and the high-risk late FGR cohorts. The low-risk late FGR group were significantly more likely to have a spontaneous vaginal delivery compared to the high-risk late FGR group. The low-risk late FGR group also had significantly less overall adverse NNO and were significantly heavier and older at delivery. There was however no significant difference in the remaining labour outcomes and in adverse maternal outcome between these two groups.

In Chapter 5: I evaluated my late FGR clinic risk stratification and management protocol by comparing the labour, maternal and neonatal outcomes with a pre-clinic cohort. The low-risk late FGR clinic group were significantly more likely to have a spontaneous vaginal delivery compared to the pre-clinic cohort. The low-risk late FGR group also had significantly less overall adverse NNO and were less likely to have evidence of intrapartum fetal compromise requiring episiotomy at the time of delivery. There was however no significant difference in the remaining labour outcomes and in adverse maternal outcome between these two groups and between the high-risk late FGR clinic and the pre-clinic cohort.

In Chapter 6: I performed a limited time series and used my late FGR clinic and pre-clinic cohort to assess whether or not adverse NNO in the high-risk group was related to iatrogenic early delivery or in fact more severe placental insufficiency in this group. I performed this task by comparing adverse NNO in high-risk late FGR delivered at 37 vs 38 weeks and low-risk delivered at 37 vs 40 weeks. I identified that adverse NNO was increased in the high-risk group at all gestations inferring that increased adverse NNO in the high-risk late FGR cohort is likely related to more severe placental insufficiency within this cohort.

7.1.2 Late FGR outcome and association with antenatal definitions

Using additional 3rd trimester USS parameters combined with EFW in SGA and AGA fetus “at risk” in the late FGR clinic such as increased UtA Doppler combined PI ≥2.5 or PI >95th centile, UmbA PI >95th centile, abnormally low CPR <5th centile for gestational age or significant drop in fetal AC ≥50 centiles compared to a 2nd trimester USS; I identified a “high-risk” FGR group at increased risk of placental insufficiency and functional adverse NNO compared to a “low-risk” FGR group at reduced risk of placental insufficiency, indicating these USS parameters can be used to predict adverse NNO and FGR independent of neonatal size.

My aim to identify reliable parameters antenatally of postnatal outcome was accomplished by a more detailed identification of the neonate affected by FGR. There was significantly increased overall adverse NNO in the high-risk compared to the low-risk FGR groups within the new UCLH late FGR clinic. Overall, there was significantly more hypoglycaemia, hypothermia, jaundice requiring phototherapy treatment, NNU admission. Overall the high-risk FGR vs the low-risk FGR babies had increased perinatal morbidity at delivery potentially due to a combination of late preterm complications (early iatrogenic term intervention) and more severe FGR related placental disease (Chapter 4).

7.1.3 Evaluation of the late FGR clinic versus the pre-clinic cohort

Evaluation of the late FGR clinic showed the low-risk late FGR clinic group vs the pre-clinic cohort were significantly more likely to have a SOL and a SOL followed by a vaginal delivery. In addition, due to the procedure of delayed delivery in the low-risk late FGR cohort this group compared to the pre-clinic cohort delivered significantly later and were significantly heavier at delivery. Furthermore, delayed delivery and avoiding early iatrogenic preterm or late term delivery in the low-risk late FGR cohort compared to the pre-clinic cohort was associated with significantly less overall adverse NNO. It is therefore possible that an appropriately identified high risk cohort might benefit early term delivery whereas a low risk cohort can be conservatively managed until the due date (Chapter 5).

7.1.4 Producing a multiparametric model to predict adverse NNO

Using a multiparametric model from real and simulated data from the late FGR clinic and the pre-clinic cohort I was able to estimate the probability of an adverse NNO < 36 weeks and > 40 weeks **See Chapter 6 multiparametric model to predict adverse NNO.** This model showed us that at any gestation low-risk pregnancies had reduced risk of adverse NNO with adverse NNO nadir at 38 to 40 weeks identifying the importance of trying to avoid early term delivery whilst allowing delayed delivery up to 41 weeks in low-risk late FGR pregnancies in order to reduce adverse NNO.

7.1.5 Future Aims

Although the late FGR clinic at UCLH is now established I remain keen to continue working closely with my dedicated PPI group, colleagues and the extended multidisciplinary team to continue to further improve the neonatal, labour and maternal outcomes in the late FGR Clinic. My MD (Res) project has shown that 3rd trimester sonographic parameters as well as maternal biochemistry and comorbidities known to be associated with placental insufficiency and adverse NNO can be used to risk stratify late FGR pregnancies and by allowing delayed delivery in the low-risk late FGR group this was associated with significantly reduced adverse NNO in the low-risk late FGR cohort compared with the high-risk late FGR cohort and the pre-clinic cohort.

In terms of future aims I am particularly interested in proposed future work involving additional sonographic parameters, maternal biochemical markers and maternal haemodynamics to further refine and improve the late FGR clinic diagnostic criteria, risk stratification and management protocols. I am particularly interested in using maternal biochemical markers including soluble fms-like tyrosine kinase to Placental growth factor (sFlt-1 to PlGF) ratio and combining this within my current late FGR clinic management pathways to potentially improve identification of high versus low-risk late FGR groups and to further guide surveillance frequency and timing of delivery within my two risk groups.

I am also interested in performing future work using placental histopathology to assess whether not the severity and type of placental lesions associated with late FGR can be used to not only further guide my current late FGR clinic risk stratification, surveillance and timing of delivery protocol but whether or not specific placental histology and lesions associated with placental histology could be used in combination with the present factors used in the late FGR clinic to improve the postnatal neonatal phenotype and diagnosis of late FGR.

In my MD (Res) project I also assessed adverse NNO between the different cohorts in the late FGR clinic as well as the pre-clinic cohort using short term adverse NNO. In the future I would be very interested to assess more long term and severe adverse NNO (including evidence of cerebral palsy, cognitive, motor, hearing or visual impairment) in line with the COSNEON study by Damhuis in 2021[142]. I feel assessing these long term and severe adverse NNO could potentially improve the current parameters used in the screening, risk stratification and the management protocols used in the UCLH late FGR.

The Truffle 2 trial is planning to assess the timing of delivery between 32 and 36+6 weeks in late preterm FGR pregnancies[321]. As a future aim I would be keen for the data reported in my thesis to potentially provide the feasibility and safety data to set up a randomised trial ideally using risk stratification based on parameters and adverse NNO associated with placental insufficiency to further investigate the optimal timing of delivery in Late FGR pregnancies >37 weeks.

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