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Published in:
Ultrasound in Obstetrics and Gynecology

DOI:
10.1002/uog.26250

Ultrasound Obstet Gynecol 2023; **62**: 796–804
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.26250.

Predictive value of fetal growth trajectory from 20 weeks of gestation onwards for severe adverse perinatal outcome in low-risk population: secondary analysis of IRIS study

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KEYWORDS: fetal growth restriction; FGR; growth velocity; placental insufficiency; SGA; slow fetal growth; small-for-gestational age

CONTRIBUTION

What are the novel findings of this work?
Slow fetal growth, defined as a decline in abdominal circumference (AC) and/or estimated fetal weight of >20 or >50 percentiles or an AC growth velocity $<10^{th}$ percentile, between $18+0$ to $23+6$ and $32+0$ to $36+6$ weeks' gestation, did not predict severe adverse perinatal outcome (SAPO) in a low-risk population. If slow fetal growth was combined with small fetal size, there was an increased risk of SAPO.

What are the clinical implications of this work?
Slow fetal growth alone does not distinguish between true fetal growth restriction (FGR) and constitutionally small fetus in a low-risk population. If slow fetal growth is suspected, the use of various diagnostic tools for impaired placental function and FGR should be considered, to improve diagnosis of the fetus at risk.

ABSTRACT

Objectives *The placental dysfunction underlying fetal growth restriction (FGR) may result in severe adverse perinatal outcome (SAPO) related to fetal hypoxia. Traditionally, the diagnostic criteria for FGR have been based on fetal size, an approach that is inherently flawed because it often results in either over- or underdiagnosis. The anomaly ultrasound scan at 20 weeks' gestation may be an appropriate time at which to set a benchmark for growth potential of the individual fetus. We hypothesized that the fetal growth trajectory from that point onwards may be informative regarding third-trimester placental dysfunction. The aim of this study was to investigate the predictive value for SAPO of a slow fetal growth trajectory between 18 + 0 to 23 + 6 weeks and 32 + 0 to 36 + 6 weeks' gestation in a large, low-risk population.*

Methods *This was a* post-hoc *data analysis of the IUGR Risk Selection (IRIS) study, a Dutch nationwide cluster-randomized trial assessing the (cost-)effectiveness of routine third-trimester sonography in reducing SAPO. In the current analysis, for the first ultrasound examination we used ultrasound data from the routine anomaly scan at 18 + 0 to 23 + 6 weeks' gestation, and for the second we used data from an ultrasound examination performed between 32 + 0 and 36 + 6 weeks' gestation. Using multilevel logistic regression, we analyzed whether SAPO was predicted by a slow fetal growth trajectory, which was defined as a decline in abdominal*

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Accepted: 7 May 2023

circumference (AC) and/or estimated fetal weight (EFW) of more than 20 percentiles or more than 50 percentiles or as an AC growth velocity (ACGV) < 10th percentile (p10). In addition, we analyzed the combination of these indicators of slow fetal growth with small-for-gestational age (SGA) (AC or EFW < p10) and severe SGA (AC/EFW < 3rd percentile) at 32 + 0 to 36 + 6 weeks' gestation.

Results *Our sample included the data of 6296 low-risk singleton pregnancies, among which 82 (1.3%) newborns experienced at least one SAPO. Standalone declines in AC or EFW of > 20 or > 50 percentiles or ACGV < p10 were not associated with increased odds of SAPO. EFW < p10 between 32 + 0 and 36 + 6 weeks' gestation combined with a decline in EFW of > 20 percentiles was associated with an increased rate of SAPO. The combination of AC or EFW < p10 between 32 + 0 and 36 + 6 weeks' gestation with ACGV < p10 was also associated with increased odds of SAPO. The odds ratios of these associations were higher if the neonate was SGA at birth.*

Conclusions *In a low-risk population, a slow fetal growth trajectory as a standalone criterion does not distinguish adequately between fetuses with FGR and those that are constitutionally small. This absence of association may be a result of diagnostic inaccuracies and/or post-diagnostic (e.g. intervention and selection) biases. We conclude that new approaches to detect placental insufficiency should integrate information from diagnostic tools such as maternal serum biomarkers and Doppler ultrasound measurements.* © *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

Fetal growth restriction (FGR) is defined as the condition in which a fetus does not reach its intrinsic growth potential. The most common underlying pathophysiological mechanism is placental insufficiency[1]. An immediate threat caused by FGR is fetal hypoxia, which carries a risk of morbidity and mortality, especially if the FGR goes undetected[2–6]. Therefore, monitoring of fetal growth and management strategies in cases of suspected FGR are key objectives of antenatal care[7–9].

Traditionally, small-for-gestational age (SGA) is the key identifier of FGR. Typically, SGA is defined as an abdominal circumference (AC), estimated fetal weight (EFW) or birth weight below the 10th percentile (< p10). However, this approach is inherently flawed, because many SGA fetuses and newborns are constitutionally small, while some fetuses and newborns may not have reached their intrinsic growth potential despite having a weight above this cut-off[8,10,11]. Also, there is a risk of inadequate assessment of fetal size and growth due to the low sensitivity and specificity of sonographic fetal biometric measurements[7].

Currently, no tool exists that weighs fetal size against the unknown entity of intrinsic growth potential. The anomaly ultrasound scan at around 20 weeks of gestation may be an appropriate time at which to set the benchmark for growth potential of the individual fetus. We hypothesized that the fetal growth trajectory from that point onwards may be informative regarding third-trimester placental dysfunction and that this may help to identify fetuses at risk of hypoxia[12,13]. However, how best to define a slow fetal growth trajectory is undecided, particularly with respect to which timepoints to use and the best cut-off for percentiles of decline (decline of > 20 or > 50 percentiles) of AC and/or EFW[1,8,14–20].

The aim of this secondary analysis of the IUGR Risk Selection (IRIS) study[7] was to examine the predictive value of a slow fetal growth trajectory between 18 + 0 to 23 + 6 and 32 + 0 to 36 + 6 weeks' gestation in predicting severe adverse perinatal outcome (SAPO). Also, as a supplementary secondary analysis, we tested the associations between slow fetal growth and the outcomes onset of labor and mode of birth.

METHODS

This was a secondary data analysis of the IRIS study, of which the methods have been described extensively[7,17]. Briefly, the IRIS study (Netherlands Trial Register NTR4367) was a Dutch nationwide stepped-wedge cluster-randomized trial examining the (cost-)effectiveness in reducing SAPO of routine third-trimester ultrasonography in a low-risk population at 28–30 and 34–36 weeks' gestation (as compared to clinically indicated ultrasonography)[7,17]. The study included 13 520 pregnant women with children born between March 2015 and August 2016.

The medical ethics review committee of the VU University Medical Center in Amsterdam approved the IRIS study (reference number: 2013.409). Written informed consent for the use and linking of maternal and child data was obtained from all participating women.

Population

In The Netherlands, hospitals provide secondary and tertiary antenatal care, whereas primary-care midwives are independent medical practitioners qualified to provide full maternity care for women with uncomplicated low-risk pregnancy. Women in primary midwife-led care at the onset of labor can choose to deliver with their midwife at home, in a birth center or in a hospital setting.

The IRIS study included women at least 18 years of age receiving midwife-led care from one of the 60 participating midwifery practices after the 20-week screening scan for anomalies and who, at that point in time, had a low-risk singleton pregnancy and provided written informed consent for data usage[17]. The observation of significant anomalies during the scan at 18 + 0 to 23 + 6 weeks' gestation was an exclusion criterion. Women with a medical condition at 18 + 0 to 23 + 6 weeks of gestation that required secondary or tertiary antenatal care were also ineligible for the IRIS study. Women who developed any medical condition

that required secondary or tertiary antenatal care during pregnancy before the study ultrasound examination between 32 + 0 and 36 + 6 weeks' gestation (essential for this *post-hoc* analysis) were excluded from the current analysis because the ultrasound data from the secondary and tertiary antenatal care providers were not available.

Ultrasound examination

Between 18 + 0 and 23 + 6 weeks' gestation, all women in The Netherlands are offered a fetal anomaly scan which includes fetal biometric measurements[21,22]. This anomaly scan was the benchmark ultrasound examination that we used for the current analysis ($n = 6296$). The IRIS study protocol did not include routine collection of anomaly-scan data.

The second ultrasound examination that we used was performed between 32 + 0 and 36 + 6 weeks' gestation in the midwifery practices and participating sonography centers of the IRIS study. Sonographers who participated in the IRIS study held a certificate for structural anomaly screening (73% of 154 participating sonographers) or passed a biometry quality test before the trial (27%). Two independent and experienced sonographers who were board members of the Dutch Professional Organization of Sonographers conducted quality assessments of the sonographers during the trial[7].

We used the reference curve of Verburg *et al.*[23] for gestational-age-specific percentiles of AC and the reference curve Hadlock-3[24] for gestational-age-specific percentiles of EFW. If more than one ultrasound examination was available between 32 + 0 and 36 + 6 weeks' gestation, the last one was used for the current analysis.

Indicators of small fetal size or slow fetal growth

The indicators of small fetal size that we tested were SGA (AC or EFW < p10) and severe SGA (AC or EFW < 3rd percentile (p3)) between 32 + 0 and 36 + 6 weeks' gestation.

Several different indicators of slow fetal growth were used: a decline of more than 20 or 50 percentiles of the AC and/or EFW between 18 + 0 to 23 + 6 and 32 + 0 to 36 + 6 weeks' gestation[1,17]; and a low AC growth velocity (ACGV), in mm/week, between 18 + 0 to 23 + 6 and 32 + 0 to 36 + 6 weeks' gestation. The ACGV difference score was calculated by subtracting the AC (in mm) at the 18 + 0 to 23 + 6-week scan (timepoint 1 (T1)) from the AC (in mm) at the 32 + 0 to 36 + 6-week scan (T2), and dividing this difference by the number of days between the scans (i.e. gestational age at T1 subtracted from gestational age at T2). This difference score was then *z*-standardized and thus transformed into a *Z*-score. Low ACGV was defined using as a cut-off *Z*-score < p10 of this low-risk population. This method is in line with the approach by Sovio *et al.*[8], in which low ACGV was also defined as a *Z*-score in the lowest 10%.

Also, we tested the associations of combinations of (severe) SGA and different indicators of slow fetal growth with SAPO. We combined: AC < p10 with a decline in AC of > 20 and of > 50 percentiles; EFW < p10 with a decline in EFW of > 20 and of > 50 percentiles; AC < p10 with ACGV < p10 and ACGV ≥ p10; and EFW < p10 with ACGV < p10 and ACGV ≥ p10.

Main outcome

The main outcome, SAPO, was the same as that used in the IRIS study[7], i.e. a composite of severe adverse fetal and neonatal outcomes, up to 7 days after birth, defined as one or more of the following: perinatal death occurring from 28 weeks of gestation until 1 week after birth; Apgar score < 4 at 5 min; impaired consciousness (coma, stupor or decreased response to pain); asphyxia, defined as cord blood arterial base excess of < −12 mmol/L; seizures on two or more occasions within 72 h after birth; requirement for assisted ventilation via endotracheal tube, lasting > 24 h and initiated within 72 h following delivery; septicemia, ascertained by blood culture; meningitis, ascertained by cerebrospinal fluid culture; bronchopulmonary dysplasia requiring oxygen after 36 completed weeks and ascertained by radiography; intraventricular hemorrhage Grade 3 or 4, diagnosed by ultrasound or autopsy; cystic periventricular leukomalacia, ascertained by ultrasonography; and necrotizing enterocolitis, diagnosed by radiography, surgery or autopsy.

Of note, due to the exclusion criteria for the current analysis, pregnancies that ended before the second ultrasound examination between 32 + 0 and 36 + 6 weeks' gestation (due to perinatal death or very premature delivery) were not included in the analysis.

Secondary outcomes

Secondary outcomes of the current study were onset of labor and mode of birth outcomes. The onset of labor outcome was divided into three categories: spontaneous onset of labor, induction of labor and prelabor Cesarean section. Prelabor Cesarean sections had various indications, such as breech presentation or previous Cesarean section. We did not differentiate between these indications. The mode of birth outcome was divided into three categories: spontaneous vaginal, assisted vaginal (vacuum or forceps) or Cesarean section during labor. Cases in which a vaginal birth was planned but, during labor, a Cesarean section was performed (due to, for example, obstructed delivery or fetal distress) were defined as Cesarean section during labor.

Statistical analysis

Descriptive statistics were calculated for baseline characteristics and ultrasound parameters (means, SDs, frequencies, percentages). We calculated the gestational-age-specific standard percentiles for birth weight using the formula of the Hoftiezer birth-weight standard[25].

Multilevel logistic regression models were used to examine the association between indicators of slow fetal

growth, small fetal size and SAPO. Models included a fixed effect for fetal indicators of a slow fetal growth trajectory and a random effect for midwifery practice to account for clustering of women within the participating midwifery practices. We did not adjust for maternal baseline characteristics. We also tested whether combinations of indicators of a slow fetal growth trajectory and small fetal size were associated with SAPO. We also aimed to examine the association of SGA (AC and/or EFW < p10) and severe SGA (AC and/or EFW < p3) measured between 32 + 0 and 36 + 6 weeks' gestation with SAPO. If the *n* was too small, we did not perform regression analysis, instead using Fisher's exact test for bivariable analyses.

Using the same logistic regression models or Fisher's exact test, we examined the association of slow fetal growth with SAPO for newborns that were appropriate-for-gestational age (AGA), defined as birth weight ≥ p10, or SGA.

Finally, we tested whether indicators of a slow fetal growth trajectory were associated with different types of onset of labor and mode of birth outcomes using multinomial logistic regression analysis.

Analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA) and Stata software, version 14 (StataCorp., College Station, TX, USA). The Hoftiezer SDSs were calculated in R, version 3.02[26]. *P*-values ≤ 0.05 (two-sided) were considered statistically significant.

RESULTS

In total, 13 520 women with a low-risk singleton pregnancy at a mean ± SD gestational age of 22.8 ± 2.4 weeks were enrolled into the IRIS study[7] between February 2015 and February 2016. For 13 046 of these pregnancies, data on gender, birth weight and gestational age at birth could be linked to data of The Netherlands' Perinatal Registry and perinatal and maternal outcomes were available[27].

The IRIS study protocol did not include routine collection of the data from the 18 + 0 to 23 + 6-week anomaly scan (the reference scan). Nevertheless, these data were available for 10 204 women, of whom 4482 were in the control group of the IRIS study and 5722 were in the intervention group. The other 2842 (22%) women, for whom reference scan data were not available or not collected, we excluded. Another 3884 (38%) women were excluded because there were no ultrasound data available from 32 + 0 to 36 + 6 weeks' gestation. The lack of these third-trimester ultrasound data was due to two main reasons: 940 (16%) women from the intervention group of the IRIS study developed a medical condition that led to referral to secondary or tertiary antenatal care prior to the planned study scan, while 2944 (66%) of those in the control group did not have a clinically indicated third-trimester scan. Finally, there was no information about the occurrence of SAPO for 24 (0.4%) of the remaining 6320 neonates, who were therefore also excluded. Thus, 6296 women were included in one or more of our main analyses. Baseline characteristics of these women and neonates are given in Table 1.

Table 2 presents the data of the ultrasound measurements. In this low-risk population, the rates of AC and EFW < p10 at 18 + 0 to 23 + 6 (median, 20 + 0) weeks' gestation were low, at 1.4% and 0.4%, respectively. At 32 + 0 to 36 + 6 (median, 34 + 4) weeks' gestation, these

Table 1 Baseline characteristics of study population of 6296 low-risk singleton pregnancies

Characteristic	*Value*
Maternal characteristics	
Maternal age (years)	30.7 ± 4.4
Ethnicity	
Dutch	4665/6293 (74.1)
Other western	713/6293 (11.3)
Non-western	915/6293 (14.5)
Data missing	3
Parity	
Nulliparous	3056/6245 (48.9)
Parous	3189/6245 (51.1)
Data missing	51
Prepregnancy BMI	
Underweight (< 18.5 kg/m^2)	214/6195 (3.5)
Normal (18.5–25.0 kg/m^2)	4077/6195 (65.8)
Overweight/obese (> 25.0 kg/m^2)	1904/6195 (30.7)
Data missing	101
Smoking	
Yes	370/6282 (5.9)
No	5912/6282 (94.1)
Data missing	14
Educational level	
Low	627/6180 (10.1)
Medium	2229/6180 (36.1)
High	3324/6180 (53.8)
Data missing	116
Gestational diabetes*	
Yes	154/6290 (2.4)
No	6136/6290 (97.6)
Data missing	6
Infant characteristics	
Sex	
Boy	3165/6295 (50.3)
Girl	3130/6295 (49.7)
Data missing	1
Birth-weight percentile (Hoftiezer)	
< p10 (SGA)	517 (8.2)
≥ p10 (AGA)	5779 (91.8)
Data missing	0
Congenital abnormality	
Yes	121 (1.9)
No	6175 (98.1)
Data missing	0
Severe adverse perinatal outcome	
Yes	82 (1.3)
No	6214 (98.7)
Data missing	0

Data are given as mean ± SD, *n*/*N* (%), *n* or *n* (%). *Women with gestational diabetes with stable blood glucose levels with dietary intervention only; if women needed insulin treatment, they were referred to secondary care and were not included in this sample. AGA, appropriate-for-gestational age; BMI, body mass index; p10, 10th percentile; SGA, small-for-gestational age.

rates increased to 2.0% of fetuses with AC < p10 and 5.2% of fetuses with EFW < p10. Approximately one in four (25.3%) fetuses experienced a decrease in AC of > 20 percentiles between the measurement at 18 + 0 to 23 + 6 weeks and that at 32 + 0 to 36 + 6 weeks' gestation, and almost one in five fetuses (18.7%) experienced such a decrease in EFW. The rates of decrease of > 50 percentiles were much lower: 3.4% for the AC and 0.7% for EFW. ACGV was < p10 in 10.0% of the fetuses.

Overall, 82 neonates in our analysis experienced at least one SAPO, of whom 14 experienced this in combination with birth weight < p10 (SGA). Table 3 shows the associations with SAPO of AC and EFW < p10 and < p3 between 32 + 0 and 36 + 6 weeks' gestation. AC < p10 as a standalone risk factor was not associated with SAPO.

Table 2 Ultrasound data from 6296 low-risk singleton pregnancies

Parameter	*Value*
AC	
18 + 0 to 23 + 6 GW	
< p10	85 (1.4)
≥ p10	6211 (98.6)
Data missing	0
32 + 0 to 36 + 6 GW	
< p3	24 (0.4)
< p10	123 (2.0)
≥ p10	6173 (98.0)
Data missing	0
EFW	
18 + 0 to 23 + 6 GW	
< p10	23/5789 (0.4)
≥ p10	5766/5789 (99.6)
Data missing	507
32 + 0 to 36 + 6 GW	
< p3	41/5770 (0.7)
< p10	302/5770 (5.2)
≥ p10	5468/5770 (94.8)
Data missing	526
Fetal growth velocity between 18 + 0 to 23 + 6 and 32 + 0 to 36 + 6 GW	
AC	
Decline in AC > 20 percentiles	1554/6148 (25.3)
Decline in AC > 50 percentiles	210/6148 (3.4)
Normal AC growth velocity	4594/6148 (74.7)
Data missing	148
EFW	
Decline in EFW > 20 percentiles	1042/5571 (18.7)
Decline in EFW > 50 percentiles	37/5571 (0.7)
Normal EFW growth velocity	4529/5571 (81.3)
Data missing	725
AC and/or EFW	
Decline in AC and/or EFW > 20 percentiles	1696/5571 (30.4)
Decline in AC and/or EFW > 50 percentiles	201/5571 (3.6)
Normal AC and/or EFW growth velocity	3875/5571 (69.6)
Data missing	725
ACGV*	
< p10	627/6288 (10.0)
≥ p10	5661/6288 (90.0)
Data missing	8

Data are given as *n* (%), *n* or *n*/*N* (%). *Z-scores of abdominal circumference growth velocity (ACGV) between 18 + 0 to 23 + 6 and 32 + 0 to 36 + 6 gestational weeks (GW). AC, abdominal circumference; EFW, estimated fetal weight; p10, 10th percentile.

However, it was related to a 7.27 (95% CI, 1.59–33.23) times higher risk of the neonate having a SGA birth weight combined with SAPO. None of the 24 fetuses with AC < p3 experienced SAPO. EFW < p10 was related to an increased risk of SAPO (odds ratio (OR), 2.49 (95% CI, 1.22–5.06), and to a 19.81 (95% CI, 6.56–59.82) times higher risk of SGA birth weight combined with SAPO. None of the 41 fetuses with EFW < p3 experienced SAPO.

Table 4 shows the associations of indicators of slow fetal growth with SAPO at any birth weight, SAPO combined with a birth weight < p10 and SAPO combined with a birth weight ≥ p10. For both AC and EFW, a standalone decline of more than 20 or 50 percentiles between 18 + 0 to 23 + 6 and 32 + 0 to 36 + 6 weeks' gestation was not associated with an increased risk of SAPO. However, if AC crossed more than 20 percentiles, there was an increased risk of the neonate being SGA at birth combined with SAPO (OR, 2.98 (95% CI, 1.04–8.51)). The final indicator of a slow fetal growth trajectory was the Z-score based on an ACGV between 18 + 0 to 23 + 6 and 32 + 0 to 36 + 6 weeks' gestation in the lowest 10% of our population (ACGV < p10). When this indicator was used alone, it was not associated with an increased risk of SAPO. However, ACGV < p10 was related to an increased risk of SAPO combined with SGA neonate (OR, 6.46 (95% CI, 2.23–18.73)).

Finally, we analyzed the predictive values of combinations of small fetal size and indicators of slow fetal growth. The results of these analyses are shown in Table 5. A decline in EFW of > 20 percentiles when the EFW was also < p10 between 32 + 0 and 36 + 6 weeks' gestation was associated with an increased risk of SAPO (OR, 2.9 (95% CI, 1.03–8.14)) (Table 5), and there was a stronger association with an increased risk of SAPO combined with SGA birth weight (OR, 12.19 (95% CI, 3.22–46.15)). The combination of ACGV < p10 between 18 + 0 to 23 + 6 and 32 + 0 to 36 + 6 weeks' gestation with AC < p10 or EFW < p10 between 32 + 0 and 36 + 6 weeks showed a significant association with SAPO (OR, 2.83 (95% CI, 1.01–7.91) and OR, 2.91 (95% CI, 1.31–6.43), respectively). Moreover, these same combinations also showed a statistically significant association with SGA at birth and SAPO (OR, 8.42 (95% CI, 1.84–38.46) and OR, 16.23 (95% CI, 5.21–50.54), respectively). Combinations of AC < p10 or EFW < p10 with a normal fetal growth velocity defined as ACGV ≥ p10 were not associated with SAPO.

The outcomes of these analyses are also summarized in Figure 1, which shows the associations (OR and 95% CI, if available) of the ultrasound-based indicators of small fetal size and slow fetal growth with SAPO.

The secondary outcomes of this study were onset of labor and the mode of birth. The results of these analyses are shown in Tables S1 and S2. In this low-risk population, 79.9% of pregnancies had spontaneous onset of labor, the rate of inductions was 14.7% and that of prelabor Cesarean section was 5.4%. We found a slight decrease in the rate of spontaneous onset of labor and a slight increase in the rate of inductions when ACGV < p10 or when there was a decline in AC and/or EFW > 50 percentiles.

Table 3 Association with severe adverse perinatal outcome (SAPO) of abdominal circumference (AC) and estimated fetal weight (EFW) < 10th percentile (p10) or < 3rd percentile (p3) between 32 + 0 and 36 + 6 weeks' gestation

Ultrasound indicator	n	*Data missing*	*SAPO (n = 82)*		*SGA neonate (BW < p10) + SAPO (n = 14)*	
			OR (95% CI)	P	*OR (95% CI)*	P
AC < p10	123	0	2.51 (0.90–6.99)	0.08	7.27 (1.59–33.23)	0.01
AC < p3	24	0	NA	—	NA	—
EFW < p10	302	526	2.49 (1.22–5.06)	0.01	19.81 (6.56–59.82)	< 0.001
EFW < p3	41	526	—	0.41*	—	0.10*

BW, birth weight; NA, not applicable, because $n = 0$; OR, odds ratio; SGA, small-for-gestational age. *Fisher's exact test because of small *n*.

Table 4 Association with severe adverse perinatal outcome (SAPO) of indicators of slow fetal growth between 18 + 0 to 23 + 6 and 32 + 0 to 36 + 6 weeks' gestation

Ultrasound indicator	n	*Data missing*	*SAPO (n = 82)*		*SGA neonate (BW < p10) + SAPO (n = 14)*		*AGA neonate (BW ≥ p10) + SAPO (n = 68)*	
			OR (95% CI)	P	*OR (95% CI)*	P	*OR (95% CI)*	P
Decline in AC > 20 percentiles	1554	148	1.17 (0.72–1.91)	0.52	2.98 (1.04–8.51)	0.04	0.92 (0.53–1.63)	0.79
Decline in AC > 50 percentiles	210	148	—	0.53*	NA	—	—	0.73*
Decline in EFW > 20 percentiles	1042	725	1.13 (0.65–1.97)	0.67	—	0.31*	1.04 (0.55–1.97)	0.90
Decline in EFW > 50 percentiles	37	725	NA	—	NA	—	NA	—
ACGV < p10	627	8	1.53 (0.83–2.85)	0.18	6.46 (2.23–18.73)	< 0.001	0.87 (0.37–2.01)	0.74

AC, abdominal circumference; ACGV, abdominal circumference growth velocity; AGA, appropriate-for-gestational age; BW, birth weight; EFW, estimated fetal weight; NA, not applicable, because $n = 0$; OR, odds ratio; p10, 10th percentile; SGA, small-for-gestational age. *Fisher's exact test because of small *n*.

Table 5 Association with severe adverse perinatal outcome (SAPO) of combinations of abdominal circumference (AC) and estimated fetal weight (EFW) < 10th percentile (p10) between 32 + 0 and 36 + 6 weeks' gestation and indicators of slow fetal growth between 18 + 0 to 23 + 6 and 32 + 0 to 36 + 6 weeks' gestation

Ultrasound indicator	n	*Missing*	*SAPO (n = 82)*		*SGA neonate (BW < p10) + SAPO (n = 14)*	
			OR (95% CI)	P	*OR (95% CI)*	P
AC < p10 and decline in AC > 20 percentiles	70	148	—	0.61*	—	0.15*
AC < p10 and decline in AC > 50 percentiles	17	148	NA	—	NA	—
EFW < p10 and decline in EFW > 20 percentiles	103	855	2.90 (1.03–8.14)	0.04	12.19 (3.22–46.15)	< 0.001
EFW < p10 and decline in EFW > 50 percentiles	8	855	NA	—	NA	—
AC < p10 and ACGV < p10	111	8	2.83 (1.01–7.91)	0.05	8.42 (1.84–38.46)	0.01
EFW < p10 and ACGV < p10	200	526	2.91 (1.31–6.43)	0.01	16.23 (5.21–50.54)	< 0.001
AC < p10 and ACGV ≥ p10	12	8	NA	—	NA	—
EFW < p10 and ACGV ≥ p10	102	526	1.51 (0.36–6.24)	0.57	9.31 (1.98–43.71)	0.01

ACGV, abdominal circumference growth velocity; BW, birth weight; NA, not applicable, because $n = 0$; OR, odds ratio; SGA, small-for-gestational age. *Fisher's exact test because of small *n*.

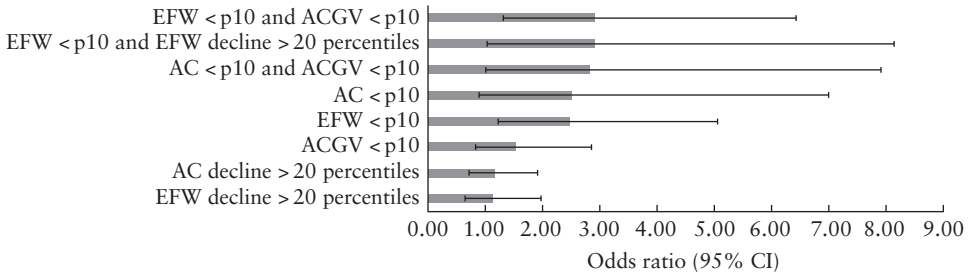

Figure 1 Associations of indicators of small fetal size and slow fetal growth with severe adverse perinatal outcome. AC, abdominal circumference; ACGV, abdominal circumference growth velocity *Z*-scores between 18 + 0 to 23 + 6 and 32 + 0 to 36 + 6 weeks' gestation; EFW, estimated fetal weight; p10, 10th percentile.

Also, the rate of prelabor Cesarean section was higher if slow fetal growth was suspected. Not all of these differences were significant. 84.0% of the women in our study population had a spontaneous vaginal birth, the rate of assisted vaginal birth was 7.8% and that of Cesarean section during labor was 8.1%. ACGV < p10 and a decline in AC and/or EFW of > 20 or > 50 percentiles were not significantly associated with higher rates of assisted vaginal delivery or Cesarean section.

DISCUSSION

In this subanalysis of the IRIS study, in a low-risk population, a slow fetal growth trajectory defined as a decline in EFW of > 20 percentiles between 18 + 0 to 23 + 6 and 32 + 0 to 36 + 6 weeks' gestation was associated with an increased risk of SAPO only if it was combined with small fetal size (EFW < p10 between 32 + 0 and 36 + 6 weeks' gestation). ACGV < p10 was associated with an increased risk of SAPO only if either AC or EFW was < p10. These associations were stronger in SGA newborns.

Furthermore, we found that a slow fetal growth trajectory defined as decline in AC of > 20 percentiles or ACGV < p10 between 18 + 0 to 23 + 6 and 32 + 0 to 36 + 6 weeks' gestation was associated with an increased risk of SAPO among SGA newborns. Overall, rates of prelabor Cesarean section were slightly higher when slow fetal growth was suspected, which is in line with the results of previous studies[28].

Our study is one of few to examine the effects of a slow fetal growth trajectory in a large, low-risk population. Our results regarding the predictive value of slow fetal growth are mostly in line with earlier studies in mixed-risk populations. Sovio *et al.*[8] also reported that ACGV < p10 between 20 weeks' gestation and the last scan before birth combined with EFW < p10 is predictive of perinatal morbidity. These findings suggest that suspicion of slow fetal growth could assist in the diagnosis of FGR and that this may contribute to more accurate identification of the fetus at risk. The Delphi definition for FGR also incorporates slow fetal growth in combination with either small fetal size or Doppler abnormalities.

Based on previous theory and evidence, we also expected to detect more SAPO in the group with a slow fetal growth trajectory and an infant considered AGA in size[8,29,30]. We hypothesize that the lack of this association in our study can be explained by the inherent 'healthy' selection bias due to the low-risk nature of our population.

Our study has several strengths, including its prospective design and a dataset based on questionnaires, a perinatal registry and hospital records, collected within a large-scale nationwide study. Another strength is that we considered different indicators of slow fetal growth. A decline of > 20 or > 50 percentiles is often used in clinical practice but this approach has some flaws. For example, in order to have a decline of > 50 percentiles, the initial AC or EFW must be > p50. A decline of > 20 percentiles is more inclusive, but the risk of false positives is increased due to the inaccuracy in biometric measurement. The high (30%) rate of decline in AC and/or EFW of > 20 percentiles in our study supports this hypothesis. The *Z*-score-based indicator ACGV < p10 is a more objective measurement, reflecting a relative drop in individual growth velocity.

Our study also has limitations. First, only severe and immediate adverse outcomes that occurred after the last ultrasound examination between 32 + 0 and 36 + 6 weeks' gestation were reported. It would have been interesting to include in the analyses less severe outcomes related to FGR, such as hypothermia and hypoglycemia. However, these data were not available. Second, this study was performed in a selected low-risk population with limited numbers of SAPO. For the current analyses, we excluded those women for whom no ultrasound data were available between 32 + 0 and 36 + 6 weeks' gestation. Reasons for this drop-out were referral to secondary or tertiary antenatal care because of complications such as pregnancy-induced hypertension, suspected FGR (defined as a decline of 20 percentiles or EFW or AC < p10 at any scan) or preterm birth. However, women who were referred after the scan between 32 + 0 and 36 + 6 weeks for abnormal fetal growth were included in our dataset. All in all, this was a low-risk population and therefore our findings may not be generalizable to a high-risk population.

Another limitation is the lack of Doppler measurements, as these play an increasingly important role in the diagnosis and treatment of FGR. Doppler measurements are not performed routinely in midwifery-led care in The Netherlands and were not performed in the IRIS study ultrasound examinations because current evidence regarding the value of routine Doppler measurements in low-risk pregnancy is not conclusive[31]. Doppler measurements were performed if SGA was suspected, but these data from secondary and tertiary care providers were not collected. In future, whether additional markers, including Doppler assessment, are of additional diagnostic value in identifying the fetus at risk should be assessed[32,33].

Finally, the composite of SAPO has some limitations. Although it is common practice to use composite outcomes in FGR studies, one might argue that some of these outcomes can be a result of both the condition, i.e. placental insufficiency, and the treatment, which is often provider-initiated (relatively) premature or early term birth[7,8,14,34–36]. We found that the group that experienced a decline in AC and/or EFW of > 50 percentiles had the lowest rate of spontaneous onset of labor and the highest rate of prelabor Cesarean section. The group with ACGV < p10 had the highest rate of inductions. As a result of these provider-initiated interventions, the increased prenatal detection of FGR may have resulted not in a lower incidence of composite outcomes at the population level but in a shift from hypoxia-related outcomes to prematurity-related outcomes. In the current study, however, asphyxia contributed most to the composite outcome ($n = 80$)[36,37].

The diagnosis and management of placental insufficiency is challenging. Biometric measurements, whether standalone, static or in a growth trajectory, do not identify adequately the risk of SAPO in a low-risk population. However, the same applies to all known prognosticators of FGR. This absence of associations may be a result of diagnostic inaccuracies or from post-diagnostic (e.g. intervention) biases.

Conclusions

We conclude that, in a low-risk population, the use of a slow fetal growth trajectory as a standalone criterion for FGR was not associated with an increased risk of SAPO. In future approaches to detect placental insufficiency, small fetal size should be integrated with other diagnostic tools, such as maternal serum biomarkers and Doppler measurements. This should help to discriminate when interventions such as induction of labor or prelabor Cesarean section are warranted. The optimal index measurement to define fetal growth potential and the subsequent fetal growth trajectory has yet to be determined. Late-onset FGR is a condition that can occur in fetuses that have grown normally until the third trimester. Therefore, measurements at this later gestational age may be better suited to use as a starting point for the fetal growth trajectory. In future research it would be interesting to re-examine the effect of a slow fetal growth trajectory in mixed and high-risk populations and to assess the predictive value of combinations of several variables such as Doppler findings and biomarkers as well as the fetal growth trajectory.

ACKNOWLEDGMENT

The authors received no specific funding for this *post-hoc* analysis. The original study was supported by a grant from The Netherlands Organization for Health Research and Development (ZonMw; grant No 209030001). This funding source had no role in study design, data collection, data analysis, data interpretation, writing of the scientific article or the decision to submit the paper for publication.

REFERENCES

1. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, Silver RM, Wynia K, Ganzevoort W. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol* 2016; **48**: 333–339.
2. Nardozza LMM, Caetano ACR, Zamarian ACP, Mazzola JB, Silva CP, Marçal VMG, Lobo TF, Peixoto AB, Araujo Júnior E. Fetal growth restriction: current knowledge. *Arch Gynecol Obstet* 2017; **295**: 1061–1077.
3. Boers KE, Vijgen SMC, Bijlenga D, van der Post JaM, Bekedam DJ, Kwee A, van der Salm PCM, van Pampus MG, Spaanderman MEA, de Boer K, Duvekot JJ, Bremer HA, Hasaart THM, Delemarre FMC, Bloemenkamp KWM, van Meir CA, Willekes C, Wijnen EJ, Rijken M, le Cessie S, Roumen FJME, Thornton JG, van Lith JMM, Mol BWJ, Scherjon SA. Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). *BMJ* 2010; **341**: c7087.
4. Figueras F, Eixarch E, Meler E, Iraola A, Figueras J, Puerto B, Gratacos E. Small-for-gestational-age fetuses with normal umbilical artery Doppler have suboptimal perinatal and neurodevelopmental outcome. *Eur J Obstet Gynecol Reprod Biol* 2008; **136**: 34–38.
5. Sharma D, Shastri S, Sharma P. Intrauterine growth restriction: antenatal and postnatal aspects. *Clin Med Insights Pediatr* 2016; **10**: 67–83.
6. Kesavan K, Devaskar SU. Intrauterine growth restriction: postnatal monitoring and outcomes. *Pediatr Clin North Am* 2019; **66**: 403–423.
7. Henrichs J, Verfaille V, Jellema P, Viester L, Pajkrt E, Wilschut J, van der Horst, Henriëtte E, Franx A, de Jonge A. Effectiveness of routine third trimester ultrasonography to reduce adverse perinatal outcomes in low risk pregnancy (the IRIS study): nationwide, pragmatic, multicentre, stepped wedge cluster randomised trial. *BMJ* 2019; **367**: l5517.
8. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. *Lancet* 2015; **386**: 2089–2097.
9. Kamphof HD, Posthuma S, Gordijn SJ, Ganzevoort W. Fetal growth restriction: mechanisms, epidemiology, and management. *Matern Fetal Med* 2022; **4**: 186–196.
10. Ganzevoort W, Thilaganathan B, Baschat A, Gordijn SJ, Gardosi J. Point: Fetal growth and risk assessment: is there an impasse? *Am J Obstet Gynecol* 2019; **220**: 74–82.
11. Kamphof HD, Gordijn SJ, Ganzevoort W, Verfaille V, Offerhaus PM, Franx A, Pajkrt E, de Jonge A, Henrichs J. Associations of severe adverse perinatal outcomes among continuous birth weight percentiles on different birth weight charts: a secondary analysis of a cluster randomized trial. *BMC Pregnancy Childbirth* 2022; **22**: 375.
12. Caradeux J, Martinez-Portilla RJ, Peguero A, Sotiriadis A, Figueras F. Diagnostic performance of third-trimester ultrasound for the prediction of late-onset fetal growth restriction: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2019; **220**: 449–459.e19.
13. Figueras F, Caradeux J, Crispi F, Eixarch E, Peguero A, Gratacos E. Diagnosis and surveillance of late-onset fetal growth restriction. *Am J Obstet Gynecol* 2018; **218**: S790–S802.e1.
14. Bricker L, Medley N, Pratt JJ. Routine ultrasound in late pregnancy (after 24 weeks' gestation). *Cochrane Database Syst Rev* 2015; **2015**: CD001451.
15. Melamed N, Baschat A, Yinon Y, Athanasiadis A, Mecacci F, Figueras F, Berghella V, Nazareth A, Tahlak M, McIntyre HD, Costa FDS, Kihara AB, Hadar E, McAuliffe F, Hanson M, Ma RC, Gooden R, Sheiner E, Kapur A, Divakar H, Ayres-de-Campos D, Hiersch L, Poon LC, Kingdom J, Romero R, Hod M. FIGO (International Federation of Gynecology and Obstetrics) initiative on fetal growth: Best practice advice for screening, diagnosis, and management of fetal growth restriction. *Int J Gynaecol Obstet* 2021; **152**: 3–57.
16. Lees CC, Stampalija T, Baschat AA, Costa FdS, Ferrazzi E, Figueras F, Hecher K, Kingdom J, Poon LC, Salomon LJ, Unterscheider J. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol* 2020; **56**: 298–312.
17. Henrichs J, Verfaille V, Viester L, Westerneng M, Molewijk B, Franx A, van der Horst H, Bosmans JE, de Jonge A, Jellema P, IRIS Study Group. Effectiveness and cost-effectiveness of routine third trimester ultrasound screening for intrauterine growth restriction: study protocol of a nationwide stepped wedge cluster-randomized trial in The Netherlands (The IRIS Study). *BMC Pregnancy Childbirth* 2016; **16**: 310–318.
18. Kiserud T, Johnsen SL. Biometric assessment. *Best Pract Res Clin Obstet Gynaecol* 2009; **23**: 819–831.
19. Grantz KL, Kim S, Grobman WA, Newman R, Owen J, Skupski D, Grewal J, Chien EK, Wing DA, Wapner RJ, Ranzini AC, Nageotte MP, Hinkle SN, Pugh S, Li H, Fuchs K, Hediger M, Buck Louis GM, Albert PS. Fetal growth velocity: the NICHD fetal growth studies. *Am J Obstet Gynecol* 2018; **219**: 285.e1–36.
20. Guihard-Costa AM, Droullé P, Larroche JC. Growth velocity of the biparietal diameter, abdominal transverse diameter and femur length in the fetal period. *Early Hum Dev* 1991; **27**: 93–102.
21. Liefers J, Atsma F. Monitor 2018. Prenatale screening op down-, edwards- en patausyndroom en het Structureel Echoscopisch Onderzoek. IQ Scientific Center for Quality of Healthcare, Radboudumc 2019. https://www.pns.nl/sites/default/files/2020-04/20200114%20Professionalsmonitor%202018%20prenatale%20screening.pdf.
22. Gitsels-van der Wal, Janneke T, Verhoeven PS, Manniën J, Martin L, Reinders HS, Spelten E, Hutton EK. Factors affecting the uptake of prenatal screening tests for congenital anomalies; a multicentre prospective cohort study. *BMC Pregnancy Childbirth* 2014; **14**: 264.
23. Verburg BO, Steegers EaP, De Ridder M, Snijders RJM, Smith E, Hofman A, Moll HA, Jaddoe VWV, Witteman JCM. New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. *Ultrasound Obstet Gynecol* 2008; **31**: 388–396.
24. Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. *Radiology* 1991; **181**: 129–133.
25. Hoftiezer L, Hukkelhoven CW, Hogeveen M, Straatman HM, van Lingen RA. Defining small-for-gestational-age: prescriptive versus descriptive birthweight standards. *Eur J Pediatr* 2016; **175**: 1047–1057.
26. R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/.
27. Perined. *Perinatale Zorg in Nederland 2015*. Utrecht: Perined, 2016.
28. Gabbay-Benziv R, Aviram A, Hadar E, Chen R, Bardin R, Wiznitzer A, Yogev Y. Pregnancy outcome after false diagnosis of fetal growth restriction. *ISO4 Standard J Matern-Fetal Neonatal Med* 2017; **30**: 1916–1919.
29. Hugh O, Gardosi J. Fetal weight projection model to define growth velocity and validation against pregnancy outcome in a cohort of serially scanned pregnancies. *Ultrasound Obstet Gynecol* 2022; **60**: 86–95.
30. MacDonald TM, Hui L, Tong S, Robinson AJ, Dane KM, Middleton AL, Walker SP. Reduced growth velocity across the third trimester is associated with placental insufficiency in fetuses born at a normal birthweight: a prospective cohort study. *BMC Medicine* 2017; **164**.
31. Alfirevic Z, Stampalija T, Medley N. Fetal and umbilical Doppler ultrasound in normal pregnancy. *Cochrane Database of Syst Rev* 2015; **2015**: CD001450.

32. Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. *Cochrane Database of Syst Rev* 2017; **2017**: CD007529.
33. Akolekar R, Panaitescu AM, Ciobanu A, Syngelaki A, Nicolaides KH. Two-stage approach for prediction of small-for-gestational-age neonate and adverse perinatal outcome by routine ultrasound examination at 35–37 weeks' gestation. *Ultrasound Obstet Gynecol* 2019; **54**: 484–491.
34. Monier I, Ego A, Benachi A, Hocquette A, Blondel B, Goffinet F, Zeitlin J. Comparison of the performance of estimated fetal weight charts for the detection of small- and large-for-gestational age newborns with adverse outcomes: a French population-based study. *BJOG* 2022; **129**: 938–948.
35. Andreasen LA, Tabor A, Nørgaard LN, Rode L, Gerds TA, Tolsgaard MG. Detection of growth-restricted fetuses during pregnancy is associated with fewer intrauterine deaths but increased adverse childhood outcomes: an observational study. *BJOG* 2021; **128**: 77–85.
36. Gordijn SJ, Ganzevoort W. Search for the best prediction model, definition and growth charts for fetal growth restriction using a composite of adverse perinatal outcomes: a catch-22? *Ultrasound Obstet Gynecol* 2022; **60**: 305–306.
37. Stampalija T, Wolf H, Mylrea-Foley B, Marlow N, Stephens KJ, Shaw CJ, Lees CC. Reduced fetal growth velocity and weight loss are associated with adverse perinatal outcome in fetuses at risk of growth restriction. *Am J Obstet Gynecol* 2022; **228**: 71.e1–100.

SUPPORTING INFORMATION ON THE INTERNET

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

Table S1 Associations between measures of low fetal growth velocity and onset of labor ($n = 6260$)

Table S2 Associations between measures of low fetal growth velocity and mode of birth ($n = 5949$)