The association of neonatal morbidity and long term neurological outcome in infants who were growth restricted and preterm at birth:secondary analyses from TRUFFLE (trial of Randomized Umbilical and Fetal Flow in Europe.

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Short title:

Neonatal morbidity and neurological outcome in preterm infants born after FGR.

Abstract

Objective: to study the relationship between neonatal morbidity (NNM)and two–years neurodevelopmental impairment (NDI) in surviving children after early fetal growth restriction (FGR).

Design: Secondary analyses of an European randomized trial (TRUFFLE) of delivery for very preterm fetuses dependent on venous Doppler or cardiotocographic criteria

Setting: Tertiary perinatal centres, participants in TRUFFLE

Population: 402 surviving children after early FGR.

Methods: Prospective data were collection from the recognition of FGR until the corrected age two years. We studied the association between NNM and NDI, retaining trial allocation in all statistical models. NNM included any of bronchopulmonary dysplasia, brain injury, sepsis or necrotising enterocolitis. NDI was a composite of Bayley cognitive score <85, cerebral palsy or severe sensory impairment.

Main Outcome Measure: NDI in relation to NNM.

Results: NNM occurred in 104 cases (26% of 402) and was more frequent in 17 of 39 infants (44%) with NDI than in the 87 of 363 infants (24%) with normal outcome (OR 2.5 (1.3 to 4.8; p=0.01). In 22 of 39 NDI cases (56%) there was no preceding NNM. NNM was inversely related to gestational age. NDI did not vary by gestational age. In multivariable analyses, cerebral ultrasound abnormalities were most strongly associated with NDI, together with trial group allocation, birth weight ratio (BWR), infant sex and Apgar score.

Conclusions: With the exception of cerebral ultrasound abnormalities, commonly used neonatal morbidities are poor markers of later neurodevelopmental impairment and should not be used as surrogate outcomes for NDI.

245 words

Tweetable abstract

Neonatal morbidities cannot be used as surrogate outcomes for neurodevelopmental impairment.

KEY WORDS

Fetal growth restriction, Prediction, Neonatal Morbidity, Neurodevelopmental Impairment

Introduction

Perinatal researchers often use neonatal morbidities as surrogate outcomes for longer-term childhood outcomes in studies of early (intra-uterine) exposures or interventions (1,2). There is evidence that specific neonatal morbidities, such as focal brain injury detected with ultrasound, bronchopulmonary dysplasia, neonatal sepsis and retinopathy are risk factors for later development. The causal pathways for these associations may involve structural injury or more subtle white matter damage, through interruption of oligodendrocyte maturation, for example by sepsis (3). However these associations are imprecise, perhaps because early alterations in brain maturation during fetal life, socio-demographic characteristics, and other environmental and family factors, mediate much of the longer term outcome (4,5,6). This might be particularly true in babies with preterm fetal growth restriction (FGR), as this condition alone may be the main risk factor for NDI, through associated alterations in brain maturation (7,8,9).

In FGR pregnancies, prolonging pregnancy may lead to fetal death or fetal brain injury, due to fetal hypoxia or prolonged malnutrition. Delivering too early may lead to neonatal death due to prematurity or to brain injury caused by related neonatal morbidities. Thus, the relative role of neonatal morbidity may be less important in determining survival without neurodevelopmental impairment following FGR.

TRUFFLE (the Trial of Randomised Fetal Flow Velocities in Europe) investigated whether ductus venosus (DV) measurement changes (as either early or late (absent A-wave) changes) combined with cardiotocography (CTG) used as a trigger for delivery, could increase the chance of healthy outcomes compared to reduced short term variation of fetal heart rate in pregnancies complicated by FGR between 26 and 32 weeks (10). The primary outcome was defined as survival without neurodevelopmental impairment (NDI) at 2 years of age corrected for preterm birth. A composite of neonatal morbidities was a secondary outcome and did not differ between study groups. In contrast, the use of DV measures was associated with increased proportions of babies surviving free of NDI.

In this secondary analyses we aimed to explore the relation between neonatal morbidity and survival with and without NDI at 2 years of age. In addition, because neonatal morbidity is strongly associated to gestational age (1), and severity of fetal growth restriction (11) we aimed to explore whether neonatal morbidity and NDI are associated similarly across gestational age and birthweight ratio subgroups. Finally we aimed to explore which prenatal and delivery factors, apart from neonatal risk factors are associated with NDI.

Methods

The design and principal outcomes for TRUFFLE have been described previously (10,12). In short, women with singleton fetuses at 26-32 weeks of gestation, with fetal abdominal circumference <10th percentile, estimated fetal weight ≥ 500 g and umbilical artery Doppler pulsatility index (PI) >95th percentile, were included in a twenty centre European study (ISRCTN 56204499). Baseline maternal and fetal data were collected via a secure internet data entry page. Study group allocation was performed in an even ratio from randomly sized blocks, stratified for gestational age (lower or higher than 29 weeks of gestation) and for participating centres. Eligible women were randomly allocated for delivery according to one of three monitoring arms: reduced cardiotocography (CTG) fetal heart rate short-term variation (STV<3.5 ms at a gestational age below 29 weeks and <4.0 ms thereafter); early ductus venosus changes (PI>95th percentile; 'DV p95'); or late ductus venosus changes ('a' wave at or below baseline; 'DV no A'). Abnormal DV measurements had to be repeated within 24 hours, if permitted by other measures of fetal condition, to demonstrate that this was a consistent observation. In all groups delivery could also be decided on 'safety net criteria' when the CTG showed recurrent decelerations, or in the DV groups when STV was very low (STV<2.6 ms at a gestational age below 29 weeks and <3.0 ms thereafter).

Gestational age was calculated using a first trimester dating ultrasound scan or, in the absence of an early scan, from the date of the last menstrual period if supported by later ultrasound findings.

The ratio of birth weight to the median (50th percentile) weight for gestational age, adjusted for maternal ethnicity, weight and length and infant sex, was calculated as a measure of the severity of FGR (BWR, birth weight ratio) following Gardosi (13). A BWR of 0.86 is comparable to P10 and a BWR of 0.68 to P2.3 on a birth weight curve.

Severe neonatal morbidity (NNM) was registered as a composite of one or more of the following severe morbidities: bronchopulmonary dysplasia (BPD), severe germinal matrix cerebral haemorrhage [GMH; intra-ventricular hemorrhage with dilation of the lateral ventricles (grade 3) or intra-parenchymal hemorrhage (grade 4)], cystic periventricular leucomalacia (PVL), proven neonatal sepsis (positive blood culture requiring treatment with antibiotics), necrotizing enterocolitis (NEC; Bell's stage 2 or greater: presence of pneumatosis or perforation on x-ray or identified by laparotomy) and bronchopulmonary dysplasia (BPD; defined as receiving supplemental oxygen at 36 weeks postmenstrual age). Neonatal data were extracted from clinical records and entered directly into the website study database.

Surviving children 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 (14). 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 (15), five points were added to Bayley II Mental developmental index (MDI) scores. If no Bayley test could be performed because of impairments, the attending paediatrician was asked to assess an estimate of cognitive delay (no delay, 3-6 months or more than 6 months delay).

All assessed children had a formal neurological examination to determine the presence of cerebral palsy (CP), which was classified using the Surveillance of Cerebral Palsy in Europe (SCPE) classification. The functional severity of CP was scored using the Gross Motor Function Classification System (GMFCS). Neurodevelopmental impairment (NDI) was defined as a Cognitive Bayley III score or corrected Bayley II MDI of <85 or an estimated cognitive delay >3 months, CP with a GMFCS >1, hearing loss requiring hearing aids or severe visual loss (legally certifiable as blind or partially sighted).

Differences between groups were compared using ANOVA, Pearson's Chi-square or Fisher exact tests as appropriate. To analyse the impact of neonatal morbidity, odds ratios and confidence intervals were calculated for neurodevelopmental impairment (NDI) and constituent disabilities. The group of 402 infants were subsequently divided into five gestational age groups (26-27, 28-29, 30-31, 32-33, >=34) and 6 BWR groups (<0.40, 0.4- , 0.5-, 0.6-, 0.7, and ≥0.8); the relation between gestational age and BWR groups, and the proportions with NNM and NDI were analyzed.

Multivariable logistic regression analysis was used to assess the association between a range of factors and outcomes. Odds ratios (OR), with 95 percent confidence limits (95%CI), were calculated. We use a dichotomous dependent variable (NDI versus no NDI) and included independent factors that were significantly associated with two years outcomes in univariate analysis. Study group was forced into in the final model.

IBM SPSS version 22 (New York, USA) was used for statistical calculations.

Results

Among the 503 births to women entered into TRUFFLE, 41 babies died before 2 years of age, neonatal information of one baby was unavailable and we excluded 59 children who were not examined at two years, leaving 402/461 (87%) survivors for this analysis (see our earlier publication (10) for flowchart). The children included were representative of the whole cohort (Table 1) over a range of factors. Ninety two percent of the Truffle cohort received antenatal corticosteroids. We have no data on placental microscopy. However, 99% of all liveborn infants were delivered by caesarean section before the onset of labour, which makes chorioamnionitis unlikely. There were no differences in demographic, obstetric or neonatal variables between the randomised fetal monitoring groups and between infants with or without follow-up at 2 years (Data were shown in our earlier paper (10))

Consistent with the main trial findings (10), among the 402 included children who survived and were examined at 2 years of age, there was a trend in the proportion without NDI across the three trial groups, being highest in the DVnoA and lowest in the STV groups (p=.02).

NNM was more common among those with NDI (24% v 44%; OR 2.5 ; 95% CI 1.3 to 4.8; p=0.01), however, in 22 of 39 infants with NDI there was no preceding neonatal morbidity (56%; 95% CI 41% to 72%.) (Table 2). For NNM to predict NDI, sensitivity was 44% and specificity was 76%. Among individual morbidities there were significantly higher rates of NDI among those with abnormal cerebral ultrasound (OR: 8.8; 95% CI 2.5 to 30.2) and bronchopulmonary dysplasia (OR: 2.7; 95% CI 1.1 to 6.3). Rates of sepsis were not significantly higher in those with NDI (OR: 1.7; 95%CI 0.8 to 3.7). There were a number of other factors that increased the risk of NDI, including male sex, exposure to maternal smoking, those with a Apgar score <7, and with lower BWR values (all p<.05). The gestational age distribution did not differ across the two groups with and without NDI.

Among those with NNM only 16% had NDI compared to 7% among those without (OR: 2.5 (1.3, 4.8); table 3). The positive predictive value thus was 16%, and negative predictive value 93%. Cerebral palsy was more frequent following NNM (OR: 6.1 (1.8, 20.8)) but other components of NDI did not differ statistically between those with or without NNM. This high OR should be placed in proper perspective given that there were only 6 infants total out of 402 with CP for what is overall a very low rate of102% of CP in the study cohort.

The proportion with NNM falls rapidly from 68% at 26-27 weeks of gestation to 11% at 34 weeks or greater (p<.001). There is a non significant reduction in NDI from 16% at 26-27w to 8% at ≥34w (p=.40; Figure 1a).

Similarly, the proportion with NDI falls from 17% at BWR <0.4 to 9% at BWR ≥0.8 (p=0.06) but there is no relationship between BWR and NNM (p 0.98; Figure 1b).

We used stepwise multivariable analysis to explore the relationship between NDI and those factors significantly associated with outcome on univariable analysis (Table 2), including trial allocation with CTG-STV allocation as the reference group. In the final model, 6 factors were independently associated with NDI at 2 years Cerebral ultrasound abnormality was the strongest negative associate (OR: 19.0; 95% CI 4.2 to 85.2) but was only present in 3% of the population, contributing 15% of the variance in 2-year outcomes. In male infants and infants with Apgar scores <7 and a lower BWR, NDI was also seen more frequently. Allocation to each DV monitoring group as part of the trial was associated with a lower frequency of NDI. A receiver operating characteristic curve (ROC) analysis had an area under the curve of 0.78 for the final model, consistent with a poor prediction.

Discussion

Main findings.

In surviving preterm infants born after severe fetal growth restriction the risk for neurological impairment was increased by the presence of severe neonatal morbidity (OR 2.5; 95% CI 1.3 to 4.8) but for 56% (95% CI 41%-72%) infants with NDI, neurodevelopmental impairment was not preceded by any of the components of our neonatal morbidity composite. Whilst the presence of neonatal morbidity was strongly associated with gestational age at birth, the proportion with NDI did not differ significantly over the gestation range. In contrast, the relationship of BWR was clearer for NDI than for NNM. Multivariable analysis identified key protective factors, including the study allocation to the two DV monitoring arms, and one major neonatal risk factor. We thus demonstrate that in preterm babies born after FGR composite neonatal morbidity appears a poor proxy outcome for NDI-free survival.

Strengths of this study were the large prospective sample of children born after fetal growth restriction, born in several European countries. Also, the use of BWR, rather than a cut-off of <p5 or <p10 for birthweight, provided further insight in the degree of FGR and it's relation to both NNM and NDI.

Limitations were the loss to follow up of 13%, that was not related to GA, BWR or NNM. NDI occurred in a rather low rate of 10%, therefore further explorations of associations of pregnancy, delivery and neonatal morbidities (the last aim of this paper) lacked power.

Interpretation.Current perinatal practice is to delay the delivery of very preterm fetuses with growth restriction to a later gestational age.(7) However delaying delivery does require close monitoring of the fetus as increasing the degree of growth restriction (reducing the BWR) is also associated with adverse outcome. Preterm birth is associated with reduced overall and regional brain volumes. Using magnetic resonance imaging (MRI), babies born after preterm FGR had lower brain volumes shortly after birth and at term-term equivalent age compared to normally grown preterm infants.(16) This deficit comprised mainly of reduced grey matter volumes, with a lesser effect on the white matter. A further study in very low birth weight infants found an association of fetal Doppler indices and 2-year development and suggested that this association was mediated through lower brain volume, which they measured at term-equivalent age using MRI (5). However, the effect of the severity of FGR (as expressed by BWR) on brain volumes in prospectively followed fetuses was not evaluated, but a progressive effect on brain growth seems plausible. Thus timing of delivery balances between the risk for neonatal morbidity by earlier delivery and NDI with increasing FGR by later delivery. Additionally we have confirmed in this multivariable analysis,

that using either of the two ductus venosus monitoring strategies in TRUFFLE is associated with reduced long-term morbidity compared to a reliance on STV on cardiotocography.

This study intended to investigate whether there was a strong relationship between NNM and NDI. We did not this strong relationship. Moreover, of all the components of NNM, in our multivariate analysis, only cerebral ultrasound abnormalities were kept into the model and were significantly associated with NDI. Cerebral ultrasound abnormalities are most frequent in the most preterm fetuses and probably a consequence of neonatal immaturity. However, this study was not designed to demonstrate increased risk of major GMH or PVL associated with FGR. Strategies that prevent brain injury would be by preventing fetal and perinatal acidosis or swings in cerebral blood pressure before delivery (17,18). It is worth noting that most cerebral ultrasound abnormalities occurred in the DV groups (4.2% in combined DV groups vs 0.6% STV group; P<0.05),(9) but this may simply reflect improved survival at low gestational ages.

We here demonstrate a larger vulnerability for males (OR 0.87 (0.77 to 0.98)) for NDI. In literature on outcomes after FGR sex differences are hardly reported (19). In 4 year old children born FGR after early-onset hypertensive pregnancy complications, abnormal neurodevelopmental outcomes was also associated with male sex (20).

In this study a rather low rate if NDI is found. Because of inconsistencies in defining FGR in literature and differentiation from small for gestational age (SGA), comparing our NDI rate to other studies is challenging (19) . Previously we suggested that a conservative approach to timing delivery in waiting for late ductus venosus changes–unless severe CTG changes defined as safetynet occur first–was associated with a more favourable 2 year (10). However, the age of two is rather early in child development and further follow up, probably at least until school age (20,21, 22,), would provide extra insight into the consequences of FGR and interventions that influence timing of delivery, because cognitive development, together with other measures of neuropsychiatric functioning can better be assessed at that age, with less emphasis on motor and social development.

Conclusion

Although, in FGR-infants, the presence of neonatal morbidity is highly associated with impairment at 2 years it appears to be a poor proxy for 'NDI' as a primary outcome, as the majority of those with NDI have no neonatal morbidity. Considering individual neonatal morbidities, the predictive value is best for cerebral ultrasound abnormalities, which are relatively infrequent compared to NDI. Until better short term markers of long term neurodevelopmental impairment are identified, perinatal studies with important neurological outcomes should plan 2-year outcome evaluations at the very least.

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Contributions of the authors to this manuscript:

A V W-L designed the study, interpreted the results and wrote the manuscript

NM and CL contributed to the study design, interpreted results and contributed to the writing of the manuscript

HW contributed to the study design, carried out all data analyses, interpreted results and contributed to the writing of the manuscript

all TRUFFLE investigators collaborated in data collection, contributed to data interpretation and writing of the manuscript.

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None of the authors have disclosures

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Ethics:

This was a prospective multicentre randomised management trial conducted in 20 European tertiary care centres with a fetal medicine unit in 4 countries (UK, Italy, Germany and the Netherlands). Patients were included from 2005 to 2010. Women were recruited by investigators with expertise in fetal assessment. Following written informed consent, participants were randomly assigned to one of three groups in a 1:1:1 ratio using secure web based randomisation). 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. The study was ratified by the ethics committees of all participating units.

References:

1. Damadaram M, Story L, Rutherford M, Kumar S. Early adverse perinatal complications in preterm growth-restricted foetuses. Aust N Z J Obstet Gyneaecol 2011;51:204-209.
2. Boers KE, Vijgen SM, Bijlenga D, van der Post JA, Bekedam DJ, Kwee A, et al. Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). BMJ. 2010;341:c7087.
3. Favrais G1, van de Looij Y, Fleiss B, Ramanantsoa N, Bonnin P, Stoltenburg-Didinger G, et al. Systemic inflammation disrupts the developmental program of white matter. Ann Neurol.;70:550-565.
4. Manuck TA, Sheng X, Yoder BA, Varner MW. Correlation between initial neonatal and early childhood outcomes following preterm birth. AJOG 2014; 210:426.e1-9
5. Leppanen M, Ekholm E, Palo P, Maunu J, Munck P, Parkkola R, et al. Abnormal antenatal Doppler velocimetry and cognitive outcome in very low birth weight infants at 2 years of age. Ultrasound Obstet Gynaecol 2010; 36:178-185.
6. Doyle LW, Anderson PJ, Battin M, Bowen JR, Brown N, Callanan C, et al. Long term follow up of high risk children: who, why and how? BMC Pediatr. 2014;14:279-294.
7. Baschat AA. Neurodevelopment after fetal growth restriction. Fetal Diagn Ther 2014; 36:136-142.
8. Levine TA, Grunau RE, McAuliffe FM, Pinnamanemi R, Foran A, Alderdice FA. Early Childhood neurodevelopment after intrauterine growth restriction: a systematic review. Pediatrics 2015;135:126-141.
9. Baschat AA, Odibo AO. Timing of delivery in fetal growth restriction and childhood development; Some uncertainties remain. AJOG. 2011;204:2-3.
10. Lees CC , Marlow N, van Wassenaer-Leemhuis AG, Arabin B, Bilardo CM, Brezinka C, et al. 2 Year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE); a randomised trial. Lancet. 2015;385:2162-72.
11. Zeitlin J, Mayass, El Ayoubi M, Jarreau PH, Draper ES, Blondel B,et al. Impact of fetal growth restriction on mortality and morbidity in a very preterm birth cohort. J Peds 2010;157:733-739.
12. Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, et al. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound Obstet Gynecol 2013; 42: 400–408.

13. Gardosi J, Mongelli M, Wilcox M, Chang A. An adjustable fetal weight standard. Ultrasound Obstet Gynecol 1995; 6:168-174.
14. Bayley N. Bayley Scales of Infant and Toddler development. San Antonio Tx: The Psychological Cooperation 2006
15. Moore T, Johnson S, Haider S, Hennessy E, Marlow N. Relationships between test scores using the second and thirs editions of the Bayley Scales in extremely preterm children. J Pediatr 2012;160:553-558.
16. Tolsa CB, Zimine S, Warfield SK, Freschi M, Sancho-Rossignol A, Lazeyras F, et al. Early alteration of structural and functional brain development in premature infants born with intrauterine growth restriction. Pediatr Res 2004; 56:132-138
17. Malin GL, Morris RK, Khan KS. Strength of association between umbilical cord pH and perinatal and long term outcomes: systematic review and meta-analysis. BMJ 2010;340:c1471.
18. Dempsey EM. Under pressure to treat? Arch Dis Child Fetal Neonatal Ed. 2015;100: F380-381.
19. Levine TA, Grunau RE, McAuliffe FM, Pinnamaneni R, Foran A, Alderdice FA. Early childhood neurodevelopment after intrauterine growth restriction: a systematic review.Pediatrics 2015;135:126-141.
20. van Wassenaer AG, Westera J, van Schie PEM, Houtzager BA, Cranendonk A, de Groot L et al. Outcome at 4.5 years of age born after expectant management of early-onset hypertensive disorders of pregnancy. AJOG 2011;204:e1-9
21. Morsing E, Åsard M, Ley D, Stjernqvist, K, Maršál K. Cognitive Function After Intrauterine Growth Restriction and Very Preterm Birth. Pediatrics 2011;127;e874-882.
22. Tideman E1, Marsál K, Ley D. Cognitive function in young adults following intrauterine growth restriction with abnormal fetal aortic blood flow. Ultrasound Obstet Gynecol. 2007;29:614-8.

Legend to figure 1a

Barplot describing rates of NNM and NDI over gestational age (GA) groups. Total numbers of each gestational group are presented above the bars. There was a significant relation between NNM and GA ($p<0.001$) , but not between NDI and GA ($p=0.40$).

Legend to figure 1b

Barplot describing rates of NNM and NDI over birth weight ratio (BWR) groups. Total numbers of each BWR group are presented above the bars. There was no significant relation between NNM and BWR ($p=0.98$) , and between NDI and BWR ($p=0.06$).