

The Role of Growth Trajectories in Classifying Fetal Growth Restriction

Edward D. Barker, PhD, Fionnuala M. McAuliffe, MD, Fiona Alderdice, PhD, Julia Unterscheider, MD, Sean Daly, MD, Michael P. Geary, MD, Mairead M. Kennelly, MD, Keelin O'Donoghue, PhD, Alyson Hunter, MD, John J. Morrison, MD, Gerard Burke, Patrick Dicker, PhD, Elizabeth C. Tully, PhD, and Fergal D. Malone, MD

OBJECTIVE: To examine the validity of a growth trajectory method to discriminate between pathologically and constitutionally undergrown fetuses using repeated measures of estimated fetal weight.

METHODS: In a prospective, observational, multicenter study in Ireland, 1,116 women with a growth-restricted fetus diagnosed participated with the objective of evaluating ultrasound findings as predictors of pediatric morbidity and mortality. Fetal growth trajectories were based on estimated fetal weight.

RESULTS: Between 22 weeks of gestation and term, two fetal growth trajectories were identified: normal (96.7%) and pathologic (3.3%). Compared with the normal trajectory, the pathologic trajectory was associated with an increased risk for preeclampsia (odds ratio [OR] 8.1, 95% confidence interval [CI] 2.6–23.4), increased umbil-

ical artery resistance at 30 weeks of gestation (OR 12.6, 95% CI 4.6–34.1) or 34 weeks of gestation (OR 28.0, 95% CI 8.9–87.7), reduced middle cerebral artery resistance at 30 weeks of gestation (OR 0.33, 95% CI 0.12–0.96) or 34 weeks of gestation (OR 0.14, 95% CI 0.03–0.74), lower gestational age at delivery (mean 32.02 weeks of gestation compared with 38.02 weeks of gestation; $P < .001$), and higher perinatal complications (OR 21.5, 95% CI 10.5–44.2). In addition, 89.2% of newborns with pathologic fetal growth were admitted to neonatal intensive care units compared with 25.9% of those with normal growth.

CONCLUSIONS: Fetal growth trajectory analysis reliably differentiated fetuses with a pathologic growth pattern among a group of women with growth-restricted fetuses. With further development, this approach could provide clarity to how we define, identify, and ultimately manage pathologic fetal growth.

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Fetal growth restriction is a major public health problem. It is associated with fetal death, neonatal death, neonatal and pediatric morbidity, and risk of cardiovascular disease in adulthood,^{1,2} and it can result in either stillbirth or neonatal death.^{3–5} When fetal growth restriction is detected, accurate and timely identification of the condition is of importance for well-being of an at-risk fetus.

The criteria for defining fetal growth restriction, however, are variable. The most common definition is an estimated fetal weight, based on ultrasound measurements, of less than the 10th percentile for a given gestational age based on a set of standardized population birth weights at various gestational ages. This approach, however, is flawed because of the arbitrary nature of the 10th percentile cut-off, the heterogeneity

From the Department of Psychology, Institute of Psychiatry, King's College London, London, United Kingdom; and the UCD Obstetrics and Gynecology, School of Medicine and Medical Science, National Maternity Hospital, University College Dublin, Royal College of Surgeons in Ireland, Coombe Women and Infants University Hospital, and Rotunda Hospital, Dublin, University College Cork, Cork University Maternity Hospital, Cork, Royal Jubilee Maternity Hospital, Belfast, National University of Ireland, Galway, and Graduate Entry Medical School, University of Limerick, Limerick; University College Dublin Center for Human Reproduction, Coombe Women and Infants University Hospital, Dublin; Epidemiology and Public Health, Royal College of Surgeons in Ireland, Dublin; and School of Nursing and Midwifery, Queens University, Belfast, Ireland.

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Corresponding author: Dr. Edward D. Barker, Department of Psychology, King's College London, Institute of Psychiatry, PO Box 077, De Crespigny Park, London, SE5 8AF, UK; e-mail: ted.barker@kcl.ac.uk.

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of pregnancies that meet this cut-off (ie, including the constitutionally small fetus), and the inaccuracies in estimated fetal weight calculations used in previous studies.⁶ Because of these limitations, an alternative approach has been to use customized growth potentials, which adjusts for maternal characteristics (eg, ethnicity, height, weight) and excludes pathologic factors (eg, smoking, and hypertension).⁶ This approach has been shown to be a better predictor of adverse outcome than use of traditional population weight standards.^{7,8} Nevertheless, a limitation of this approach is that the percentiles are based on a given point in gestation, which still may confuse the constitutionally small with the pathologically small fetus because overall fetal development, based on multiple gestation points, is not assessed. The adequacy of the less than 10th percentile cut-off to distinguish between these two groups has implications for subsequent effective fetal surveillance and management.

The current study sought to examine the usefulness of a complimentary analytic strategy to differentiate the pathologically small fetus from the constitutionally small fetus using the growth mixture model.^{9,10} A growth mixture model tests the extent to which, for a repeatedly assessed outcome, a population may consist of a mixture of growth trajectories that are distinct in underlying etiology and long-term functioning.¹¹ We tested the degree to which a growth mixture model could identify at least two estimated fetal weight growth trajectories, the constitutionally small fetus and the pathologically small fetus.

MATERIALS AND METHODS

This study was performed as a prespecified secondary analysis of the Prospective Observational Trial to Optimise Pediatric Health study conducted by the Perinatal Ireland Research Consortium, a nationwide collaborative research network comprising the seven largest academic obstetric centers in Ireland. The trial is a multicenter, prospective, observational study that was initiated in March 2010. The primary aims of the Prospective Observational Trial to Optimise Pediatric Health study were to evaluate multivessel Doppler changes in fetuses with estimated fetal weight less than the 10th percentile and the significance of these changes, and to correlate them with short-term and long-term pediatric morbidity. The study was powered to address these primary aims. Eligibility criteria included singleton pregnancies between 24 0/7 weeks of gestation and 36 6/7 weeks of gestation with estimated fetal weights less than 10th percentile for gestation and structural and chromosomal normality after birth. Institutional Review Board approval was

obtained at each center, and participants gave written informed consent.

Participants (N=1,116 determined by a priori power analysis for the primary study) underwent serial ultrasound assessments of biometric parameters and Doppler assessment of multiple fetal vessels every 2 weeks, including the umbilical artery, middle cerebral artery, ductus venosus, aortic isthmus, and myocardial performance index. Outcome data that were collected included maternal and obstetric characteristics, delivery and birth weight outcomes, and perinatal morbidity and mortality data. At enrollment, the expectant mothers underwent health assessments that included blood pressure, height, weight, body mass index (BMI, calculated as weight (kg)/[height (m)]²), smoking and alcohol intake. Obstetric management, including fetal surveillance, was standardized across all seven centers. This consisted of fetal growth assessment every 2 weeks and, if deemed necessary by the managing consultant, more frequent evaluation with umbilical arterial Doppler, biophysical profile, cardiotocography, or both. Decision to deliver was at the discretion of the individual consultant obstetrician and was generally based on abnormal cardiotocography findings. Antenatal corticosteroids were administered between 24 0/7 weeks of gestation and 36 0/7 weeks of gestation if delivery was thought to be likely within 1 week.

The developmental trajectories were based on estimated fetal weight, which was obtained by ultrasound assessment. On average, the participants in the study underwent 4.78 ultrasound assessments (standard deviation 2.31, range 1–11). The fetal growth mixture models were performed for estimated fetal weight. To maximize power for the analysis, estimated fetal weight was averaged on a monthly basis, at 23–26 weeks of gestation (n=414), 27–30 weeks of gestation (n=571), 31–34 weeks of gestation (n=880), 35–38 weeks of gestation (n=920), and 39–42 weeks of gestation (n=264).

Validity measures for the estimated fetal weight growth trajectories included the following: maternal health characteristics that were noted at enrollment (eg, BMI, history of preeclampsia); Doppler assessments of the umbilical artery, absent end diastolic flow in the umbilical artery, and middle cerebral artery; fetal biometry (eg, femur length, head circumference); and perinatal complications at delivery. The Doppler assessments were averaged on a monthly basis during the same weeks when estimated fetal weight was assessed. Analyses were restricted to those points during gestation with a sufficient number of women with Doppler assessments per fetal growth trajectory (more than 20) to allow comparisons. With regard to perinatal outcomes, “composite adverse



perinatal complications” were defined as a composite outcome of intraventricular hemorrhage, periventricular leucomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, or death.

The analysis proceeded with three main steps. In the first step, we estimated trajectories of estimated fetal weight in a growth mixture model. In general, growth mixture modeling is a type of analysis of repeated measures (in this case, estimated fetal weight) that can test the degree to which a mixture of different developmental trajectories can appropriately describe the overall pattern of development and estimate the proportion of individuals who follow the different developmental trajectories, which are represented as groups (1=in the trajectory, 0=not in the trajectory). More specifically, this type of modeling assumes that a given population of interest may not be homogeneous but could consist of subpopulations that differ in patterns of growth (eg, increasing, not increasing, and decreasing). Of note, in growth mixture models, different trajectories are assumed to have different underlying etiologies and outcomes.¹¹ Therefore, this type of model is well-suited for differentiating normal fetal growth from pathologic fetal growth, particularly within a population of women who are at risk for having small-for-gestational-age fetuses. That is, growth mixture models can identify different patterns of fetal growth that could approximate normal or pathologic fetuses, and one can then test the degree to which risks, such as preeclampsia, associate more with one pattern of growth than the other.

The optimal number of fetal growth trajectories was chosen using two criteria. The first was the relative fit of the models, through the Bayesian information criterion and the Lo-Mendell-Rubin likelihood ratio test.¹² Lower Bayesian information criterion values indicate a more parsimonious model. The Lo-Mendell-Rubin likelihood ratio test provides a k-1 likelihood ratio-based method for determining the ideal number of trajectories; a low *P* value (*P*<.05) indicated better fit to the data. Moreover, we also assessed the entropy statistic, a measure of classification accuracy (ie, accuracy of being assigned to one trajectory rather than another), with values closer to 1 indexing greater precision (range 0–1) and with the recommendation that sufficient accuracy is indicated by 0.80 or more.¹³ The second criterion is that each model was estimated using 100 random perturbations of starting values for 20 iterations. The ending values from the 10 optimizations with the highest log likelihood were used as the starting values for the final stage optimization. A model was considered stable

when random perturbations of starting values were replicated. The criteria for choosing the optimal number of trajectories were used in a hierarchical manner.¹⁴ That is, as long as the stability criterion was met, the model with an entropy at the acceptable value (0.80) and the higher number of fit statistics in agreement was chosen.

In the second step, we examined characteristics of the women at the different estimated fetal weight trajectories. In the third step, differences in the estimated fetal weight trajectories in Doppler abnormalities and perinatal outcomes were evaluated. Odds ratios and 95% confidence intervals were used to estimate risk for pathologic fetal growth and the uncertainty regarding the risk estimates. *P*=.05 was considered statistically significant. All analyses were performed with Mplus software 6.1.

RESULTS

Figure 1 contains the two-trajectory model of estimated fetal weight. The two-trajectory model was chosen because it had the best fit to the data; fit statistics are available from the first author on request. The two trajectories identified were fetuses with pathologic growth (3.3%; n=37) and fetuses with normal growth (96.7%; n=1,079).

Table 1 contains characteristics of the women by the pathologic growth and normal growth trajectories. No significant differences were noted between women whose fetuses exhibited pathologic growth and those whose fetuses exhibited normal growth in terms of height or European ethnicity. Compared with mothers of fetuses with normal growth, mothers of fetuses with pathologic growth were on average older and had higher BMI but had lower gestational age at enrollment in the study (Table 1). Compared with the normal growth trajectory group, women who had a fetus in the pathologic growth trajectory group had a higher incidence of preeclampsia during this pregnancy and had higher diastolic blood pressure.

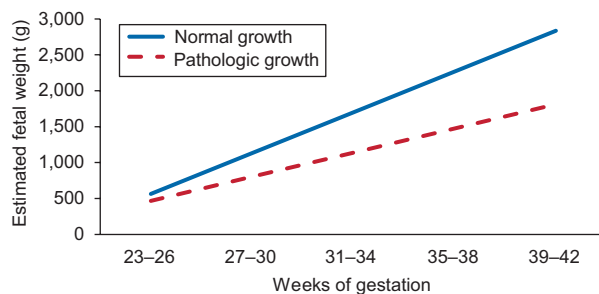


Fig. 1. Growth trajectories of estimated fetal weight. Barker. *Identifying Pathologic Fetal Growth*. *Obstet Gynecol* 2013.



Table 1. Maternal Characteristics by Fetal Growth Trajectory

Characteristic	Fetal Growth Trajectory		OR (95% CI)
	Pathologic	Normal	
Age (y)	31.76±5.51	29.88±5.69	1.054* (1.002–1.11)
Height (cm)	161.57±6.12	161.87±11.65	0.998 (0.98–1.01)
Weight (kg)	67.30±14.50	63.57±13.12	1.018 (0.98–1.04)
BMI (kg/m ²)	25.79±5.43	24.07±4.69	1.067* (1.01–1.13)
Western European ethnicity	89.2 (33/37)	82.5 (874/1,060)	1.756 (0.61–5.02)
Gestational age at enrollment (wk)	27.86±2.94	30.17±3.92	0.850* (0.79–0.92)
Maternal health status at enrollment			
Preeclampsia	10.8 (4/37)	1.5 (16/1,079)	8.053* (2.55–23.40)
Systolic blood pressure (mm Hg)	116.74±12.40	113.13±13.52	1.019 (0.99–1.04)
Diastolic blood pressure (mm Hg)	73.03±11.19	68.03±9.33	1.050* (1.02–1.09)
Drank alcohol	0 (0/37)	1.9 (21/1,079)	NA
Smoker	24.3 (9/28)	23.4 (252/1,079)	1.054 (0.49–2.27)

OR, odds ratio; CI, confidence interval; BMI, body mass index; NA, not able to be estimated because of zero frequency in pathologic growth group.

Data are mean±standard deviation or % (yes/total) unless otherwise specified.

* $P < .05$.

With regard to systolic blood pressure, note that odds ratios are multiplicative and, hence, an increase in three units of blood pressure (ie, $1.05 \times 1.05 \times 1.05$) indicates a 15.76% increase in odds of a pathologic fetal growth pattern.

The Doppler parameters are described in Table 2. Three general patterns of results are highlighted here. Compared with the normal growth trajectory group, fetuses in the pathologic growth trajectory group displayed decreased resistance in middle cerebral artery at 27–30 weeks of gestation and 31–34 weeks of gestation, increased pulsatility in the umbilical artery at 27–30 weeks of gestation and 31–34 weeks of gestation, and higher incidence of absent end-diastolic flow

at 27–30 weeks of gestation and 31–34 weeks of gestation. Of note, in general, the odds for the pathologic growth trajectory compared with the normal growth fetal trajectory increased with gestation across the Doppler parameters.

Table 3 describes data regarding abdominal circumference, femur length, head circumference, abdominal circumference measurements, and perinatal complications. Fetuses in the pathologic growth trajectory group had delayed growth for all measurements. For example, femur length, on average, was approximately 4 weeks delayed for the pathologic growth trajectory group compared with the normal growth trajectory group (ie, average femur for

Table 2. Doppler Parameters by Fetal Growth Trajectory

Doppler Parameter	Fetal Growth Trajectory		OR (95% CI)
	Pathologic	Normal	
Middle cerebral artery pulsatility index at 27–30 wk of gestation	1.75±0.45 (n=21)	2.09±0.98 (n=190)	0.334* (0.117–0.957)
Middle cerebral artery pulsatility index at 31–34 wk of gestation	1.64±0.44 (n=19)	1.97±0.50 (n=370)	0.140* (0.027–0.740)
Umbilical artery pulsatility index at 27–30 wk of gestation	1.94±0.91 (n=23)	1.13±0.27 (n=525)	12.579* (4.64–34.11)
Umbilical artery pulsatility index at 31–34 wk of gestation	1.57±0.69 (n=20)	1.05±0.21 (n=844)	28.022* (8.956–87.682)
Umbilical artery absent end diastolic flow at 27 wk of gestation	56.0 (14/25)	3.3 (17/521)	37.751* (14.97–95.21)
Umbilical artery absent end diastolic flow at 31 wk of gestation	45.0 (9/20)	2.2 (18/834)	37.077* (13.67–100.55)

OR, odds ratio; CI, confidence interval.

Data are mean±standard deviation or % (yes/total) unless otherwise specified.

* $P < .05$.



Table 3. Other Measures of Fetal Growth and Perinatal Complications

Measure	Fetal Growth Trajectory		OR (95% CI)
	Pathologic	Normal	
Fetal growth			
Femur length at 27–30 wk of gestation (mm)	42.61±3.74 (n=26)	51.41±2.83 (n=539)	0.474* (0.38–0.59)
Femur length at 31–34 wk of gestation (mm)	49.47±4.01 (n=25)	59.61±2.74 (n=852)	0.353* (0.26–0.48)
Head circumference at 27–30 wk of gestation (mm)	239.08±16.14 (n=26)	258.56±11.15 (n=539)	0.875* (0.82–0.88)
Head circumference at 31–34 wk of gestation (mm)	268.83±14.16 (n=25)	290.14±10.24 (n=850)	0.856* (0.90–0.97)
Abdominal circumference at 27–30 wk of gestation (mm)	195.33±12.97 (n=27)	226.38±10.96 (n=544)	0.804* (0.76–0.85)
Abdominal circumference at 31–34 wk of gestation (mm)	223.54±16.04 (n=25)	264.03±12.03 (n=855)	0.800* (0.69–0.93)
Perinatal complications			
Composite adverse neonatal outcomes	45.9% (20, 37)	3.8% (41, 1,079)	21.52* (10.50–44.10)
NICU admission	89.2% (33, 37)	25.9% (279, 1,079)	23.67* (8.31–67.40)
Gestational age at delivery (wk)	32.02±3.42 (n=37)	38.02±2.74 (n=1,079)	0.672* (0.62–0.73)

OR, odds ratio; CI, confidence interval; NICU, neonatal intensive care unit.

Data are mean±standard deviation or % (yes/total) unless otherwise specified.

* $P<.05$.

pathologic growth at 30 weeks of gestation was approximately the same as normal growth at 26 weeks of gestation). With regard to perinatal complications, compared with the normal growth trajectory group, the pathologic growth trajectory group had an increased incidence of adverse perinatal outcomes and lower gestational age at birth.

In addition, 89.2% of newborns with pathologic fetal growth were admitted to neonatal intensive care units compared with 25.9% of those with normal growth.

DISCUSSION

In a prospective sample of pregnant women whose fetuses had growth restriction diagnosed, the present study assessed the extent to which growth trajectory analysis using a growth mixture model could differentiate pathologically small from constitutionally small fetuses. Two fetal growth trajectories were identified, pathologic growth (3.3%) and normal growth (96.7%). Using maternal characteristics and ultrasound and Doppler assessments, we found high validity for the pathologic growth and normal growth trajectories.

There are three main advantages to this approach, in comparison with percentiles, that are based on ad hoc but reasonable decision criteria for categorizing fetal growth as pathologic (ie, less than the 10th percentile of estimated fetal weight). First, the identification of an abnormal growth trajectory is made with reference to fit statistics that help differentiate abnormal

from normal growth patterns. Of note, ex ante specified rules, such as pathologic growth being defined as being less than the 10th percentile of estimated fetal weight, have no formal basis for calibrating the precision of individual classifications of pathologic growth.^{9,11} In the present analysis, the fit statistics (ie, Bayesian information criterion and entropy) suggested that two fetal growth trajectories, normal growth and pathologic growth, best-described estimated fetal weight within this population of pregnant women.

Second, the pathologic growth and normal growth trajectories are based entirely on the data available and not in reference to population-based criteria;¹⁵ therefore, they may define pathologic fetal growth based on local sample characteristics more accurately. For example, within the present sample, women with fetuses exhibiting pathologic growth had higher BMI, higher diastolic blood pressure, and greater incidence of preeclampsia. Such a maternal health profile is consistent with increased essential hypertension and metabolic placental disease but is specific to the Prospective Observational Trial to Optimise Pediatric Health study participants, who all had growth-restricted fetuses.

Third, the growth trajectory method can be advantageous in that the fetal growth trajectories were based on repeated assessments of estimated fetal weight in the last two trimesters of gestation, which may translate into a more coherent and systematic developmental framework in comparison with fetal growth percentiles based on a single point in gestation.⁹



This study has generated an abnormal growth curve that could be used to identify the pathologically growth-restricted fetus as opposed to the constitutionally small fetus. Although this study raises the possibility of developing normal and pathologic growth curves for the fetus, this requires further validation with large samples of pregnant women to fully explore its clinical application in comparison with traditional fetal assessment methods in the management of suspected fetal growth restriction.

The present study has several limitations. First, this study includes a cohort of prenatally identified women with growth-restricted fetuses rather than a cohort of normal fetuses. Fetuses identified as being above the 10th percentile with poor growth velocity could be considered to have pathologic growth; therefore, the trajectory method reflects a conservative estimate of pathologic growth, or perhaps has identified those fetuses at the very severe end of the spectrum of pathologic growth. This is supported by the finding that 2–5% of the fetuses with normal growth demonstrated absent end-diastolic flow in the umbilical artery, which is associated with a significant risk of fetal hypoxia and acidosis. Second, the Doppler assessments were low in frequency and temporally concentrated at the end of the second trimester and the beginning of the third trimester. Future studies assessing the degree to which the current findings extend across a wider gestational age range will provide valuable data regarding growth restriction that are not limited by the traditional 10th percentile cut-off. Third, the demographic data regarding smoking and drinking were quite limited in detail; therefore, they may not have captured the effects of other substance use on fetal development.¹⁶ Fourth, the gestational age at birth is likely to have contributed to the higher number of neonatal intensive care unit admissions in the pathologic growth group. Further research is needed to examine the relative contributions of gestational age, growth, and other risk factors that might contribute to neonatal intensive care unit admission. Fifth, at a statistical level, we need to average the estimated fetal weight on a monthly basis to model the data, thus creating a margin of error. As with other growth curves, the development of this approach will require more validation with large datasets to explore these limitations.

In conclusion, the present study offers a new method with which to evaluate fetal growth restriction through the use of a growth trajectory method, which is commonly used in nonobstetric research. The method has been widely (and successfully) implemented in developmental psychopathology research to enable the identification of individuals who evinced abnormal

behavioral or psychiatric development, and has associated predictive risks with long-term outcomes.^{17–20} Moreover, many commonly used statistical software packages, such as Mplus,²¹ SAS,²² STATA,²³ and R, could be used to estimate these fetal growth trajectories. Therefore, this type of analysis should be easily accessible to researchers and clinicians in the medical community, but the involvement of statisticians, or researchers trained in statistics, may be necessary. The current results highlight that this approach can reliably differentiate fetuses with pathologic growth among a group of at-risk fetuses with estimated fetal weight less than the 10th percentile for a given gestational age. This method could provide an alternative approach to how we define, identify, and ultimately manage pathologic fetal growth.

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