2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial

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Summary

Background No consensus exists for the best way to monitor and when to trigger delivery in mothers of babies with fetal growth restriction. We aimed to assess whether changes in the fetal ductus venosus Doppler waveform (DV) could be used as indications for delivery instead of cardiotocography short-term variation (STV).

Methods In this prospective, European multicentre, unblinded, randomised study, we included women with singleton fetuses at 26–32 weeks of gestation who had very preterm fetal growth restriction (ie, low abdominal circumference [<10th percentile] and a high umbilical artery Doppler pulsatility index [>95th percentile]). We randomly allocated women 1:1:1, with randomly sized blocks and stratified by participating centre and gestational age (<29 weeks *vs* ≥29 weeks), to three timing of delivery plans, which differed according to antenatal monitoring strategies: reduced cardiotocograph fetal heart rate STV (CTG STV), early DV changes (pulsatility index >95th percentile; DV p95), or late DV changes (A wave [the deflection within the venous waveform signifying atrial contraction] at or below baseline; DV no A). The primary outcome was survival without cerebral palsy or neurosensory impairment, or a Bayley III developmental score of less than 85, at 2 years of age. We assessed outcomes in surviving infants with known outcomes at 2 years. We did an intention to treat study for all participants for whom we had data. Safety outcomes were deaths in utero and neonatal deaths and were assessed in all randomly allocated women. This study is registered with ISRCTN, number 56204499.

Findings Between Jan 1, 2005 and Oct 1, 2010, 503 of 542 eligible women were randomly allocated to monitoring groups (166 to CTG STV, 167 to DV p95, and 170 to DV no A). The median gestational age at delivery was 30·7 weeks (IQR 26·1–40·6) and mean birthweight was 1019 g (SD 322). The proportion of infants surviving without neuroimpairment did not differ between the CTG STV (111 [77%] of 144 infants with known outcome), DV p95 (119 [84%] of 142), and DV no A (133 [85%] of 157) groups (p_{trend}=0·09). 12 fetuses (2%) died in utero and 27 (6%) neonatal deaths occurred. Of survivors, more infants where women were randomly assigned to delivery according to late ductus changes (133 [95%] of 144, 95%, 95% CI 90–98) were free of neuroimpairment when compared with those randomly assigned to CTG (111 [85%] of 131, 95% CI 78–90; p=0.005), but this was accompanied by a non-significant increase in perinatal and infant mortality.

Interpretation Although the difference in the proportion of infants surviving without neuroimpairment was non-significant at the primary endpoint, timing of delivery based on the study protocol using late changes in the DV waveform might produce an improvement in developmental outcomes at 2 years of age.

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Introduction

When a fetus is diagnosed with early onset growth restriction, the main priority for the obstetrician, fetal medicine specialist, neonatologist, and parent is for the fetus to be delivered in optimum condition and survive the neonatal period. Nevertheless, outcomes in later life relating to neurodisability are of potentially greater importance than survival, are rarely reported, and cannot be inferred from whether or not complications occur in the neonatal period.[1] Most studies of early onset fetal growth restriction have focused on short-term neonatal outcomes[2–4] and only one, the GRIT study,[5] was both randomised and reported infant follow-up at 2 years and the age at which the infant began school. The GRIT study randomly allocated women to early or delayed delivery when signs of fetal compromise were present, but the obstetrician was in equipoise as to whether delivery was indicated. Neonatal outcomes,[6] childhood morbidity at 2 years,[7] and at morbidity at school age[8] did not show benefit for either group, thus not further informing management.

Several methods exist for surveillance of the at-risk fetus—eg, cardiotocography, arterial and venous Doppler examination, and biophysical profiles.[9] The temporal

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sequence of these changes is variable,[10] but generally, the more severe the growth restriction is, the more pronounced the Doppler changes are.[11] No consensus exists for what is the best way to monitor growth restriction, what is the most appropriate trigger for delivery, and no trials of the importance of different criteria for delivery exist. In the preterm growth restricted fetus, the decision to deliver is usually made only when signs of substantial worsening of the fetal condition are observed by visual or qualitative assessment of a cardiotocograph tracing or changes in biophysical status because these changes correlate with fetal hypoxaemia.[12] One prospective cohort study[13] comparing short-term variation of fetal heart rate, Doppler of the umbilical artery, middle cerebral artery, and ductus venosus in early preterm pregnancies complicated by fetal growth restriction concluded that the abnormal ductus venosus pulsatility index was the best discriminating variable for neonatal outcome.

We therefore postulated that changes in the fetal ductus venosus Doppler waveform, which generally develop after those in the umbilical artery, might be used as indications for delivery instead of cardiotocograph short-term variation. To test this hypothesis, we designed a three group randomised trial to establish whether the assessment of the ductus venosus waveform could be a better method than cardiotocograph with short-term variation calculation alone to trigger delivery of the very preterm (before 32 week) growth restricted fetus.

Methods

Study design and participants

The Trial of Umbilical and Fetal Flow in Europe (TRUFFLE) study was a prospective, multicentre, randomised management trial done in 20 European tertiary care centres with a fetal medicine unit in five countries (Germany, Italy, the Netherlands, Austria, and the UK). Participants were included from Jan 1, 2005, to Oct 1, 2010, but not all hospitals started recruiting at the same time.[14] Women were recruited by investigators with expertise in fetal assessment using secure web based randomisation. Women were eligible for inclusion in this study if they were admitted to hospital with singleton pregnancies and were diagnosed with fetal growth restriction, defined as a fetal abdominal circumference below the 10th percentile on the reference chart[15] and abnormal umbilical artery Doppler with a pulsatility index above the 95th percentile of the Doppler reference chart[16] with or without reversed or absent end-diastolic flow. Pregnancies had a gestational age assigned from crown rump length before 14 weeks or biparietal diameter between 14·0 weeks and 22·0 weeks.

At inclusion, gestational age was between 26 weeks and 31·9 weeks (ie, 182–223 days), estimated fetal weight was more than 500 g (fetal weight was estimated according to the four variables head circumference, abdominal circumference, biparietal diameter, and femur length model),[17] and with a normal ductus venosus waveform with a pulsatility index (PI) below the 95th percentile.[18] Additionally, short-term variation after 1 h of cardiotocograph tracing had to be greater than 3·5 ms between 26·0 weeks and 28·9 weeks, and more than 4 ms between 29·0 weeks and 31·9 weeks.[19]

Women were not eligible if delivery was known, planned, or impending; any obvious major fetal structural abnormality existed; previous invasive prenatal testing showed any fetal karyotype abnormality; or if they were younger than 18 years of age. Patients provided written informed consent. The study was ratified by the ethics committees of all participating units.

An independent Data Monitoring Committee reviewed the accruing trial data annually, and recommended at each meeting whether the trial should continue as

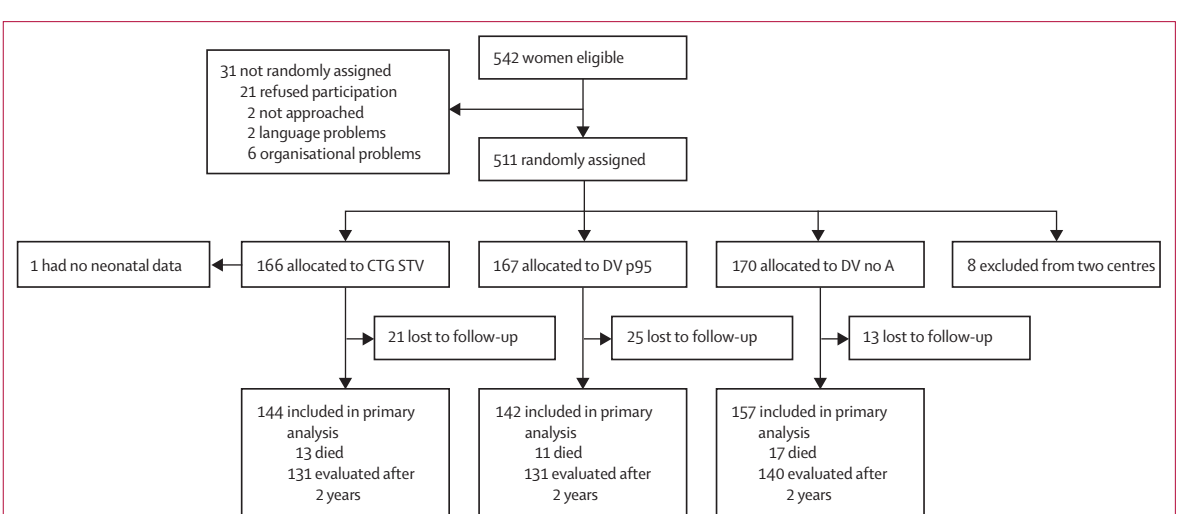

Figure 1: **Trial profile**

planned, undergo design modification, or stop recruiting on safety grounds, or because the effectiveness of one or other group had been proved to a very high level of statistical significance. They made decisions by consensus. There were no formal interim analyses or stopping rules.

Randomisation and masking

Participants were randomly assigned to one of three groups in a 1:1:1 ratio to establish the timing of delivery of their fetus with severe early onset fetal growth restriction. Baseline maternal and fetal data were collected with a secure internet data entry page. Eligible patients were allocated through the study website. Allocation to groups was done with randomly sized blocks, stratified for gestational age (<29 weeks *vs* ≥29 weeks) and for participating centres. Concealment of the allocated monitoring regime was not possible, and clinicians responsible for the care of the women entered in the study and women themselves were aware of the treatment allocation. However, the paediatrician doing the follow-up examination was masked to follow-up assessment and data entry allocation.

Procedures

The intervention was delivery of the fetus according to the criteria of the randomisation group. In group one (cardiotocograph short-term variation [CTG STV]), the timing of delivery was assessed with the criteria for reduced STV (STV <3·5 ms at <29 weeks of gestation or STV <4 ms at ≥29 weeks of gestation). In cases where corticosteroids had been given for fetal lung maturity, no decision regarding delivery was made on the grounds of reduced variation from 24 h to 72 h after the first intramuscular dose because corticosteroid administration is known to lead to transient reduced STV. Umbilical artery Doppler measurements were taken in this group, but no waveform measurements of the ductus venosus were recorded.

In groups two and three, timing of delivery was based on abnormalities of the ductus venosus waveform. Women in group two delivered on the basis of early ductus venosus changes (pulsatility index >95th percentile [DV p95])[18] and women in group three delivered on the basis of late ductus venosus changes (A wave indicated no or reversed flow [DV no A]). Abnormal measurements should be confirmed by a second measurement at least 24 h later (measurements were repeated as often as needed).

Monitoring in all groups included umbilical artery Doppler and CTG was recommended at least once a week, but could be more frequent according to local policy. Safety net criteria for delivery applied to all patients irrespective of randomised group if the cutoff rescue value of STV for delivery based on CTG at 26·0 to 28·9 weeks less than 2·6 ms; if short-term variation less than 3 ms at 29·0 to 32·0; or if, irrespective of STV, spontaneous repeated persistent unprovoked decelerations on CTG occurred. Note that these STV limits are lower than those set for delivery in group one (CTG STV).

After 32 weeks, the decision to deliver was based on local criteria (for example abnormal cardiotocograph pattern, low short-term variation, or high umbilical artery Doppler pulsatility index or absent or reversed

	CTG STV	DV p95	DV no A	Total
Study population				
Entered into study	170	170	171	511
Excluded at short-term analysis*	4	3	1	8
Randomly allocated treatment	166	167	170	503
Fetal death	2 (1%)	4 (2%)	6 (4%)	12 (2%)
Neonatal death	10 (6%)	6 (4%)	11 (6%)	27 (5%)
Neonatal data missing	1 (1%)	0	0	1 (<1%)
Death <2 years age	1 (1%)	1 (1%)	0	2 (<1%)
Alive at 2 years	152 (92%)	156 (93%)	153 (90%)	461 (92%)
Lost or refused follow-up†‡	21 (14%)	25 (16%)	13 (8%)	59 (13%)
Assessed for neurodevelopment (primary outcome population)†	131 (86%)	131 (84%)	140 (92%)	402 (87%)
Bayley not feasible because of behaviour or impairment§	5 (4%)	3 (2%)	1 (1%)	9 (2%)
No Bayley test done; other information of child's condition used	7 (5%)	3 (2%)	4 (3%)	14 (3%)
Bayley second edition done	5 (4%)	9 (7%)	9 (6%)	23 (6%)
Bayley third edition done as per protocol	114 (87%)	116 (89%)	126 (90%)	356 (89%)
Demographic characteristics				
Maternal age, years	31 (5)	31 (6)	31 (6)	31 (6)
Caucasian ethnicity	135 (81%)	138 (83%)	150 (88%)	423 (84%)
Nulliparous	101 (61%)	103 (62%)	115 (68%)	319 (63%)
Body-mass index, kg/m²	25 (5)	25 (6)	24 (5)	25 (6)
Smoking during pregnancy	31 (19%)	24 (12%)	22 (13%)	77 (15%)
Diabetes	3 (2%)	3 (2%)	3 (2%)	9 (2%)
Chronic hypertension	14 (8%)	23 (14%)	19 (11%)	56 (11%)
Renal morbidity	5 (3%)	5 (3%)	1 (1%)	11 (2%)
Other medical disease	33 (20%)	29 (17%)	29 (17%)	91 (18%)
Any gestational hypertensive morbidity	98 (59%)	100 (60%)	105 (62%)	303 (60%)
Pre-eclampsia—HELLP	58 (35%)	68 (41%)	69 (41%)	195 (39%)
Gestational age at entry, weeks	29·3 (27·9–30·1)	29·1 (27·9–30·3)	29·1 (27·9–30·4)	29·1 (27·9–30·3)
Estimated fetal weight by ultrasound, g	868 (201)	887 (229)	887 (221)	881 (217)
Umbilical artery pulsatility index	2·0 (0·6)	2·0 (0·5)	2·0 (0·5)	2·0 (0·5)
Absent or reversed end diastolic flow	62 (37%)	70 (42%)	77 (45%)	209 (42%)
U/C ratio	1·4 (0·6)	1·5 (0·6)	1·5 (0·6)	1·5 (0·6)
Ductus venosus pulsatility index	0·6 (0·1)	0·6 (0·1)	0·6 (0·1)	0·6 (0·1)
Short-term variation fetal heart rate, ms	6·4 (1·9)	6·7 (2·4)	6·7 (2·2)	6·6 (2·2)

Data are n, n (%), mean (SD), or median (IQR). U/C ratio=umbilical artery pulsatility index to median cerebral artery pulsatility index ratio. CTG STV=cardiotocography short term variation. DV p95= early ductus venous changes (pulsatility index >95th percentile). DV no A=late ductus venous changes (A wave at or below baseline). *Two centres were excluded because they had not reported any outcomes. †Percentage of surviving infants. ‡Results include five children with severe congenital abnormalities for whom developmental information was not reported (two with trisomy 21, one with fragile X syndrome, one with 4-P-Q syndrome, and one with microcephaly). §Results include two children with severe congenital abnormalities with developmental information (one multiorgan syndrome with severe delay and one hypoplastic cerebellum with moderate delay).

Table 1: **Baseline characteristics**

For the **protocol** see http://www.thelancet.com/protocol-reviews/02PRT-34

umbilical flow) as ductus venosus waveforms were no longer taken into consideration.

The protocol recommended delivery if reversed umbilical artery end diastolic flow occurred at a gestation of 30 weeks or more or if there was absent umbilical artery end diastolic flow at 32 weeks.

The timing of maternal prophylactic steroid administration was according to local protocols. Two doses of intramuscular 12 mg betamethasone were given, the second 12–24 h after the first. Repeat doses of steroids were not recommended.

For all study patients, the intention was for delivery to occur within 24 h of the decision being made. If there was a protocol violation in timing of delivery, then the patient was analysed according to the original randomised group. We did an intention to treat analysis for all patients for whom we had data.

Outcomes

The primary outcome for this trial was survival without neurodevelopmental impairment at 2 years of age, corrected for prematurity. Surviving infants and their parents were invited to the follow-up clinics in each of the participating institutions. Development was assessed using the Bayley III Scales of Infant and Toddler Development.[20] Trained psychologists or paediatricians masked to study group provided the cognitive scales. Published normative scores[21] were used in all centres and instructions translated locally. The cognitive scale assesses abilities such as sensorimotor development, exploration, and manipulation, object relatedness, concept formation, memory, and simple problem solving. The cognitive outcome is reported as the composite cognitive scale with a normed mean of 100 and a SD of 15. For some children only the second edition of the Bayley Scales was available. To compensate for discrepancies between editions of the Bayley Scales, five points were added to Bayley II Mental developmental index (MDI) scores to correct.[22] If no Bayley test could be done because of impairments, the attending paediatrician was asked to fill in an estimate of cognitive delay (no delay, 3–6 months delay, or more than 6 months delay).

All infants had a formal neurological examination to establish the presence of cerebral palsy, which was classified using the Surveillance of Cerebral Palsy in Europe (SCPE) classification. The functional severity of cerebral palsy was scored using the Gross Motor Function Classification System (GMFCS).[23] Neurodevelopmental impairment was defined as a cognitive Bayley III score or corrected Bayley II mental development index score of less than 85 or an estimated cognitive delay of more than 3 months, cerebral palsy, with a GMFCS of more than 1, hearing loss needing hearing aids, or severe visual loss (legally certifiable as blind or partially sighted).

Apart from these neurosensory and developmental measures, medical history between first discharge home and age of assessment was recorded and anthropometry done (height, weight, and head circumference). Three hypotheses were tested for the primary outcome. First, the hypothesis that in preterm growth restricted fetuses, timing delivery when the fetal ductus venosus Doppler pulsatility index reaches the 95th percentile increases the rate of normal infant neurological outcome compared with delivery timing based on cardiotocograph fetal heart short-term variation alone. Second, the hypothesis that in preterm growth restricted fetuses, timing delivery when the fetal ductus venosus Doppler pulsatility index reaches a late stage of abnormality (A wave reaching the baseline) increases the rate of normal infant neurological outcome compared with delivery timing based on cardiotocograph fetal heart short-term variation alone. And third, the hypothesis that in preterm growth restricted fetuses, delaying delivery until the fetal ductus venosus Doppler pulsatility index reaches a late stage of abnormality (A wave reaching the baseline) increases the rate of normal infant neurological outcome compared with delivering when the fetal ductus venosus Doppler pulsatility index reaches the 95th percentile. The protocol was published on *The Lancet*'s website in 2004, with a revision to the primary outcome published in 2007); the primary outcome was revised to include developmental assessment using the Bailey Scales of Infant and Toddler Development (third edition) scale instead of the Griffiths Mental Development Scales.

	CTG STV (n=166)	DV p95 (n=167)	DV no A (n=170)	Total (n=503)
Any hypertensive morbidity	117 (70%)	124 (74%)	121 (71%)	362 (72%)
Preeclampsia—HELLP	80 (48%)	83 (50%)	88 (52%)	251 (50%)
Antihypertensive medication	80 (48%)	90 (54%)	92 (54%)	262 (52%)
Magnesium treatment	29 (18%)	24 (14%)	33 (19%)	86 (17%)
Antenatal corticosteroid	149 (90%)	156 (93%)	156 (92%)	461 (92%)
Interval to delivery days	7 (0·5–61)	7 (0·5–56)	9 (0·5–88)	8 (0·5–88)
Fetal death	2 (1%)	4 (2%)	6 (4%)	12 (2%)
Delivered using criteria off protocol at <32 weeks				
Fetal condition*	13 (8%)	19 (11%)	23 (14%)	55 (11%)
Maternal pre-eclampsia	17 (10%)	15 (9%)	22 (13%)	54 (11%)
Delivery indication ≥32 weeks, local protocol	46 (28%)	51 (31%)	50 (29%)	147 (29%)
Gestational age at delivery, weeks	30·6 (29·0–32·0)	30·7 (29·0–32·4)	30·7 (29·4–32·1)	30·7 (29·1–32·1)
Neonatal characteristics, liveborn	164 (99%)	163 (98%)	164 (96%)	491 (98%)
Birthweight, g	998 (288)	1036 (356)	1023 (320)	1019 (322)
Male sex	81 (49%)	77 (47%)	86 (52%)	244 (50%)
Apgar score <7 at 5 min	16 (10%)	14 (9%)	21 (13%)	51 (10%)
Umbilical arterial pH				
Data available	138 (83%)	131 (78%)	135 (79%)	404 (80%)
Median	7·26 (6·8–7·4)	7·26 (6·8–7·4)	7·26 (7·0–7·4)	7·26 (6·8–7·4)
<7·0	4 (3%)	1 (1%)	0 (0%)	5 (1%)

Data are n (%), mean (SD), or median (IQR). CTG STV=cardiotocography short term variation. DV p95=early ductus venous changes (pulsatility index >95th percentile). DV no A=late ductus venous changes (A wave at or below baseline). *Results include clinical suspicion of impending fetal compromise.

Table 2: **Obstetric data after study entry and neonatal data at delivery**

The secondary outcome was a composite of adverse neonatal outcome defined as fetal or postnatal death (between trial entry in-utero and discharge home from neonatal services) or one or more of the following severe morbidities: bronchopulmonary dysplasia, severe germinal matrix cerebral haemorrhage (GMH; intraventricular haemorrhage with dilation of the lateral ventricles [grade 3] or intraparenchymal haemorrhage [grade 4]),[24] cystic periventricular leukomalacia,[25] proven neonatal sepsis, or necrotising enterocolitis.[26] Bronchopulmonary dysplasia was defined as a need for supplemental oxygen at 36 weeks' postmenstrual age, sepsis as positive blood or liquor culture needing treatment with antibiotics, and necrotising enterocolitis as the presence of pneumatosis or perforation on radiograph or disease identified by laparotomy. Neonatal data were extracted from clinical records and entered directly into the website study database.

Maternal hypertension was defined as a blood pressure of more than 140/90 mm Hg and proteinuria as more than 0·3 g/L on 24 h collection of urine. Hypertensive disorders were defined as chronic if hypertension existed at or before 20 weeks' gestation or needed treatment before pregnancy or as gestational if the onset of hypertension occurred after 20 weeks in the absence of proteinuria. Pre-eclampsia was defined as hypertension and proteinuria. HELLP syndrome was defined as alanine aminotransferase concentrations of more than 70 IU/L with platelet concentrations of less than 100×10^9 platelets per L and with evidence of haemolysis from blood film or lactate dehydrogenase concentrations of more than 600 IU/L.

To ensure quality control of Doppler measurements, prior to study commencement, investigators from each unit submitted ductus venosus images for blinded scoring by two members of the quality control group. When scores were lower than 4 or 6 for submitted images, repeat image submissions were needed.

To ensure quality control of short-term variation calculation, all patients underwent cardiotocograph monitoring, done using equipment that allows waveform analysis with Oxford Sonicaid 8002 or equivalent Dawes-Redman software based algorithm. The recordings were at least 45 min in duration.

From all centres at least one paediatrician or psychologist participated in a training course for Bayley III assessment and measurements were subsequently validated by an independent psychologist to reach more than 90% item agreement before commencing testing. These courses were organised before the first child was 2 years of age. Complete Bayley score forms were checked by a paediatrician not involved in any of the assessments.

Study data were entered using a secure website by the investigators. Investigators could only view data from cases randomised in their own centre. Developmental outcome data were entered in a separate database under supervision of an independent paediatrician not involved in the treatment of the children.

Statistical analysis

To detect a difference in the primary outcome (survival without neurodevelopmental impairment), from 50% in the controls to 66·6% in either of the intervention groups with 80% power at 5% statistical significance; the study needed assessment of 450 infants (150 in each group). We assumed a loss to follow-up of 10% on the basis of discussions with other investigators and therefore aimed to recruit 500 women.

The statistical analysis was planned before treatment allocation was revealed. Comparison of the primary outcome between the groups was planned by 6-group χ^2 analysis. If this analysis gave a statistically significant result then post-hoc two by two analyses were done between the three groups to explore intergroup differences. Data analysis was done with IBM SPSS version 20 (NY, USA).

	CTG STV (n=166)	DV p95 (n=167)	DV no A (n=170)	Total (n=503)
Fetal death no intervention*	2 (1%)	1 (1%)	2 (1%)	5 (1%)
Unexpected death†	0	3 (2%)	4 (2%)	7 (1%)
Livebirth	164 (99%)	163 (98%)	164 (96%)	491 (97%)
Neonatal death	10 (6%)	6 (4%)	11 (7%)	27 (6%)
Death due to congenital abnormality	0	0	2 (1%)	2 (1%)
Overall mortality	12 (7%)	10 (6%)	17 (10%)	39 (8%)
Neonatal data missing	1 (1%)	0	0	1 (<1%)
Survival at discharge	153 (92%)	157 (94%)	153 (90%)	463 (92%)
Neonatal morbidity				
Received mechanical ventilation	72 (44%)	63 (39%)	69 (42%)	204 (42%)
Received supplemental oxygen	98 (60%)	96 (59%)	103 (63%)	297 (61%)
BPD >28 days	32 (20%)	28 (17%)	31 (19%)	91 (19%)
BPD >36 weeks‡	16 (10%)	17 (10%)	16 (10%)	49 (10%)
Sepsis (proven)‡	33 (20%)	31 (19%)	23 (14%)	87 (18%)
NEC pneumatosis‡	3 (2%)	3 (2%)	1 (1%)	7 (1%)
Perforation‡	2 (1%)	2 (1%)	5 (3%)	9 (2%)
GMH grade III or IV‡	0 (0%)	4 (2%)	8 (5%)	12 (2%)
PVL grade II or III‡	1 (1%)	2 (1%)	2 (1%)	5 (1%)
Death following severe morbidity†	10 (6%)	6 (4%)	9 (5%)	25 (5%)
Adjusted age of survivors at discharge, days§	−9 (−39 to 170)	−7 (−37 to 99)	−10 (−38 to 169)	−9 (−39 to 170)
Survival following severe neonatal morbidity (% of survivors)	38 (25%)	42 (27%)	38 (25%)	118 (25%)
Survival without severe neonatal morbidity (% of all study entrants)	115 (69%)	115 (69%)	115 (68%)	345 (69%)

Data are n (%) or median (IQR). BPD=bronchopulmonary dysplasia. NEC=necrotising enterocolitis. GMH=germinal matrix haemorrhage. PVL=cystic periventricular leucomalacia. CTG STV=cardiotocography short term variation. DV p95=early ductus venous changes (pulsatility index >95th percentile). DV no A= late ductus venous changes (A wave at or below baseline). *Parents declined delivery despite this being indicated according to study criteria. †Fetal death not anticipated between scheduled follow-up appointments. ‡Components of severe morbidity: BPD (supplemental oxygen at 36 weeks' gestational age), GMH (grade III or IV), PVL (grade II or III), NEC, or proven sepsis. §Adjusted age at discharge calculated from expected date of delivery at 40 weeks' gestation.

Table 3: **Short-term fetal and neonatal outcomes**

	CTG STV (n=166)	DV p95 (n=167)	DV no A (n=170)	Total (n=503)
Infants with known outcome*	144 (87%)	142 (85%)	157 (92%)	443 (88%)
Survivors assessed for neurodevelopment†	131 (86%)	131 (84%)	140 (92%)	402 (87%)
Survival without impairment	111	119	133	363
Percentage of assessed surviving infants‡	85%	91%	95%	90%
Percentage of all infants with known outcome§	77%	84%	85%	82%
Components of abnormal outcome				
Perinatal or infant death before 2 years*¶	13 (8%)	11 (7%)	17 (10%)	41 (8%)
Impairments at 2 years¶	20 (15%)	12 (9%)	7 (5%)	39 (10%)
Cerebral palsy (GMFCS >grade 1)¶	5 (4%)	1 (1%)	0 (0%)	6 (1%)
Neurosensory impairment¶	3 (2%)	1 (1%)	1 (1%)	5 (1%)
DQ <85¶	13 (10%)	8 (6%)	5 (4%)	26 (6%)
No test result, but reported impaired¶	7 (5%)	3 (2%)	1 (1%)	11 (3%)

Data are n (%). GMFCS=Gross Motor Function Classification System. DQ=developmental quotient. MDI=mental developmental index. *Percentage of all infants, including infants with adjusted Bayley 2 MDI scores (MDI + 5 points). †Percentage of surviving infants. ‡Linear association, p=0·004; χ^2 DV no A versus CTG STV, p=0·005. §Linear association, p=0·09; χ^2 DV no A versus CTG STV, p=0·09. ¶Percentage of assessed infants.

Table 4: **Primary outcome at 2 years corrected age**

See Online for appendix

This study is registered with ISRCTNRegistry.com, number 56204499.

Role of the funding source

The funder of the study in each country had no role in the study design, data collection, data analysis, and interpretation of data, or in writing the report. The corresponding author had full access to all the data from the study and had final responsibility for the decision to submit for publication.

Results

511 women were included in the study, of whom eight were subsequently excluded because they were entered in two centres from which no delivery or outcome data could be obtained (figure 1, table 1). 461 infants (92%) were alive at 2 years and complete follow-up data were available from 402 (87%; table 1). At delivery, 362 (72%) of 503 women had a hypertensive condition (table 2). Antenatal corticosteroids were given to 461 (92%) of women (table 2).

The median gestation at delivery was 30·7 weeks (IQR 29·1–32·1) and mean birthweight was 1019 g (SD 322 g; table 2). 55 (11%) of 503 were delivered because of fetal condition assessed differently from the study protocol, which could be based on visual assessment of the cardiotocograph in the absence of fetal heart rate short term variation analysis, clinical signs of placental abruption, or any other clinical suspicion of fetal condition abnormality by the attending obstetrician. 54 (11%) of 503 babies were delivered because of maternal condition (severe pre-eclampsia) and 147 (29%) at or after 32 weeks based on local criteria, indicating delivery to be necessary.

491 (98%) of babies were liveborn, and 463 (92%) of 503 survived until reaching their first discharge home. 345 (69%) of 503 all infants survived without severe neonatal morbidity (table 3). We identified no difference in baseline variables (tables 1, 2) or short-term outcomes (table 3) between the three study groups.

Two infants died after discharge before the age of 2 years, both from sequelae of their neonatal illness. Of the remaining 461 survivors at 2 years, 59 (13%) did not participate in follow-up. The gestational age at birth, birthweight, and short-term morbidity of infants of non-participants were similar to those of children that attended follow-up (appendix).

At 2 years of age, corrected for prematurity, 402 children were assessed as part of the study (after exclusion of 8 children with no data); 356 children completed the Bayley III cognitive test, 23 had a Bayley II mental development index recorded, and a further 23 children did not complete a formal assessment but we classified their outcome based on reliable information about their neurological and developmental normality or abnormality. Nearly half of the children in this last group attended testing but were unable to complete the test because of behaviour or neuromotor impairments.

Of the 443 infants with known outcomes, 111 (77%) of 144 infants who were allocated to the CTG STV survived without impairment compared with 119 (84%) of 142 allocated to the DV p95 group and 133 (85%) of 157 allocated to the DV no A group (p_{trend}=0·09; table 5, appendix). A small number of deaths occurred in each group before the corrected age of two years (2 deaths after discharge included): 13 (8%) of 166, 11 (7%) of 167, and 17 (10%) of 170; p_{trend}=0·35 (table 2). By contrast, impairment in survivors was recorded in 20 (15%) of 131 allocated to CTG STV, 12 (10%) of 119 allocated to DV p95, and seven (5%) of 133 allocated to DV no A (p_{trend}=0·004). Post-hoc comparison showed improved outcome in survivors for DV no A compared with the CTG STV (p=0·005; appendix). Prevalence of the individual components of the composite primary outcome (table 4) did not differ but individual components were of low frequency.

A further post-hoc breakdown of the components of the outcome assessment is shown in table 5; the severity of any outcome did not differ between allocated groups. Mean Bayley III cognitive scores and growth measures were below the anticipated population means, indicating preterm birth.

Enrolment to the study was stratified into categories of less than 29 weeks or more than 29 weeks of gestation. For babies entered before 29 weeks, mortality was 31 (14%) of 227 compared with only ten (4%) of 276 in the higher gestational age group. However, the proportion of surviving infants with abnormal neurodevelopment of those with known outcome (n=443) was similar in both gestational age groups (17 [8%] of 202 and 22 [9%] of 241;

figure 2). These differences were not statistically significant. The interval between study entry and delivery between the three randomisation groups did not differ (table 2, appendix).

We addressed the issue of missing data using multiple imputation to generate 14 imputation sets using all the variables described in tables 1–5. Pooled analysis of the imputation sets did not show significant changes in terms of neurodevelopmental outcome at 2 years in survivors.

Discussion

To our knowledge, this study is the first multicentre, randomised management trial to report outcomes in a large cohort of women whose fetuses had early onset growth restriction, being both small for gestational age and with evidence of fetoplacental insufficiency based on raised umbilical artery Doppler impedance (panel). Women were enrolled before giving birth and managed according to one of three prespecified management strategies. The proportion of infants who survived without neurodevelopmental impairment between the three groups did not differ; however, the direction of effect in mortality across the three groups differed from the direction of effect in impairment in survivors such that neurodevelopmental impairment was least frequent in survivors randomly assigned to the DV no A group compared with those in the CTG STV group (p_{trend} across the three groups of 0·004). Thus, deferring of delivery until the ductus venosus A wave has disappeared (unless delivery is mandated earlier by the CTG safety net criteria) compared with delivery based only on CTG STV possibly changes results in a small excess of antenatal deaths but also in substantially improved survival without impairment at 2 years of age, corrected for prematurity.

As might be expected, perinatal mortality was dependent on the gestational age at enrolment (figure 2) but the proportion with abnormal neurological outcome was similar within the trial groups independently of gestation. Delivery based on CTG STV was associated with the lowest proportion of survivors without impairment, irrespective of whether enrolment occurred before or after 29 weeks.

Allocation in this trial resulted in three well balanced groups in terms of important factors such as gestational age, birthweight, infant sex, and hypertensive disorder in the mother. The interval between enrolment and delivery was similar between the three groups implying that reported differences in outcome were unlikely to be due only to delaying delivery in one group. Those assessing outcome at 2 years were masked to trial groups and used a single scale from the Bayley III scales as the cognitive assessment because this was not language dependent and avoided bias from using a test that was not standardised in all languages, although instructions to the child needed translating. Furthermore, 96% of the assessments were done using assessors validated to a high standard in the administration of the Bayley III cognitive scale; for those few children in whom the older second edition of the scale was used, mental development index scores were adjusted in a prespecified manner to compensate for the higher scores seen when using the Bayley III scales. Neurological assessment and classification of neuromotor outcome was also done using the same assessment process and classification procedure agreed during training of assessors. All outcome information was checked for accuracy by an independent paediatric expert before entry into the central study database. The follow-up rate was high for such a large and complex trial. Characteristics of infants lost for follow-up were similar to those that were reviewed and the results were checked for potential bias using imputation techniques.

	CTG STV (n=166)	DV p95 (n=167)	DV no A (n=170)	Total (n=503)
Survivors at 2 years	152 (92%)	156 (93%)	153 (90%)	461 (92%)
Survivors assessed for neurodevelopment	131 (86%)	131 (84%)	140 (92%)	402 (87%)
No Bayley score, but other information available	12 (9%)	6 (5%)	5 (4%)	23 (6%)
Bayley third edition cognitive as per protocol	114 (87%)	116 (89%)	126 (90%)	356 (89%)
Bayley second edition	5 (4%)	9 (7%)	9 (6%)	23 (6%)
Cognitive composite score*	99 (12)	98 (12)	100 (12)	99 (12)
<75	1 (1%)	2 (2%)	2 (1%)	5 (1%)
75–84	12 (9%)	6 (5%)	3 (2%)	21 (5%)
85–94	25 (21%)	28 (21%)	30 (21%)	83 (21%)
≥95	81 (68%)	89 (68%)	100 (71%)	270 (67%)
Neurosensory outcome data				
Cerebral palsy (GMFCS >grade 1)	5 (4%)	1 (1%)	0	6 (1%)
Motor function: GMFCS† grade 1	1 (1%)	4 (3%)	1 (1%)	6 (1%)
Grade 2	2 (2%)	0	0	2 (<1%)
Grade 3	3 (2%)	0	0	3 (1%)
Grade 4	0	0	0	0
Grade 5	0	1 (1%)	0	1 (<1%)
Normal vision‡	113 (97%)	117 (94%)	130 (97%)	360 (96%)
Impaired (refractive error or squint)	3	6	3	12 (3%)
No useful vision	1	1	1	3 (1%)
Normal hearing‡	118 (98%)	126 (98%)	135 (100%)	379 (98%)
Loss corrected with aids (moderate or severe)	1	2	0	3 (1%)
Loss not corrected with aids (profound)	3	0	0	3 (1%)
Normal communication‡	94 (81%)	110 (89%)	127 (94%)	331 (89%)
Vocabulary <5 words	22 (19%)	12 (11%)	8 (6%)	42 (11%)
No communication with words or signs	0	1	0	1 (0%)
Growth§				
Height mean *Z* score	−0·34 (1·14)	−0·38 (1·03)	−0·26 (1·11)	−0·32 (1·09)
Weight mean *Z* score	−1·39 (1·28)	−1·30 (1·86)	−1·35 (1·31)	−1·35 (1·51)
Head circumference mean *Z* score	−0·49 (1·12)	−0·56 (1·11)	−0·40 (1·07)	−0·48 (1·10)

GMFCS=Gross Motor Function Classification System. MDI=mental developmental index. *Data includes adjusted Bayley 2 MDI scores (MDI + 5 points). †Gross Motor Function Classification System.[21] ‡Information not available in all cases. §Calculated using American Centers for Disease Control and Prevention standards.

Table 5: **Developmental and neurosensory outcomes in survivors to 2 years**

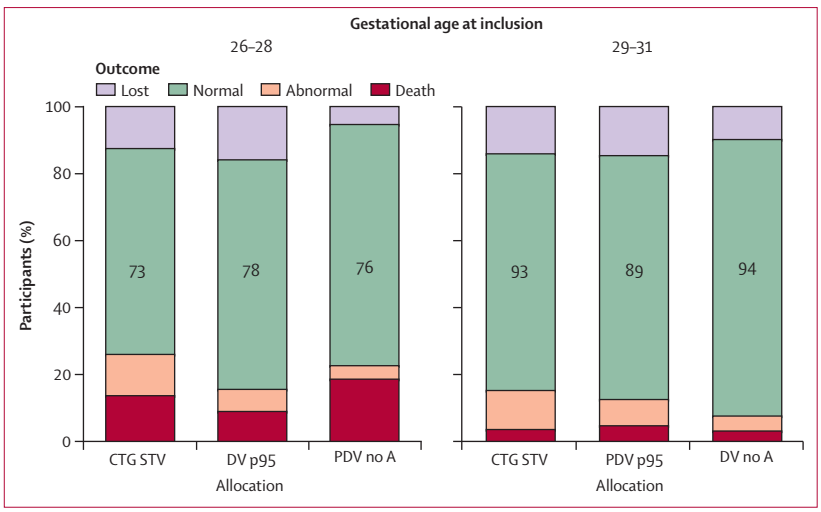

Figure 2: **Outcome for all cases**
The bars present the percentages for the three allocation groups, separately for those cases included before 29 weeks and for those at 29 weeks or later. The total number of cases for the subgroups is presented in the middle of each bar.

One major challenge in doing a trial in this area is the difficulty in reliance on one marker to trigger delivery. Delivery was indicated for maternal indication in 54 (11%) of 503 with severe pre-eclampsia or HELLP syndrome. Many women had hypertension on enrolment (303 [60%] of 503) and this percentage increased (362 [72%]) by the time of delivery. In 55 (11%) women, the diagnosis of fetal distress was not based on study protocol, but on visual CTG assessment because computerised assessment was not available at that time, or there was insufficient time for a complete computerised assessment because of acute deterioration of fetal condition. In the remaining women, the delivery was indicated as specified in the protocol, although in about half of these women the safety-net criteria were used. Safety net indicated delivery was most prevalent in the late ductus venosus group (DV no A; 33%), less so in the early ductus venosus group (DV p95; 23%), and least in the CTG STV group (15%). Further exploratory analysis is needed to understand the effects of per protocol and safety net indications on outcomes. Although the criteria for delivery were precisely described in our protocol, inevitably, in a large clinical management trial, deviations from protocol did occur.

Only one previous trial that randomly allocated delivery timing in fetal growth restriction has been done (GRIT). GRIT recruited a similar number of women between 1996 and 2002. By contrast with the clear delivery indications used in TRUFFLE, GRIT allocated women to immediate or delayed delivery based on clinical judgment using a Bayesian design. GRIT reported that 17% of their cohort died or had severe neuromorbidity compared with 18% in TRUFFLE but the median gestation at delivery for GRIT was more than 1 week later than in babies in this TRUFFLE study.[6,7] Outcomes between the two GRIT trial groups at 2 years or at school age did not differ and thus GRIT did not give any specific clues as to the optimum timing or indications for delivery. Entry to GRIT was predicated on the attending obstetrician being in equipoise about delivery. The use of clear entry and delivery criteria in TRUFFLE resulted in a more homogeneous group of babies recruited from clinicians in 20 units who had shared training and validation for their fetal assessment techniques to achieve a standardised approach to management in the prenatal period. The TRUFFLE study was targeted at a lower gestational age, where exact timing of delivery is probably more important. Furthermore, the Bayley III assessment is more recent and better standardised compared with the Griffiths Scales used in GRIT.

We have previously reported TRUFFLE neonatal cohort outcomes based upon the gestational age at enrolment. The TRUFFLE neonatal cohort is a high-risk group with 8% mortality and in whom 25% met criteria for severe neonatal morbidity.[14] Other studies have reported very high rates of bronchopulmonary dysplasia[3] and poorer 2 year neurodevelopmental outcomes[27] in preterm fetal growth restriction; these findings are not borne out by the prospectively collected TRUFFLE data. Furthermore, when analysed by randomised group (table 3), the neonatal outcomes (as death or severe neonatal morbidity or combined) did not differ between the three groups. These data are by contrast with a previous case series of severe fetal growth restriction where substantially higher rates of death or neonatal morbidity were associated with an absent or reversed A wave in the ductus venosus.[2]

We were also encouraged by the low prevalence of neuroimpairment in this cohort. Outcomes for very preterm fetuses with identified fetal growth restriction in TRUFFLE seem to be much better than appreciated previously; 82% of children with known outcome survived without impairment. We had predicted much higher rates of poor outcome in designing TRUFFLE; however, good outcomes could possibly be more frequent in those populations entered into randomised trials than in those receiving standard care. In this case, delivery was predicated on specific criteria and clinical monitoring was very frequent. Comparison with other studies is difficult as the TRUFFLE cohort was identified at a very low gestational age. In GRIT, 83% of infants survived without disability but deaths were twice as frequent as impairment, which was defined using an older developmental test that tended to produce much higher scores in modern populations, and thus might have been an underestimate. By contrast, data from a cohort of 113 women with fetal growth restriction delivered by abnormal biophysical profile or maternal condition between 2000 and 2008, with a similar gestational age at delivery to TRUFFLE, identified 26% mortality and 30% of survivors with abnormal neuromotor outcomes;[28] only 44% survived without impairment. A randomised controlled trial of volume expansion in preeclampsia or gestational hypertension[29] included 210 women in

2001–03, delivery was at an average of 32 weeks, and the mean birthweight was 1280 g, 90% of infants were small for gestational age. Perinatal mortality was 12% and at 1 year, and 74% survived with no impairment.

Assessment of children at later ages might be more accurate to identify the range of impairments associated with preterm birth and with fetal growth restriction. Follow-up at school age for the GRIT trial was undertaken but problems with assessment of populations educated in different systems and in different languages and the lack of population availability for follow-up in many countries precluded a high follow-up rate.[8] Around 80% of survivors had known outcome and outcomes between the study groups did not differ. Follow-up of a small cohort of children born after fetal growth restriction identified and monitored with Doppler ultrasound has shown significant cognitive deficits compared with gestation matched appropriately grown babies and term controls.[30] Thus, the optimistic outcomes we have reported might underestimate the burden of impairment seen in middle childhood when the children are in education.

We showed no significant difference in survival without neurodisability at 2 years using three defined triggers for delivery. The primary outcome is, however, a composite of both death and neurodisability. At the time of study inception, we had not anticipated that the two components of the composite primary outcome might diverge: a small non-significant increase in deaths in the DV no A group was offset by a statistically significant reduction in neurodevelopmental impairment in the surviving infants in that group. In view of the small number of perinatal deaths, statistical modelling of the contributory factors is not possible. Nevertheless, the difference (albeit not significant) in perinatal mortality between the CTG STV and DV groups is reduced when lethal congenital abnormality and non-intervention is excluded (table 3). Furthermore, in six of seven unexpected fetal deaths the CTG immediately before death was above the CTG STV study group intervention cut-off, hence they might have occurred had the cases been included in the CTG STV group. The deaths could not have been directly attributed to allocation to one of the ductus venosus groups in any of these cases. In this context, the three-fold incidence of neuroimpairment was significantly lower in surviving infants (5% *vs* 15%) where delivery was based on late ductus venosus changes compared with CTG STV.

Eligibility for inclusion required that delivery of the fetus was not imminent; we randomised 94% of women eligible constituting about 0·2% of all deliveries in participating units during the study duration, which compares to an incidence of 0·4% for fetal growth restriction with or without pre-eclampsia delivery irrespective of degree of urgency before 32 weeks reported in a prospective, observational, multicentre study of uterine artery Doppler screening.[31] Hence, the findings of our study can be generalised to women presenting to fetal maternal and obstetric services in which a diagnosis of very preterm fetal growth restriction is made and there is still time to plan a strategy for fetal monitoring. Implementation of the protocol that we describe needs access both to computerised CTG equipment to allow STV to be calculated and the expertise to do fetal ductus venosus Doppler measurements in a reproducible way. Both monitoring modalities have become integral to the UK guidance for the management of the small-for-gestational-age baby.[32]

Although these findings cannot necessarily be generalised to later gestations, a conservative approach to timing delivery in waiting for late ductus venosus changes—unless severe CTG changes defined as safety net occur first—is associated with a more favourable 2 year outcome in early onset fetal growth restriction.

***Panel:* Research in context**

Systematic review

Before developing the protocol, we did a systematic review to search for randomised trials assessing timing of delivery based on antenatal monitoring strategies, in growth restricted or small for gestational age (SGA) preterm fetuses. We searched Medline (Ovid) from its inception to March 31, 2003 with the keywords "randomised", "preterm", "growth restriction" or "small for gestational age", or "SGA" and "fetal" or "intrauterine". The search was updated in July 1, 2014, after completion of the study. No language restrictions were applied. From the 44 citations retrieved, only one randomised trial assessed timing of delivery in fetal growth restriction before 36 weeks: the GRIT study.[6] This study showed that when the clinician was in equipoise over delivery timing in fetal growth restriction no differences in short or long-term outcome between immediate and delayed delivery existed.

Interpretation

The outcomes of antenatally diagnosed very preterm growth restriction are better than assumed with 92% of infants surviving from the time of diagnosis to discharge home. Furthermore, although survival without neuroimpairment did not differ between groups, neuroimpairment at 2 years in our study was less frequent in the infants of women randomly assigned to delivery based on late ductus venosus changes compared with those randomly assigned to delivery based on computerised cardiotocograph (CTG) changes. Previous observational and retrospective studies have suggested that a worse outcome is associated with late ductus venosus changes and these studies have informed management. By contrast, our findings support waiting for late ductus venosus changes before delivery because no increase in hypoxia mediated deaths occurred and neuroimpairment is less frequent than when delivery is based on computerised CTG changes.

Contributors

CCL, NM, AvW-L, BA, CMB, CB, JBD, SC, AD, JJD, TF, EF, WG, KH, PM, EO, ATP, DS, KTMS, BT, TT, AV, GHAV, and HW met at least annually in 2002–14 and were all involved in the inception, design, and conduct of the study. CCL coordinated meetings and circulated drafts of the manuscript, which all authors contributed to HW coordinated data collection and analysis and prepared the tables. NM and AvW-L led the paediatric follow-up design of the study and AvW-L was the independent paediatrician who assessed the paediatric outcome forms.

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Declaration of interests

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