Defining the residual risk of adverse perinatal outcome in growth-restricted fetuses with normal umbilical artery blood flow

Vicky O'Dwyer, MD; Gerard Burke, FRCOG; Julia Unterscheider, MD; Sean Daly, MD; Michael P. Geary, MD; Mairead M. Kennelly, MD; Fionnuala M. McAuliffe, MD; Keelin O'Donoghue, PhD; Alyson Hunter, MD; John J. Morrison, MD; Patrick Dicker, PhD; Elizabeth C. Tully, PhD; Fergal D. Malone, MD

OBJECTIVE: We sought to determine the cause of adverse perinatal outcome in fetal growth restriction (FGR) where umbilical artery (UA) Doppler was normal, as identified from the Prospective Observational Trial to Optimize Pediatric Health (PORTO). We compared cases of adverse outcome where UA Doppler was normal and abnormal.

STUDY DESIGN: The PORTO study was a national multicenter study of >1100 ultrasound-dated singleton pregnancies with an estimated fetal weight <10th centile. Each pregnancy underwent intensive ultrasound, including multivessel Doppler. UA Doppler was considered abnormal when the pulsatility index was >95th centile or end-diastolic flow was absent/reversed. Adverse perinatal outcome was defined as a composite of intraventricular hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, or death.

RESULTS: In all, 57 (5.0%) of the 1116 fetuses had an adverse perinatal outcome. Nine (1.3%) of 698 fetuses with normal UA Doppler had an adverse outcome, compared with 48 (11.5%) of 418 with abnormal UA Doppler ($P < .0001$). There were 2 perinatal deaths in the normal group and 6 in the abnormal group ($P = .01$). The perinatal deaths in the normal group were 1 case of pulmonary hypoplasia after prolonged preterm rupture of the membranes from 12 weeks' gestation and a case of placental abruption. Gestation at delivery was 33 ± 3 vs 31 ± 4 weeks ($P = .05$) and mean birthweight was 1830 ± 737 vs 1146 ± 508 g ($P = .001$) in the respective groups. Neonatal sepsis was the commonest adverse outcome in both groups: 0.1% and 0.4%, respectively ($P = .01$).

CONCLUSION: Adverse perinatal outcome is uncommon in FGR with normal UA Doppler. The cases we identified were associated with heterogenous pathologies. FGR with normal UA blood flow is a largely benign condition.

Key words: adverse perinatal outcome, fetal growth restriction, umbilical artery Doppler

Cite this article as: O'Dwyer V, Burke G, Unterscheider J, et al. Defining the residual risk of adverse perinatal outcome in growth-restricted fetuses with normal umbilical artery blood flow. Am J Obstet Gynecol 2014;211:420.e1-5.

Fetal growth restriction (FGR) caused by maternal, fetal, and placental pathologies is associated with significant morbidity and mortality. The aim of identifying growth-restricted fetuses in pregnancy is to improve perinatal outcomes through intensive sonographic fetal surveillance and optimal timing of delivery.[1]

The American Congress of Obstetricians and Gynecologists and the Royal College of Obstetricians and Gynecologists in the United Kingdom recommend the use of sonographic measurement of abdominal circumference or an estimated fetal weight (EFW) <10th centile to identify fetuses that are growth restricted and at risk of adverse perinatal outcome.[2-4] Acknowledging the limitations of this cutoff to predict perinatal outcome, the main Prospective

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

Received March 10, 2014; revised May 28, 2014; accepted July 20, 2014.

Financial support was provided by the Health Research Board and Friends of the Rotunda.

The authors report no conflict of interest.

Corresponding author: Vicky O'Dwyer, MD. vickyodwyer@rcsi.ie

0002-9378/$36.00 • © 2014 Published by Elsevier Inc. • http://dx.doi.org/10.1016/j.ajog.2014.07.033

Observational Trial to Optimize Pediatric Health (PORTO) analysis showed that infants at particular risk of adverse perinatal outcome are those with EFW <3rd centile or with abnormal umbilical artery (UA) Doppler studies with EFW <10th centile.[5]

A recent review of randomized and quasirandomized trials found that the use of UA Doppler in growth-restricted fetal surveillance reduced the incidence of obstetric interventions, such as induction of labor and cesarean section, and perinatal mortality.[6]

The national multicenter PORTO study identified a small number of adverse outcomes in small fetuses with normal Doppler. Since the finding of a small fetus with normal umbilical blood flow is a common clinical scenario, affecting about 7% of the obstetric population, we wanted to document the precise causes of those adverse perinatal outcomes, and to determine whether the spectrum of causes differs between those cases with and without abnormal UA Doppler.

TABLE 1
Delivery details analyzed by umbilical artery Doppler measurement

Variable	Adverse outcome and normal UA Doppler (n = 9)	Adverse outcome and abnormal UA Doppler (n = 48)	*P* value
Gestational age at delivery, wk	33 ± 3	31 ± 4	.06
Birthweight, g	1830 ± 737	1146 ± 508	.001
Female sex	5 (56%)	17 (36%)	.64
Spontaneous onset of labor	1 (11%)	0	.16
Induction of labor	0	6 (13%)	.57
Mode of delivery			
Spontaneous vaginal	0	4 (9%)	.36
Operative vaginal	0	1	.66
Elective cesarean	3 (33%)	12 (26%)	.69
Emergency cesarean	6 (67%)	27 (57%)	.61
Indication for delivery			
Maternal	2 (22%)	13 (28%)	.74
Nonreassuring fetal testing	7 (78%)	46 (98%)	.01
Other	0	3 (6%)	.002
Apgar score <7[5]	1 (11%)	6 (13%)	.57
Cord pH	7.2 ± 0.2	7.2 ± 0.1	.20
NICU admission	9 (100%)	43 (91%)	.36

NICU, neonatal intensive care unit; *UA*, umbilical artery.

O'Dwyer. Adverse perinatal outcome in growth-restricted fetuses with normal umbilical artery Doppler. Am J Obstet Gynecol 2014.

Materials and Methods

The PORTO study was a multicenter prospective observational study conducted in Ireland's 7 largest obstetric hospitals. The study was conducted from January 2010 through June 2012. During this time period 1200 ultrasound-dated singleton pregnancies between 24+0 and 36+6 weeks' gestation and with an EFW >500 g were recruited. FGR was defined as an EFW <10th centile. The Hadlock-4 formula was used to calculate EFW from head circumference, biparietal diameter, abdominal circumference, and femur length. Fetuses with major structural or chromosomal abnormalities were excluded from the analysis. Institutional review board approval was obtained and all participants gave written informed consent.

Baseline demographic details were recorded at enrollment. Women with FGR pregnancies underwent serial sonographic evaluation of EFW at 2-weekly intervals until birth. Biophysical profile scoring, amniotic fluid volume evaluation, and multivessel Doppler assessment including UA Doppler were performed at each sonogram. Abnormal UA Doppler was defined as a pulsatility index >95th centile or absent or reversed end-diastolic flow. When UA Doppler was abnormal, patients were admitted to hospital for daily electronic fetal heart rate monitoring and corticosteroids were administered to promote fetal lung maturation between 24-36 weeks' gestation. Decisions regarding management and delivery were made by the lead clinician treating each patient, but were not prespecified by the study design. However, all women were delivered ≤34 weeks' gestation when there was absent end-diastolic flow in the UA Doppler. Tertiary-level neonatal care facilities were available in all 7 trial centers.

Adverse perinatal outcome was defined as a composite of intraventricular hemorrhage, periventricular leukomalacia, hypoxic ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, and death. These outcomes were defined using the Vermont Oxford Network manual (http://www.vtoxford.org/tools/manualofoperationspart2.pdf).

Fisher exact test was used to compare the adverse outcomes in normal vs abnormal UA Doppler groups (Tables 1 and 2). A *P* value < .05 was considered statistically significant.

Results

Of 1200 recruited pregnancies with FGR, 32 (2.7%) were excluded due to chromosomal and/or structural abnormalities and 52 (4.2%) were lost to follow-up or delivered in another hospital. This resulted in 1116 patients completing the study protocol. Table 3 outlines the maternal demographics and fetal characteristics in the groups with normal and abnormal UA Doppler measurements. Maternal demographics were similar between the 2 groups. However, in the normal UA Doppler