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Reduced growth velocity at term is associated with adverse neonatal outcomes in non-small for gestational age infants★

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ABSTRACT

Objectives: To investigate the association between decreased growth velocity at term, measured by estimated fetal weight z-score change, and adverse neonatal outcome and operative birth for intrapartum fetal compromise in a cohort of non-small for gestational age infants.
Study design: A prospective observational study was conducted at Mater Mothers' Hospital, Brisbane, Australia. Serial ultrasound assessment was undertaken every two weeks from 36 weeks gestation until delivery to determine estimated fetal weight on 436 women with uncomplicated pregnancies. Intrapartum and neonatal outcomes were recorded. The outcome measures were adverse neonatal outcome [severe acidosis (cord pH < 7.0, base deficit ≤-12 mmol/L and/or lactate >6 mmol/L), low Apgar score (<7 at 5 min) or neonatal intensive care unit admission] and operative delivery for intrapartum fetal compromise. Estimated fetal weight z-score change was compared between those with and without adverse neonatal outcome and operative delivery for intrapartum fetal compromise using Generalised Linear Mixed Models.
Results: The estimated fetal weight z-score per week declined for infants with the adverse neonatal outcome whilst those without demonstrated an increase [-0.04 (0.18) vs. 0.02 (0.21), p = 0.02]. There was no difference in estimated fetal weight z-score change per week in those with and without operative delivery for intrapartum fetal compromise.
Conclusion: Reduced growth velocity in non-small for gestational age fetuses at term is associated with an increased risk of adverse neonatal outcomes.

Introduction

Reduced birthweight (BW) at term is associated with an increased risk of poor perinatal outcomes with small for gestational age (SGA) infants at significant risk for stillbirth, neonatal death and serious neonatal morbidity [1]. However, more recent data [2–6] suggests that a proportion of fetuses with estimated weights >10th centile may in fact have suboptimal growth rendering them vulnerable to adverse perinatal sequelae. These infants are also at increased risk of operative birth and neonatal morbidity [7,8].

Conventionally, the definition of SGA is either an estimated fetal weight (EFW) by ultrasound or BW <10th centile for gestational age. However, simply using a weight threshold to identify fetuses at higher risk of adverse perinatal outcome will miss some cases where the decline in growth velocity also confers an increased risk even when the EFW is >10th centile for gestation. This approach of categorising risk on the basis of a dichotomous variable does not account for the dynamic nature of fetal weight gain nor the incremental risk of adverse outcomes associated with decreasing weight centiles.

The aim of this study was to investigate the association between the change in EFW z-score per week at term in a cohort of low risk women with non-SGA fetuses that had adverse neonatal outcomes and required operative delivery for intrapartum fetal compromise (Op-IFC). We hypothesized that the intrauterine growth velocity of these fetuses would be reduced despite having an EFW >10th centile.

★ The study was conducted at Mater Research Institute – University of Queensland, Level 3 Aubigny Place, Raymond Terrace, South Brisbane, Queensland, 4101, Australia.

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Study design

The data for this study were collected from a blinded, prospective, panel study in women attending the Mater Mother's Hospital in Brisbane from May 2014 to May 2016. These women were recruited as part of another study assessing the cerebroplacental ratio and placental growth factor in late pregnancy [9,10]. Women with uncomplicated, non-anomalous, singleton pregnancies planning a vaginal birth were invited to participate when they attended routine antenatal appointments from 28 weeks' gestation. Women with hypertension, known SGA fetus, previous caesarean or maternal age <18 or >50 years were ineligible, and those with incomplete data or medical complications which developed after recruitment were excluded from analysis. Ethical and governance approvals were granted by the Mater Human Research Ethics Committee and Research Governance Office (Ref no: HREC/13/MHS/173). Signed informed consent was obtained from all participants at enrolment.

Gestational age was established from a first trimester ultrasound scan. Women attended for ultrasound assessment every two weeks from 36 weeks (± 1 week) until delivery. Fetal biometry was measured in accordance with established protocols [11]. EFW and EFW z-scores were calculated using Hadlock's C formula [12] and WHO reference charts [13], respectively.

Women and clinicians were blinded to the ultrasound findings. Labour and delivery were managed according to local protocols and guidelines. As one of the outcomes of this study was to identify the risk of intrapartum fetal compromise, women that did not have continuous intrapartum fetal heart rate monitoring were excluded.

The outcome measures were a composite of adverse neonatal outcomes (ANO) and operative delivery for intrapartum fetal compromise. Adverse neonatal outcomes were severe acidosis (cord pH < 7.0, base deficit ≤−12 mmol/L and/or lactate >6 mmol/L), low Apgar score (<7 at 5 min) or neonatal intensive care unit (NICU) admission]. Emergency operative delivery was defined as (Caesarean or instrumental birth) for an abnormal intrapartum fetal heart rate pattern [14] as contemporaneously determined by the supervising obstetrician.

Statistical analysis

To account for the variability in EFW between genders and for each gestational week, z-scores were calculated against population reference centiles [13]. The change in EFW z-scores between ultrasounds was calculated by subtracting the z-score of the last ultrasound from that of the first scan. The z-score difference per week was then calculated (difference in z-score/difference in gestational days)*7.

Continuous variables are reported as mean (standard deviations) with Pearson's Correlation coefficients used to assess for correlations with a change in EFW z-scores per week. Categorical variables are reported as percentage (number) with differences in change of EFW z-score per week assessed using t-tests. Differences or correlations that were found to be significant at $P < 0.05$ were investigated further. Data was changed to a longitudinal format and the slopes for EFW z-scores at first and second scan were modelled using Generalised Linear Mixed Models (GLMM) incorporating terms for the random intercept and random slope as well as an interaction term for gestational age. This allowed for the measure of differences in the ratio of change. To test for group differences in the rate of change per gestational age on an additive scale, EFW slope was calculated from the partial derivative of the expected EFW slope taken from the GLMM interaction with respect to gestational age. A Wald test was used to assess for significant differences in slope between the groups. All statistical analysis was performed using Stata, StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

Results

During the study period 436 women met the inclusion criteria for this study. Participant characteristics of the final study cohort are shown in Table 1. The change in EFW z-score per gestational week was not associated with any differences in maternal characteristics (Table 1). Seventy-three (73/436, 16.7%) infants were born with the ANO, of which 87.7% (64/73) were acidotic, 6.9% (5/73) had a low Apgar score and 24.7% (18/73) were admitted to the NICU. Umbilical artery cord gas analysis was performed in 55.5% (242/436) of deliveries. Infants that experienced the ANO were more likely to be born to nulliparous women (18.3% vs. 5.6%, p = 0.02) and were delivered at a later gestation (40.7 weeks, IQR 39.1–40.7 weeks vs. 40.0 weeks, IQR 39.6–41.1 weeks, p < 0.001).

The change in EFW z-score was compared between those with and without the ANO and Op-IFC outcomes (Table 2). Infants that experienced the ANO had a greater decrease in their EFW z-score per week compared to those that did not have this complication [−0.04 (SD 0.18) vs. 0.02 (SD 0.21), p = 0.02] (Fig. 1). There was however no difference in EFW z-score change for infants that required Op-IFC birth. The EFW z-score of infants that were admitted to the NICU decreased [−0.08 (SD 0.14)] compared to those that were not admitted [0.02 (SD 0.21)] (p = 0.07). A similar trend was also seen for infants that were acidotic at birth although this change was again not significant [-0.03 (SD 0.18) vs. 0.02 (SD 0.21, p = 0.06).

The Generalised linear mixed models showed a significant interaction between the ANO and gestational age for the EFW z-scores (-0.06, 95%CI: −0.10 to −0.02, p = 0.01) (Fig. 2). The slope of the partial derivative for the cohort without the ANO was 0.01 (95% CI −0.01 to 0.03, p = 0.17) whilst the cohort with the ANO had a slope of -0.05 (95%CI −0.09 to −0.01, p = 0.02). This suggests that

Table 1
Maternal characteristics by EFW z-score change per week.

Maternal characteristic	Entire cohort	EFW z-score change per week		P Value
		Yes	No	
Age	29.8 (4.5)	0.06		0.26*
BMI	23.8 (4.5)	−0.03		0.58*
Caucasian ethnicity	61.5% (268/436)	0.01 (0.20)	0.02 (0.22)	0.58
Assisted reproduction	2.5% (11/436)	0.01 (0.21)	−0.06 (0.25)	0.32
Nulliparous	87.6% (382/436)	0.01 (0.20)	0.06 (0.26)	0.14
Diabetes	8.0% (35/436)	0.03 (0.24)	0.01 (0.21)	0.65
Smoking	9.4% (41/436)	−0.03 (0.21)	0.01 (0.21)	0.28

EFW, estimated fetal weight; BMI, body mass index.
Entire cohort reported as percentage (N).
Age and BMI are reported as mean (standard deviation) with *t*-test (*Pearson Correlation Coefficient).

Table 2
EFW z-score change per week for intrapartum and perinatal outcomes.

Perinatal outcome	Entire cohort	EFW z-score change per week		P Value
		Yes	No	
Male fetus	48.6% (212/436)	0.03 (0.20)	−0.004 (0.21)	0.16*
Method of birth				
SVD	50.9% (222/436)	0.01 (0.23)	0.01 (0.19)	0.92*
Instrumental	30.3% (132/436)	0.01 (0.19)	0.01 (0.22)	0.76*
Instrumental IFC	14.7% (64/436)	−0.02 (0.17)	0.02 (0.22)	0.27*
Instrumental other	15.6% (68/436)	0.03 (0.21)	0.01 (0.21)	0.46*
Emergency CS	18.8% (82/436)	0.02 (0.19)	0.01 (0.21)	0.63*
Emergency CS IFC	4.1% (18/436)	0.02 (0.25)	0.01 (0.21)	0.91*
Emergency CS other	14.7% (64/436)	0.02 (0.17)	0.01 (0.21)	0.64*
NICU	4.1% (18/436)	−0.08 (0.14)	0.02 (0.21)	0.07*
Respiratory distress	11.0% (48/436)	−0.004 (0.19)	0.01 (0.21)	0.63*
Apgar <7 at 5 minutes	2.1% (9/436)	−0.05 (0.11)	0.01 (0.21)	0.34*
Acidosis	14.7% (64/436)	−0.03 (0.18)	0.02 (0.21)	0.06*
ANO	16.7% (73/436)	−0.04 (0.18)	0.02 (0.21)	0.02*

EFW, estimated fetal weight; *SVD*, spontaneous vaginal delivery; *IFC*, intrapartum fetal compromise; *CS*, caesarean section; *NICU:* Neonatal Intensive Care Unit; *ANO:* Adverse Neonatal Outcome (Acidosis, Apgar score <7 at 5 min, NICU admission).
Entire cohort reported as percentage (N). * Data reported as mean (standard deviation) with *t*-test.

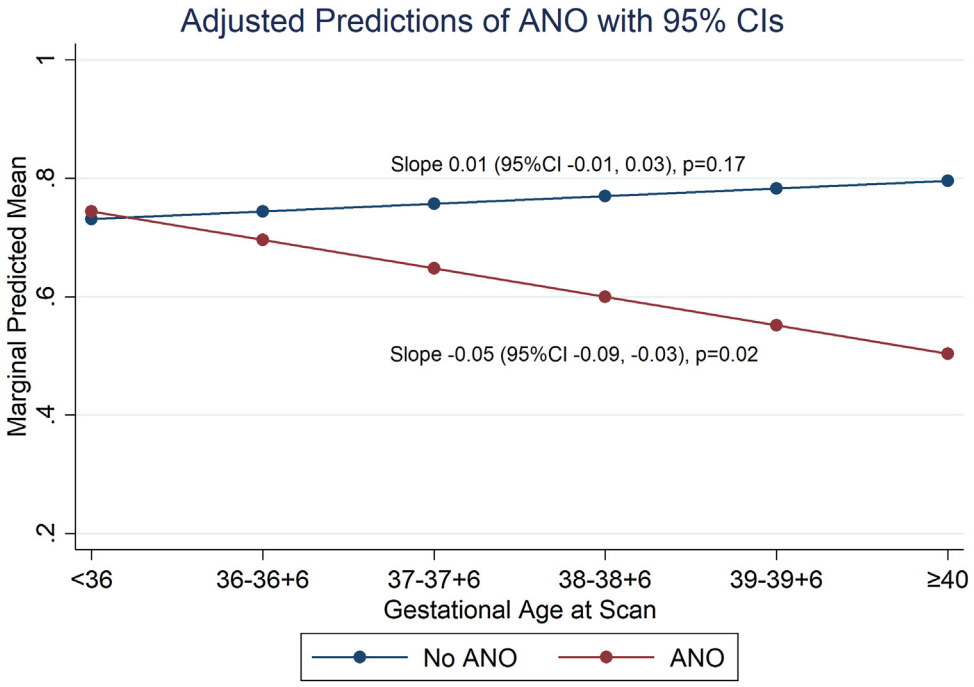

Fig. 1. Predicted mean change of estimated fetal weight by gestational age in weeks for the adverse neonatal outcome.
ANO: adverse neonatal outcome.

for each gestational age week, fetuses without the ANO experienced no difference in their EFW z-score against the WHO population standard whilst those with the ANO experienced a decrease. The Wald test found a significant difference between the slopes of 0.06 (95%CI 0.02 to 0.10, p = 0.01) for those with and without the ANO.

Discussion

Principal findings

The results of this study demonstrate that growth velocity declined in infants with adverse neonatal outcomes as reflected by the negative EFW z-score change per gestational week, compared to those without the ANO. Whilst the rate of decline in EFW, corrected for gestation, from 28 to 36 weeks' gestation in fetuses with growth restriction has been previously demonstrated [15], similar changes have not been shown in a term cohort over a relatively short duration. Our results suggest that some fetuses exhibit subtle decline in growth velocity at term which may be responsible for the increased risk of intrapartum compromise and adverse perinatal outcomes.

We have previously shown that some women at term, with apparently normally grown fetuses have evidence of abnormal fetal cardiac function [16–18] and cerebral circulation [3,10,19–21] and low levels of placental growth factor (PlGF) [22] and that these are associated with an increased risk of intrapartum compromise and adverse neonatal outcomes. Fetuses with late onset growth restriction or SGA are at risk of a variety of adverse short- and long-term outcomes. These include caesarean section for intrapartum fetal compromise, neonatal acidosis, NICU admission [23], composite neonatal morbidity [1,24], cerebral palsy [25], and an

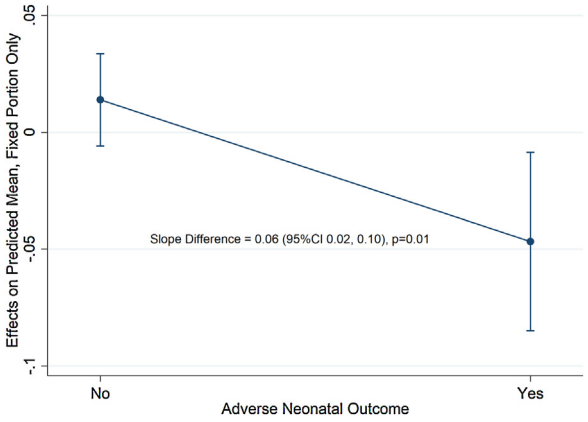

Fig. 2. Predicted slope gradients of estimated fetal weight per gestational week for the adverse neonatal outcome.

increased risk of poor school performance [26]. Although the results of previous studies are primarily in SGA populations, the results from our study suggests that term non-SGA fetuses with declining growth velocity may also be at risk of some of these complications albeit to not as severe a degree.

Recent studies [6,27] have suggested that the cerebroplacental ratio (CPR) may be used as a surrogate marker for fetal growth - a low CPR indicative of a fetus that has failed to reach its growth potential. A low CPR is associated with a variety of intrapartum and perinatal complications including operative birth for fetal compromise, admission to NICU, acidosis and perinatal death [2–4,28]. Additionally, the magnitude of change of the CPR in late pregnancy also appears to be a risk factor for various adverse pregnancy outcomes [29].

Fetuses that fail to reach their growth potential are at increased risk of stillbirth and adverse neonatal sequelae [30,31]. Given that stillbirth rates in Australia and other high income countries have not decreased significantly in decades [32], novel ways to identify the compromised but currently undetected at-risk fetus are necessary. However, our results, whilst demonstrating that term perturbations of fetal growth are evident in some apparently appropriately grown infants and that this is associated with adverse intrapartum and neonatal outcomes are not yet translatable into the clinical setting. Paradoxically, they highlight the practical difficulties in identifying an at-risk cohort. In a real-world setting none of our study participants would necessarily have been identified as high risk and thus would not have received a late pregnancy ultrasound, let alone multiple assessments to assess fetal growth velocity. Retrospective classification of the study cohort was undertaken according to the Delphi consensus definition [33], resulting in two fetuses (0.5%) meeting the definition of late onset FGR based on EFW <3rd centile at assessment.

The concept of assessing fetal growth velocity is not new, however late pregnancy ultrasound has yet to be shown to improve perinatal outcomes. Unlike women with known risk factors (hypertension, diabetes mellitus, previous FGR etc.), routine ultrasound to assess fetal growth is generally not performed in low risk women unless there are concerns about fetal size on clinical examination or symphyseal-fundal height assessment. Cochrane reviews do not support the use of either routine late pregnancy ultrasound or umbilical artery Doppler assessment in low-risk populations [34,35]. However, these reviews are often limited by small sample size, use of surrogate outcomes, and most importantly, ultrasound scans that were often performed too remote from term, thereby potentially missing late onset growth restriction. A recent study by Sovio et al showed that late pregnancy ultrasound in low risk women tripled the detection rate for SGA babies at term suggesting the potential utility of such an assessment [36]. The results from this study and others clearly show that while perinatal risks are inversely proportional to weight, identifying a vulnerable fetus remains difficult and should continue to remain the focus of research in attempts to mitigate adverse late perinatal outcomes.

Strengths and limitations

The strengths of this study are the prospective design, low risk study cohort, relatively large sample size and broad range of characteristics of participants. This study reflects the population of women at term in our institution and suggests that our findings may possibly be applicable and relevant to other similar high-income healthcare settings. Additionally, the blinding of ultrasound findings from participants and obstetric caregivers and technical rigour in data collection and analysis reduces potential bias. However, whilst the high level of ultrasound operator expertise is a strength of this study this may not necessarily be replicated in all other settings. We recognise the general limitations for the accuracy of ultrasound determination of fetal weight particularly at the extremes of weight. Other limitations relate to the impracticality of performing serial scans at term.

Additionally, in our study the overall spontaneous vaginal delivery rate was 50.3%. Whilst this figure is relatively low compared to Europe and the United Kingdom [37], our figures are consistent with Australian national data [38]. Our study population also consisted a high number of nulliparous women (87.6%), a group which is known to have higher rates of instrumental vaginal and emergency caesarean deliveries when compared to the rest of the birthing population [38].

Conclusion

The findings for this study demonstrate that subtle decreases in fetal growth velocity are detectable and associated with poorer neonatal outcomes. They highlight the difficulty in identifying non-SGA at-risk fetuses late in pregnancy.

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