

When is the ideal time for a preterm fetus to be delivered?

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LIST OF ABBREVIATIONS Growth Restriction Intervention Trial (GRIT)

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In August 2004, *The Lancet* published data on brain development in survivors of the multicentred GRIT. The aim of this study¹ was to identify compromised fetuses between 24 and 36 weeks gestation and answer the question whether it was safer to deliver them immediately or to delay until there was no clinical doubt that delivery was necessary. Five-hundred and eighty-eight such fetuses were identified in 69 hospitals in 13 European countries. Two-hundred and ninety-six were randomly assigned to immediate delivery and 292 to delayed delivery. The median interval between randomisation and delivery in the immediate delivery group was 0.9 days, and 4.9 days in the delay group. The authors had previously reported on the stillbirths and neonatal deaths in these pregnancies,² and identified similar mortality before discharge between immediate and delayed delivery groups.

The main outcome measures of the current report were death and disability at or beyond two years of age. These outcome measures were recorded in 98% of immediate births and 97% of delayed births. Overall rates of death and disability were similar: 19% of immediate births and 16% of delayed births. In the subgroup of infants born at gestation less than 31 weeks, the outcomes appeared to improve by delaying the delivery where possible.

Obstetricians and midwives have the unenviable task of looking after patients whom they cannot see. The mother's health is often considered to be their primary responsibility, but both professions have the added burden of caring for single or multiple fetuses, and can monitor their progress only indirectly. The wellbeing of the pregnancy can be judged by the mother's health, her own weight gain and the absence of acute maternal disease (including hypertension or vaginal bleeding). In addition, fetal size can be judged by the obstetrician's hands, and

the heart rate monitored by auscultation. Biochemical tests such as urinary oestriol concentrations have failed to live up to the promise of monitoring placental function and have largely been abandoned. Ultrasound and heart rate monitoring by cardiotocography help assess fetal wellbeing more effectively.

The challenge of monitoring fetal health is particularly serious in the presence of growth-restriction. Such a fetus has few metabolic reserves, and sudden death in pregnancy may be unheralded. Labour is an intermittently hypoxic event, and anaerobic metabolism may not be an option where stores of fat and glycogen are inadequate. More recently placental and fetal arterial Doppler flow-velocity waveforms have guided decision making. These have proved particularly effective in assessing the growth-restricted pregnancy and are a useful adjunct in assessment of the very preterm fetus where cardiotocographical monitoring may be unhelpful.

The GRIT study is in many ways an astonishing achievement, representing as it does the gathering of data in 13 countries over a seven-year period. It implies that in 548 situations the obstetrician found himself or herself unable to decide whether to deliver immediately or not. The success of follow-up indicates excellent organisation, and the paediatricians describing outcomes did not know to which study group an individual fetus had been allocated.

From a neonatologist's point of view, the GRIT study group chose an unexpected range of gestational ages to study. The 24-week gestation baby is very different from that at 36 weeks. In the absence of severe congenital abnormalities, the current infant mortality after 32 weeks' gestation is low: the causes of this rare event include asphyxia, necrotising enterocolitis and infection. Because

of the availability of intratracheal replacement surfactant, significant respiratory distress syndrome is rare in this group. Obstetricians should therefore have a low threshold for delivery in this relatively mature group if the fetus appears to show signs of compromise. By contrast, before 32 weeks, and particularly in the extreme preterm infant, there is a much higher mortality, and the levels of morbidity have recently been emphasised in the Epicure Study,³ in which 49% of surviving infants born at less than 26 weeks' gestation had some disability at 30 months of age and 19% were severely disabled.

It is in this immature group of infants that one might expect to find benefits in delaying time of delivery. With every week that passes there should be a decreasing occurrence of serious neonatal complications including intraventricular haemorrhage, retinopathy of prematurity and sepsis. On the other hand, delay may expose the growth-restricted fetus to ischaemic injury of the brain, resulting in asphyxia, periventricular leucomalacia and intraventricular haemorrhage, as well as the significant risk of intra-uterine death. This surely is the group where the main challenge lies. The authors of the GRIT study did examine a subgroup of infants at 24–30 weeks' gestation and demonstrated that the immediate delivery group had higher cerebral palsy rates (10% vs 0%) and more infants with a Griffiths Developmental Quotient of less than 71 (10% vs 4%), but the numbers were too small to achieve statistical significance. Regrettably sample size is often the limiting factor in such epidemiological studies.

REFERENCES

1 The GRIT study group. Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomized controlled trial. *Lancet* 2004; **364**:513–20.

In essence this study has shown a small increase in fetal death if the obstetrician delays delivery, and a small increase in neonatal death if early delivery is chosen. The most important information from this study may emerge from detailed follow-up of the surviving children.

Nevertheless this was an admirable trial, even though it does not inform obstetricians about when, in an individual case, the optimal time of delivery should be. The art of clinical medicine is once again found to be paramount, until a new and reliable method of fetal monitoring can be found.

KEYPOINTS

- GRIT studied 588 at-risk fetuses in 13 European countries.
- Death and disability at or beyond two years of age was the same when the delivery was carried out at once (within about a day) or only when delivery was clearly needed (within about five days).
- Infant mortality at or after 32 weeks of pregnancy is low and immediate delivery can be supported for at-risk fetuses.
- Infant mortality before 32 weeks rises steadily due to immaturity of the fetus and in this study delaying delivery did seem to be beneficial. However, the study sample was too small for this result to be statistically significant.
- It is essential that further information on neuro-developmental outcome be obtained in the coming years.

2 GRIT Study Group. A randomized trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation. *BJOG* 2003; **110**:27–32.

3 EPICure Study Group. Neurologic and developmental disability after extremely preterm birth. *N Engl J Med* 2000; **343**(6):429–30.