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Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE)

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ABSTRACT

Objectives *Few data exist for counseling and perinatal management of women after an antenatal diagnosis of early-onset fetal growth restriction. Yet, the consequences of preterm delivery and its attendant morbidity for both mother and baby are far reaching. The objective of this study was to describe perinatal morbidity and mortality following early-onset fetal growth restriction based on time of antenatal diagnosis and delivery.*

Methods *We report cohort outcomes for a prospective multicenter randomized management study of fetal growth restriction (Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE)) performed in 20 European perinatal centers between 2005 and 2010. Women with a singleton fetus at 26–32 weeks of gestation, with abdominal circumference < 10th percentile and umbilical artery Doppler pulsatility index > 95th percentile, were recruited. The main outcome measure was a composite of fetal or neonatal death or severe morbidity: survival to discharge with severe brain injury, bronchopulmonary dysplasia, proven neonatal sepsis or necrotizing enterocolitis.*

Results *Five-hundred and three of 542 eligible women formed the study group. Mean ± SD gestational age at diagnosis was 29 ± 1.6 weeks and mean ± SD estimated fetal weight was 881 ± 217 g; 12 (2.4%) babies died* in utero. *Gestational age at delivery was 30.7 ± 2.3 weeks, and birth weight was 1013 ± 321 g. Overall, 81% of deliveries were indicated by fetal condition and 97% were by Cesarean section. Of 491 liveborn babies, outcomes were available for 490 amongst whom there were 27 (5.5%) deaths and 118 (24%) babies suffered severe morbidity. These babies were smaller at birth (867 ± 251 g) and born earlier (29.6 ± 2.0 weeks). Death and severe morbidity were significantly related to*

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gestational age, both at study entry and delivery and also with the presence of maternal hypertensive morbidity. The median time to delivery was 13 days for women without hypertension, 8 days for those with gestational hypertension, 4 days for pre-eclampsia and 3 days for HELLP syndrome.

Conclusions *Fetal outcome in this study was better than expected from contemporary reports: perinatal death was uncommon (8%) and 70% survived without severe neonatal morbidity. The intervals to delivery, death and severe morbidity were related to the presence and severity of maternal hypertensive conditions.*

INTRODUCTION

The timing of delivery of a baby with early preterm fetal growth restriction (FGR) poses the obstetrician with a serious dilemma. To deliver early potentially exposes the neonate to morbidity associated with immaturity, whereas to deliver too late risks serious additional morbidity secondary to critical fetal hypoxia with a worsening of the fetal condition. There is little information in relation to risk of intrauterine fetal death or neonatal prognosis as most studies comprise small or retrospective cohorts of babies and hence the risks of poor outcome are not easily generalizable at the time of antenatal diagnosis of early-onset FGR. Furthermore, those studies that describe perinatal mortality and morbidity use obstetric and neonatal parameters that are present immediately before birth[1–3], an obvious confounding attribute of which is that the parameters themselves may dictate the clinical urgency for delivery. At the time the diagnosis of early preterm FGR is made, the gestational age at delivery and birth weight are, of course, still unknown as the interval between diagnosis and delivery cannot be predicted.

The technique most frequently used for fetal surveillance and assessment of necessity to deliver is cardiotocography (CTG). Assessment of the fetal heart rate, variability and the presence of accelerations and decelerations is performed visually and fetal condition is classified semi-objectively as 'reassuring' or 'not reassuring'. Computerized analysis of the signal provides an objective assessment, expressed as short-term variability (STV)[4–7]. Although umbilical artery Doppler clearly identifies an 'at-risk' fetus, changes in the ductus venosus Doppler waveform may have a better association with subsequent neonatal morbidity than that based on umbilical Doppler abnormality in early preterm FGR[2,3,8,9].

We recruited women at very preterm gestations to a European multicenter study on FGR, in which management was delivery based on the results of ductus venosus Doppler or CTG-STV monitoring according to one of three randomized arms and the primary outcome was infant development at the age of 2 years. When designing the study, the Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) investigators had detailed discussions regarding the ethical consequences of the study and hence the three management protocols were designed in such a way that differences in short-term outcome between the groups were highly unlikely[10].

To facilitate counseling and inform clinical management, we explored the association between obstetric characteristics and short-term perinatal outcomes in women who were included in the TRUFFLE study. As long-term follow-up is not yet complete, randomization allocation has not been unblinded and therefore is not disclosed. The study cohort data analysis is for short-term perinatal outcome and therefore focuses on the questions most pertinent to a diagnosis of FGR. These are: how long will it take until the baby has to be delivered, what factors are important in prolonging gestation and what is the risk of severe neonatal morbidity after delivery?

METHODS

Setting

This was a prospective multicenter unblinded management trial conducted in 20 European tertiary-care centers with a fetal medicine unit, in five countries (Austria, Germany, Italy, The Netherlands and the UK). Patients were included from 2005 to 2010, but not all hospitals started recruiting at the same time.

Participants

Eligible participants were women over 18 years of age capable of giving informed consent, with a singleton pregnancy at 26 + 0 to 31 + 6 weeks of gestation diagnosed with FGR. This was defined as fetal abdominal circumference below the 10th percentile according to local standards and abnormal umbilical artery Doppler pulsatility index (PI) above the 95th percentile based on local standards, irrespective of the presence of absent or reversed end-diastolic flow. In all cases, the estimated fetal weight was > 500 g[11]. Short-term variation after 1 h of CTG tracing had to be > 3.5 ms at 26–28 weeks and > 4 ms at 29–31 weeks with ductus venosus PI < 95th percentile[12]. Gestational age was assigned from measurement of crown–rump length prior to 14 weeks or biparietal diameter between 14 + 0 and 21 + 6 weeks. Women were not eligible if there was known, planned or impending delivery, major fetal structural abnormality or invasive prenatal testing showing fetal karyotype abnormality.

The intervention was delivery of the fetus according to the criteria of the randomization group, determined by the CTG criteria of reduced short-term variation, early abnormalities of the ductus venosus waveform (PI > 95th centile) or late ductus venosus changes (absent or negative A-wave). In all groups, delivery could be undertaken based on a maternal indication, such as severe pre-eclampsia, or clear CTG abnormalities, such as recurrent late decelerations. After 32 + 0 weeks, the timing of delivery was according to local management protocol. For all patients, the intention was to deliver within 24 h

after the decision to deliver was made with timing of maternal steroids according to local protocols. Repeat doses of steroids were never given.

Outcome variables

The primary outcome for this study was a composite of fetal or postnatal death (between trial entry *in utero* and first discharge home from neonatal services) or one or more of the following severe morbidities: bronchopulmonary dysplasia, severe cerebral germinal matrix hemorrhage (intraventricular hemorrhage with dilation of the lateral ventricles (Grade III) or intraparenchymal hemorrhage (Grade IV)), cystic periventricular leukomalacia, proven neonatal sepsis or necrotizing enterocolitis. Bronchopulmonary dysplasia was defined as a need for supplemental oxygen to maintain oxygen saturations of >90% at 36 weeks postmenstrual age; sepsis as positive blood culture requiring treatment with antibiotics; and necrotizing enterocolitis as the presence of pneumatosis or perforation on X-ray 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 blood pressure > 140/90 mmHg and proteinuria as > 0.3 g/L on a 24-h collection of urine. Hypertensive disorders were defined as chronic if hypertension existed prior to 20 weeks' gestation or required treatment prior to 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 > 70 iu/L with platelets $< 100 \times 10^9$/L and with evidence of hemolysis from blood film or lactate dehydrogenase (LDH) > 600 U/L.

Statistical methods

Groups were compared two-sided for statistical significance by ANOVA, the Mann–Whitney *U*-test or Pearson's chi-square test, as appropriate. The association of demographic, clinical and diagnostic parameters at study inclusion with the composite endpoint was first explored by univariate analysis. Those parameters that reached statistical significance in univariate analysis were entered in a multivariate logistic regression analysis to adjust for association between parameters and to calculate odds ratios (ORs). The interval between inclusion and delivery was explored by Kaplan–Meier analysis for comparison of different risk parameters. Logistic regression analysis was started with all parameters in the model, and the probability for removal from the model was set at 0.1. Statistical calculations were performed using Statistical Package for the Social Sciences (SPSS program, version 20.0; IBM Corp., New York, NY, USA).

Research governance

These data are reported according the STROBE statement for reporting cohort studies[13]. TRUFFLE was ratified by the Ethics Committees of all participating units, and all patients gave written consent for study inclusion. The protocol underwent review by the Lancet[14] and was published online in 2003 with an amendment published in 2007 after revision of the primary outcome: for the randomized study, we estimated that 562 women needed to be recruited to allow 450 infant assessments at 2 years of age. The randomized trial was registered with the International Standard Randomized Controlled Trial Number Register (ISRCTN56204499)[15]. An independent Data Monitoring Committee reviewed data for patient safety and performed interim analyses for efficacy and futility.

RESULTS

Five-hundred and eleven women were recruited of 542 eligible for study inclusion. Thirty-one women were assessed as eligible for the study but were not entered. For eight participants in two centers, baseline and follow-up obstetric and neonatal outcome data were either substantively incomplete or absent, despite all attempts at contact; these two centers were excluded from the analysis. The study cohort therefore comprised 503 women and their fetuses from 20 centers. Demographic and baseline obstetric characteristics of the women recruited are shown in Table 1. In one case, neonatal, but not obstetric, data were missing. Maternal and neonatal outcome data are presented in Table 2.

Antenatal fetal death occurred in 12 (2.4%) cases. In five of these, the parents decided against intervention or withdrew from medical treatment (median gestational age at inclusion 27 + 2 weeks; range 26 + 1 to 29 + 1); estimated fetal weight 707 g (599–947 g). The fetal deaths were unexpected in the other seven (1.3%) cases, in one following placental abruption.

Four-hundred and ninety babies were liveborn. All deliveries were medically indicated and 81% were for fetal indication. Twenty-seven (5.5%) infants died during the original neonatal admission before they could be discharged home for the first time; in two of these, death was caused by an antenatally undiagnosed lethal congenital abnormality. Table 3 details the major contributors to severe morbidity in relation to the gestational age at study entry, which were sepsis (18%) and bronchopulmonary dysplasia (10%). Relatively infrequent were germinal matrix hemorrhage (2%) and cystic periventricular leukomalacia (1%). One-hundred and fifty-seven (31%) babies met the criteria for the composite outcome of death or severe morbidity. Table 4 details outcomes in relation to time of delivery; overall, 345 (70%) of liveborn babies survived without severe morbidity.

The gestational age at both study entry and delivery were strongly related to infant outcome (Figures 1 and 2 respectively). Compared with the remaining women, mothers of babies meeting the criteria for the composite outcome of death or severe morbidity were recruited earlier (28 + 3 weeks *vs* 29 + 3 weeks). At study entry, estimated fetal weight was lower (798 g *vs* 918 g)

Table 1 Demographic, medical, obstetric and diagnostic data at study entry for all women and those who subsequently had the composite poor outcome*

Variable	*All included* (n = *503*)	*Death or severe morbidity* (n = *157*)
Maternal age (years)	31 ± 6	31 ± 5
Caucasian ethnicity	423 (84)	139 (89)
Nulliparous	319 (63)	107 (68)
Body mass index (kg/m^2)	25 ± 6	26 ± 6‡
Smoking	77 (15)	23 (15)
Diabetes	9 (2)	2 (1)
Chronic hypertension	56 (11)	18 (12)
Renal morbidity	11 (2)	3 (2)
Other medical disease†	91 (18)	31 (20)
Pre-eclampsia-HELLP	195 (39)	70 (45)
Any gestational hypertensive morbidity	303 (60)	108 (69)‡
Antihypertensive medication	217 (43)	78 (50)‡
Magnesium for pre-eclampsia	48 (10)	16 (10)
GA at entry (weeks + days)	29+0 ± 11§	28+3 ± 11‡§
Estimated fetal weight (g)	881 ± 217	798 ± 210‡

Data are given as *n* (%) or mean ± SD. *Composite poor outcome comprised fetal or neonatal death or severe morbidity (bronchopulmonary dysplasia (oxygen after gestational age of 36 weeks), germinal matrix hemorrhage (Grade III and Grade IV), periventricular leukomalacia (Grade II and Grade III), necrotizing enterocolitis or proven sepsis). †Including liver, thyroid, thrombo-embolic or autoimmune conditions. ‡$P < 0.05$. §SD given in days. GA, gestational age.

Table 2 Obstetric and neonatal data at delivery for all women and for those who subsequently had the composite poor outcome*

Variable	*All included* (n = *503*)	*Death or severe morbidity* (n = *157*)
Maternal/pregnancy characteristics		
Pre-eclampsia-HELLP	262 (52)	91 (58)
Any hypertensive morbidity	368 (73)	124 (79)†
Antihypertensive medication	262 (52)	92 (59)†
Magnesium for pre-eclampsia	86 (17)	29 (19)
Corticosteroids for fetal maturation	461 (92)	145 (92)
Interval to delivery (days)	8 (0.5–88)	4 (0.5–61)
GA at delivery (weeks + days)	30+5 ± 16‡	29+4 ± 144†‡
Delivery indication		
Fetal condition	409 (81)	125 (80)
Maternal	64 (13)	20 (13)
Other	30 (6)	12 (8)
Mode of delivery		
Cesarean	486 (97)	148 (94)
Vaginal	17 (3)	9 (6)
Fetal death		
No intervention planned	5 (1)	5 (3)
Unexpected	7 (1)	7 (4)
Neonatal characteristics		
Birth weight (g)	1013 ± 321	867 ± 251†
Male gender	250 (50)	91 (58)†
Apgar score < 7 where liveborn	51 (10)	24 (17)†
Arterial pH (*n* = 404)	7.25 ± 0.08	7.23 ± 0.08†
Arterial pH		
≥ 7.0 to < 7.2	64 (16)	35 (29)†
< 7.0	5 (1)	2 (2)†

Data are given as *n* (%), mean ± SD or median (range). *Composite poor outcome comprised perinatal death (fetal or neonatal death) or severe morbidity: bronchopulmonary dysplasia (oxygen after gestational age of 36 weeks), germinal matrix hemorrhage (Grade III and Grade IV), periventricular leukomalacia (Grade II and Grade III), necrotizing enterocolitis or proven sepsis. †$P < 0.05$. ‡SD given in days. GA, gestational age.

and they more frequently suffered from hypertensive morbidity (gestational hypertension, pre-eclampsia or HELLP syndrome) (69% *vs* 56%). The time between inclusion and delivery was shorter (median 4 days *vs* 11 days). This median interval was shortest in cases with fetal death (3 days), slightly longer when severe neonatal morbidity or neonatal death occurred (4 days) and significantly longer when severe neonatal morbidity was absent (11 days). Babies with composite poor outcome (death or severe morbidity) were more likely to be delivered at an earlier gestation (29 + 4 weeks *vs* 31 + 2 weeks), have lower birth weight (867 g *vs* 1079 g), have an Apgar score below 7 (15% *vs* 8%) and lower umbilical pH (7.23 *vs* 7.25).

The most important independent determinants of the composite poor outcome (death or severe morbidity) were the presence of gestational hypertensive morbidity at study entry (OR = 1.70; 95% CI, 1.11–2.62), gestational age at study entry (OR= 0.80 per week of gestation; 95% CI, 0.65–0.99) and estimated fetal weight at study inclusion (OR = 0.84 per 100 g of estimated fetal weight; 95% CI, 0.72–0.99). Women with gestational hypertensive morbidity at inclusion had a significantly shorter median interval from inclusion to delivery (5 (range, 0.5–49) days) than did women without hypertensive morbidity (13 (range, 0.5–88) days) (Figure 3). The median duration of this interval was associated with the severity of the hypertensive condition: 8 days for gestational hypertension; 4 days for pre-eclampsia; and 3 days for HELLP syndrome (Figure 3). The babies of mothers with hypertensive morbidity at study entry were more likely to be delivered at an earlier gestation (30 + 1 weeks *vs* 31 + 4 weeks) and to have a lower birth weight (979 g *vs* 1063 g).

In the time between study entry and delivery, the number of women with any gestational hypertensive condition increased by 13%. At delivery, 368 (73%) women had a hypertensive condition, of whom 180 (49%) had pre-eclampsia, 80 (22%) had HELLP syndrome and two developed eclampsia. Notwithstanding this, only 64 (24%) of the 262 babies with mothers with pre-eclampsia, HELLP syndrome or eclampsia were delivered solely on maternal indication.

DISCUSSION

In this prospective multicenter study of 503 women identified at presentation with a diagnosis of FGR at very preterm gestational ages, we report low rates of antenatal and neonatal death. In this very high-risk group, over two-thirds survive without severe neonatal morbidity. The proportion surviving with neuromorbidity was low

Table 3 Perinatal mortality and severe morbidity according to gestational age at study entry

Variable	*Gestational age at study entry*			
	26–27 weeks	*28–29 weeks*	*30–31 weeks*	*Total*
n	133	204	166	503
Fetal death				
No intervention	4 (3)	1 (1)	0	5 (1)
Unexpected	3 (2)	4 (2)	0	7 (1)
Live birth*	126 (95)	198 (97)*	166 (100)	490 (97)
Neonatal death	15 (12)	10 (5)	2 (1)	27 (6)
Death with congenital anomaly	0	2	0	2
Overall mortality	22 (17)	15 (7)	2 (1)	39 (8)
Survival if liveborn	111 (88)	188 (94)	164 (98)	463 (95)
Neonatal morbidity				
Ventilated	90 (71)	76 (38)	38 (23)	204 (42)
Oxygen	79 (77)	128 (65)	72 (43)	297 (61)
BPD				
>28 days	54 (43)	31 (16)	6 (4)	91 (19)
>36 weeks†	34 (27)	13 (7)	2 (1)	49 (10)
Sepsis				
Clinical suspicion	30 (24)	26 (13)	11 (7)	67 (14)
Proven†	27 (21)	35 (18)	25 (15)	87 (18)
NEC				
Pneumatosis†	4 (3)	3 (2)	0 (0)	7 (1)
Perforation†	3 (2)	5 (3)	1 (1)	9 (2)
GMH Grade III or IV†	6 (5)	5 (3)	1 (1)	12 (2)
PVL Grade II or III†	2 (2)	1 (1)	2 (1)	5 (1)
Death following severe morbidity†	14 (11)	8 (4)	2 (1)	24 (5)
Adjusted age at discharge relative to EDD (days)‡	+12 (−22 to 68)	−4 (−39 to 170)	−10 (−37 to 64)	−9 (−39 to 170)
Severe morbidity (% of survivors)†	46 (37)	44 (22)	28 (17)	118 (24)
Survival without severe morbidity (% of all study entrants)	65 (49)	144 (71)	136 (82)	345 (69)

Data are given as *n*, *n* (%) or median (range). Percentages for neonatal mortality and morbidity were calculated from total number of liveborn infants. *One case with missing neonatal data was not included. †Severe morbidity: BPD (oxygen after gestational age of 36 weeks), 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. BPD, bronchopulmonary dysplasia; EDD, expected date of delivery; GMH, germinal matrix hemorrhage; NEC, necrotizing enterocolitis or proven sepsis; PVL, cystic periventricular leukomalacia.

(3%); most severe neonatal morbidity was caused by acquired infection or by bronchopulmonary dysplasia. All fetuses in this study had evidence of significant FGR but were eligible for care if delivery was to be indicated. There was standardization of management strategies up to 32 weeks of gestation.

Overall, 8% of babies died after a diagnosis of FGR, with approximately one-third of deaths occurring before delivery and two-thirds occurring in the neonatal period. Antepartum deaths were caused either by a decision for non-intervention, because the prognosis was considered too poor (five of 12 cases), or were unanticipated. This is perhaps not unexpected as the study population comprises a very preterm group at high risk of intrauterine hypoxia, in whom sudden fetal death is thought to be common. As might be expected and is reported in other studies[1,16], the vast majority of women had a Cesarean delivery. Male babies rather than female babies were more likely to meet the criteria for composite morbidity in a 3:2 ratio, consistent with the known male vulnerability to neonatal mortality and morbidity at low gestational ages[17,18].

The major determinant of adverse outcome was maternal hypertension, the presence of which shortened the interval from antenatal diagnosis of FGR to delivery. Women with HELLP syndrome were delivered earliest, followed by those with pre-eclampsia and gestational hypertension. It has been suggested that the interval between the first occurrence of umbilical Doppler abnormalities and fetal heart-rate changes[19,20] or subsequent fetal Doppler deterioration[21] is shorter in FGR with maternal hypertension or pre-eclampsia. Thus, in the context of maternal hypertensive disease, it is the proportion of maternal indication deliveries that increase. These findings, although intuitive, provide evidence to underpin the close monitoring of maternal blood pressure and proteinuria that is mandated when a diagnosis of early-onset FGR is made.

The prospective study against which these data can be meaningfully compared is the multicenter Growth Restriction Intervention Trial (GRIT)[16]. Five-hundred and forty-eight women with 'compromised' pregnancies were recruited at 24–36 weeks' gestation from 69 hospitals in 13 European countries between 1996 and 2002; outcomes on 487 liveborn babies were reported. They were randomly allocated to early (median 0.9 days from randomization) or late (median 4.9 days from randomization) delivery; most babies were affected by FGR. The overall outcomes for neonatal morbidity and mortality were similar between the immediate and deferred delivery groups with the median delivery gestation being 32 weeks,

Table 4 Perinatal mortality and severe morbidity amongst live births according to gestational age at delivery

	Gestational age at birth					
	26–27 weeks	*28–29 weeks*	*30–31 weeks*	*32–33 weeks*	*≥ 34 weeks*	*Total*
*n**	43	131	169*	103	44	490
Neonatal death	8 (19)	12 (9)	5 (3)	1 (1)	1 (2)	27 (6)
Death with congenital anomaly	0 (0)	0 (0)	0 (0)	1 (1)	1 (2)	2 (1)
Survival	35 (81)	119 (91)	164 (97)	102 (99)	43 (98)	463 (94)
Neonatal morbidity						
Ventilated	41 (95)	84 (64)	57 (34)	16 (16)	6 (14)	204 (42)
Oxygen	39 (91)	108 (82)	101 (60)	39 (38)	10 (23)	297 (61)
BPD						
>28 days	27 (63)	49 (37)	13 (8)	1 (1)	1 (2)	91 (19)
>36 weeks†	16 (37)	25 (19)	6 (4)	1 (1)	1 (2)	49 (10)
Sepsis						
Clinical suspicion	10 (23)	27 (21)	22 (13)	7 (7)	1 (2)	67 (14)
Proven†	14 (33)	31 (24)	28 (17)	10 (10)	4 (9)	87 (18)
NEC						
Pneumatosis†	0	4 (3)	2 (1)	0	1 (2)	7 (1)
Perforation†	0	5 (4)	2 (1)	1 (1)	1 (2)	9 (2)
GMH Grade III or IV†	3 (7)	7 (5)	2 (1)	0	0	12 (2)
PVL Grade II or III†	2 (5)	0	2 (1)	1 (1)	0	5 (1)
Died following severe morbidity†	8 (19)	11 (8)	5 (3)	0 (–)	0 (–)	24 (5)
Adjusted age at discharge relative to EDD (days)‡	+12 (−22 to 68)	−4 (−39 to 170)	−10 (−37 to 64)	−12 (−28 to 51)	−8 (−31 to 81)	−9 (−39 to 170)
Severe morbidity†	22 (51)	46 (35)	33 (20)	12 (12)	5 (11)	118 (24)
Survival without severe morbidity	13 (30)	73 (56)	131 (78)	90 (87)	38 (86)	345 (70)

Data are given as *n*, *n* (%) or median (range). *One case with missing neonatal data not included. †Severe morbidity: BPD (oxygen after gestational age of 36 weeks), 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. BPD, bronchopulmonary dysplasia; EDD, expected date of delivery; GMH, germinal matrix hemorrhage; NEC, necrotizing enterocolitis or proven sepsis; PVL, cystic periventricular leukomalacia.

and birth weight of 1200 g for the immediate delivery group and 1400 g for the deferred delivery group. Overall, 36 (7%) babies died in the neonatal period and the proportion with intraventricular hemorrhage was 15%, 5% had cystic periventricular leukomalacia and 6.1% had necrotizing enterocolitis; neither bronchopulmonary dysplasia nor sepsis was reported separately. These morbidities were therefore more common in the GRIT babies compared with the TRUFFLE cohort, although in our study babies were born on average just over 1 week earlier and were approximately 300 g lighter, and thus may be considered to be at higher risk. GRIT found no differences between the early or delayed delivery groups in terms of perinatal death, or 2-year[22] or school-age outcomes[23]. However, antenatal surveillance was not standardized: it is reasonable to hypothesize that by improving antenatal surveillance, as in TRUFFLE, a reduction in antenatal mortality might be achieved without worsening neonatal outcome.

Another, more recent, study from American and European centers compared outcomes in which ductus venosus Doppler was normal *vs* abnormal in 604 severely FGR babies born before 33 weeks' gestation (median gestational age = 29 weeks) and admitted to the neonatal unit[2]. Importantly, and in contrast to TRUFFLE, cases were not collected prospectively from the point of antenatal diagnosis. The babies were born, on average, 1 week earlier than in TRUFFLE and weighed slightly less, but it is reasonable to compare gestation-specific outcomes. If FGR is diagnosed at 26–27 weeks, we report that 17% of babies die before or after birth and 19% die if delivery occurs at 26–27 weeks, which contrasts with the previous report of 43% for delivery at 26 weeks. By contrast, after 30 weeks, we found that FGR is associated with mortality lower than 3%, in contrast to the previously reported mortality, of 17%, after delivery at 30 weeks[2].

A study of 180 babies with birth weight < 10th percentile, < 34 weeks and with abnormal umbilical Doppler, delivered between 1997 and 2004 in one of the larger units subsequently recruiting to TRUFFLE, and immediately prior to TRUFFLE commencing recruitment, offers further comparison. The mean gestational age at delivery was 30.2 weeks and mean birth weight was 875 g[24]. The overall mortality in that study was 14% and severe morbidity 28.3% compared to 5% and 25%, respectively, in this report; the definition of severe morbidity was similar but also included retinopathy of prematurity.

In this context, it is interesting to note the recently reported outcomes from EPICure 2 for appropriately grown babies born in 2006; at 26 weeks, 78% survived and 50% survived without major neonatal morbidity[18].

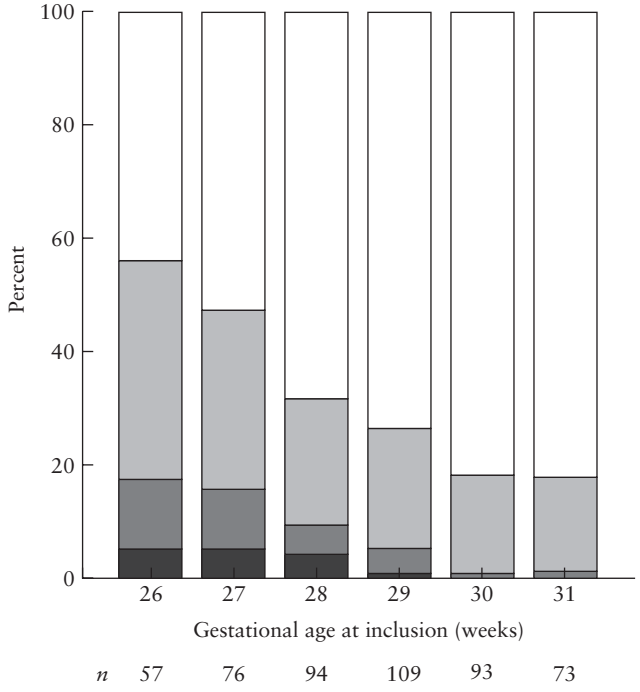

Figure 1 Outcome for fetuses according to gestational age at inclusion. '*n*' indicates total number of infants represented in each bar (one case is missing). Severe morbidity is defined as bronchopulmonary dysplasia (36 weeks), germinal matrix hemorrhage of Grade III or IV, cystic periventricular leukomalacia of more than Grade I, proven sepsis or necrotizing enterocolitis. □, No severe morbidity; ▒, severe morbidity; ■, neonatal death; ■, fetal death.

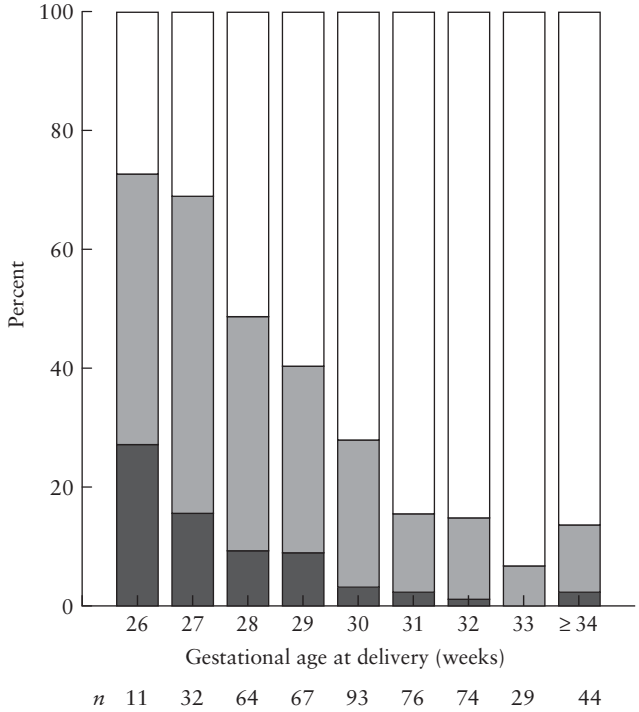

Figure 2 Outcome of live births ($n = 490$) according to gestational age at delivery. '*n*' indicates total number of infants represented in each bar (one case is missing). Severe morbidity is defined as bronchopulmonary dysplasia (36 weeks), germinal matrix hemorrhage of Grade III or IV, cystic periventricular leukomalacia of more than Grade I, proven sepsis or necrotizing enterocolitis. □, No severe morbidity; ▒, severe morbidity; ■, neonatal death.

This contrasts with our findings at 26–27 weeks of 81% survival but only 30% survival without severe morbidity. In EPICure 2, the birth weight standard deviation score was a predictor for bronchopulmonary dysplasia and for retinopathy of prematurity, but not for mortality, which seems consistent with these findings. The similarity in mortality for studies that were almost exactly contemporary, but one reporting on FGR and the other not, suggests that growth restriction may specifically modify morbidity risk.

A consensus antenatal monitoring and delivery protocol was used for women entered into TRUFFLE with close fetal monitoring involving CTG and Doppler parameters. As a result of this, 97% of women in TRUFFLE had Cesarean deliveries, compared with 98% and 85% in the cohorts reported by Baschat[2] and GRIT[16], respectively. Outcome in relation to mode of delivery was not reported in GRIT, but this suggests that, for some deliveries, a less interventional approach may be reflected in worse neonatal outcomes. The proportion delivered by Cesarean section will also be related to indication for delivery and we have shown a close relationship of the timing of delivery to the maternal hypertensive condition and a higher likelihood of maternal indication for delivery with greater severity of the hypertensive disorder, which for GRIT would not have been the case.

This study has several important strengths. Women were recruited prospectively from 2005 to 2010, hence reflecting contemporary neonatal medicine and obstetric practice. The entry criteria reflected the ultrasound and Doppler findings most commonly used to describe 'genuine' FGR as the babies were both small and showed evidence of fetoplacental impairment with raised umbilical artery PI. Indeed, only two babies were subsequently found to have major congenital abnormalities. Thus, the results are broadly generalizable to those women referred for specialist follow up of early-onset FGR between 26 and 32 weeks. Although the trigger for delivery was one of three different arms, this was randomly allocated and all three arms reflect practice current both at the inception of the study and now. Ascertainment of outcome was high, reflecting the philosophy of the group, whose investigators met on average twice per year from 2002 to 2012. The investigators achieved a high measure of agreement for a common monitoring policy, despite their own preferences in practice, met stringent criteria for the use of Doppler assessments and were co-located with a specialist neonatal facility whose specialists collaborated closely in the study. In only eight pregnancies were we unable to acquire outcome data; exclusion of all cases from these two centers prevented a possible selection bias.

A potential criticism is that women were randomized to one of three management arms and we report the outcomes of the entire cohort. However, as the three randomized arms reflect closely current fetal medicine practice, reporting the aggregated data is an appropriate

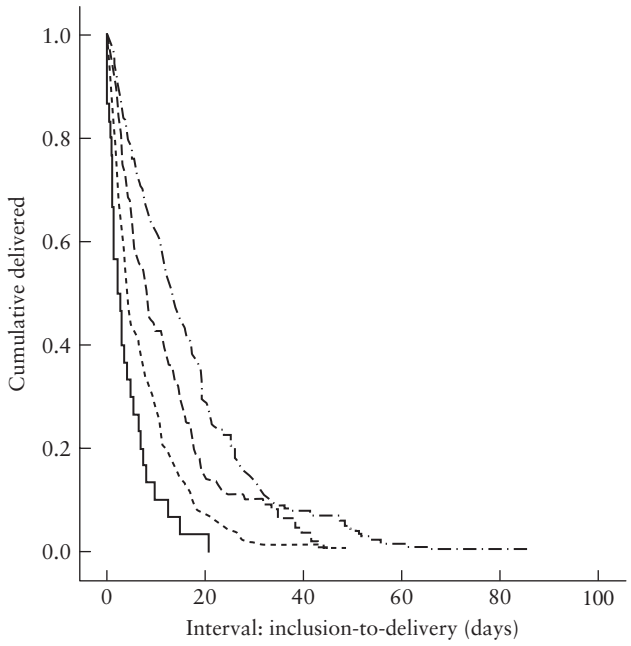

Figure 3 Kaplan–Meier analysis of interval between inclusion and delivery, presented separately for women with and those without hypertensive morbidity on inclusion. Differences between groups were statistically significant. ——, HELLP; - - - -, pre-eclampsia; – – – – –, gestational hypertension; —·—, no hypertensive morbidity.

reflection of outcomes expected in day-to-day clinical practice. We do not disclose outcome by randomized group in advance of reporting the primary outcome to avoid any possible influence on practice in the interim. Our aim in this paper is rather, given the paucity of prospective reports of outcome in FGR restriction for large cohorts, to describe perinatal outcomes in contemporary practice.

In summary, we describe somewhat better than expected perinatal outcomes in this high-risk group of fetuses, which are likely to be attributable to developments both in neonatal care and in antenatal monitoring. Delivery at 26 weeks of gestation still carries significant mortality and morbidity, similar to that in national birth cohorts, and the converse is true for delivery after 30 weeks. Maternal hypertension, in particular its severity, shortens the interval to delivery and influences neonatal outcome negatively. These data provide contemporary information to support counseling in respect of short-term outcomes for women at the time of antenatal diagnosis and separately at delivery.

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