

OBSTETRICS

Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study

Julia Unterscheider, MD; Sean Daly, MD; Michael Patrick Geary, MD; Mairead Mary Kennelly, MD; Fionnuala Mary McAuliffe, MD; Keelin O'Donoghue, PhD; Alyson Hunter, MD; John Joseph Morrison, MD; Gerard Burke, FRCOG; Patrick Dicker, PhD; Elizabeth Catherine Tully, PhD; Fergal Desmond Malone, MD



OBJECTIVE: The objective of the Prospective Observational Trial to Optimize Pediatric Health in Intrauterine Growth Restriction (IUGR) (PORTO Study), a national prospective observational multicenter study, was to evaluate which sonographic findings were associated with perinatal morbidity and mortality in pregnancies affected by growth restriction, originally defined as estimated fetal weight (EFW) <10th centile.

STUDY DESIGN: Over 1100 consecutive ultrasound-dated singleton pregnancies with EFW <10th centile were recruited from January 2010 through June 2012. A range of IUGR definitions were used, including EFW or abdominal circumference <10th, <5th, or <3rd centiles, with or without oligohydramnios and with or without abnormal umbilical arterial Doppler (pulsatility index >95th centile, absent or reversed end-diastolic flow). Adverse perinatal outcome, defined as a composite outcome of intraventricular hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, and death was documented for all cases.

RESULTS: Of 1116 fetuses, 312 (28%) were admitted to neonatal intensive care unit and 58 (5.2%) were affected by adverse perinatal outcome including 8 mortalities (0.7%). The presence of abnormal umbilical Doppler was significantly associated with adverse outcome, irrespective of EFW or abdominal circumference measurement. The only sonographic weight-related definition consistently associated with adverse outcome was EFW <3rd centile ($P = .0131$); all mortalities had EFW <3rd centile. Presence of oligohydramnios was clinically important when combined with EFW <3rd centile ($P = .0066$).

CONCLUSION: Abnormal umbilical artery Doppler and EFW <3rd centile were strongly and most consistently associated with adverse perinatal outcome. Our data call into question the current definitions of IUGR used. Future studies may address whether using stricter IUGR cutoffs comparing various definitions and management strategies has implications on resource allocation and pregnancy outcome.

Key words: definition, intrauterine growth restriction, perinatal morbidity and mortality, small for gestational age

Cite this article as: Unterscheider J, Daly S, Geary MP, et al. Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. *Am J Obstet Gynecol* 2013;208:290.e1-6.

From the Departments of Obstetrics and Gynecology (Drs Unterscheider, Tully, and Malone) and Epidemiology and Public Health (Dr Dicker), Royal College of Surgeons in Ireland; the Department of Obstetrics and Gynecology (Dr Daly) and University College Dublin Center for Human Reproduction (Dr Kennelly), Coombe Women and Infants University Hospital; the Department of Obstetrics and Gynecology, Rotunda Hospital (Dr Geary); and the Department of Obstetrics and Gynecology, University College Dublin School of Medicine and Medical Science, National Maternity Hospital (Dr McAuliffe), Dublin; the Department of Obstetrics and Gynecology, University College Cork, Cork University Maternity Hospital, Cork (Dr O'Donoghue); the Department of Obstetrics and Gynecology, Royal Jubilee Maternity Hospital, Belfast (Dr Hunter); the Department of Obstetrics and Gynecology, National University of Ireland, Galway (Dr Morrison); and the Department of Obstetrics and Gynecology, Mid-Western Regional Maternity Hospital, Limerick (Dr Burke), Ireland.

Received Nov. 20, 2012; revised Jan. 29, 2013; accepted Feb. 3, 2013.

The PORTO Study was conducted by the Perinatal Ireland Research Consortium, a nationwide collaborative research network composed of the 7 largest academic obstetric centers in Ireland. The study was funded by the Health Research Board of Ireland and Friends of the Rotunda.

The authors report no conflict of interest.

Presented in oral format at the 33rd annual meeting of the Society for Maternal-Fetal Medicine, San Francisco, CA, Feb. 11-16, 2013.

The racing flag logo above indicates that this article was rushed to press for the benefit of the scientific community.

Reprints: Julia Unterscheider, MD, Royal College of Surgeons in Ireland, Rotunda Hospital, Parnell Square, Dublin 1, Ireland. juliaunterscheider@rcsi.ie.

0002-9378/\$36.00 • © 2013 Mosby, Inc. All rights reserved. • <http://dx.doi.org/10.1016/j.ajog.2013.02.007>

Inadequate fetal growth affects up to 10% of all pregnancies. While the majority of such pregnancies will have a physiologically normal fetus that is simply small for gestational age (SGA), the ability to differentiate such a fetus from the pathologically growth-restricted fetus is limited. Pregnancies affected by intrauterine growth restriction (IUGR) pose a major public health problem and are associated with increased neonatal morbidity and mortality.¹ In addition, through fetal programming, adverse intrauterine environment may increase disease risk in adulthood leading to hypertension, diabetes, coronary heart disease, and stroke.²

The most commonly adopted definition to describe a fetus that has not reached its target weight based on sonographic estimated fetal weight (EFW) for a certain gestation is an abdominal circumference (AC) or EFW measurement

<10th centile. The American Congress of Obstetricians and Gynecologists (ACOG)³ and Royal College of Obstetricians and Gynecologists (RCOG)⁴ agree that at this cutoff the risk of perinatal morbidity and mortality increases. ACOG considers amniotic fluid an “important diagnostic and prognostic parameter in fetuses with IUGR,” whereas the RCOG notes that amniotic fluid assessment has “minimal value in diagnosing” growth restriction. Both guidelines agree that umbilical artery (UA) Doppler is not a reliable screening technique for IUGR, but is a useful assessment tool once IUGR is diagnosed. The Society of Obstetricians and Gynecologists of Canada⁵ uses an EFW <10th centile for diagnosis of SGA and suggests that UA and uterine artery Doppler studies in combination with ultrasound of the placental morphology is useful to establish a more refined diagnosis of IUGR.

The use of customized fetal growth charts⁶ has been proposed for more appropriate identification of fetal growth restriction taking into account anthropomorphic variables of the mother and fetus. However, these are not universally available or used in routine clinical practice in Ireland. The Hadlock formula⁷ is the most widely accepted method of estimating fetal weight using a composite sonographic measurement of fetal head, abdomen, and femur.

Ireland has the highest birth rate in Europe with >72,000 singleton births per year.⁸ The 7 academic obstetric centers that participated in the Prospective Observational Trial to Optimize Pediatric Health in IUGR (PORTO Study) deliver approximately 70% of these infants. In 2010, 5.1% of singletons were born with low birthweight, defined as <2500 g at >37 weeks' gestation, and the overall perinatal mortality rate corrected for fetal anomalies was 6.5 per 1000 births.⁸

The objective of this study was to evaluate which sonographic parameters are associated with perinatal morbidity and mortality in pregnancies affected by IUGR, defined as EFW <10th centile, to establish more explicit criteria for diagnosis of IUGR. Our data link various sonographic findings with respective pregnancy outcomes. It challenges the

reader to rethink the cutoffs used for IUGR definition. Further studies are needed to address optimal management and intervention strategies comparing these various IUGR definitions.

MATERIALS AND METHODS

The PORTO Study is a multicenter prospective study conducted at 7 academic obstetric centers in Ireland. For the purpose of the study, IUGR was defined as EFW <10th centile based on sonographic measurements of fetal biparietal diameter, head circumference, AC, and femur length (Hadlock-4). The diagnosis was made by conventional population-based growth standards⁷ as customized centile charts were not available at the time of this analysis. From January 2010 through June 2012, the PORTO Study recruited 1200 consecutive ultrasound-dated singleton pregnancies. Inclusion criteria were a gestational age (GA) between 24 0/7 and 36 6/7 weeks' and an EFW \geq 500 g. Fetuses with major structural and/or chromosomal abnormalities were excluded retrospectively from the final analysis. Institutional review board approval was obtained at each participating site, and all study participants gave written informed consent.

Referral to the study occurred if small fetal size was suspected due to clinical evaluation in the antenatal setting. A PORTO Study research sonographer then confirmed that EFW was <10th centile, and performed a detailed sonogram of the fetal anatomy and uterine artery Doppler at enrollment. Baseline demographic data were recorded. All eligible pregnancies underwent serial sonographic evaluation of fetal weight at intervals of every 2 weeks until birth. All normally formed fetuses underwent evaluation of amniotic fluid volume; biophysical profile scoring; multivessel Doppler of UA, middle cerebral artery, ductus venosus, umbilical vein, and aortic isthmus; and myocardial performance index at every subsequent contact with the research sonographers. All prenatal and ultrasound data were contemporaneously transferred to an ultrasound software system (Viewpoint; MDI Viewpoint, Jacksonville, FL) and up-

TABLE 1
Maternal demographics and fetal characteristics (n = 1116)

Characteristic	Value
Age, y	30 \pm 6
White European ethnicity	907 (83%)
Spontaneous conception	1100 (99%)
Maternal height, cm	162 \pm 12
Maternal weight at booking, kg	64 \pm 13
BMI, kg/m ²	24.1 \pm 4.7
Smokers	261 (23%)
Hypertensive disease/preeclampsia	134 (12%)
GA at enrollment, wk	30.1 \pm 3.9
GA at delivery, wk	37.8 \pm 3.0
Weight at delivery, g	2495 \pm 671
NICU admission	312 (28%)
Apgar score <7 ⁵	13 (1%)
Stillbirths	4 (1:280)
Neonatal deaths	4 (1:280)

Continuous variables are summarized with mean \pm SD and categorical variables with n (%).

BMI, body mass index; GA, gestational age; NICU, neonatal intensive care unit.

Unterscheider. Optimizing the definition of IUGR. *Am J Obstet Gynecol* 2013.

loaded onto a live World Wide Web-based central consolidated database.

In cases of absent end-diastolic flow (AEDF) or reversed end-diastolic flow in the UA, the patient was admitted to hospital and a daily computerized short-term variation cardiocardiogram was carried out. Corticosteroids for fetal lung maturation were administered between 24-36 weeks' gestation if delivery was thought to be likely within 1 week. Delivery was prompted by fetal (eg, nonreassuring fetal testing) or maternal (eg, deterioration of preeclampsia, antepartum hemorrhage) reasons, however the ultimate management decisions relating to timing and mode of delivery were at the discretion of the lead clinician managing each case and were not prespecified by the study design. There was however general agreement among clinicians in Ireland to deliver AEDF cases by 34 weeks' gestation. Tertiary-level neonatal care facilities were available in all 7 sites.

TABLE 2
Predictors of adverse perinatal outcome

Predictor	n = 1116	Adverse outcome (n = 58)	Normal outcome (n = 1058)	P value	Adjusted P value ^a
EFW <3rd	826	51 (6.2%)	775 (93.8%)	.0131	.3409
EFW <5th	1047	55 (5.3%)	992 (94.7%)	.7428	.0894
AC <3rd	909	52 (5.7%)	857 (94.3%)	.0988	.9027
AC <5th	998	53 (5.3%)	945 (94.7%)	.6194	.2589
AC <10th	1080	56 (5.2%)	1024 (94.8%)	.9215	.1921
EFW <3rd + oligohydramnios	127	13 (10.2%)	114 (89.8%)	.0066	.4623
EFW <5th + oligohydramnios	189	13 (6.9%)	176 (93.1%)	.2533	.7184
EFW <10th + oligohydramnios	231	15 (6.5%)	216 (93.5%)	.3189	.4362
AC <3rd + oligohydramnios	180	14 (7.8%)	166 (92.2%)	.0885	.2251
AC <5th + oligohydramnios	205	14 (6.8%)	191 (93.2%)	.2439	.3263
AC <10th + oligohydramnios	231	14 (6.1%)	217 (93.9%)	.5067	.4508
EFW <3rd + abnormal UA	251	42 (16.7%)	209 (83.3%)	< .0001 ^b	.0163
EFW <5th + abnormal UA	346	45 (13.0%)	301 (87.0%)	< .0001 ^b	.0220
EFW <10th + abnormal UA	413	47 (11.4%)	366 (88.6%)	< .0001 ^b	.0136
AC <3rd + abnormal UA	315	42 (13.3%)	273 (86.7%)	< .0001 ^b	.0046
AC <5th + abnormal UA	353	43 (12.2%)	310 (87.8%)	< .0001 ^b	.0108
AC <10th + abnormal UA	400	46 (11.5%)	354 (88.5%)	< .0001 ^b	.0031

Abnormal UA refers to absent or reversed end-diastolic flow in UA or pulsatility index >95th centile. Oligohydramnios refers to amniotic fluid index <8 cm or amniotic fluid deepest pool <2 cm. Adverse perinatal outcome was defined as adverse composite outcome of intraventricular hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, and death.

AC, abdominal circumference; EFW, estimated fetal weight; UA, umbilical artery Doppler.

^a Derived from multivariate analysis adjusting for gestational age at delivery; ^b Statistically significant after adjusting for multiple comparisons (Bonferroni-adjusted significance level of 0.3%, P value < .003). Fisher exact test was used in cases where table cell contained <5 observations.

Unterscheider. Optimizing the definition of IUGR. *Am J Obstet Gynecol* 2013.

Pediatric outcomes for infants not requiring neonatal intensive care were recorded by the research sonographers and uploaded onto the database. Infants requiring neonatal intensive care unit (NICU) admission had their outcomes recorded by neonatology medical or nursing staff. Adverse perinatal outcome was defined as a composite outcome of intraventricular hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, and death. Given that all study sites were members of the Vermont Oxford Network,⁹ definitions for intraventricular hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia, and sepsis were standardized across all centers derived from the Vermont Oxford Network manual. The outcomes were analyzed based on

various IUGR definitions including EFW or AC <10th, <5th, or <3rd centiles, with or without associated oligohydramnios (defined as amniotic fluid volume of <8 cm or deepest vertical pocket <2 cm) and with or without abnormal UA Doppler (defined as pulsatility index >95th centile, AEDF or reversed end-diastolic flow).¹⁰

A sample size calculation was performed. Depending upon the baseline rates of outcomes considered, the study had sufficient power (80%) with a sample size of 1100 to show a risk reduction in 2 equally exposed groups (550 vs 550) of 8% for an outcome with a 30% overall baseline rate in our study population, and 2% for an outcome with a 5% overall baseline rate. For a subanalysis with a 2:1 study exposure partition of 1100 pregnancies (733 vs 367 pregnancies) the study would also determine an 8% and 4% reduction in base-

line outcome rates of 30% and 5%, respectively.

Use of statistics

Prior to statistical analysis, all ultrasound and outcome data were screened for anomalous records or potential outliers and followed up by research sonographers for resolution. Statistical comparisons were performed using the χ^2 test of association. Fisher exact test was used in cases where a table cell contained <5 observations. Demographics and baseline characteristics were presented using summary statistics (Table 1). Three centile cutoffs (3rd, 5th, and 10th) for EFW and AC, in addition to the presence of oligohydramnios or abnormal Doppler, were considered a priori as predictors of adverse perinatal outcomes, NICU admission, and perinatal mortality (Tables 2-4). Predictors were considered over the course of a pregnancy, eg, EFW <3rd

TABLE 3
Predictors of admission to neonatal intensive care unit

Predictor	n = 1116	NICU admission (n = 312)	No admission (n = 804)	P value	Adjusted P value ^a
EFW <3rd	826	267 (32.3%)	559 (67.7%)	< .0001 ^b	.1038
EFW <5th	1047	300 (28.7%)	747 (71.3%)	.0435	.4764
AC <3rd	909	275 (30.3%)	634 (69.7%)	.0003 ^b	.1890
AC <5th	998	294 (29.5%)	704 (70.5%)	.0011 ^b	.1043
AC <10th	1080	306 (28.3%)	774 (71.7%)	.1249	.9728
EFW <3rd + oligohydramnios	127	66 (52.0%)	61 (48.0%)	< .0001 ^b	.0008 ^b
EFW <5th + oligohydramnios	189	73 (38.6%)	116 (61.4%)	.0003 ^b	.0463
EFW <10th + oligohydramnios	231	78 (33.8%)	153 (66.2%)	.0272	.2409
AC <3rd + oligohydramnios	180	69 (38.3%)	111 (61.7%)	.0007 ^b	.0165
AC <5th + oligohydramnios	205	73 (35.6%)	132 (64.4%)	.0069	.0469
AC <10th + oligohydramnios	231	75 (32.5%)	156 (67.5%)	.0863	.2534
EFW <3rd + abnormal UA	251	147 (58.6%)	104 (41.4%)	< .0001 ^b	< .0001 ^b
EFW <5th + abnormal UA	346	158 (45.7%)	188 (54.3%)	< .0001 ^b	.0974
EFW <10th + abnormal UA	413	169 (40.9%)	244 (59.1%)	< .0001 ^b	.3945
AC <3rd + abnormal UA	315	149 (47.3%)	166 (52.7%)	< .0001 ^b	.0205
AC <5th + abnormal UA	353	159 (45.0%)	194 (55.0%)	< .0001 ^b	.0168
AC <10th + abnormal UA	400	166 (41.5%)	234 (58.5%)	< .0001 ^b	.1294

Abnormal UA refers to absent or reversed end-diastolic flow in UA or pulsatility index >95th centile. Oligohydramnios refers to amniotic fluid index <8 cm or amniotic fluid deepest pool <2 cm. AC, abdominal circumference; EFW, estimated fetal weight; NICU, neonatal intensive care unit; UA, umbilical artery Doppler.

^a Derived from multivariate analysis adjusting for gestational age at delivery; ^b Statistically significant after adjusting for multiple comparisons (Bonferroni-adjusted significance level of 0.3%, P value < .003). Fisher exact test was used in cases where table cell contained <5 observations.

Unterscheider. Optimizing the definition of IUGR. *Am J Obstet Gynecol* 2013.

centile at any time after recruitment. Using a nominal 5% level of statistical significance, comparisons were made using a Bonferroni-corrected significance level of 0.3% (17 comparisons of predictors). The adjusted P values in Tables 2-4 were derived from a multivariate analysis adjusting for GA at delivery. SAS version 9.2 (SAS Institute, Cary, NC) was used for data management and statistical analysis.

RESULTS

Of 1200 recruited pregnancies with EFW <10th centile, 32 (2.7%) were excluded due to chromosomal and/or structural abnormalities, 13 (1%) withdrew their consent, 13 (1%) delivered outside Ireland, and 26 (2.2%) were lost to follow-up. This resulted in 1116 patients completing the study protocol.

The mean maternal age was 30 years with 83% of mothers being of white European descent. This is consistent with

the demographic profile of the overall obstetric population attending for antenatal care in Ireland⁸ reflecting an unselected group of recruited pregnancies. The mean GA at enrollment to the study was 30.1 weeks and the mean GA at delivery was 37.8 weeks. Table 1 outlines maternal demographics and fetal characteristics.

One in 20 infants was affected by the composite adverse perinatal outcome and 1 in 4 infants required admission to the NICU reflecting a truly at-risk population. Table 2 describes the predictors of adverse perinatal outcome. The majority of fetuses (72%, n = 800) with an EFW <10th centile had a normal perinatal outcome, meaning they neither required admission to NICU nor were they affected by morbidity or mortality. Infants with EFW <3rd centile had rates of composite adverse outcome of 6.2% (51/826) while the cohort with EFW in the 3rd-10th centiles had a rate of 2% (5/

254). Mean infant birthweight was 2495 g. In all, 58 infants (5.2%) had an adverse perinatal outcome. Whenever abnormal UA Doppler was found there was a significant increased risk of adverse perinatal outcome. The strong statistical significance for abnormal Doppler velocimetries in Table 2 arises from the considerable reduction in false-positive results associated with abnormal Doppler. EFW or AC cutoffs <5th or <10th centiles were not significantly linked to adverse perinatal outcome. An EFW <3rd centile alone was found to be statistically significant (at the nominal 5% significance level). However, in those who did not have an adverse outcome (n = 1058), 775 (73.3%) had an EFW <3rd centile at any stage during the study period as compared to 209 (19.8%) who had an EFW <3rd centile plus an abnormal UA Doppler.

Irrespective of the EFW or the AC measurement, the strongest and most

TABLE 4
Predictors of perinatal mortality

Predictor	n = 1116	Perinatal mortality (n = 8)	No mortality (n = 1108)	P value	Adjusted P value ^a
EFW <3rd	826	8 (1.0%)	818 (99.0%)	.1209	.9533
EFW <5th	1047	8 (0.8%)	1039 (99.2%)	.4662	.9751
AC <3rd	909	8 (0.9%)	901 (99.1%)	.3640	.9684
AC <5th	998	8 (0.8%)	990 (99.2%)	.3290	.9676
AC <10th	1080	8 (0.7%)	1072 (99.3%)	.6043	.9816
EFW <3rd + oligohydramnios	127	3 (2.4%)	124 (97.6%)	.0525	.2249
EFW <5th + oligohydramnios	189	3 (1.6%)	186 (98.4%)	.1392	.2612
EFW <10th + oligohydramnios	231	4 (1.7%)	227 (98.3%)	.0622	.0660
AC <3rd + oligohydramnios	180	3 (1.7%)	177 (98.3%)	.1242	.2168
AC <5th + oligohydramnios	205	3 (1.5%)	202 (98.5%)	.1677	.2367
AC <10th + oligohydramnios	231	3 (1.3%)	228 (98.7%)	.3735	.2579
EFW <3rd + abnormal UA	251	6 (2.4%)	245 (97.6%)	.0023	.6429
EFW <5th + abnormal UA	346	6 (1.7%)	340 (98.3%)	.0123	.9855
EFW <10th + abnormal UA	413	6 (1.5%)	407 (98.5%)	.0576	.9180
AC <3rd + abnormal UA	315	6 (1.9%)	309 (98.1%)	.0079	.4246
AC <5th + abnormal UA	353	6 (1.7%)	347 (98.3%)	.0146	.5619
AC <10th + abnormal Doppler	400	6 (1.5%)	394 (98.5%)	.0282	.7112

Abnormal UA refers to absent or reversed end-diastolic flow in UA or pulsatility index >95th centile. Oligohydramnios refers to amniotic fluid index <8 cm or amniotic fluid deepest pool <2 cm. AC, abdominal circumference; EFW, estimated fetal weight; UA, umbilical artery Doppler.

^a Derived from multivariate analysis adjusting for gestational age at delivery.

Unterscheider. Optimizing the definition of IUGR. *Am J Obstet Gynecol* 2013.

significant association with adverse perinatal outcome in the overall population was found when an abnormal UA Doppler was present. Even after multivariate analysis adjusting for GA at delivery expressed by respective *P* values in Table 2, abnormal Doppler remained significantly associated with adverse perinatal outcome. The only sonographic weight-related definition consistently associated with adverse perinatal outcome was an EFW <3rd centile (*P* = .0131), although this did not reach the Bonferroni-corrected significance level of 0.3%. The presence of oligohydramnios was only important when combined with an EFW <3rd centile (*P* = .0066).

As outlined in Table 3, 28% (n = 312) of the cohort required admission to the NICU with a median length of stay of 13 days. Table 3 demonstrates better predictive ability of fetal biometry markers (EFW <3rd centile, AC <3rd or <5th centiles) for NICU admission in the absence of abnormal Doppler. However as

with predictors of adverse perinatal outcome, whenever abnormal Doppler was present, the risk of NICU admission was significantly increased irrespective of the biometry cutoff used.

There were 4 stillbirths and 4 neonatal deaths in this cohort of nonanomalous infants corresponding to a perinatal mortality rate of 7.2 per 1000 births. As demonstrated in Table 4, all 8 perinatal deaths occurred in the setting of an EFW <3rd centile. The lack of statistical significance associated with any of the cutoffs used in Table 4 reflects the small number of deaths in the overall cohort.

COMMENT

The appropriate management of IUGR pregnancies relies on accurate identification and diagnosis. The optimal definition of growth restriction, in particular the differentiation between physiological (SGA) and pathological (IUGR) small fetal size, is one of the most com-

mon, controversial, and complex problems in modern obstetrics.

There is agreement internationally that an EFW <10th centile for gestation should alert clinicians to potential small fetal size. However, our data call into question whether having an EFW <10th centile on its own really matters in predicting adverse perinatal outcome. Our data suggest that all fetuses with an EFW <3rd centile, or those fetuses with a combination of EFW <10th centile and abnormal UA Doppler, are at increased risk of either adverse perinatal outcome or NICU admission when compared to those with EFW or AC <10th or <5th centiles or normal UA Doppler indices. Whether a composite morbidity rate of 2% in the group of infants with EFW in the 3rd-10th centiles is acceptable to clinicians to change their utilization of antenatal surveillance is debatable. Until such time that patients identified with various cutoffs are subjected to a randomized trial or a blinded trial the ques-

tion regarding optimal IUGR definition, surveillance, and intervention cannot be answered satisfactorily. In contrast to the ACOG bulletin on IUGR, we found that amniotic fluid abnormalities per se do not significantly increase the risk for adverse outcome.

A major strength of this study is the prospective study design. It took only 2 years to recruit 1200 pregnancies in 7 centers, all of which were subjected to a high degree of fetal surveillance using the most advanced Doppler techniques available, which were performed by a small group of trained research sonographers. While the study was multicenter in nature, inconsistencies in assessment were overcome with regular training sessions of the cohort of research sonographers by experienced maternal-fetal medicine specialists. All sonographers used the same ultrasound equipment (Voluson E8; GE Healthcare, Buckinghamshire, UK) and underwent regular quality assurance assessments. Another strength of the study is that the cohort reflects a true at-risk population with 1 in 20 infants affected by composite adverse perinatal outcome and 1 in 4 infants requiring admission to the NICU. A possible weakness of our study relates to the slightly late GA at which IUGR pregnancies were enrolled (mean GA at enrollment was 30 weeks). This might underestimate the true implications of IUGR as most later-gestation pregnancies generally have a better perinatal prognosis.

A possible weakness of our study is that we had no ability to compare our IUGR cohort to an appropriately grown reference population. Therefore a firm conclusion regarding when it is reasonable to

avoid fetal surveillance for the SGA fetus cannot be drawn from our data. Also, there may be some limitations in generalizing our results to the US population, given that the majority of our patients were white European women with a mean body mass index of 24. Additionally, there are some minor variations in clinical practice between our population and the US population, such as the administration of corticosteroids for IUGR fetuses up until 36 weeks' gestation in our population as recommended by the RCOG.¹¹ We also acknowledge that our perinatal outcomes are not solely a reflection of ultrasound parameters and that respective pregnancy outcomes must always be seen in the context of mode and frequency of antenatal surveillance and interventions such as administration of steroids and timely delivery, especially given that we did not use preset criteria for delivery.

In conclusion, the terminology currently used to describe inadequate fetal growth is inconsistent and confusing; therefore a clear definition of SGA and IUGR is needed to improve outcomes for this cohort. Our data provide evidence from a large prospective cohort of >1100 pregnancies with small fetal size that correlates various sonographic parameters with perinatal outcome. Pregnancies at increased risk of adverse outcome are those with associated abnormal UA Doppler and in particular those with EFW <3rd centile with or without accompanying oligohydramnios. ■

ACKNOWLEDGMENTS

We thank Fiona Manning, original Perinatal Ireland research manager, and the team of Perinatal Ireland research sonographers Fiona Cody, Hilda O'Keefe, Emma Doolin, Cecelia Mulcahy, Azy

Khalid, Phyl Gargan, Annette Burke, Edel Varden, Wendy Ooi, and Amanda Ali.

REFERENCES

1. Badawi N, Kurinczuk JJ, Keogh JM, et al. Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ* 1998;317:1549-53.
2. Barker DJ. Adult consequences of fetal growth restriction. *Clin Obstet Gynecol* 2006; 49:270-83.
3. American College of Obstetricians and Gynecologists. Intrauterine growth restriction. Washington, DC: American College of Obstetricians and Gynecologists; 2000.
4. Royal College of Obstetricians and Gynecologists. The investigation and management of the small-for-gestational-age fetus (guideline no. 31). London: Royal College of Obstetricians and Gynecologists; 2002.
5. Lausman A, McCarthy FP, Walker M, Kingdom J. Screening, diagnosis, and management of intrauterine growth restriction. *J Obstet Gynaecol Can* 2012;34:17-28.
6. Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customized antenatal growth charts. *Lancet* 1992;339:283-7.
7. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements—a prospective study. *Am J Obstet Gynecol* 1985; 151:333-7.
8. Perinatal Statistics Report, Economic and Social Research Institute (ESRI) on behalf of the Department of Health and the Health Service Executive Ireland, June 2010. Available at: www.esri.ie. Accessed Feb. 25, 2013.
9. Horbar JD. The Vermont Oxford Network: evidence-based quality improvement for neonatology. *Pediatrics* 1999;103:350-9.
10. Archaya G, Wilsgaard T, Berntsen GK, Maltau JM, Kiserud T. Reference ranges for serial measurements of umbilical artery Doppler indices in the second half of pregnancy. *Am J Obstet Gynecol* 2005;192:937-44.
11. Royal College of Obstetricians and Gynecologists. Antenatal corticosteroids to reduce neonatal morbidity (guideline no. 7). London: Royal College of Obstetricians and Gynecologists; 2010.