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Why we miss fetal growth restriction: Identification of risk factors for severely growth-restricted fetuses remaining undelivered by 40 weeks gestation

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Why we miss fetal growth restriction: Identification of risk factors for severely growth restricted fetuses remaining undelivered by 40 weeks' gestation.

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**Why we miss fetal growth restriction:
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Abstract

BACKGROUND

Severe fetal growth restriction (FGR) is a leading cause of adverse perinatal morbidity and mortality, however in Victoria, 35% of severely growth-restricted infants are undelivered by 40 weeks' gestation.

AIMS

We aimed to identify factors associated with failure to deliver severely growth-restricted fetuses by 40 weeks' gestation.

METHODS

We conducted a retrospective case-control study of term singletons born <3rd centile for gestation at a single tertiary centre (2010-2017). Infants with a planned delivery for FGR between 37.0–39.6 weeks' gestation ("planned birth" group; n=187) were compared with those undelivered by 40.0 weeks' ("undelivered" group; n=233). Variables assessed included the presence of risk factors for FGR, model of care, symphyseal-fundal height measurements and third-trimester ultrasounds.

RESULTS

An equivalent proportion of women were 'high-risk' for FGR on history (31.3% vs 38.0%, $p=0.187$) in the planned and undelivered groups. Women booked under low-risk models (shared care and midwifery-led care) were significantly more likely to be in the undelivered group compared to those booked under traditional collaborative models (79.8% vs 37.4%, $p<0.001$). Women in the undelivered group were less likely to have received a third-trimester ultrasound (93.0% vs 40.3%, $p<0.001$), however were more likely to have had a reassuring ultrasound with an EFW or AC >10th centile (78.7% vs 16.1%, $p<0.001$).

CONCLUSIONS

Failure to deliver the severely growth-restricted fetus before 40.0 weeks' is more likely to occur in the following situations: 1) failure to receive an indicated third-trimester ultrasound; 2) the presence of falsely reassuring third-trimester ultrasound scan; and 3) booking under a low-risk rather than traditional collaborative models of care.

Introduction

Fetal growth restriction (FGR) is the pathological failure of a fetus to reach its biologically determined growth potential.¹ Antenatal detection of FGR is a critical objective of maternity care, given that it is a significant cause of perinatal morbidity and mortality, and the single largest cause of unexplained stillbirth.²⁻⁴ Previous studies have demonstrated a seven-fold increase in adverse neonatal outcomes in fetuses with birthweight <3rd centile for gestational age.⁵ Complications include short-term neonatal morbidity such as intraventricular haemorrhage, necrotising enterocolitis and sepsis.^{6,7} Long-term sequelae include increased risk of cerebral palsy, cardiovascular and cerebrovascular disease, metabolic syndrome, type 2 diabetes mellitus and mental illness.⁸⁻¹⁰

Antenatal diagnosis of FGR has undeniable benefits. Intensive fetal surveillance (both antenatal and intrapartum) together with optimising timing of birth may reduce adverse perinatal outcomes by up to four-fold.¹¹⁻¹³ However, the antenatal detection of FGR remains extremely challenging. Universal third-trimester ultrasound has been shown to detect less than two-thirds of growth-restricted infants, with even lower detection rates if relying on clinical suspicion alone.¹⁴

Given that adverse outcomes of FGR are known to rapidly increase with advancing gestation,¹⁵ the Victorian Department of Health has nominated 'severe intra-uterine growth restriction in a singleton pregnancy undelivered by 40 weeks' as a key performance indicator in the assessment of maternity care quality. However, during 2015-2016, over one-third of fetuses <3rd centile born in Victorian public hospitals remained undelivered at 40 weeks'.¹⁶ The performance indicator only includes infants born <3rd centile, as this group is less likely to be constitutionally small, and less reasonably undelivered, than the small-for-gestational-age (SGA) fetus between the 3rd and 10th centiles.

We aimed to identify which factors were associated with fetuses <3rd centile for birthweight being undelivered by 40 weeks' gestation, with a view to develop strategies to reduce the adverse consequences of undiagnosed severe FGR.

Methods

Study Population

We conducted a retrospective case-control study at a single tertiary maternity centre in Victoria, the Mercy Hospital for Women (MHW), comparing those pregnancies in which severe FGR was diagnosed antenatally and delivered prior to 40 weeks' gestation, with severely growth-restricted infants undelivered by that time. Data was collected over a seven-year period, from 1 March 2010 to 28 February 2017. Severe FGR was defined as <3rd centile for gestation and gender, using Australian population birthweight centiles for singleton infants (Dobbins, 2012),¹⁷ which are those currently used in the Victorian Perinatal Services Performance Indicators.

All singleton infants born <3rd centile at 40.0 weeks' gestation or later were identified as the cases ('undelivered' group). Controls were defined as singleton, term, infants <3rd centile intentionally delivered by planned caesarean section or induction of labour, between 37.0 – 39.6 weeks' gestation, with a documented indication for delivery being suspected placental insufficiency ('planned birth' group). Women who underwent spontaneous labour prior to 40.0 weeks' gestation were excluded, as it was uncertain whether a conscious decision to deliver based on suspected fetal growth restriction would have occurred or not. Women who had an elective caesarean section or induction prior to 40.0 weeks' gestation were also excluded, if growth restriction or suspected placental insufficiency was not documented as a reason for delivery, as delivery timing may have been unrelated to the discovery of growth restriction.

Multiple pregnancies and congenital fetal anomalies (major structural malformations, major chromosomal or metabolic disorders) were excluded. Women with no first-trimester ultrasound were excluded, to ensure all had an accurately dated pregnancy.

Data Source

Cases and controls were identified using the Birthing Outcomes System (BOS), a database in which midwives record patient characteristics, delivery indications and birthing outcomes as part of routine maternity care. Individual medical records were used to obtain medical, obstetric and antenatal history and to determine model of care. Information about antenatal appointments and continuity of care was checked against the Inpatient Management (IPM) system, which contains an electronic catalogue of each maternity visit at the hospital by

patients. Ultrasound reports were obtained from Clinical Patient Folder (CPF), a system recording all clinical investigations.

Outcome Measures

(i) **Baseline Characteristics and Risk Factors for FGR on History**

Baseline characteristics assessed included maternal age, body mass index (BMI), height, parity, gestational age at delivery and mode of conception. Known risk factors for FGR were documented, including previous SGA infants <10th centile or <3rd centile, previous stillbirth, pregnancy interval <6 or >60 months, pregnancy-associated plasma A protein (PAPP-A) <0.4 MoM, pre-eclampsia, gestational hypertension, gestational diabetes mellitus and smoking, alcohol or illicit drug use during pregnancy. Medical conditions were recorded including essential hypertension, pre-existing diabetes mellitus, autoimmune disease (systemic lupus erythematosus, antiphospholipid syndrome), thrombophilias, cardiovascular disease, chronic pulmonary disease, renal insufficiency, congenital infections, iron deficiency anaemia and thalassaemia. Risk factors were considered to be ‘major’ or ‘minor’ in accordance with international obstetric guidelines.¹⁸ We defined women as ‘high-risk’ for FGR if they had at least 3 minor risk factors, or 1 major risk factor.¹⁸

(ii) **Models of Care**

Four major maternity models of care were identified at the MHW, which align with national and international antenatal care structures;¹⁹⁻²¹ general practitioner (GP) shared care, midwife-led care, traditional collaborative care by public obstetricians and midwives, and care by a private obstetrician. In accordance with Victorian maternity care frameworks,²² GP shared care and midwife-led care were grouped as ‘low-risk’ models. Traditional collaborative care and private obstetric care were grouped as ‘mixed-risk’ models, as they cared for both low and high-risk patients.

The model of care the woman was allocated to at her first antenatal booking visit, as well as the predominant model of care in the third-trimester (beyond 28 weeks’) was recorded. If the woman was transferred from a low-risk to a mixed-risk model, this was noted. Continuity of care was defined as seeing the same type of health professional (either midwives, GPs or obstetricians) or the same individual health professional (exact same midwife, GP or obstetrician), over at least three of the five consecutive visits prior to birth and prior to 39 weeks’.

(iii) Symphyseal Fundal Height (SFH) Measurements

The last three SFH measurements prior to birth, and prior to 39 weeks' gestation, were recorded. We assessed whether the fundal height had been measuring significantly behind dates or remained static. The former was defined as a SFH of at least 3cm less than the current gestational age and the latter as no growth in SFH over two or more consecutive measurements, with at least a two-week gap between the visits.

(iv) Third-Trimester Ultrasound

We assessed whether third-trimester ultrasound biometry was performed and the mean number of scans performed if one was conducted. As per international guidelines, one major risk factor or three minor risk factors were considered indications for a third-trimester ultrasound.¹⁸ Ultrasound estimations of fetal weight (EFW) and abdominal circumference (AC) were separately assessed with respect to: <10th centile, <25th centile or 'slowed growth' (centile decreasing by ≥ 25 centiles).

Statistical Analysis

Means, standard deviations, medians or percentages of the total were used to describe outcomes of interest. Chi-squared tests were used for analysis of categorical variables, and the unpaired Student's t-test for analysis of continuous variables that approximated a normal distribution. Statistical significance was regarded as a p-value <0.05. Statistical analysis was performed using GraphPad Prism Version 7.0c, 2017.

Ethics

Ethics approval was granted by the Human Research Ethics Committee at the Mercy Hospital for Women (approval project number R16:18).

Results

Over the 7-year period, 466 infants were identified who met the inclusion criteria. Of these, 46 were excluded, due to an inaccurately dated pregnancy (n=25), no antenatal record available (n=14), fetal malformation (n=6) and multiple pregnancy (n=1); leaving 420 available for analysis. Additionally, patients under shared care (n=36) or private care (n=35) at booking visit were excluded from the analysis of continuity of care and SFH measurement, due to incomplete information in their histories.

Baseline Characteristics

Maternal age, parity, height, BMI and mode of conception were equivalent in the planned birth and undelivered groups (Table 1). As expected, the mean gestational age at delivery was greater in the undelivered group (40.6 weeks') compared to the planned birth group (38.3 weeks'), demonstrating a significantly earlier gestation at delivery if FGR was detected.

Risk Factors on Maternal History

Overall, an equivalent number of women in both groups were considered high-risk based on medical or obstetric risk factors (Table II). Further, women were equally as likely to smoke, drink alcohol, or have had a previous SGA baby <10th centile. Women who used illicit substances during pregnancy were more likely to be in the planned birth group (11 (5.9%) vs 2 (0.9%) women, $p=0.008$). All women who had a low PAPP-A were in the planned birth group (8 (4.3%) vs 0 (0%), $p=0.005$).

Models of Maternity Care

Table III demonstrates that almost 80% of women undelivered by 40.0 weeks' were booked under low-risk models, compared with only 20% booked under mixed-risk models. However, women having a planned birth were much more likely to have been booked in a mixed-risk model (117 (62.6%) vs 70 (37.4%), $p<0.001$). If a woman was booked under low-risk care, and did not spontaneously labour or get delivered for another reason, she had a 73% (186 of 256) chance of remaining undelivered by 40.0 weeks' gestation, compared with a 27% chance (47 of 164) of being undelivered if booked under collaborative models.

Symphyseal Fundal Height Measurements

Planned birth for FGR was strongly associated with a fundal height measuring below the expected gestation prior to birth on any of the last three measurements (126 of 167 (75.5%) vs 61 of 179 (34.1%), $p <0.001$) and on the most recent measurement (110 of 167 (65.9%) vs 47 of 179 (26.3%), $p<0.0001$); and with static fundal growth on any of the last three measurements (53 of 167 (31.7%) vs 26 of 179 (14.5%), $p<0.0001$) (Table 4).

Third-Trimester Ultrasound Scans

Table 4 shows that receiving a third-trimester ultrasound was significantly associated with planned birth for FGR (174 (93.0%) vs 94 (40.3%), $p<0.001$). An equivalent proportion of women were high-risk for FGR and warranted a third-trimester ultrasound in both the cases and controls (73 (31.3%) vs 71 (38.0%)). All women with an ultrasound indicated on history

received one in the planned birth group, compared to approximately half of those delivering after 40.0 weeks' (71 of 71 (100%) vs 38 of 73 (52.1%), $p < 0.001$).

The presence of falsely reassuring fetal size on ultrasound was strongly associated with being in the undelivered group. Of the undelivered group, 78.7% (74 of 94) were falsely reassured by an EFW or AC $> 10^{\text{th}}$ centile on all third-trimester ultrasounds, compared with only 16.1% (28 of 174) of those with a planned birth having all scans within normal limits ($p < 0.001$). It is noteworthy that of those in the undelivered group that had a third-trimester ultrasound, 61.7% (58 of 94) had a fetus measuring $< 25^{\text{th}}$ centile for EFW or AC on at least one scan ($p < 0.001$). Of those women that had at least two ultrasounds, significantly more of undelivered group had ultrasound evidence of crossing growth centiles (15/ 39 (38.6%) vs 12/ 116 (10.3%), $p < 0.001$).

Discussion

Our study provides insights into the factors leading to severe FGR being undelivered by 40.0 weeks' gestation. We identified key factors that differed between women in whom birth was planned before 40.0 weeks' and those who were undelivered past 40.0 weeks'.

Approximately one third of women in the study were defined as high-risk for FGR on the basis of underlying risk factors. This proportion did not differ between the planned birth and undelivered groups. We had hypothesised initially that women with multiple risk factors for FGR would be more easily identified and thus less likely to be missed, however this was not the case. This can at least in part be explained by the presence of risk factors failing to trigger an indicated third-trimester ultrasound in almost 50% of women in whom a scan was indicated.

Two risk factors were independently associated with detection of FGR; low PAPP-A and use of illicit substances during pregnancy. At the study centre, a specific guideline for women with PAPP-A < 0.4 MOM recommends a third-trimester ultrasound. This contrasts with other obstetric or medical risk factors that frequently failed to trigger an indicated scan, and may reflect the importance of a local guideline endorsed by the hospital's obstetricians and midwives. Women using illicit substances are cared for in a dedicated high-risk unit that includes heightened fetal surveillance and a low threshold for delivery before 40 weeks' gestation.

A low-risk model of maternity care was strongly associated with an increased likelihood of being in the undelivered group. This was true for both the model of care at booking, and also the model of care during the third-trimester. Importantly, this was irrespective of the presence or absence of underlying risk factors. The relative absence of third-trimester ultrasounds in the undelivered group suggests that a very small baby was not suspected.

Previous studies, including two small Australian randomised controlled trials (RCTs) and a Cochrane review,²³⁻²⁶ found no differences in serious perinatal outcomes between midwifery-led models compared to conventional collaborative models. However, serious adverse obstetric outcomes are so infrequent that small but important differences will seldom be demonstrable using RCT methodology. Severe FGR is strongly associated with stillbirth but is much more frequent, and this may be why we have detected differences not seen in other studies.

As anticipated, those with planned birth for FGR were more likely to have had reduced or static symphyseal-fundal height measurements identified. It may be that healthcare providers in collaborative-care models see FGR more frequently and have a higher index of suspicion.

Also as expected, those women who received a third-trimester ultrasound were significantly more likely to be in the planned birth group. Moreover, if an ultrasound was indicated based on history, every woman in the planned birth group received it, compared to only half of women in the undelivered group. These findings provide compelling arguments for the need for clear guidelines stipulating the indications for performing third-trimester growth scans.

Finally, we observed that of those women who had a third-trimester ultrasound and had a planned birth, the vast majority had at least one scan with EFW or AC $\leq 10^{\text{th}}$ centile. Conversely, only one in five of those of women in the undelivered group had an ultrasound with EFW or AC $\leq 10^{\text{th}}$ centile, although almost two-thirds had a fetus measuring $\leq 25^{\text{th}}$ centile for EFW or AC on ultrasound. Given the margin of error inherent in ultrasound, it is important to maintain a high level of clinical suspicion for FGR among the subpopulation that are close to, but not less than, the 10^{th} centile. As FGR at term can be the result of late-onset pathology, it is also important not to be falsely reassured by ultrasounds performed early in the third-trimester, as they may not be representative of later fetal size. Those in the undelivered group were more likely to have crossed centiles on ultrasound, indicating slowing of growth while still remaining within normal parameters in their most recent

ultrasound. This demonstrates that decelerating fetal growth is an area necessitating stronger clinical suspicion and consideration for delivery.

Strengths and Limitations of Study

We believe our findings make a significant contribution to the literature as we are not aware of any studies of severely growth restricted ($< 3^{\text{rd}}$ centile) term singletons, that have compared those born by planned birth with those going up to or beyond their due date. Our study incorporates a large sample size, in a single centre, representative of contemporary obstetric practice. An inherent limitation of the study is its retrospective design. To ensure accuracy of our records, we used multiple data sources, including paper medical histories and three electronic databases. However, some information was difficult to obtain, including symphyseal height and ultrasound data from the history of women in shared or private care. We were also unable to take into consideration the role of maternal choice in the timing of delivery. It is possible that women who seek out low-risk models of care may also be those less inclined to accept interventions by induction or caesarean section even in the event of an identified small fetus, and that there is a proportion of women in whom early delivery was offered and declined.

Conclusions

Severe FGR is an area of national public health significance associated with such perinatal morbidity and mortality that birth of the infant $< 3^{\text{rd}}$ centile at or after 40.0 weeks' has been adopted by the Victorian Department of Health as a maternity care performance indicator. We identified key differences in the care that the severely growth restricted ($< 3^{\text{rd}}$ centile), term singleton fetus with planned birth before 40.0 weeks' received compared to those undelivered at or beyond 40.0 weeks'. Women were much more likely to have been cared for under 'low-risk' models in the undelivered group, irrespective of the woman's underlying risk factors for FGR. This provides a strong argument for education and up-skilling of low-risk carers, as they are an essential part of our maternity workforce. Women were also much less likely to have had a third-trimester ultrasound in the undelivered group; even if clinically indicated. If an ultrasound was performed, it was more likely to be falsely reassuring. Our findings identify targetable areas for improvements in maternity care in the hospital.

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Table I: Baseline Characteristics

Characteristic	Undelivered (n=233)	Planned birth (n=187)	p-value
Maternal age (y)	31.62 (4.68)	31.28 (5.05)	0.463
Age 35-40 (%)	44 (18.9)	42 (22.5)	0.435
Age >40 (%)	10 (4.3)	3 (1.6)	0.195
Gestation at delivery (weeks)	40.6 (0.55)	38.3 (0.73)	<0.0001
Nulliparity (%)	166 (71.2)	119 (63.6)	0.120
Maternal height (cm)	157.1 (6.61)	159.1 (6.10)	0.369
BMI (kg/m ²)	23.4 (4.60)	23.6 (4.85)	0.651
BMI 30-35 (%)	22 (9.4)	15 (8.0)	0.610
BMI >35 (%)	6 (2.6)	7 (3.7)	0.687
IVF conception (%)	7 (3.0)	2 (1.1)	0.307

Continuous variables are summarised with mean (SD) and categorical variables with n (%).BMI; body mass index, IVF; in vitro fertilisation.

Table II: Association between risk factors on history and detection of fetal growth restriction.

Outcome	Undelivered (n=233) (%)	Planned birth (n=187) (%)	P value
Overall Risk Category†			
Low-Risk	160/233 (68.7)	116/187 (62.1)	0.187
High-Risk	73/233 (31.3)	71/187 (38.0)	
Medical Risk Factors	28/233 (12.0)	20/187 (10.7)	0.788
Essential hypertension	3/233 (1.29)	0/187 (0)	0.33
Pre-existing diabetes mellitus	0/233 (0)	0/187 (0)	-
Autoimmune disease	2/233 (0.86)	2/187 (1.07)	0.776
Thrombophilias	2/233 (0.86)	0/187 (0)	0.578
Other‡	7/233 (3)	14/187 (7.49)	0.062

Obstetric Risk Factors			
Previous SGA <10 th centile	35/67 (52.2)	41/68 (60.3)	0.441
Previous FGR <3 rd centile	20/67 (29.9)	25/68 (36.8)	0.503
Previous stillbirth	2/67 (1.5)	2/68 (2.9)	0.99
Pregnancy interval <6 or >60 months	1/233 (0.4)	2/187 (1.1)	0.848
Low PAPP-A <0.4 MoM	0/233 (0)	8/187 (4.3)	0.005
Preeclampsia/ gestational hypertension	14/233 (6.0)	10/187 (5.4)	0.937
Gestational diabetes mellitus	14/233 (6.0)	16/187 (8.6)	0.414
CMV or toxoplasmosis infection	0/233 (0)	0/187 (0)	-
Smoking	24/233 (10.3)	22/187 (11.8)	0.749
Alcohol consumption	11/233 (4.7)	6/187 (3.2)	0.594
Illicit substance use	2/233 (0.9)	11/187 (5.9)	0.008

†High risk; 3 minor or 1 major risk factors for FGR, low risk; 0-2 minor risk factors for FGR. ‡ Other: Cardiac disease, chronic pulmonary disease, renal insufficiency, iron deficiency and thalassaemia

Table III: Association between models of maternity care and detection of fetal growth restriction.

	Undelivered (n=233) (%)	Planned birth (n=187) (%)	p-value
Model of care at booking			
Low-risk	186 (79.8)	70 (37.4)	<0.001
Mixed-risk	47 (20.2)	117 (62.6)	
Model of care in third trimester			
Low-risk	163 (69.6)	49 (26.2)	<0.001
Mixed-risk	70 (30.0)	138 (73.8)	

Table IV: Association between symphyseal fundal height, third-trimester ultrasound and detection of fetal growth restriction.

Outcome	Undelivered (n=233) (%)	Planned birth (n=187) (%)	P-value
Symphyseal Fundal Height			
Fundus < dates on last 3 measurements†	61/179 (34.1)	126/167 (75.5)	<0.001

Fundus < dates on most recent measurement	47/179 (26.3)	110/167 (65.9)	<0.001
Static growth on last 3 measurements‡	26/179 (14.5)	53/167 (31.7)	<0.001
Performance of Third- Trimester Ultrasound			
Scan performed	94/233 (40.3)	174/187 (93.0)	<0.001
Mean number of scans performed (SD) §	1.6 (0.82)	2.5 (1.32)	<0.001
Mean gestation at first scan (weeks) (SD)	33.2 (3.14)	32.4 (3.47)	0.0656
Mean gestation at most recent scan (weeks)	35.2 (2.27)	36.3 (1.51)	<0.001
Scan performed if indicated on history	38/73 (52.1)	71/71 (100)	<0.001
Third Trimester Ultrasound Parameters §			
EFW or AC ≤ 10th centile on any scan	20/94 (21.3)	146/174 (83.9)	<0.001
EFW or AC ≤ 25th centile on any scan	58/94 (61.7)	156/174 (89.7)	<0.001
EFW or AC ≤ 10th centile on most recent scan	15/94 (16.0)	134/174 (77.1)	<0.001
EFW or AC ≤ 25th centile on most recent scan	53/94 (56.4)	144/174 (82.8)	<0.001
Crossing of growth centiles††	15/39 (38.6)	12/116 (10.3)	<0.001

† Fundus measuring at least 3cm less than the expected equivalent gestation on any of the last 3 SFH measurements prior to birth.‡ No growth in SFH over two or more consecutive measurements gestations, with at least a two-week gap between visits.§ Out of those that received an ultrasound. †† Fetus crossing ≥ 25 centiles for EFW or AC on any two consecutive scan in the third trimester.