Timing of delivery in fetal growth restriction and childhood development: some uncertainties remain

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In this issue, Walker et al present long-term outcomes of children who were assigned randomly to immediate vs delayed delivery in the growth restriction intervention trial (GRIT). GRIT is the first randomized trial for delivery timing in perinatal fetal growth restriction (FGR). Understanding its background and details of the study design are important prerequisites to appreciate the significance of their findings.

In the early 1990s, surveillance tests that were used for FGR management included traditional or computerized fetal heart rate analysis, umbilical artery Doppler scanning, and biophysical profile scoring. The prevailing concern was that progressive intrauterine hypoxemia and acidemia increase the risk for irreversible developmental delay. Because prolonged monitoring carried the risk of such fetal compromise and early delivery increased risks for prematurity-related morbidity and death, the optimal timing of delivery had been a central issue in FGR management. Although the degree of fetal compromise could be estimated with any available surveillance test, thresholds and appropriate delivery triggers were unclear. Justification for a randomized trial on delivery timing was based on formal assessment of the collective and balanced uncertainty among experts in antenatal surveillance around this issue, which is an important difference from most trials that are designed to address universally agreed equipoise among experts. Furthermore, because experts also demonstrated uncertainty about the best test to trigger delivery, GRIT was designed to compare solely the effect of delivery timing, irrespective of the surveillance modality used for this purpose. Another unique feature of GRIT is the Bayesian approach used for monitoring and data interpretation. In brief, the Bayesian procedure involves the use of archetypal “skeptical” and “enthusiastic” priors. A skeptical prior would be an obstetrician who does not believe that delivery timing has consequences; an enthusiastic prior can either be an enthusiast for immediate or for deferred delivery. In this approach, results of the trial are released to the investigators regularly to “update” their opinions and possibly convert skeptics to enthusiasts. The assumption is that each investigator can make an informed opinion and change their priors.

FGR singletons or twins between 24-36 weeks’ gestation were eligible for trial entry if responsible clinicians were uncertain about delivery timing and if umbilical artery Doppler scans had been recorded. Randomization was to immediate delivery (within 48 hours, allowing for steroid administration) or delay until the physician believed that delivery could no longer be safely deferred. Main outcome measures were perinatal death and Griffith’s developmental quotient at age 2 years. More than 500 women were recruited with balanced allocation into each arm. Delivery delay averaged 4.9 days overall, but delay was almost 1 week for women who were assigned randomly after 30 weeks’ gestation. Deaths before discharge (approximately 10%) were identical in both groups; total cesarean section deliveries were more frequent when immediate delivery was required. Ninety-eight percent of the women completed 2-year follow-up evaluation, which showed a comparable rate of death or disability (16-19%) in both arms. Most disability (10% vs 0% cerebral palsy rate) was observed in deliveries at <31 weeks’ gestation because of prematurity-associated morbidity. No additional predictors were identified. At 6-13 years of follow-up observation, Walker et al report standardized evaluations of cognition, language, behavior, and motor ability in just over one-half of the original study cohort. No differences were observed in the rate of severe disability and the scores in individual developmental domains, which are comparable to other preterm cohorts. Overall, the authors conclude that obstetricians who are unsure about delivery timing in FGR are prepared to delay approximately 4 days; although such delay causes some stillbirths, earlier delivery produces an almost equal number of additional neonatal deaths. These similar mortality rates suggested randomization at a correct equivocal threshold between delivery and delay. They also suggest that delivery was timed appropriately to minimize deaths but probably too early to reduce prematurity-related brain damage. The 2-year outcomes did not support the concept that obstetricians could improve brain development through delivery before terminal hypoxemia. The current study strengthens this point even further: judgments that are made around the time of delivery have little impact on longer-term neurodevelopment.

There have been many criticisms about GRIT: enrollment over almost 8 years, inability to track the total screened population, lack of specific delivery triggers, and the use of Bayesian monitoring. The current study by Walker et al may be affected...
by selection bias due to the examination of a select subset of the original study sample. However, focusing on these limitations detracts from important lessons that can be learned from GRIT and recent observational data. Our assumptions about long-term fetal impacts of placental disease were based largely on the premise that fetal metabolic deterioration precedes abnormal neurodevelopment and that early intervention could modify this cascade. This is incorrect; by the time FGR is clinically apparent, many fetal organs (including the brain) have already been subjected to abnormal blood flow and nutrient partitioning. Supported by their own data and studies quoted in the article, Walker et al1 also come to the conclusion that neurodevelopment is affected already before the cascade of fetal deterioration occurs, which leaves a limited scope for effective prevention by merely changing delivery timing.

How about the short-term impacts of delivery timing? We now know that with worsening placental function, the fetus may exhibit a sequence of cardiovascular abnormalities and finally abnormal biophysical parameters that parallel the progression of hypoxemia to academia.3 The rate of this progression is determined by the severity of placental disease and is faster with earlier onset FGR,5 which explains the longer randomization time to delivery interval for patients who are enrolled at >30 weeks’ gestation in GRIT.5 We now can also quantify the impact of prematurity in placenta-based FGR and have learned that gestational age has such a strong impact on neonatal outcome that it overrides the effects of fetal deterioration until the early third trimester.5 Because these prenatal and postnatal features of FGR cannot be altered currently, managing obstetricians may be forced to raise their delivery thresholds according to neonatal risks and allow the fetus to get “sicker” to gain time. In GRIT, such delay resulted in significantly increased stillbirths (9/282 delayed arm vs 2/294 with immediate delivery; Fisher’s exact test, \( P = .035 \)). Conversely, immediate delivery significantly increased neonatal deaths if it occurred at <30 weeks’ gestation (immediate delivery, 17/25 prematurity-related deaths; delayed delivery, 8/23 prematurity-related deaths; \( \chi^2 \) test, \( P = .04 \)).5

The currently underway randomized “trial of umbilical and fetal flow in Europe” compares ductus venosus Doppler scanning and computerized cardiotocography as specific delivery triggers for their ability to affect long-term outcomes. Based on our knowledge today, we can anticipate similar neurodevelopment in both arms. Given our inability to modify the clinical course and developmental impacts of early-onset FGR, the most promising avenue to truly affect outcomes will be prevention. Significant advances have been made in the first-trimester screening and prevention of placental dysfunction.7 When early FGR develops, delay risks stillbirth, although delivery risks neonatal death. Divon et al8 already demonstrated that integrated Doppler scanning and biophysical monitoring could avoid acidemia and stillbirth, even with markedly diminished umbilical artery end-diastolic blood flow. Until we focus our research to clarify appropriate monitoring intervals that recognize accelerating fetal disease and increase our accuracy to predict the balance between fetal and neonatal risks, uncertainties about delivery timing will remain.

REFERENCES