Prediction of adverse neonatal outcomes using size centiles and conditional growth centiles

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Conflict of interest

The authors did not report any conflict of interest.

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ABSTRACT

Objective: To test whether adding conditional growth centiles to size centiles of estimated fetal weight improves prediction of adverse neonatal outcomes in pregnancies with a small for gestational age (SGA) fetus or pregnancies at risk.

Methods: This prospective longitudinal study included pregnant women at risk of or diagnosed with an SGA ($\leq 5^{th}$ centile) fetus. They underwent serial ultrasound measurements and the final two were included in the regression analysis. Adverse outcomes were birth < 37 weeks, operative delivery due to fetal distress, 5-min Apgar score < 7, newborn hypoglycemia (glucose < 2.0 mmol/L), admission to the neonatal intensive care unit, and perinatal mortality. A combined outcome variable 'any adverse outcome' included one or more adverse outcomes.

Results: Complete biometric data were obtained for 211 women. Conditional growth and size centiles contributed independently in the prediction of adverse outcomes. Combining conditional growth and size centiles improved significantly the prediction of outcomes compared with size centiles alone (e.g. for 'any adverse outcome': $P = 0.023$, log-likelihood test). For 'any adverse outcome' the specificity of 78% (95%CI: 70-84%) using size centiles as predictor was improved to 94% (89-97) when conditional growth centiles was added, while the sensitivity was not significantly changed, i.e. 60% (49-69) vs. 39% (30-50), respectively.

Conclusion: Size centiles and conditional growth centiles contribute independently in the prediction of adverse neonatal outcome, and their combination further improves the prediction model. The results support an increased use of conditional growth centiles in the monitoring of fetuses at risk.

INTRODUCTION

Fetuses that are small for gestational age (SGA) are convincingly associated with increased risk of adverse perinatal outcomes[1-3]. Ultrasound assessment of fetal size is thus important in clinical management. An extension would be serial measurements to monitor growth, and constructing individual growth trajectories has been attempted[4]. Another method utilizes the serial ultrasound measurements for quantifying individual fetal growth using conditional centiles[5-8]; in the following we address this method and use the expression 'conditional growth centile'. The method uses a previous measurement to condition individualized ranges for the subsequent measurement[9]. These ranges are narrower and shifted toward the initial centile compared with reference ranges for the entire population. However, the literature on such centiles is scarce and controversial[10-13]. Slow growth of the fetal biparietal diameter (BPD) was indeed associated with an increased risk of perinatal death[10], and slow growth of the fetal abdominal area was found to be superior to the fetal abdominal area alone for predicting cesarean delivery due to fetal distress and newborn admission to a neonatal intensive care unit (NICU)[14]. However, according to Iraola *et al.*[12], growth centiles seem to be inferior to customized centiles in predicting adverse neonatal outcomes, and another retrospective study found no benefits of using conditional growth centiles over conventional size centiles[13].

Intuitively, conditional growth centile ≤ 5th should reflect slow intrauterine growth, and therefore be a marker of perinatal risk separate from SGA. Thus, the aim of the present study was to determine whether adding conditional growth centiles to centiles of estimated fetal weight (EFW) improves the prediction of adverse neonatal outcomes compared with the SGA classification alone.

METHODS

This prospective longitudinal study was carried out from May 2010 to June 2014 at the Fetal Medicine Unit, Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway. The study was approved by the Regional Committee for Medical and Health Research Ethics (approval no. REC West 2010/686), and all the included women gave their written informed consent to participate. Women with a singleton pregnancy who were referred for a 24-week ultrasound evaluation due to risk of having an SGA fetus, and pregnant women having had an ultrasound examination for any clinical indication and diagnosed with an SGA fetus, i.e. EFW ≤ 5th centile were invited to participate in the study. Women who were invited to participate due to high risk had previously experienced preeclampsia and/or had given birth to an SGA (≤ 5th centile) newborn[8], had a chronic maternal disease such as hypertension, renal failure, systemic and rheumatic disease, or had a discrepancy of ≥ 14 days between the gestational age set by their last menstrual period (LMP) and that calculated via ultrasound. Women with pre-gestational diabetes were not included. Exclusion criteria were congenital malformations and chromosomal aberrations.

Gestational age was based on ultrasound scanning of fetal head circumference (HC) at gestational week 17–20[15] (n = 120) unless a first-trimester scan of crown rump length[16] had determined fetal age (n = 82), or if the day of conception was known due to conception via in vitro fertilization (n = 9). Voluson 730 Expert E6 and E8 (GE Medical

Systems, Kretz Ultrasound, Zipf Austria) ultrasound scanners were used for the measurements. The measurements included biometry of the fetal HC[15,17], abdominal circumference (AC)[17], and femur length[17,18]. EFW was calculated according to Combs formula[19]. Repeated examinations were performed with intervals of 2–6 weeks, depending upon the clinical need. Participants who had submitted to one ultrasound measurement only were not included in the analysis. A size centile of EFW was calculated at each visit and a conditional growth centile was calculated for the last biometry conditioned by the previous biometry with at least a 14 days interval (Figure 1)[8]. The terms for calculating size and conditional growth centiles[8] had been integrated in an electronic spreadsheet. In the analysis we used both the 5th and 10th centile for fetal size and growth[8]. For birth weight centiles a population based reference chart was used[20].

The decision concerning the timing and mode of delivery was made by the clinicians in line with national and local guidelines. SGA as an isolated finding was not indication for preterm delivery. Above 37 weeks gestation a policy of expectant management was followed until 39-40 weeks if no additional factors appeared. The overall cesarean rate in the department was 12.5% at the time of the study. Birth outcomes (gestational age, birth weight, information about labor and delivery, Apgar score, and admission to the NICU) were collected from clinical records after birth. Newborns with gestational age < 34 weeks were routinely transferred to the NICU. Blood sample was taken of the newborns from all participants for glucose testing within 2 hours after delivery. The following were considered to be adverse outcomes for the newborn: preterm birth (< 37 weeks of gestation), operative delivery (including cesarean delivery and vaginal instrumental delivery) due to fetal distress, admission to the NICU, 5-min Apgar score < 7, hypoglycemia (glucose < 2.0 mmol/L), and perinatal mortality. A combined outcome variable of ‘any adverse outcome’ was also used, which was established if at least one component was abnormal. Delivery due to fetal distress was indicated by pathological fetal Doppler findings, CTG abnormalities or due to fetal echocardiographic events (S-T analysis, STAN[21]) during labor. Labor at ≥ 36 weeks gestation in risk pregnancies was monitored by fetal echocardiography.

We estimated the necessary study size by an interim analysis using the “any adverse outcome” variable when the first 80 infants had been delivered. We used the log-likelihood test to assess whether adding conditional growth centile ≤ 5^{th} to a model with size ≤ 5^{th} centile significantly improved the model ($P < 0.05$) and estimated that a sample of 160 women was needed. To allow for potential withdrawals, exclusions, and incomplete data for some participants, the sample was expanded to 220 women. Log-binomial regression analysis was used to assess whether size centiles and conditional growth centiles were associated with the outcomes, shown as Relative Risk. To test whether size and conditional growth centiles had independent association with the outcomes, when adjusted for each other, both parameters were included in the model and results were shown as adjusted Relative Risk. Log-likelihood testing, which is used for comparing the goodness of fit of two models, was used to test the hypothesis that the addition of conditional growth centile to the size centile for the last measurement improved the prediction of adverse outcomes compared with that based on size centile alone. Sensitivity and specificity were used to demonstrate the effect. Possible collinearity between size and conditional growth centiles was assessed using variance inflation factor (VIF)[22]. Statistical analyses were carried out using SPSS 22 (Statistical Package for the Social Sciences, SPSS, Chicago, IL, USA), and the threshold for statistical significance was set at $P < 0.05$.

RESULTS

Of the 227 women who were invited to enroll in the study, seven declined to participate. Another three participants were excluded because of fetal malformations and one woman withdrew when she moved out of the area. Five women were not included in the statistical analysis due to missing serial biometric measurements. Thus, 211 participants were eligible for the analyses: 159 with a high risk of having an SGA fetus and 52 diagnosed with an SGA fetus. Among the high-risk participants, 71 had had a prior pregnancy with preeclampsia, 132 had given birth to a newborn with a birth weight ≤5th centile, nine were included due to maternal disease (i.e. systemic lupus erythematosus, chronic renal failure, and chronic hypertension), and two were included because of a discrepancy of ≥ 14 days between the LMP and ultrasound fetal age dating. Of the 159 high-risk pregnancies, 54 had more than one cause for inclusion. Maternal characteristics and birth outcomes of the study population are listed in Table 1; 201 (95.3%) of the women were Caucasian.

In total, 999 biometric assessments were carried out for the 211 participants (median 5 per woman; range 2–8). The ultrasound biometry was carried out by 38 doctors in the department, all with basic training in biometry but with varying degree of expertise. The median interval between the last two examinations was 21 days (range 7–59). In six cases two biometric measurements were available but with less than 14 days apart. At the final visit, 80 fetuses (37.9%) had an EFW ≤ 5th centile and 100 fetuses (47.4%) had an EFW ≤ 10th centile. Using these cut offs there was consistency between the ultrasound EFW centiles[8] and birth weight centiles[20] in 67 (80.7%) and 91 (84.3%) cases, respectively. Gestational hypertension appeared in 11 (5.2%) participants and pre-eclampsia in 34 (16.1%).

Complete outcome data were available for all, except for 40 (19%) missing neonatal glucose levels. A total of 89 neonates (42.2%) had at least one adverse outcome, 50 (23.7%) were born prematurely, 48 (22.7%) were admitted to NICU and 50 (23.7%) had an operative delivery due to fetal distress, 39 by cesarean section and 11 by instrumental vaginal delivery. Among the 151 women who had a vaginal cephalic delivery we found a significantly increased risk of instrumental vaginal delivery due to fetal distress in those with birthweight ≤ 10th centile (8/61) compared with those with a birthweight > 10th centile (3/90), RR 3.93 (95% Cl 1.09 – 14.24) p = 0.037. Ten newborns (4.7%) had a 5-min Apgar score of < 7 and 23 (of 171) (13.5%) had hypoglycemia. Hypoglycemia occurred in one newborn of women who had gestational diabetes (n = 10). There were two perinatal deaths, giving a neonatal mortality rate of 0.9%, both were born alive but were severely growth restricted and born extremely prematurely (25^{+3} and 26^{+5} weeks).

Four of the 50 women with a preterm delivery had a spontaneous start of labor; the remaining 46 had either an induced labor (*n* = 22) or a primary cesarean delivery (*n* = 24), of which 21 were emergency cesarean deliveries (i.e. within 24 hours after making the decision). Delivery mode and indications of the preterm and term deliveries are given in Table 2. The median gestational age at delivery in the preterm group was

36^{+3} weeks in those who were induced, and 31^{+3} weeks in those having a primary cesarean delivery. None were delivered preterm due to SGA alone; additional factors such as preeclampsia, abnormal cardiotocography, or fetal Doppler abnormalities were always present prior to decision for induction or cesarean delivery. The frequency of extreme preterm delivery (< 28 weeks) was 2.4% (n = 5), 15 (9.5%) fetuses were delivered between 28 and 33^{+6} weeks, and 30 were late preterm births (34-36^{+6} weeks).

Collinearity between size centiles and conditional growth centiles was well below accepted level, i.e. VIF below 1.5 for the 5^{th} and the 10^{th} centiles[22]. In the model conditional growth centile ≤ 5 and ≤ 10 exerted independent effects on the following adverse outcomes in the model: preterm birth, operative delivery due to fetal distress, admission to the NICU, and the 'any adverse outcome' variable (Table 3 and 4). Size centile ≤ 5 had independent association to operative delivery due to fetal distress and 'any adverse outcome' when adjusted for conditional growth centile (Table 3). When cut off was set to 10^{th} centile, size had independent association to admission to NICU as well (Table 4). Adding conditional growth centile to size centile ≤ 5 in the model resulted in a significant improvement, as estimated by log-likelihood test, in the prediction of preterm birth, operative delivery due to fetal distress, admission to the NICU, and 'any adverse outcome' (Table 3). The 10^{th} centile for SGA, commonly used as a cutoff in clinical practice and research, showed similar results (Table 4).

The sensitivity for size centile ≤ 5 as predictor of 'any adverse outcome' was 60% (95%CI: 49-69) and was not significantly changed when adding conditional growth centile in the model (39% (95%CI: 30-50)). On the other hand side, the specificity of

78% (95%Cl: 70-84) when using size centile ≤ 5 as predictor was significantly improved to 94% (95%Cl: 89-97) when conditional growth centile ≤ 5 was added in the model.

DISCUSSION

Generally, fetal size and growth are strongly related. Here we showed that they also have independent effects on a prediction model for adverse outcomes. Secondly, we found that combining the two parameters improves prediction. These results suggest that there is potential clinical usefulness in introducing conditional growth centiles into the surveillance of SGA pregnancies and those at risk thereof.

Although the study was not designed for testing the precision of predictors, we used specificity and sensitivity to illustrate the effects of the model. While sensitivity was not significantly changed by adding conditional growth centile to the size centile in the model, specificity improved from 78 to 94%. In healthcare systems where cesarean section and other obstetric interventions are common, it would be a valuable achievement to identify more precisely the SGA fetuses at low risk of adverse outcome since they would need less surveillance and interventions.

We did not exclude from the analyses cesarean section and other outcomes caused by maternal indications or other indications than fetal, but the analysis method we chose was able to discern the effects of size centiles and conditional growth centiles. However, the precision of the prediction (e.g. specificity and sensitivity used for illustration in the present study) may be affected. Removing from the analysis prematurity caused by cesarean for maternal indication, such as severe pre-eclampsia, would have skewed the analysis for the following reasons. Severe pre-eclampsia occurred both in the SGA group and the normally sized group. In the SGA group all indications for intervention were a combination of SGA and additional conditions, while in the normally sized group maternal indications (e.g. severe pre-eclampsia) alone could lead to intervention. Removal of these intervention outcomes would affect only the normally sized group. Secondly, it is likely that pre-eclampsia influences fetal development and the likelihood of adverse outcome also in the normally sized group.

The large number of doctors (38) performing the measurements in the present study increased the variation, but also the external validity. We believe the results are valid for other departments but restricted to high-risk populations. Extrapolating to low-risk settings would require another differently designed study. This is illustrated by the sizable proportion of normally grown fetuses of this study. Few of these exhibited low conditional growth centiles (Figure 1); five when cut off was set to the 5th centile and six when the cut off was the 10th centile. To explore the incidence of adverse outcomes in such a group would require a differently powered study.

Hutcheson *et al.* did not find a significant improvement in predicting adverse outcomes when comparing the use of conditional growth centiles with the use of size centiles[13]. The present study is not comparable with that study, since we explored the combined effects of centiles for size and conditional growth centiles compared with SGA classification alone. Secondly, Hutcheson *et al.* retrospectively examined an unselected population, all pregnancies lasted beyond gestational week 32, calculation of

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conditional centile was based on birth weight given their EFW at gestational week 32, and more severe outcome variables were investigated. In contrast, the present study was prospective and used only prenatal assessment for the risk calculation in a high-risk group, and therefore more relevantly reflects the usefulness of growth surveillance.

The Danish study showing that low fetal BPD growth between the first and second trimesters increased the risk of perinatal death before 34 weeks of gestation[10], reported seven perinatal deaths among 7642 pregnancies before 34 weeks. Four of the seven fetuses had a BPD growth rate ≤ 10^{th} conditional centile. The two newborn that died in our study were growth restricted. However, relative risk for perinatal mortality could not be estimated in the present study due to lack of events in the reference group.

Estimation of intrauterine fetal EFW using ultrasound imaging is associated with an uncertainty of 7.5–18.8%[23], which is a problem when trying to identify the small fetus. When extending to growth assessment that requires two or more measurements, the problem grows. Mongelli M. *et al.* showed a false positive rate in ultrasound diagnose of fetal growth restriction (defined as no apparent growth in fetal AC between two measurements) of 11.8% in gestational week 28 and an increase with advancing gestational age, with a false positive rate of 22% at week 36[24]. The false positive rate decreased with increasing time interval, and they recommended an interval of at least 3 weeks to minimize the false positive rate of fetal growth restriction. To control for such errors we used intervals of minimum two weeks with a median of 21 days between the examinations.

Information of size and conditional growth centiles were available to the managing clinician, but in line with local and national guidelines, no pregnancy was induced or delivered preterm on the basis of fetal smallness alone. It is therefore likely that there was little risk of bias concerning outcomes. However, information of fetal size and conditional growth centile may have influenced the examination frequency increasing the probability of abnormal CTG and Doppler findings leading to earlier intervention and prematurity in some cases. IUGR is closely related to hypertensive disorders, which was a contributing indication for delivery in 11 (50%) of the preterm inductions and in 14 (58%) of preterm cesarean deliveries. Thus maternal hypertensive disorders influenced the total number of preterm births.

It has previously been shown that SGA is associated with an increased risk of intra-partum fetal distress compared with AGA[25-27] and a correspondingly increased risk of cesarean delivery[14,28,29]. The increased risk of vaginal instrumental delivery due to fetal distress in the second stage of labor found in our study for those with birth weight ≤ 10th centile corroborates with such studies.

While it is intuitive that a low conditional growth centile should be an important parameter when managing pregnancies at risk of growth restriction, the existing literature does not unequivocally support its use. The present results should encourage its use in clinical practice and research particularly since well-documented reference ranges and models for calculating conditional centiles during longitudinal observations are now available[8,17].

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REFERENCES

1. Kramer MS, Olivier M, McLean FH, Willis DM, Usher RH. Impact of intrauterine growth retardation and body proportionality on fetal and neonatal outcome. *Pediatrics* 1990; **86**: 707-713.
2. Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A. Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford Network. *Am J Obstet Gynecol* 2000; **182**: 198-206.
3. McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth weight in relation to morbidity and mortality among newborn infants. *N Engl J Med* 1999; **340**: 1234-1238.
4. Simon NV, Deter RL, Kofinas AD, Cavanaugh SH, Shearer DM. Small-for-menstrual-age infants: different subgroups detected using individualized fetal growth assessment. *J Clin Ultrasound* 1994; **22**: 3-10.
5. Royston P. Calculation of unconditional and conditional reference intervals for foetal size and growth from longitudinal measurements. *Stat Med* 1995; **14**: 1417-1436.
6. Royston P, Altman DG. Design and analysis of longitudinal studies of fetal size. *Ultrasound Obstet Gynecol* 1995; **6**: 307-312.
7. Owen P, Donnet ML, Ogston SA, Christie AD, Howie PW, Patel NB. Standards for ultrasound fetal growth velocity. *Br J Obstet Gynaecol* 1996; **103**: 60-69.
8. Johnsen SL, Rasmussen S, Wilsgaard T, Sollien R, Kiserud T. Longitudinal reference ranges for estimated fetal weight. *Acta Obstet Gynecol Scand* 2006; **85**: 286-297.
9. Owen P, Ogston S. Conditional centiles for the quantification of fetal growth. *Ultrasound Obstet Gynecol* 1998; **11**: 110-117.
10. Pedersen NG, Figueras F, Wojdemann KR, Tabor A, Gardosi J. Early fetal size and growth as predictors of adverse outcome. *Obstet Gynecol* 2008; **112**: 765-771.
11. Smith-Bindman R, Chu PW, Ecker JL, Feldstein VA, Filly RA, Bacchetti P. US evaluation of fetal growth: prediction of neonatal outcomes. *Radiology* 2002; **223**: 153-161.
12. Iraola A, Gonzalez I, Eixarch E, Meler E, Illa M, Gardosi J, Gratacós E, Figueras F. Prediction of adverse perinatal outcome at term in small-for-gestational age fetuses: comparison of growth velocity vs. customized assessment. *J Perinat Med* 2008; **36**: 531-535.

13. Hutcheon JA, Egeland GM, Morin L, Meltzer SJ, Jacobsen G, Platt RW. The predictive ability of conditional fetal growth percentiles. *Paediatr Perinat Epidemiol* 2010; **24**: 131-139.

14. Owen P, Harrold AJ, Farrell T. Fetal size and growth velocity in the prediction of intrapartum caesarean section for fetal distress. *Br J Obstet Gynaecol* 1997; **104**: 445-449.

15. Johnsen SL, Rasmussen S, Sollien R, Kiserud T. Fetal age assessment based on ultrasound head biometry and the effect of maternal and fetal factors. *Acta Obstet Gynecol Scand* 2004; **83**: 716-723.

16. Robinson HP. Sonar measurement of fetal crown-rump length as means of assessing maturity in first trimester of pregnancy. *BM J* 1973; **4**: 28-31.

17. Johnsen SL, Wilsgaard T, Rasmussen S, Sollien R, Kiserud T. Longitudinal reference charts for growth of the fetal head, abdomen and femur. *Eur J Obstet Gynecol Reprod Biol* 2006; **127**: 172-185.

18. Johnsen SL, Rasmussen S, Sollien R, Kiserud T. Fetal age assessment based on femur length at 10-25 weeks of gestation, and reference ranges for femur length to head circumference ratios. *Acta Obstet Gynecol Scand* 2005; **84**: 725-733.

19. Combs CA, Jaekle RK, Rosenn B, Pope M, Miodovnik M, Siddiqi TA. Sonographic estimation of fetal weight based on a model of fetal volume. *Obstet Gynecol* 1993; **82**: 365-370.

20. Skjaerven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. *Acta Obstet Gynecol Scand* 2000; **79**: 440-449.

21. Amer-Wahlin I, Hellsten C, Noren H, Hagberg H, Herbst A, Kjellmer I, Lilja H, Lindoff C, Månsson M, Mårtensson L, Olofsson P, Sundström AK, Maršál K. Cardiotocography only versus cardiotocography plus ST analysis of fetal electrocardiogram for intrapartum fetal monitoring: a Swedish randomised controlled trial. *Lancet* 2001; **358**: 534-538.

22. Williams R. Multicollinearity. http://www3.nd.edu/~rwilliam/ 2015.

23. Nahum GG, Stanislaw H. Ultrasonographic prediction of term birth weight: how accurate is it? *Am J Obstet Gynecol* 2003; **188**: 566-574.

24. Mongelli M, Ek S, Tambyrajia R. Screening for fetal growth restriction: a mathematical model of the effect of time interval and ultrasound error. *Obstet Gynecol* 1998; **92**: 908-912.

25. Lin CC, Moawad AH, Rosenow PJ, River P. Acid-base characteristics of fetuses with intrauterine growth retardation during labor and delivery. *Am J Obstet Gynecol* 1980; **137**: 553-559.

26. Low JA, Boston RW, Pancham SR. Fetal asphyxia during the intrapartum period in intrauterine growth-retarded infants. *Am J Obstet Gynecol* 1972; **113**: 351-357.

27. Low JA, Pancham SR, Worthington D, Boston RW. The incidence of fetal asphyxia in six hundred high-risk monitored pregnancies. *Am J Obstet Gynecol* 1975; **121**: 456-459.

28. Sylvestre G, Fisher M, Westgren M, Divon MY. Non-reassuring fetal status in the prolonged pregnancy: the impact of fetal weight. *Ultrasound Obstet Gynecol* 2001; **18**: 244-247.

29. Figueras F, Eixarch E, Gratacos E, Gardosi J. Predictiveness of antenatal umbilical artery Doppler for adverse pregnancy outcome in small-for-gestational-age babies according to customised birthweight centiles: population-based study. *BJOG* 2008; **115**: 590-594.

Table 1. Maternal characteristics and birth outcomes of the total study population, and in those without and those with adverse outcomes.

Characteristic	Median (range) or n (%)			***P****
	Total study population (n = 211)	Non adverse outcomes (n = 122)	Adverse outcomes (n = 89)	
Maternal				
Age (years)	30 (17–43)	30 (21–42)	30 (17–43)	**0.926**
Height (cm)	165 (148–179)	165 (148–179)	164 (148–176)	**0.095**
Pre-pregnancy weight (kg)	63 (44–120)	62 (45–114)	65 (44–120)	**0.005**
BMI (kg/m^2)	22.9 (17.2–41.5)	22.6 (17.2–41.4)	24.1 (17.5–41.5)	**<0.001**
Parity ≥1	174 (83%)	114 (93%)	60 (67%)	**<0.001**
Smoking	17 (8%)	5 (4%)	12 (14%)	**0.013**
Chronic maternal disease†	12 (6%)	4 (3%)	8 (9%)	**0.077**
Birth outcomes				
Gestational age at delivery ($weeks^{+days}$)	39^{+2} (25^{+3}–42^{+3})	40^{+0} (37^{+4}-$42^{3)}$	36^{+5} (25^{+3}–40^{+6})	**<0.001**
Newborn birth weight (g)	2890 (440–4340)	3200 (2320–4340)	2270 (440–4135)	**<0.001**
Birth weight ≤ 5^{th} centile	83 (39%)	27 (22%)	56 (63%)	**<0.001**
Birth weight ≤ 10^{th} centile	108 (51%)	41 (34%)	67 (75%)	**<0.001**
Newborn length (cm)	48 (28–54)	49 (43–54)	45 (28–53)	**<0.001**
Ponderal index (kg/m^3)	26.1 (17.6–32.4)	27.0 (21.5–32.4)	24.5 (17.6–29.7)	**<0.001**
Placenta weight (g)	500 (120–1100)	550 (300–1100)	425 (120–900)	**<0.001**
Male infants	103 (49%)	60 (49%)	43 (48%)	**0.901**

* Chi-square test for categorical variables and independent t-test for continuous variables are used to compare characteristics between those without and those with adverse outcomes. †Pre-gestational hypertension (n = 7), rheumatic disorder (n = 2), chronic renal failure (n =2), congenital valvular defect (n =1).

Table 2. Delivery mode in preterm and term deliveries and indications for preterm and term iatrogenic deliveries.

	Preterm delivery	Term delivery
Delivery mode of total study population	(n = 50)	(n = 161)
Spontaneous vaginal delivery	13 (26%)	126 (78%)
Elective cesarean delivery	3 (6%)	5 (3%)
Emergency cesarean delivery	29 (58%)	17 (11%)
Vaginal instrumental delivery	5 (10%)	13 (8%)
Indications for iatrogenic deliveries	(n = 46)	(n = 77)
EFW ≤5th centile alone	0 (0%)	24 (15%)
EFW ≤5th centile + abnormal Doppler/CTG and/or HT*/PE	31 (62%)	19 (12%)
PE	8 (16%)	7 (4%)
Maternal indications†	3 (6%)	12 (7%)
Other indications‡	4 (4%)	15 (9%)

EFW, estimated fetal weight. HT, hypertension. PE, pre-eclampsia.

* Includes both pre-gestational hypertension and gestational hypertension

† Includes complicated obstetric history, maternal request, previous uterine surgery, breach presentation, severe hyperemesis and severe chronic maternal disease.

‡ Includes gestational diabetes, hypertension, post term, rupture of membranes, placental abruption, oligohydramnios and advanced maternal age in combination with gestational age > 41^{+2}

Table 3. Log-binomial regression analysis of size and conditional growth centiles ≤ 5 of estimated fetal weight and their combination in the prediction of preterm birth, operative delivery due to fetal distress, admission to NICU and any adverse outcome.

Outcome	Exposure	Total (n)	Outcome n (%)	Relative risk	95% CI	Adjusted* relative risk	95% CI
Preterm birth							
Size	≤ 5th centile	80	31 (38.8)	2.67	1.62–4.40	1.80	0.99-3.27
	> 5th centile	131	19 (14.5)	1	Reference	1	Reference
Conditional growth	≤ 5th centile	47	23 (48.9)	2.97	1.89-4.67	2.08[†]	1.20-3.58
	> 5th centile	164	27 (16.5)	1	Reference	1	Reference
Operative delivery due to fetal distress							
Size	≤ 5th centile	80	37 (46.3)	4.66	2.64–8.22	2.63	1.34-5.17
	> 5th centile	131	13 (9.9)	1	Reference	1	Reference
Conditional growth	≤ 5th centile	47	29 (61.7)	4.82	3.05-7.62	2.72[†]	1.58-4.70
	> 5th centile	164	21 (12.8)	1	Reference	1	Reference
NICU							
Size	≤ 5th centile	80	32 (40.0)	3.28	1.92–5.57	1.74	0.85-3.56
	> 5th centile	131	16 (12.2)	1	Reference	1	Reference
Conditional growth	≤ 5th centile	47	26 (55.3)	4.12	2.59-6.57	2.89[†]	1.52-5.49
	> 5th centile	164	22 (13.4)	1	Reference	1	Reference
Any adverse outcome							
Size	≤ 5th centile	80	53 (66.3)	2.41	1.75–3.32	1.81	1.22-2.67
	> 5th centile	131	36 (27.5)	1	Reference	1	Reference
Conditional growth	≤ 5th centile	47	37 (78.7)	2.48	1.90-3.25	1.73[†]	1.24-2.40
	> 5th centile	164	52 (31.7)	1	Reference	1	Reference

*The two independent covariates, size centile and conditional growth centiles, are both included in the analysis

[†]Inclusion of conditional growth centiles in the model in addition to size centiles significantly improved the prediction of preterm birth, (P = 0.023), operative delivery due to fetal distress (P = 0.028), admission to NICU (P = 0.022), and any adverse outcome (P = 0.023), log-likelihood test

CI, confidence interval

Table 4. Log-binomial regression analysis of size and conditional growth centiles ≤ 10 of estimated fetal weight and their combination in the prediction of preterm birth, operative delivery due to fetal distress, admission to NICU and any adverse outcome.

Outcome	Exposure	Total (n)	Outcome n (%)	Relative risk	95% CI	Adjusted* relative risk	95% CI
Preterm birth							
Size	≤ 10th centile	100	37 (37.0)	3.16	1.78-5.59	2.02	0.94-4.34
	> 10th centile	111	13 (11.7)	1	Reference	1	Reference
Conditional growth	≤ 10th centile	69	30 (43.5)	3.09	1.90-5.03	2.00[†]	1.04-3.85
	> 10th centile	142	20 (14.1)	1	Reference	1	Reference
Operative delivery due to fetal distress							
Size	≤ 10th centile	100	41 (41.0)	5.06	2.59-9.87	2.59	1.06-6.34
	> 10th centile	111	9 (8.1)	1	Reference	1	Reference
Conditional growth	≤ 10th centile	69	35 (50.7)	4.80	2.82-8.18	2.72[†]	1.34-5.53
	> 10th centile	142	15 (10.6)	1	Reference	1	Reference
NICU							
Size	≤ 10th centile	100	37 (37.0)	3.73	2.02-6.92	2.16	1.03-4.50
	> 10th centile	111	11 (9.9)	1	Reference	1	Reference
Conditional growth	≤ 10th centile	69	31 (44.9)	3.75	2.24-6.29	2.39[†]	1.29-4.43
	> 10th centile	142	17 (12.0)	1	Reference	1	Reference
Any adverse outcome							
Size	≤ 10th centile	100	62 (62.0)	2.55	1.77-3.66	1.96	1.23-3.14
	> 10th centile	111	27 (24.3)	1	Reference	1	Reference
Conditional growth	≤ 10th centile	69	47 (68.1)	2.30	1.71-3.11	1.51[†]	1.03-2.20
	> 10th centile	142	42 (29.6)	1	Reference	1	Reference

* The two independent covariates, size centile and conditional growth centiles, are both included in the analysis

[†]Inclusion of conditional growth centiles in the model in addition to size centiles significantly improved the prediction of preterm birth, (*P* = 0.015), operative delivery due to fetal distress (*P* = 0.014), admission to NICU (*P* = 0.024), and any adverse outcome (*P* = 0.012), log-likelihood test

CI, confidence interval

FIGURE LEGEND

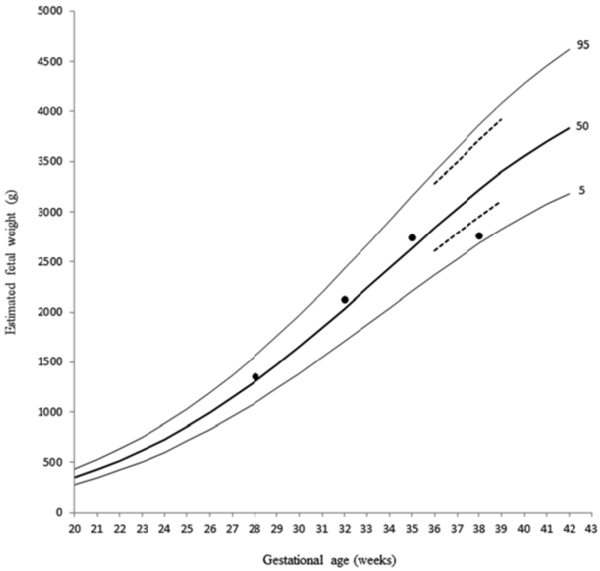

Figure 1. Serial biometry measurements of estimated fetal weight (EFW) for one of the participants (black dots) plotted on reference ranges for male fetal sex with 5th, 50th and 95th centiles (black rules). The second last EFW assessment at 35 weeks (2746g, size centile 64) was used for calculating the individual conditional growth range for the last measurement at 38 weeks (broken rules for 5th and 95th conditional growth centiles). The last EFW of 2760g corresponds to 11th centile for size and the conditional growth centile of 1.