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Management of late-onset fetal growth restriction: pragmatic approach

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KEYWORDS: late fetal growth restriction; risk classification; timing of delivery; ultrasound management

CONTRIBUTION

What are the novel findings of this work?
Appropriate antenatal risk classification using ultrasound including Doppler parameters in pregnancies with late-onset fetal growth restriction (FGR) allows fetuses at low risk of *in-utero* compromise to benefit from expectant management, with associated low neonatal and maternal morbidity.

What are the clinical implications of this work?
Risk stratification in late FGR pregnancy and pragmatic management based on a novel protocol for timing of surveillance and delivery could be implemented into clinical practice to reduce intervention in low-risk cases, with potential advantages in the neonatal period and long term.

ABSTRACT

Objectives *There is limited prospective evidence to guide the management of late-onset fetal growth restriction (FGR) and its differentiation from small-for-gestational age. The aim of this study was to assess prospectively a novel protocol in which ultrasound criteria were used to classify women with suspected late FGR into two groups: those at low risk, who were managed expectantly until the anticipated date of delivery, and those at high risk, who were delivered soon after 37 weeks of gestation. We also compared the outcome of this prospective cohort with that of a historical cohort of women presenting similarly with suspected late FGR, in order to evaluate the impact of the new protocol.*

Methods *This was a prospective study of women with a non-anomalous singleton pregnancy at ≥ 32 weeks' gestation attending a tertiary hospital in London, UK, between February 2018 and September 2019, with estimated fetal weight (EFW) ≤ 10th centile, or EFW > 10th centile in addition to a decrease in fetal abdominal circumference of ≥ 50 centiles compared with a previous scan, umbilical artery Doppler pulsatility index > 95th centile or cerebroplacental ratio < 5th centile. Women were classified as low or high risk based on ultrasound and Doppler criteria. Women in the low-risk group were delivered by 41 weeks of gestation, unless they subsequently met high-risk criteria, whereas women in the high-risk group (EFW < 3rd centile, umbilical artery Doppler pulsatility index > 95th centile or EFW between 3rd and 10th centiles (inclusive) with abdominal circumference drop or abnormal Dopplers) were delivered at or soon after 37 weeks. The primary outcome was adverse neonatal outcome and included hypothermia, hypoglycemia, neonatal unit admission, jaundice requiring treatment, suspected infection, feeding difficulties, 1-min Apgar score < 7, hospital readmission and any severe adverse neonatal outcome (perinatal death, resuscitation using inotropes or mechanical ventilation, 5-min Apgar score < 7, metabolic acidosis, sepsis, and cerebral, cardiac or respiratory morbidity). Secondary outcomes were adverse maternal outcome (operative delivery for abnormal fetal heart rate) and severe adverse*

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neonatal outcome. Women managed according to the new protocol were compared with a historical cohort of 323 women delivered prior to the implementation of the new protocol, for whom management was guided by individual clinician expertise.

Results *Over 18 months, 321 women were recruited to the prospective cohort, of whom 156 were classified as low risk and 165 were high risk. Adverse neonatal outcome was significantly less common in the low-risk compared with the high-risk group (45% vs 58%; adjusted odds ratio (aOR), 0.6 (95% CI, 0.4–0.9); P = 0.022). There was no significant difference in the rate of adverse maternal outcome (18% vs 24%; aOR, 0.7 (95% CI, 0.4–1.2); P = 0.142) or severe adverse neonatal outcome (3.8% vs 8.5%; aOR, 0.5 (95% CI, 0.2–1.3); P = 0.153) between the low- and high-risk groups. Compared with women in the historical cohort classified retrospectively as low risk, low-risk women managed under the new protocol had a lower rate of adverse neonatal outcome (45% vs 58%; aOR, 0.6 (95% CI, 0.4–0.9); P = 0.026).*

Conclusions *Appropriate risk stratification to guide management of late FGR was associated with a reduced rate of adverse neonatal outcome in low-risk pregnancies. In clinical practice, a policy of expectantly managing women with a low-risk late-onset FGR pregnancy at term could improve neonatal and long-term development. Randomized controlled trials are needed to assess the effect of an evidence-based conservative management protocol for late FGR on perinatal morbidity and mortality and long-term neurodevelopment.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Late-onset fetal growth restriction (FGR) is associated with stillbirth, fetal compromise during labor and neonatal morbidity[1,2]. In late pregnancy (≥ 32 weeks of gestation), pathological smallness may not be evident on ultrasound[3]. Furthermore, fetuses with estimated fetal weight (EFW) > 10th centile may also be at high risk of compromise, whilst a proportion of fetuses who are small-for-gestational-age (SGA) may be constitutionally small with low risk of adverse outcome[4–6]. A Delphi survey defined late FGR as a fetus at ≥ 32 weeks that is particularly small (EFW or abdominal circumference (AC) < 3rd centile) or has growth failure (drop in EFW or AC centile) or abnormal fetal Dopplers[7]. This definition of FGR depends on the local fetal growth chart used and its application to clinical decision-making at term has not been validated in prospective studies.

There is no international consensus on how to define the severity of late-onset FGR or on the optimal monitoring policy or timing of delivery, with guidance on the latter varying from 37 to 39 weeks of gestation[1,2,8,9]. A Cochrane review identified only two studies comparing delivery with expectant management in term fetuses at risk of *in-utero* compromise or late FGR, showing no difference in perinatal outcome[10]. Retrospective research indicates that ultrasound parameters and biomarkers can be applied safely to late-FGR pregnancies in order to distinguish a high-risk SGA fetus that requires delivery at 37 weeks from a low-risk SGA fetus that can continue *in-utero* development[11].

The aim of this study was to evaluate prospectively the ability of a novel ultrasound management protocol (Appendix S1) to differentiate between fetuses with suspected late FGR at high risk of *in-utero* compromise from those at low risk of complications that could potentially be managed conservatively by delaying delivery until 41 weeks' gestation. The secondary aim was to compare the outcome of this prospective cohort with that of a historical cohort of women presenting similarly with suspected late FGR, for whom management was guided by individual clinician expertise.

METHODS

This was a prospective study of women with a non-anomalous singleton pregnancy and suspected late FGR, with an ultrasound scan performed at or after 32 weeks' gestation, referred to University College London Hospital, London, UK, between February 2018 and September 2019. Women were included if EFW was ≤ 10th centile on a customized[12] or population[13] fetal growth chart, or if EFW was > 10th centile in addition to umbilical artery Doppler pulsatility index (PI) > 95th centile (Schaffer H and Staudach A, Doppler Refernzkurven, pers. comm., 1997), cerebroplacental ratio (CPR) < 5th centile[14] or a decrease in fetal AC of ≥ 50 centiles compared with a second-trimester ultrasound scan[15].

A secondary analysis was performed, in which the outcome of this prospective patient cohort managed under the new protocol was compared with that of a historical cohort of women subject to the same inclusion criteria but recruited prior to the implementation of the new clinical management policy in 2017–2018. Women in the historical cohort were managed according to individual clinician expertise and were recruited retrospectively and consecutively in order to achieve a comparison group similar in number to the prospective cohort to make up the required sample size.

In our analysis, we included all pregnancies that were dated on ultrasound, using first-trimester crown–rump length[16,17] or second-trimester head circumference[18], or by the date of embryo transfer in the case of assisted conception. We excluded from analysis any pregnancy with evidence of structural, chromosomal or genetic abnormality diagnosed ante- or postpartum. Each woman's gynecological, obstetric and medical history was reviewed to identify maternal comorbidity and risk factors associated with FGR. Gynecological risk factors included the presence of multiple fibroids, a single fibroid ≥ 5 cm, uterine anomaly (bicornuate, unicornuate, didelphys

or septate uterus) or previous surgery for a uterine anomaly. Obstetric risk factors associated with FGR included pre-eclampsia, pregnancy-induced hypertension, gestational diabetes mellitus or antepartum hemorrhage. Obstetric risk factors relating to a past pregnancy included delivery of a SGA infant or placental abruption. Medical risk factors associated with FGR included chronic hypertension, diabetes mellitus Type 1 or 2, ulcerative colitis, Crohn's disease, celiac disease, sickle cell disease, human immunodeficiency virus infection, rheumatoid arthritis, nephrectomy, complicated renal disease, sleeve gastrectomy, protein S deficiency, homozygous Factor 5 Leiden thrombophilia, antiphospholipid syndrome, complex or cyanotic cardiac conditions or scleroderma.

Ultrasound examinations were performed in line with local, national and international guidelines[19–24] by sonographers competent in growth and Doppler scanning who underwent a dedicated 2-year program of training in obstetric ultrasound and fetal medicine[25]. At each visit, the woman's blood pressure was measured using an automatic V100 DINAMAP™ sphygmomanometer (GE Healthcare, Zipf, Austria) and urinalysis was performed using Labstix® reagent strips (Siemens, Munich, Germany). Pre-eclampsia and pregnancy-induced hypertension were diagnosed in accordance with international consensus[26]. Ultrasound was performed to measure fetal biometry, amniotic fluid and fetomaternal Dopplers. CPR and umbilical and uterine (UtA) artery Doppler PI were measured according to specific ultrasound methodology and standards[21,24,27,28]. EFW (g) was calculated based on biparietal diameter, head circumference, AC and femur length, using Hadlock's formula[29], and was plotted on customized[12] and population[13] fetal growth charts to calculate the EFW centile. Reproducibility of fetal biometry and Doppler measurements is reported elsewhere[25,30].

Low-risk late FGR was defined as: (1) EFW between the 3rd and 10th centiles (inclusive), with normal first-trimester pregnancy-associated plasma protein-A (PAPP-A) (> 0.4 multiples of the median (MoM)), normal second- or third-trimester UtA-PI, normal CPR (≥ 5th centile) and no fetal AC drop across ≥ 50 centiles; or (2) EFW > 10th centile, with a significant drop in fetal AC of ≥ 50 centiles compared with a second-trimester ultrasound scan or CPR < 5th centile[15,31]. Low-risk women were managed expectantly until 41 weeks, unless they met subsequently high-risk criteria.

High-risk late FGR was defined as: (1) EFW < 3rd centile[32]; (2) EFW between the 3rd and 10th centiles (inclusive) plus at least one of low PAPP-A (≤ 0.4 MoM)[33], increased second-trimester combined sum (of both arteries) UtA-PI (> 2.5) or mean UtA-PI > 95th centile at ≥ 32 weeks[34], CPR < 5th centile[31], or fetal AC drop across ≥ 50 centiles[15]; or (3) fetus of any size with umbilical artery Doppler PI > 95th centile[32]. High-risk women were delivered at or soon after 37 weeks.

A core set of outcomes was established in accordance with international consensus and the consultation of experts[35,36]. Birth-weight centiles were calculated according to both international standards[37] and customized birth-weight charts[38]. Adverse maternal outcome was considered if operative delivery for abnormal fetal heart monitoring in labor was required (either instrument-assisted vaginal delivery or emergency Cesarean section).

The primary outcome was adverse neonatal outcome and included any of the following: hypoglycemia, defined as serum glucose < 2.5 mmol; hypothermia, defined as temperature < 36.5°C; jaundice requiring phototherapy treatment or exchange transfusion, according to the bilirubin treatment threshold set by the UK National Institute for Health and Care Excellence (NICE); suspected infection with increased inflammatory markers and negative blood cultures; difficulties in establishing breastfeeding; 1-min Apgar score < 7; admission to neonatal unit; readmission to hospital for FGR-related complications, such as hypoglycemia, hypothermia, jaundice, poor feeding and weight loss of ≥ 10%; and any of the severe adverse neonatal outcomes detailed below.

Severe adverse fetal/neonatal outcome included any of the following: intrauterine or neonatal death; advanced cardiac or respiratory neonatal resuscitation, involving use of inotropes or mechanical ventilation; 5-min Apgar score < 7; severe metabolic acidosis, defined as cord blood pH < 7.0 and base deficit > 12 mmol/L; sepsis, defined as clinical sepsis and positive blood cultures, necrotizing enterocolitis or meningitis; and severe cerebral, respiratory or circulatory morbidity. Severe cerebral morbidity included intracerebral hemorrhage Grade 3 or 4, periventricular leukomalacia Grade 2 or 3, hypoxic ischemic encephalopathy or seizures. Severe respiratory morbidity included respiratory support for more than 1 week, mechanical ventilation, meconium aspiration and persistent pulmonary hypertension of the newborn. Severe circulatory morbidity included hypotensive treatment or ductus arteriosus treatment and disseminated intravascular coagulation[3,39].

Labor was induced by promoting cervical ripening using either prostaglandin E2 vaginal gel (2 mg) for a maximum of two doses at 6 h apart or slow-release prostaglandin E2 vaginal pessary (10 mg). If onset of labor did not occur within 12–24 h, oxytocin induction was initiated after artificial rupture of membranes. Indication for operative vaginal delivery for abnormal fetal heart rate followed NICE abnormal cardiotocography guidelines[40].

The study design, analysis and reporting adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations[41]. Statistical package for the social sciences (SPSS; IBM Corp., Armonk, NY, USA) and R (R Foundation for Statistical Computing Platform, Vienna, Austria) were used for data analysis. Continuous data were identified as normally distributed if the skewness and kurtosis *Z*-scores were between −1.96 and 1.96, the *P*-value for the Shapiro–Wilk test for normality was > 0.05, and graphical representations, including histograms, normal Q–Q plots and box-and-whiskers plots, showed evidence of symmetrical distribution. When the above tests did not confirm normality, data were presented as median (interquartile range (IQR)) and

compared using the non-parametric Mann–Whitney *U*-test. Pearson's chi-square test was used to test for association, except when the expected cell count was less than five, in which case Fisher's exact test was used. Multiple logistic regression analysis was performed to adjust for significant differences in characteristics between the two groups.

Based on previous pilot and observational data[3,39,42], we calculated that, in order to detect a significant reduction in composite adverse neonatal outcome of more than 15% between the low- and high-risk groups, a sample size of 152 women per group would be required (alpha 0.05; power 80%).

Using a model-based approach, we estimated the probability score of adverse neonatal outcome at different gestational ages (GA), presented on a scale from 0 to 1, where 0 is the lowest and 1 the highest risk of adverse neonatal outcome. We fitted a logistic regression model using data from the new cohort with a specified combination of risk factors. Namely, GA (in weeks) was used as a continuous variable and low/high-risk women were represented by a dichotomous variable. A non-linear relationship with GA was captured by adding a quadratic term. Thus, this model illustrates the estimated risk that is conferred to low- and high-risk women at different stages of pregnancy. To estimate the probability of adverse neonatal outcome prior to 36 weeks and after 40 weeks of gestation, we fitted a model using observed data from the new cohort, applied the model to the historical cohort and simulated data had the pregnancy ended earlier than 36 weeks or continued beyond the due date (Appendix S2).

The new protocol for management of late FGR was approved by local hospital clinical governance and implemented as part of routine clinical service. The study was approved and registered with the hospital governance team as a quality improvement project prior to commencement; therefore, the requirement for ethical approval and individual patient consent was waived.

RESULTS

Between February 2018 and September 2019, 364 women were referred to the late-FGR clinic for management under the new protocol. After excluding fetuses with structural or chromosomal abnormalities ($n = 2$), those not meeting criteria for abnormal growth ($n = 31$) and cases with no follow-up data ($n = 10$), 321 pregnancies were included in the final analysis. The characteristics and corresponding risk stratification of this prospective cohort is summarized in Table S1. There were 156 (48.6%) pregnancies in the low-risk group and 165 (51.4%) pregnancies in the high-risk group. The two groups were comparable over a range of demographic variables but differed in underlying gynecological and obstetric risk factors (Table 1), which were adjusted for in subsequent comparisons. As anticipated, a higher proportion of women had EFW $\leq 10^{th}$ customized centile in the high-risk group.

Low-risk women were twice as likely as women in the high-risk group to have spontaneous onset of labor (48.1% *vs* 26.1%; adjusted odds ratio (aOR), 2.4 (95% CI, 1.5–3.9); $P < 0.001$) and were more likely to have spontaneous labor with subsequent unassisted vaginal delivery (31.4% *vs* 19.4%; aOR, 1.7 (95% CI, 1.0–3.0); $P = 0.033$) (Table 2). There was no significant difference in the rate of adverse maternal outcome (17.9% *vs* 24.2%; aOR, 0.7 (95% CI, 0.4–1.2); $P = 0.142$). Similar proportions in each group had instrumental or emergency Cesarean delivery for abnormal fetal heart-rate monitoring.

Neonates in the low-risk group weighed almost 300 g more than did those in the high-risk group (median, 2840 *vs* 2558 g; $P < 0.001$) and were delivered 10 days later (median, 39 + 5 *vs* 38 + 2 weeks; $P < 0.001$) (Table 3).

Only 14 (4.4%) women, of whom one was in the low-risk group and 13 were in the high-risk group, were delivered before 37 weeks of gestation, due mainly to pre-eclampsia or spontaneous preterm labor. In both groups, some women were not delivered according

Table 1 Maternal demographic and clinical characteristics of 321 pregnancies with late-onset fetal growth restriction in prospective cohort, according to risk category

Characteristic	*Low risk* (n = *156*)	*High risk* (n = *165*)	P
Age (years)	33 (29–36)	33 (30–36)	0.596
Body mass index (kg/m^2)	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 risk factor	10 (6.4)	12 (7.3)	0.760
Past obstetric risk factor*	34 (21.8)	37 (22.4)	0.892
Current obstetric risk factor†	13 (8.3)	33 (20.0)	0.003
Gynecological risk factor	5 (3.2)	14 (8.5)	0.045
Pre-eclampsia	1 (0.6)	12 (7.3)	0.003
Gestational diabetes mellitus	11 (7.1)	13 (7.9)	0.779
EFW $\leq 10^{th}$ population centile	86 (55.1)	90 (54.5)	0.964
EFW $\leq 10^{th}$ customized centile	73 (46.8)	109 (66.1)	< 0.001
CPR $< 5^{th}$ centile	6 (3.8)	11 (6.7)	0.255
AC drop $\geq$ 50 centiles	16 (10.3)	13 (7.9)	0.459

Data are given as median (interquartile range) or *n* (%). *Including delivery of small-for-gestational-age infant or placental abruption. †Including pre-eclampsia, pregnancy-induced hypertension, gestational diabetes mellitus or antepartum hemorrhage. AC, abdominal circumference; CPR, cerebroplacental ratio; EFW, estimated fetal weight.

to protocol. Low-risk women were delivered before 38 weeks in 15% of cases due to maternal choice, spontaneous labor or elective Cesarean section. In the high-risk group, 34% of women were delivered after 38 weeks because they declined intervention, met high-risk criteria after 37 weeks or were awaiting elective Cesarean section scheduled at 39 weeks.

There was no significant difference in neonatal condition at birth (5-min Apgar score or cord arterial pH) (Table 3) and only one infant in each group had cord arterial pH < 7.1. There were no intrauterine or neonatal deaths in either group. The rate of birth weight < 3rd population centile was relatively low (8.3% in the low-risk group and 35.8% in the high-risk group).

Low-risk infants were less likely to develop adverse neonatal outcome compared with high-risk infants (44.9% *vs* 57.6%; aOR, 0.6 (95% CI, 0.4–0.9); $P = 0.022$) (Table 4). Specifically, they were less likely to develop hypothermia or hypoglycemia, receive treatment for hyperbilirubinemia or require admission to the neonatal unit (Table 4, Figure 1). There was no significant difference in the rate of severe adverse neonatal outcome between the low- and high-risk groups (3.8% *vs* 8.5%; aOR, 0.5 (95% CI, 0.2–1.3); $P = 0.153$) (Table 4, Figure 2).

We compared outcomes between women managed according to the new protocol and 323 women managed according to individual clinician expertise prior to implementation of the new clinical policy (old protocol). Low-risk women managed under the new protocol were delivered later (median (IQR), 39 + 5 (38 + 5 to 40 + 2) *vs* 39 + 1 (38 + 1 to 40 + 1) weeks' gestation; $P = 0.023$) and had a lower prevalence of birth weight < 3rd population centile (8.3% *vs* 17.6%; $P = 0.012$) compared with low-risk women managed under the old protocol (Table S2). Among those classified as high-risk, GA at delivery was earlier in women managed according to the new *vs* old protocol (median (IQR), 38 + 2 (37 + 5 to 39 + 0) *vs* 38 + 5 (37 + 4 to 39 + 6); $P = 0.02$) (Table S3). There was a reduction in the risk of adverse neonatal outcome in low-risk women managed according to the new *vs* old protocol (44.9% *vs* 57.8%; aOR, 0.6 (95% CI, 0.4–0.9); $P = 0.026$), whereas in high-risk women, no significant difference was observed (57.6% *vs* 63.2%; odds ratio, 0.8 (95% CI, 0.5–1.3); $P = 0.319$).

There was no difference in the rates of severe adverse neonatal outcome and adverse maternal outcome between old and new cohorts in both the low- and high-risk groups (Tables S2 and S3). We simulated the occurrence of adverse neonatal outcome with delivery before 36 weeks and after 41 weeks' gestation. When these simulated data were combined with our observed data from both the new and old cohorts, we observed that, at any GA, the probability score of adverse neonatal outcome was lower

Table 2 Maternal and labor outcomes in 321 pregnancies with late-onset fetal growth restriction in prospective cohort, according to risk category

Outcome	*Low risk* (n = *156*)	*High risk* (n = *165*)	*OR* *(95% CI)*	P	*aOR** *(95% CI)*	P
Spontaneous onset of labor	75 (48.1)	43 (26.1)	2.6 (1.6–4.2)	< 0.001	2.4 (1.5–3.9)	< 0.001
Induction of labor	61 (39.1)	84 (50.9)	0.6 (0.4–0.99)	0.034	0.6 (0.4–1.0)	0.065
Unassisted VD	80 (51.3)	72 (43.6)	1.4 (0.9–2.1)	0.170	1.3 (0.8–2.0)	0.235
Spontaneous onset of labor and unassisted VD	49 (31.4)	32 (19.4)	1.9 (1.1–3.2)	0.013	1.7 (1.0–3.0)	0.033
Adverse maternal outcome	28 (17.9)	40 (24.2)	0.7 (0.4–1.1)	0.128	0.7 (0.4–1.2)	0.142
Instrumental delivery for abnormal FHR	9 (5.8)	12 (7.3)	0.8 (0.3–1.9)	0.589	0.8 (0.3–1.9)	0.566
Emergency Cesarean section for abnormal FHR	19 (12.2)	28 (17.0)	1.0 (0.4–2.4)	0.991	0.6 (0.3–1.2)	0.173
Elective Cesarean section	15 (9.6)	21 (12.7)	0.7 (0.4–1.5)	0.377	0.8 (0.4–1.7)	0.575

Data are given as *n* (%), unless specified otherwise. *Adjusted for presence of gynecological risk factors and obstetric risk factors pertaining to current pregnancy. aOR, adjusted odds ratio; FHR, fetal heart rate; OR, odds ratio; VD, vaginal delivery.

Table 3 Neonatal characteristics of 321 pregnancies with late-onset fetal growth restriction in prospective cohort, according to risk category

Characteristic	*Low risk* (n = *156*)	*High risk* (n = *165*)	P
BW (g)	2840 (2663–3054)	2558 (2266–2735)	< 0.001
GA at delivery (weeks)	39 + 5 (38 + 5 to 40 + 2)	38 + 2 (37 + 5 to 39 + 0)	< 0.001
BW population centile	8 (5–11)	5 (3–9)	< 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 customized centile	9 (5–16)	5 (1–10)	< 0.001
BW ≤ 10th customized centile	87 (55.8)	129 (78.2)	< 0.01
BW < 3rd customized 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)	1.00
Cord arterial pH	7.26 (7.21–7.30)	7.27 (7.22–7.32)	0.523

Data are given as median (interquartile range) or *n* (%). BW, birth weight; GA, gestational age; NNU, neonatal unit.

on average in the low-risk group compared with the high-risk group. The risk of adverse neonatal outcome was highest prior to 37 weeks of gestation, reached a nadir at 39–40 weeks and increased again after 41 weeks (Figure 3). The probability of adverse outcome appeared to be higher on average for the high- *vs* low-risk group, however this did not reach statistical significance (average OR, 1.229 (credible interval, 0.723–2.079)). Despite there being an overlap in SD between the two groups, the average nadir in the high-risk group was equivalent to the probability at 38 and 40 weeks of gestation in the low-risk group.

Table 4 Neonatal outcome (NNO) of 321 pregnancies with late-onset fetal growth restriction in prospective cohort, according to risk category

Outcome	*Low risk* (n = *156*)	*High risk* (n = *165*)	*OR (95% CI)*	P	*aOR* (95% CI)*	P
GA at delivery						
≥ 39 weeks	110 (70.5)	42 (25.5)	7.0 (4.3–11.4)	< 0.001	6.7 (4.1–11.1)	< 0.001
≥ 40 weeks	68 (43.6)	6 (3.6)	20.5 (8.5–49.1)	< 0.001	19.9 (8.3–48.2)	< 0.001
≥ 41 weeks	12 (7.7)	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
Hypoglycemia	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
Length of stay 3 or 4 days	5 (3.2)	14 (8.5)	0.3 (0.1–1.0)	0.033	0.3 (0.1–0.9)	0.04
Length of stay ≥ 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
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 are given as *n* (%), unless specified otherwise. *Adjusted for presence of gynecological and obstetric risk factors pertaining to current pregnancy. aOR, adjusted odds ratio; GA, gestational age; NNU, neonatal unit; OR, odds ratio.

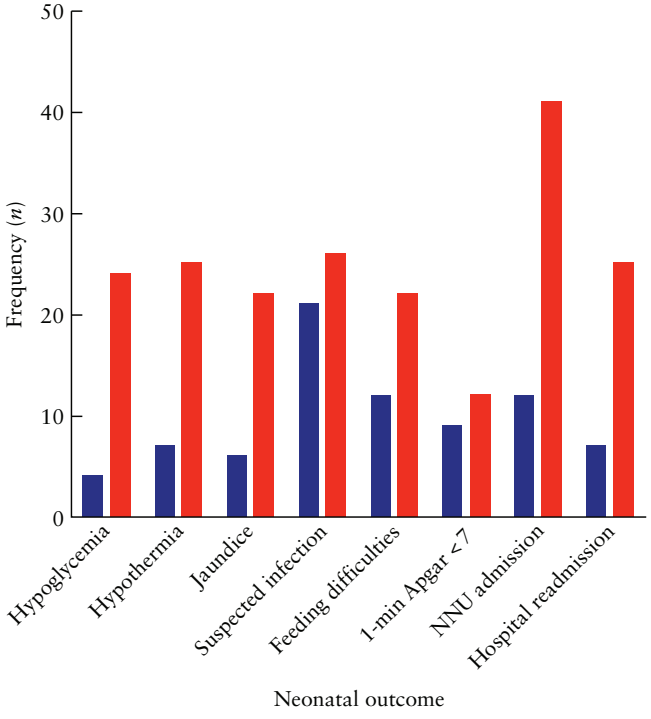

Figure 1 Frequency of adverse neonatal outcome in low-risk (■) and high-risk (■) pregnancies with late fetal growth restriction managed under new protocol. NNU, neonatal unit.

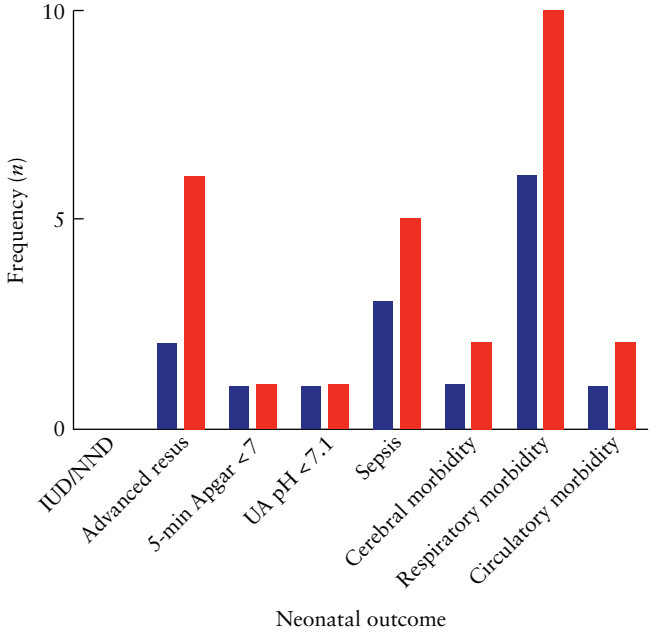

Figure 2 Frequency of severe adverse neonatal outcome in low-risk (■) and high-risk (■) pregnancies with late fetal growth restriction managed under new protocol. Advanced resus, neonatal resuscitation requiring mechanical ventilation or use of inotropes; IUD, intrauterine death; NND, neonatal death; UA, umbilical artery.

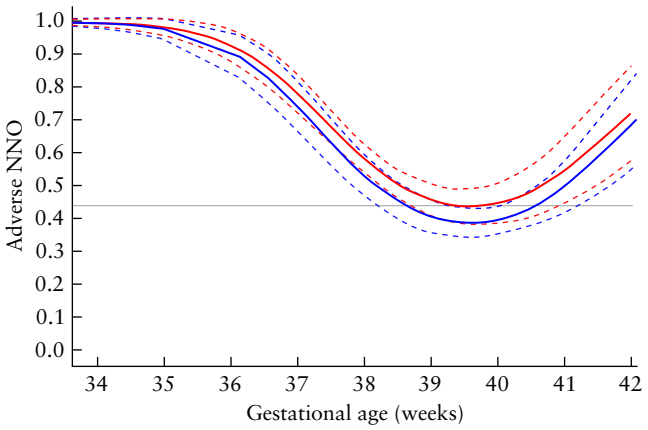

Figure 3 Fitted Bayesian logistic regression model showing estimated probability of adverse neonatal outcome (NNO) in low-risk (——) and high-risk (——) pregnancies with late fetal growth restriction as a function of gestational age. Estimations were applied to new and historical cohorts and to simulated data. Bands (dashed lines) represent SD around predictive posterior probability. Nadir of average lowest probability of adverse outcome in high-risk group is indicated by gray solid line.

DISCUSSION

This study showed that appropriate risk assessment in pregnancies with suspected late-onset FGR allowed women considered at low risk of placental impairment to be managed conservatively. Avoidance of iatrogenic early delivery in the low-risk group explains the observed increase in GA at delivery in these women, and contributed to their higher neonatal birth weights, without affecting maternal outcome. In the low- and high-risk groups, the rate of emergency Cesarean section for abnormal fetal heart rate was 12% and 17%, respectively, and the cumulative rate of emergency Cesarean section was 22% and 30%, respectively.

Infants in the low-risk group were significantly less likely to experience neonatal morbidity, including hypothermia, hypoglycemia or neonatal unit admission. A key challenge in the management of late FGR is balancing the risk of prematurity, if delivery is expedited, against the risk of further *in-utero* compromise and potential stillbirth if conservative management is adopted. We observed late prematurity complications in late growth-restricted fetuses delivered beyond 37 weeks, as has been shown in other studies[43,44].

International guidelines differ in their recommended timing of delivery for FGR fetuses[1,2,8,9,45,46]. Few studies have examined the management of late preterm or term FGR pregnancies[11,42]. The GRIT and TRUFFLE randomized controlled trials recruited a minority of late preterm fetuses (210 and 147 cases, respectively). In the GRIT study, no difference was observed in perinatal outcome between delayed and immediate deliveries, however detailed classification of FGR cases was not performed antenatally and the timing of delivery in the delayed group was left to the discretion of the individual clinician[47]. Meanwhile, the population of the TRUFFLE-1 trial[48] is not comparable with that of this study, as most women in this study had normal umbilical artery Doppler and most were delivered beyond 37 weeks' gestation. However, no stillbirths were recorded in the TRUFFLE-1 trial beyond 32 weeks and 12% of infants delivered after 34 weeks had adverse neonatal outcome, supporting the hypothesis that strategies for risk classification and delivery should be adopted in late preterm and term FGR.

A Cochrane meta-analysis did not report any benefit in delivering the near-term fetus with signs of compromise compared with waiting until the due date[10]. Two randomized trials[42,49] were included in this synthesis, of which the largest was the DIGITAT trial[42], comparing induction of labor at 36 weeks with conservative management in women with a small fetus. This trial reported no difference in neonatal outcome between groups; however, the difference in GA and birth weight between the groups was minimal (< 150 g, compared with a 300-g difference in this study), and most pregnancies had normal umbilical artery Doppler, while we stratified our population on the basis of multiparameter Doppler evaluation. Again, no stillbirths were reported in women managed conservatively after 38 weeks' gestation[42].

Our findings support the results of non-randomized retrospective studies. One such study used a similar protocol of risk stratification for small fetuses at 37 weeks of gestation[11]. We hypothesized that a similar approach could be adopted from 32 weeks and studied it in a prospective manner. Moreover, Meler *et al.*[50] reported consistent findings in a retrospective study of more than 1100 fetuses. It differs from the present analysis in that this study was prospective, included fetuses with EFW > 10th centile and a drop in AC centile, and included additional important metabolic outcomes in the definition of adverse neonatal outcome. Despite these differences, the rate of severe adverse neonatal outcome in the study of Meler *et al.*[50] was comparable with that in this study, both in the low-risk group (2.8% *vs* 3.8%) and in the high-risk group (6.5% *vs* 8.5%). However, the rate of birth weight < 3rd centile was lower in this study, probably due to our inclusion of fetuses at risk of FGR who had a drop in AC centile, which is a population less likely to have low birth weight, and due to our conservative management of low-risk pregnancies.

The TRUFFLE group reported the outcome of more than 800 pregnancies with late preterm FGR[39]. The rate of severe adverse neonatal outcome (11%) was higher compared with that in our study. This could be due to a lack of characterization of FGR and unnecessary iatrogenic prematurity, as only 53% of babies were delivered beyond 37 weeks of gestation.

We acknowledge a number of limitations in this study. Women were eligible for inclusion if EFW was > 10th centile and CPR was abnormal. These pregnancies are at low risk of placental insufficiency and could have affected the results; however, they accounted for only one case (< 1%). Moreover, the protocol was not adhered to fully, as some women were delivered after 38 weeks in the high-risk group and before 39 weeks in the low-risk group. This applied in a minority of cases and reflects a

real-life scenario. Additionally, the study was not powered sufficiently to explore differences in severe adverse neonatal outcome. For this purpose, the TRUFFLE-2 trial is ongoing[51]. However, the TRUFFLE-2 protocol contains no indication on the timing of delivery after 37 weeks and is therefore unlikely to answer this question.

The adverse outcomes observed could be due to either FGR or late prematurity. It is possible that later delivery in the high-risk group could lead to a better outcome by reducing the impact of prematurity. Meanwhile, delivery prior to the due date in the low-risk group could improve the outcome by shortening the effect of chronic placental insufficiency. To answer this question fully would require a clinical trial.

However, we were able to explore these hypotheses using our observational data in two ways. First, low-risk women managed according to the new protocol had a better outcome compared with low-risk women managed as per the old protocol. This could be because the latter cohort was delivered earlier, introducing an element of iatrogenic prematurity. Similarly, high-risk women managed according to the old protocol were delivered later in gestation and had a non-significant increase in adverse neonatal outcome compared with high-risk women managed under the new protocol. Therefore, in the high-risk group, delivery prior to the due date may benefit neonatal outcome. Second, we developed a predictive model to explore the probabilities of adverse neonatal outcome related to delivery between 34 and 42 weeks' gestation, using both observed and simulated data. At any GA, low-risk women appeared to have, on average, a lower risk of adverse neonatal outcome compared with the high-risk group. Despite the overlap in SD, the average probability of adverse neonatal outcome in the high-risk group reached a nadir at 39 weeks of gestation, which was equivalent to the probability at 38 and 40 weeks in the low-risk group. This suggests that the low-risk group suffered disproportionately from late prematurity rather than exposure to chronic placental insufficiency, and by delaying delivery beyond 40 weeks, the probability score can match that of the high-risk group.

In conclusion, this study demonstrates that late-onset FGR pregnancies can be classified as high- or low-risk of adverse outcome, and that women considered to be low-risk based on ultrasound criteria could be managed conservatively, with delivery delayed beyond 40 weeks of gestation. A randomized controlled trial is needed to verify this hypothesis.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 New clinical management protocol for pregnancies with late-onset fetal growth restriction

Appendix S2 Description of development of Bayesian logistic model to estimate probability of developing adverse neonatal outcome at different gestational ages

Table S1 Sonographic and biochemical characteristics and corresponding risk classification of 321 non-anomalous singleton pregnancies with late fetal growth restriction in prospective cohort, according to whether they were managed expectantly (low-risk group) or with delivery at 37–38 weeks (high-risk group)

Tables S2 and S3 Maternal demographic characteristics, maternal and labor outcomes, birth details and neonatal outcome in low-risk (Table S2) and high-risk (Table S3) pregnancies with late fetal growth restriction in old *vs* new cohort