Outcome in early-onset fetal growth restriction is best combining computerized fetal heart rate analysis with ductus venosus Doppler: insights from the Trial of Umbilical and Fetal Flow in Europe

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Introduction

Advances in neonatal care over the last few decades have resulted in improved survival of preterm infants even at very early gestational ages.[1] However, morbidity, neurological impairment, and decrements in intellectual and social performance are still prevalent and strongly associated with gestational age at birth.[2,3] The situation becomes even more critical if prematurity is determined by the need to rescue the fetus from an unfavorable intrauterine environment—as is the case in placental insufficiency. The outcome of these infants will not only depend on the degree of prematurity but also on the severity of fetal growth restriction (FGR).[4-6] Given

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BACKGROUND: Early-onset fetal growth restriction represents a particular dilemma in clinical management balancing the risk of iatrogenic prematurity with waiting for the fetus to gain more maturity, while being exposed to the risk of intrauterine death or the sequelae of acidosis.

OBJECTIVE: The Trial of Umbilical and Fetal Flow in Europe was a European, multicenter, randomized trial aimed to determine according to which criteria delivery should be triggered in early fetal growth restriction. We present the key findings of the primary and secondary analyses.

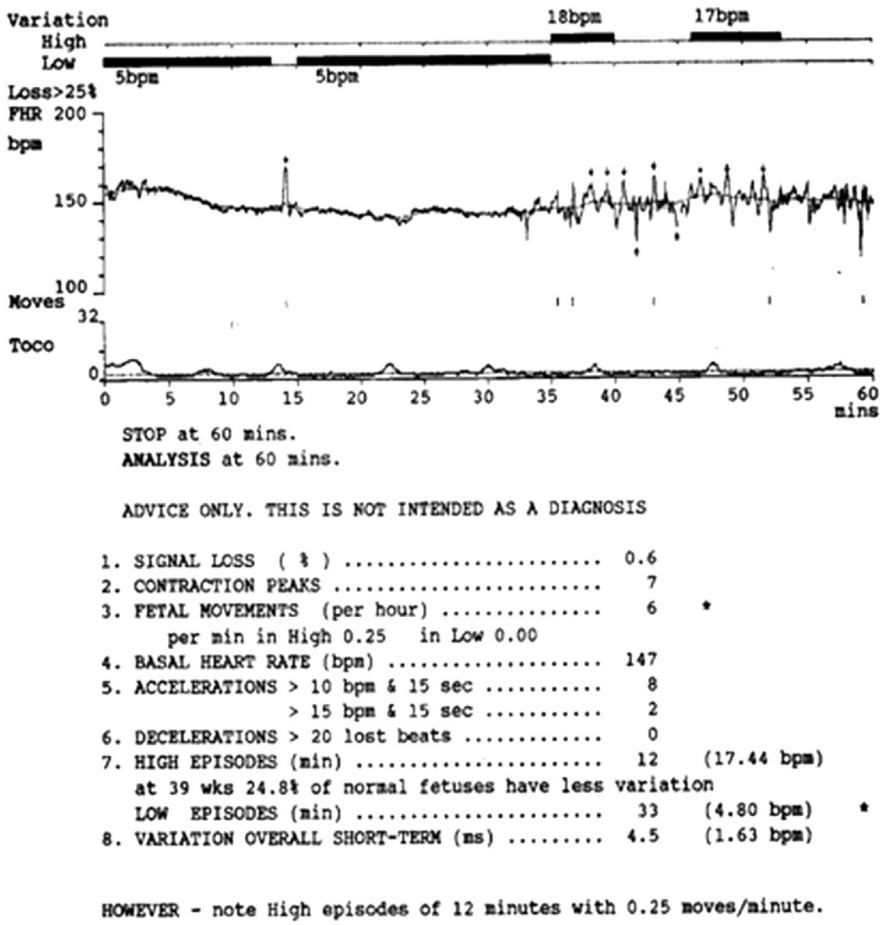
STUDY DESIGN: Women with fetal abdominal circumference <10th percentile and umbilical pulsatility index >95th percentile between 26-32 weeks were randomized to 1 of 3 monitoring and delivery protocols. These were: fetal heart rate variability based on computerized cardiotocography; and early or late ductus venosus Doppler changes. A safety net based on fetal heart rate abnormalities or umbilical Doppler changes mandated delivery irrespective of randomized group. The primary outcome was normal neurodevelopmental outcome at 2 years.

RESULTS: Among 511 women randomized, 362/503 (72%) had associated hypertensive conditions. In all, 463/503 (92%) of fetuses survived and cerebral palsy occurred in 6/443 (1%) with known outcome. Among all women there was no difference in outcome based on randomized group; however, of survivors, significantly more fetuses randomized to the late ductus venosus group had a normal outcome (133/144; 95%) than those randomized to computerized cardiotocography alone (111/131; 85%). In 118/310 (38%) of babies delivered <32 weeks, the indication was safety-net criteria: 55/106 (52%) in late ductus venosus, 37/99 (37%) in early ductus venosus, and 26/105 (25%) in computerized cardiotocography groups. Higher middle cerebral artery impedance adjusted for gestation was associated with neonatal survival without severe morbidity (odds ratio, 1.24; 95% confidence interval, 1.02—1.52) and infant survival without neurodevelopmental impairment at 2 years (odds ratio, 1.33; 95% confidence interval, 1.03—1.72) although birthweight and gestational age were more important determinants.

CONCLUSION: Perinatal and 2-year outcome was better than expected in all randomized groups. Among survivors, 2-year neurodevelopmental outcome was best in those randomized to delivery based on late ductus venosus changes. Given a high rate of delivery based on the safety-net criteria, deciding delivery based on late ductus venosus changes and abnormal computerized fetal heart rate variability seems prudent. There is no rationale for delivery based on cerebral Doppler changes alone. Of note, most women with early-onset fetal growth restriction develop hypertension.

Key words: antepartum surveillance, cardiotocography, intrauterine growth restriction, neurodevelopmental handicap, perinatal outcome, Trial of Umbilical and Fetal Flow in Europe, umbilical artery Doppler

FIGURE 1
Computerized cardiotocography readout



One-hour recording of the fetal heart rate (FHR) with computerized Dawes and Redman analysis. Bullet point 8 in the figure shows short-term variation used in the Trial of Umbilical and Fetal Flow in Europe as the cardiotocography criterion for deciding upon delivery in severe fetal growth restriction.

FHR, fetal heart rate; *IVC*, inferior vena cava; *SVC*, superiro vena cava; *toco*, tocography.

Frusca. TRUFFLE study of early fetal growth restriction. Am J Obstet Gynecol 2018.

that no targeted treatment exists for FGR, delivery is the only intervention that can prevent severe hypoxemia and acidosis, and eventually intrauterine death. Thus, optimal monitoring and timing of delivery remains crucial in the management of early-onset FGR.[7]

The issue of timing of delivery had first been addressed by the Growth Restriction Intervention Trial, which reported on 587 babies.[8,9] This study randomized women with compromised small babies to immediate delivery or expectant management, based on equipoise of the clinician regarding optimal management. Early reports indicated that an expectant policy (time to delivery 4.9 days) seemed associated with a more favorable neurodevelopmental outcome than immediate delivery (0.9 days). At school age, however, no difference was found between immediate or delayed delivery.[10] From this or other studies there is no clear evidence to support delayed above early delivery.[11] A significant limitation of the Growth Restriction Intervention Trial was that neither gestational limits nor clinical criteria for monitoring and timing of delivery were defined. The only entry criterion for the study was the clinician's uncertainty on whether to deliver or continue the pregnancy.

Monitoring early FGR and timing delivery has been undertaken in a variety of ways, including biophysical profile scoring[12] and umbilical artery (UA) Doppler,[13] although there is little evidence underlying the use of either technique. Different UA Doppler patterns identify different degrees of impaired placental function. Absent end-diastolic velocities (AED) or reversed end-diastolic velocities (RED) indicate impairment of the fetoplacental circulation and presage fetal deterioration.[13] Longitudinal studies conducted on high-risk pregnancies have shown that the transition from AED to RED may be slow and gradual in early FGR, nevertheless, both AED and RED have been associated not only with increased fetal and neonatal mortality but also with a higher incidence of long-term neurological impairment when compared with FGR fetuses with positive end-diastolic velocities in the umbilical circulation.[14,15]

Since the early 2000s, attention has moved to assessment of the ductus venosus (DV) (Figures 1 and 2) and computerized cardiotocograph (cCTG) analysis of fetal heart rate short-term variation (STV) to guide timing of delivery in FGR (Figure 3).[16] A longitudinal observational study of FGR fetuses monitored by Doppler and cCTG showed that <32 weeks' gestation, DV Doppler abnormalities (Figure 4) in some cases preceded the onset of a low STV, and that continuing pregnancy until the cCTG becomes abnormal in these cases was associated with a significantly higher perinatal mortality and worse composite perinatal outcome.[17] In particular, mortality was higher if both DV and cardiotocography (CTG) were abnormal than when only one was abnormal. Another multicenter study on a large cohort of FGR pregnancies followed up longitudinally also demonstrated that intact survival increased by 1-2% for every extra day spent in utero up to 32 weeks.[18] The balance in early-onset FGR is between, on the one hand, prolonging pregnancy to reduce prematurity-related complications, and in the other, timely intervention, to prevent mortality and limit morbidity.[19-21]