Predictable progressive Doppler deterioration in IUGR: does it really exist?

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OBJECTIVE: An objective of the Prospective Observational Trial to Optimize Pediatric Health in IUGR (PORTO) study was to evaluate multivessel Doppler changes in a large cohort of intrauterine growth restriction (IUGR) fetuses to establish whether a predictable progressive sequence of Doppler deterioration exists and to correlate these Doppler findings with respective perinatal outcomes.

STUDY DESIGN: More than 1100 unselected consecutive ultrasound-dated singleton pregnancies with estimated fetal weight (EFW) less than the 10th centile were recruited between January 2010 and June 2012. Eligible pregnancies were assessed by serial Doppler interrogation of umbilical (UA) and middle cerebral (MCA) arteries, ductus venosus (DV), aortic isthmus, and myocardial performance index (MPI). Intervals between Doppler changes and patterns of deterioration were recorded and correlated with respective perinatal outcomes.

RESULTS: Our study of 1116 nonanomalous fetuses comprised 7769 individual Doppler data points. Five hundred eleven patients (46%) had an abnormal UA, 300 (27%) had an abnormal MCA, and 129 (11%) had an abnormal DV Doppler. The classic pattern from abnormal UA to MCA to DV existed but no more frequently than any of the other potential pattern. Doppler interrogation of the UA and MCA remains the most useful and practical tool in identifying fetuses at risk of adverse perinatal outcome, capturing 88% of all adverse outcomes.

CONCLUSION: In contrast to previous reports, we have demonstrated multiple potential patterns of Doppler deterioration in this large prospective cohort of IUGR pregnancies, which calls into question the usefulness of multivessel Doppler assessment to inform frequency of surveillance and timing of delivery of IUGR fetuses. These data will be critically important for planning any future intervention trials.

Key words: Doppler, intrauterine growth restriction, sequential changes, umbilical artery

A progressive predictable sequence of placental and fetal Doppler changes has been described as an adaptive mechanism to a suboptimal intrauterine environment in pregnancies affected by intrauterine growth restriction (IUGR). The surveillance and management of IUGR secondary to placental dysfunction is facilitated by umbilical artery (UA) Doppler assessment, and this is widely accepted as the primary ultrasound surveillance tool in such pregnancies.1-3 Several studies have contributed to the understanding of longitudinal Doppler changes occurring in IUGR.4-6 Knowledge about temporal deterioration in maternal and fetal vessels is desired to inform frequency of surveillance and...
timing of delivery. However, these studies have been either retrospective or comprised small patient numbers. Furthermore, it is important to note that in fact most of these papers describing a temporal sequence refer to Doppler abnormalities within a population of IUGR fetuses rather than a predictable progressive sequence occurring within the individual fetus. It is plausible therefore that such prior population data may not actually be applicable to the longitudinal surveillance of the individual fetus in clinical practice.

Longitudinal cumulative-onset time curves of Doppler abnormalities describing a time-dependent change of various vessels are thought to follow one certain predictable pattern from the following: (1) abnormal blood flow in the uterine arteries, (2) increased resistance in the umbilical arteries, (3) compensatory flow in the middle cerebral artery (MCA) indicating cerebral redistribution, (4) absent end-diastolic flow in the UA, which is followed by (5) absent a-wave in the ductus venosus (DV), (6) abnormalities in the pulmonary and aortic outflow tracts, and finally (7) reversed a-wave in the DV.4

These compensatory and decompensatory changes have resulted in debate on the benefit of assessing vessels other than the UA in the setting of IUGR. Although some data suggest a role for DV Doppler to inform timing of delivery in severe IUGR, evidence from a large randomized trial is still awaited.7

Similarly, although reports suggest a role for abnormal aortic isthmus (AoI) Doppler in the setting of IUGR,8 the recently published Society for Maternal-Fetal Medicine clinical guideline on Doppler assessment of the IUGR fetus9 states that Doppler studies other than the UA should be reserved solely for research protocols. The same guideline acknowledges that there “does appear to be a natural progression of changes in the Doppler of UA, MCA, and DV with a large variability in manifestation.”

The goal of the prospective multicenter Prospective Observational Trial to Optimize Pediatric Health in IUGR (PORTO) study was to evaluate the optimal surveillance of fetuses with an estimated fetal weight (EFW) less than the 10th centile.10 The objective of this particular analysis was to study Doppler changes in multiple vessels including UA, MCA, DV, AoI, and myocardial performance index (MPI) and to establish whether a predictable progressive sequence of Doppler deterioration exists at the level of the individual fetus and to determine any added benefit in applying these Doppler assessments in IUGR informing surveillance intervals and timing of delivery.

**Materials and Methods**

The PORTO trial is a multicenter prospective study conducted at 7 academic obstetric centers in Ireland. For the purpose of the study, IUGR was defined as an EFW below the 10th centile based on sonographic measurements of fetal biparietal diameter, head circumference, abdominal circumference, and femur length (Hadlock-4).11

Between January 2010 and June 2012, the PORTO study recruited 1200 consecutive ultrasound-dated singleton pregnancies. Dating occurred either by crown-rump length measurement prior to 14 weeks’ gestation or by composite measurement of biparietal diameter (BPD), head circumference, abdominal circumference, and femur length from 14 0/7 to 22 0/7 weeks’ gestation. Inclusion criteria were a gestation between 24 0/7 and 36 6/7 weeks and an EFW of 500 g or more. Fetuses with major structural and/or chromosomal abnormalities were excluded from the final analysis. Institutional review board approval was obtained at each participating site, and all study participants gave written informed consent.

Referral for consideration for enrollment to the study occurred if small fetal size was suspected because of clinical evaluation in the antenatal setting. A PORTO research sonographer then confirmed that the EFW was below the 10th centile and performed a detailed evaluation of the fetal anatomy and uterine artery Doppler at enrollment. All eligible pregnancies underwent serial sonographic evaluation of fetal weight at 2 weekly intervals until birth, and

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**TABLE**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)/mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal demographics and fetal characteristics (n = 1116)</strong></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>30 ± 6</td>
</tr>
<tr>
<td>Ethnicity (white European)</td>
<td>907 (83%)</td>
</tr>
<tr>
<td>Spontaneous conception</td>
<td>1100 (99%)</td>
</tr>
<tr>
<td>Maternal height, cm</td>
<td>162 ± 12</td>
</tr>
<tr>
<td>Maternal weight at booking, kg</td>
<td>64 ± 13</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.1 ± 4.7</td>
</tr>
<tr>
<td>Smokers</td>
<td>261 (23%)</td>
</tr>
<tr>
<td>Hypertensive disease/preeclampsia</td>
<td>134 (12%)</td>
</tr>
<tr>
<td>GA at enrolment, wks</td>
<td>30.1 ± 3.9</td>
</tr>
<tr>
<td>GA at delivery, wks</td>
<td>37.8 ± 3.0</td>
</tr>
<tr>
<td>Weight at delivery, g</td>
<td>2495 ± 671</td>
</tr>
<tr>
<td>NICU admission</td>
<td>312 (28%)</td>
</tr>
<tr>
<td>Adverse perinatal outcome</td>
<td>57 (5%)</td>
</tr>
<tr>
<td>Apgar score &lt;76</td>
<td>13 (1%)</td>
</tr>
<tr>
<td>Stillbirths</td>
<td>3 (1:370)</td>
</tr>
<tr>
<td>Neonatal deaths</td>
<td>3 (1:370)</td>
</tr>
</tbody>
</table>

Continuous variables are summarized with mean ± SD and categorical variables with n (percentage).

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

all normally formed fetuses underwent evaluation of amniotic fluid volume, biophysical profile scoring (BPP), and multivessel Doppler of the UA, MCA, DV, AoI, and MPI at every subsequent contact with the research sonographers until delivery. This occurred at a minimum of 2 weekly intervals but more frequently, even daily, if deemed necessary.

A report of all sonographic findings was filed in the patient’s case record and made available to the managing clinician. All prenatal and ultrasound data were contemporaneously transferred to an ultrasound software system (Viewpoint; MDI Viewpoint, Jacksonville, FL) and uploaded onto a live web-based central consolidated database.

An abnormal UA Doppler assessment was defined as a pulsatility index (PI) above the 95th centile, (intermittently) absent (AEDF) or reversed end-diastolic flow (REDF). MCA abnormalities were defined as a PI less than the fifth centile.12 DV was recorded as being abnormal with a PI greater than the 95th centile, and absent or reversed a-wave flow.13 AoI Doppler was considered abnormal according to gestational age—based reference ranges described by Del Rio et al.14 MPI was measured in the left ventricle assessing individual isovolumetric contraction (ICT) and relaxation times (IRT) over the period between opening and closure of the semilunar valves (ejection time [ET]) (ICT + IRT/ET).15 A cerebroplacental Doppler ratio less than 1 was considered abnormal.

A small group of 10 research sonographers performed all Doppler studies. Initial structured training was provided by maternal-fetal medicine subspecialists, and quality assurance assessments with periodic resubmission of images were carried out at regular intervals. To minimize the intra- and interobserver variability, all ultrasound assessments were carried out by one single sonographer per center. All data were interpreted using published, standardized references for various Doppler findings, therefore eliminating misinterpretation of data.

In cases of AEDF or REDF in the UA, the patient was admitted to the hospital, and a daily computerized short-term variation cardiotocograph (CTG) was

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**FIGURE 1**

**Cumulative frequencies of Doppler abnormalities (n = 1116)**

![Graph showing cumulative frequencies of Doppler abnormalities](image)

Figure 1 outlines how long each of the Doppler abnormalities were present prior to delivery, expressed as a cumulative percentage of Doppler abnormalities occurring in the full cohort of 1116 pregnancies with an EFW less than the 10th centile.

EFW, estimated fetal weight.


**FIGURE 2**

**Mean time-to-delivery interval for each Doppler (n = 1116)**

![Bar chart showing mean time-to-delivery interval](image)

Figure 2 outlines the mean time from first Doppler abnormality to delivery for each interrogated vessel: UA, MCA, DV, AoI, and MPI.

AoI, abnormal aortic isthmus; DV, ductus venosus; MCA, middle cerebral arteries; MPI, myocardial performance index; UA, umbilical arteries.

carried out. Corticosteroids for fetal lung maturation were administered between 24 and 36 weeks’ gestation if delivery was thought to be likely within 1 week. The impact of steroid administration on Doppler variation was not examined. Decisions relating to timing and mode of delivery were left to the discretion of the lead clinician managing each case. Although such management decisions were not prespecified by the study design, there was, however, general agreement among the clinicians in Ireland to deliver the AEDF cases by 34 weeks’ gestation. The tertiary-level neonatal care facilities were available in all 7 sites.

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 admission had their outcomes recorded by neonatal medical or nursing staff. Adverse perinatal outcome was defined as a composite outcome of intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), hypoxic ischemic encephalopathy (HIE), necrotizing enterocolitis (NEC), BPD, sepsis, and death. Given that all study sites were members of the Vermont Oxford Network, definitions for IVH, PVL, HIE, NEC, BPD, and sepsis were standardized across all centers derived from the Vermont Oxford Network manual. The prediction of adverse outcome was evaluated by any Doppler abnormality during the study period.

**Use of statistics**
Prior to statistical analysis, all ultrasound and outcome data were screened for anomalous records or potential outliers and followed up with sonographers for resolution. Statistical comparisons were performed using the \( \chi^2 \) test of association. SAS version 9.2 (SAS Institute, Cary, NC) was used for these analyses.

**FIGURE 3**
Doppler deterioration for various sequences (n = 1116)

Various patterns of Doppler deterioration occurring in a truly sequential manner are outlined. **A**, Pattern 1 describes a sequential deterioration for vessels UA → MCA → DV; **B**, pattern 2 describes a sequential deterioration for vessels UA → DV → MCA; and **C**, pattern 3 describes a sequential deterioration for vessels MCA → UA → DV. DV, ductus venosus; MCA, middle cerebral arteries; UA, umbilical arteries.

Cary, NC) was used for data management and statistical analysis.

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

The mean maternal age was 30 years, the mean body mass index was 24 kg/m², and the vast majority of women were of white European descent. This is consistent with the demographic profile of the overall obstetric population attending for antenatal care in Ireland, reflecting an unselected group of recruited pregnancies. Twenty-three percent were smokers and 12% were affected by hypertensive disease or preeclampsia. The mean gestational age (GA) at enrollment to the study was 30.1 weeks and the mean GA at delivery was 37.8 weeks. The Table outlines maternal demographics and fetal characteristics.

Our study of 1116 fetuses with an EFW less than the 10th centile comprised 7769 individual Doppler data points gathered for as long as 17 weeks of surveillance on some patients, with an average of 7.7 weeks. Five hundred eleven patients (46%) had an abnormal UA Doppler waveform in the study; 70 patients had an UA AEDF and 8 had an UA REDF. The mean time to delivery for patients with abnormal UA Doppler, (intermittent) AEDF, and REDF was 26, 13, and 4 days, respectively. Three hundred of the study population (27%) had an abnormal MCA, 133 (12%) had an abnormal MPI, 129 (11%) had an abnormal DV, and 59 (5%) had an abnormal AoI.

The frequency of Doppler deterioration for each vessel and the timing to delivery is outlined in Figure 1. It is important to point out that these are cumulative frequencies seen in the entire study population of 1116 fetuses, and given that there may or may not be a significant overlap between these abnormalities, we cannot conclude that this represents the main sequence of progressive deterioration at the individual fetal patient level.

To emphasize this point further, Figure 2 represents the mean time from first diagnosis of Doppler abnormality until delivery. If there was a single dominant sequence of deterioration in Doppler abnormalities in the setting of IUGR, we would have expected to see a gradual shortening in the time from first diagnosis to delivery for each of the relevant Doppler findings. In contrast, what we actually found was no overall pattern of Doppler deterioration in each of these vessels. For example, although the mean time from diagnosis to delivery for an abnormal UA was 26 days, the mean time from diagnosis to delivery for abnormal DV was 37 days and 39 days for an abnormal MPI.

Our data demonstrate that there are in fact various patterns of Doppler deterioration occurring in a truly sequential manner, meaning that an initial abnormal Doppler finding was followed by another and another in one and the same fetus over time. Given that we interrogated 5 fetal vessels in our study, there are 120 different potential sequences; we have, however, restricted our description of this point to 3 patterns to illustrate this concept (Figure 3, A-C).

If we analyze the classic sequence (pattern 1: UA → MCA → DV), thought to be the single most common pattern of deterioration in IUGR, our data show that 46% (n = 511) of the overall cohort developed an abnormal UA Doppler. Eight percent (n = 87) had a sequence of an abnormal UA and MCA Doppler, and only 0.8% (n = 9) in our cohort showed a sequential change in all 3 vessels. A similar sequence applies for patterns 2 (UA → DV → MCA) and 3 (MCA → UA → DV).

To summarize these findings, Figure 4 combines various patterns of Doppler deterioration. If the sequence of deterioration from UA to MCA to DV was the most important, we would expect to see a relatively flat line such that almost all patients with an abnormal umbilical artery Doppler would next have an abnormal middle cerebral artery Doppler and would next have an abnormal ductus venosus Doppler. In actual fact, what we found was that all 6 possible sequences of Doppler deterioration were similarly represented in our dataset.

Interestingly, even when we focused on a selected group of 113 fetuses who had such severe IUGR that required delivery prior to 34 weeks, we still could not identify one single predominant pathway or sequence of deterioration. Average gestational age at presentation for all 6 Doppler sequences was 24-27 weeks, showing no statistical significance when analyzing the progression in relation to gestational age at enrollment (P = .1835, Kruskal-Wallis test).

Correlation of Doppler findings with respective perinatal morbidity and mortality outcomes shows that an abnormal umbilical artery Doppler is by far the most likely test to be associated with adverse outcome, capturing 86% of all recorded adverse outcomes (Figure 5). Second, the next most useful vessel is an abnormal middle cerebral artery Doppler, capturing 51% of all adverse outcomes. If significant time and effort are placed into searching for other Doppler abnormalities such as DV, AoI, and MPI, this will only pick up a relatively small proportion of remaining adverse perinatal outcomes.

COMMENT
Despite the large amount of published literature on ultrasound in the setting of IUGR, the optimal surveillance pattern and timing of delivery remains the focus of much debate and research, with no internationally accepted approach to management.

In this large prospective cohort of IUGR pregnancies, we have demonstrated multiple potential patterns of Doppler deterioration. The classic sequence from abnormal UA to MCA to DV exists but no more frequently than any of the other potential patterns.

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 10 trained research
sonographers. Although the study was multicenter in nature, inconsistencies in assessment were overcome with regular training sessions of the small 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.

A possible weakness of our study relates to the slightly late gestational age at which IUGR pregnancies were enrolled to the study (mean GA at enrollment was 30 weeks). This might underestimate the true scope of the problem.

Evidence from randomized controlled trials as to whether additional Doppler interrogation is of benefit in optimizing the timing of delivery in IUGR is lacking. The practical challenges of performing randomized trials in the setting of severe IUGR are so difficult that they may not be able to inform clinical practice. The PORTO study was initially designed as a study with both observational and randomized arms, with the aim being to randomize IUGR pregnancies with umbilical artery AEDF to either advanced Doppler surveillance or short-term variation CTG surveillance. However, the randomized arm of the study had to be discontinued after 12 months of recruitment because of a lack of eligible cases, despite access to a large national obstetric population.

Of the fetal vessels studied, abnormal UA and MCA Doppler remain the strongest predictors of adverse outcome, with only marginal added benefit to DV and cardiac indices. Multivessel Doppler may be beneficial as an adjunct assessment tool in the evaluation of IUGR to optimize timing of delivery; however, our study questions whether a logical sequence of deterioration in these vessels exists, therefore making any interpretation of Doppler deterioration challenging.

A potential criticism relating to our study design may be that there were no prespecified delivery criteria, and therefore, fetuses affected by IUGR were delivered at different time points of their disease progression, making it difficult to draw conclusions from our data. It is accepted that ours was not an intervention trial but an observational study of real-world clinical practice. Given the large number of cases and individual Doppler measurements gathered in our study (1116 fetuses with 7769 individual Doppler data points), we believe that we have sufficient data to be able to make robust statements about the natural history of temporal Doppler changes. These data will be critically important for planning future intervention trials. In the absence of evidence from such randomized or intervention trials, assessment of fetal well-being by CTG, biophysical profile scoring, amniotic fluid index, UA, and MCA Doppler will remain the standard of care. These findings should greatly simplify IUGR surveillance, which may have a significant implication for resource utilization in contemporary obstetric practice.

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**Figure 4**
Combination of pathways of Doppler deterioration (n = 1116)

**Figure 5**
Doppler abnormalities capturing adverse perinatal outcome (n = 57)

Doppler interrogation of the UA and MCA remains the most useful and practical tool in identifying fetuses at risk of adverse perinatal outcome, capturing 88% of all adverse outcomes.

CPR, cerebroplacental ratio; MCA, middle cerebral arteries; UA, umbilical arteries.

REFERENCES