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Neurodevelopmental outcomes at five years after early-onset fetal growth restriction: Analyses in a Dutch subgroup participating in a European management trial

A. Pels[a,*], O.C. Knaven[a], B.J. Wijnberg-Williams[b], M.J.C. Eijsermans[c], S.M. Mulder-de Tollenaer[b], C.S.H. Aarnoudse-Moens[e], C. Koopman-Esseboom[c], J. van Eyck[f], J.B. Derks[d], W. Ganzevoort[a], A.G. van Wassenaer-Leemhuis[e]

[a] Department of Obstetrics and Gynecology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
[b] Department of Pediatrics, Isala Hospital, Zwolle, the Netherlands
[c] Child Development & Exercise Center, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands
[d] Department of Obstetrics, Gynecology and Neonatology, Wilhelmina Children's Hospital University Medical Center, Utrecht, the Netherlands
[e] Department of Pediatrics, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
[f] Department of Obstetrics and Gynecology, Isala Hospital, Zwolle, the Netherlands

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ABSTRACT

Objective: The objective of this study is to explore developmental outcomes at five years after early-onset fetal growth restriction (FGR).
Study design: Retrospective data analysis of prospective follow-up of patients of three Dutch centres, who participated in a twenty centre European randomized controlled trial on timing of delivery in early-onset FGR. Developmental outcome of very preterm infants born after extreme FGR is assessed at (corrected) age of five.
Results: Seventy-four very preterm FGR children underwent follow-up at the age of five. Mean gestational age at birth was 30 weeks and birth weight was 910 g, 7% had a Bayley score <85 at two years. Median five years' FSIQ was 97, 16% had a FSIQ < 85, and 35% had one or more IQ scores <85. Motor score ≤ 7 on movement ABC-II (M-ABC-II-NL) was seen in 38%. Absent or reversed end-diastolic flow, gestational age at delivery, birthweight and neonatal morbidity were related to an FSIQ < 85. Any abnormal IQ scale score was related to birthweight, male sex and severity of FGR, and abnormal motor score to male sex and bronchopulmonary dysplasia (BPD).
Conclusions: Overall, median cognitive outcome at five years was within normal range, but 35% of the children had any abnormal IQ score at age five, depending on the IQ measure, and motor impairment was seen in 38% of the children. GA at delivery, birthweight, EDF prior to delivery and neonatal morbidity were the most important risk factors for cognitive outcomes.

Introduction

In fetal growth restriction (FGR) the fetus does not reach its genetic growth potential.

Utero-placental insufficiency is the most common cause with possibly critical consequences for both mother and fetus [1]. In early-onset placental insufficiency abnormal Doppler measurements and an asymmetrical growth are seen. A variety of definitions is found in literature, varying between an antenatal diagnosis reflecting the placental dysfunction and a postnatal diagnosis based on birthweight [2–5]. The latter probably includes the fetus who is small-for-gestational-age (SGA) rather than the fetus with FGR and is less likely to identify the fetuses at risk of adverse outcomes.

Early-onset FGR, defined as below 32 weeks of gestation, is associated with an increased risk of neonatal morbidity and mortality [6–9]. Of all pregnancies complicated by FGR, roughly 5–10% result in stillbirth or neonatal death [10]. Delivery is indicated when signs of deteriorating of the fetal condition are noticed and the fetal condition is shortly expected to be compromised.

The Trial of Randomized Umbilical and Fetal FLow in Europe (TRUFFLE) study investigated three different monitoring and

* Corresponding author at: Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands.
E-mail address: a.pels@amc.uva.nl (A. Pels).

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management strategies in patients with early-onset FGR. Survival without impairment in these three groups was 77–85% at two years of age. In the surviving infants of the group in which timing of delivery was based on late ductus venosus changes there was a significant reduction in neurodevelopmental impairment at the age of two years [11].

Unfortunately, cognitive and motor outcome of preterm children at two years has a low sensitivity in predicting cognitive deficit at later school age [12,13]. Formal follow-up at early school age was not part of the study protocol in the TRUFFLE study. However, in some NICU follow-up clinics in the Netherlands, children were invited for neonatal follow-up at five years of age according to a national guideline. This enabled us to evaluate these outcomes in Dutch TRUFFLE children.

The present analysis aims to investigate the neurodevelopmental outcome data of this cohort of very preterm early-onset growth restricted children at five years of age and compare them with the two years neurodevelopmental outcome data.

Material and methods

The design of the TRUFFLE study has been previously described [9,11,14]. The original TRUFFLE study was a prospective, multicenter, unblinded management trial in twenty European tertiary-care centres. Patients included were women over 18 years of age with a singleton pregnancy at 26–32 weeks of gestation, diagnosed with FGR based on a fetal abdominal circumference <10th percentile, an umbilical artery Doppler PI >95th percentile and an estimated fetal weight (EFW) of >500 g. Study participants were randomly allocated to three study groups in which timing of delivery was determined on different criteria (short term variation on cardiotocography, ductus venosus pulsatility index or late ductus venosus changes). Additionally, delivery could be decided when safety-net criteria required it. All parents consented to take part in the developmental follow-up as part of the TRUFFLE study and according to the local neonatal follow-up program that was considered standard care. The trial was conducted according to the principles of the Declaration of Helsinki Medical [15], Dutch legislation regarding medical research involving human subjects [16,17] and Good Clinical Practice Guidelines (GCP) [18].

The population of this analysis comprised all surviving children of the original TRUFFLE cohort born in one of three Dutch clinics (AMC, Amsterdam; Isala, Zwolle; and UMC Utrecht). The TRUFFLE study investigated the neurodevelopmental outcomes of children in all participating countries and centres at two years of age [11]. Children and their parents were contacted for a follow-up appointment at five years of age as part of standard follow-up in three centres in The Netherlands, based on criteria of gestational age and birth weight or pragmatic reasons. In AMC Amsterdam, children were invited for follow-up if they had a birthweight below 1000 g or a GA at delivery below 30 weeks. Isala Zwolle invited children with a birthweight below 1500 g or a GA at delivery below 32 weeks. In UMC Utrecht the criteria for invitation for follow-up was a GA at delivery below 28 weeks.

Baseline characteristics

Perinatal data were already reported in the original TRUFFLE study [9]. Severe neonatal morbidity was defined as presence of at least one of the following: bronchopulmonary dysplasia (BPD), defined as the need for supporting oxygen at 36 weeks of postmenstrual age [19–24], severe intraventricular haemorrhage (defined as grade III or IV) [25], cystic periventricular leukomalacia, culture-proven neonatal sepsis, necrotizing enterocolitis (Bell's ≥ stage 2) [26]. Birth weight ratio (BWR) was measured following Gardosi et al. [27] and defined as the ratio of birthweight to the 50th percentile weight, adjusted for maternal ethnicity, weight, length and infant sex. A BWR of 0.86 is comparable to the 10th percentile and a BWR of 0.68 to the 2.3rd percentile on a birthweight curve [27].

To investigate the influence of the parental education level on neurodevelopmental outcome, the highest completed education of mother was rated. Educational level was rated "low" when the highest completed level of education was primary school or low level secondary school ('VMBO'). Parents who graduated from middle or high level secondary school ('HAVO' or 'VWO') or low or middle level vocational education ('MBO') were rated "middle level of education". Parents were rated "high level of education" when they graduated from high level vocational education ('HBO') or university.

Neurodevelopmental assessment and outcomes

A trained psychologist and a paediatrician or pediatric physical therapist assessed the children attending the outpatient clinic. Cognitive development was assessed using the Wechsler Preschool and Primary Scale of Intelligence-III-NL (WPPSI^{TM} - III-NL) [28,29]. Outcome was reported as quotient and composite score, with a mean of 100 and a standard deviation of 15. Full Scale IQ (FSIQ) was reported as well as scores on IQ scales: verbal IQ (VIQ), performance IQ (PIQ), processing speed quotient (PSQ) and general language index (ATI). A score lower than 85 (<1 SD) was considered to be abnormal. All scores were based on the age corrected for prematurity.

To establish cerebral palsy (CP), patients underwent a neurological examination. CP was classified using Surveillance of Cerebral Palsy in Europe (SCPE) [30] Severity of CP was scored using the Gross Motor Function Classification System (GMFCS) [31].

Neurodevelopmental impairment (NDI) was defined as a WPPSI-III FSIQ-score <85, CP with a GMFCS ≥ 1, hearing loss requiring a hearing aid or severe visual loss (partially sighted or legally certifiable as blind).

Motor impairment was assessed using the Movement Assessment Battery for Children-II-NL (M-ABC-II-NL) [32]. Outcome was reported as the overall motor score and scores on the three subscales: manual dexterity, ball skills and balance skills. A total score ≤ seven points was considered to be abnormal. The total motor score of six children that underwent M-ABC-I were converted to the M-ABC-II-NL. For these six children the total, but not the subscales m-ABC-I score was converted to the second version.

Behavioural and emotional problems were assessed using the Child Behavior Checklist (CBCL) [33]. A total CBCL score was considered to be borderline clinical (= mildly abnormal) in the range of 60–63 and clinical (=abnormal) when > 63 points [33].

Statistical analysis

Statistical analysis was performed using IBM SPSS version 23. Baseline characteristics of our study group were compared to the patient population not seen at the age of five years, to detect the possibility of selection bias. Depending on the sample size, chi-square's test or fisher's test were used to compare frequencies of nominal variables. To compare numerical data, an unpaired *t*-test (in normally distributed data) or Mann-Whitney U test (in non-normally distributed data) was used.

Ethical approval

Multicentre Research Ethics Committee approved the TRUFFLE trial in September 2005 (ref: 05/Q0803/152).

Results

A total of 503 women were included in the original trial. Of these women, the three participating clinics conducting the five year follow-up, together contributed a total of 191 women (Fig. 1). Ninety-nine children met the above described respective selection criteria based on which patients were invited to participate in the five year follow-up consult. Eleven children were seen at five years of age because of their participation in the two years' follow-up in TRUFFLE but without fulfilling the strict inclusion criteria for five years follow-up, following the Dutch follow-up guideline, were included as well. Our final study population consisted of 74 children.

Maternal, perinatal and environmental characteristics of children assessed during follow-up are presented in Table 1. When comparing the maternal and perinatal characteristics of the children assessed in the current follow-up study to the characteristics of the 503 infants of the original TRUFFLE cohort [11], in this cohort more women were hypertensive (82% versus 72%) and had more often preeclampsia or HELLP (62% versus 50%). The children had a slightly lower GA at delivery (29.7 versus 30.7 weeks) and a lower birthweight (910 versus 1019 g) and slightly more severe neonatal morbidity (31% versus 25%).

Characteristics of children assessed during follow-up at the age of five years were compared to characteristics of children in the participating centres not assessed at follow-up (Table 1). In line with the applied follow-up criteria, children assessed at five years had a statistically significant lower birthweight and lower GA at birth than the children who were not assessed at the age of five. Also the assessed patient group showed a shorter interval between randomisation and delivery. Bronchopulmonary dysplasia (BPD) was more often present in this group than among the children that were not evaluated at five years of age. Of the patients evaluated at five year, five out of 74 (6,8%) had a

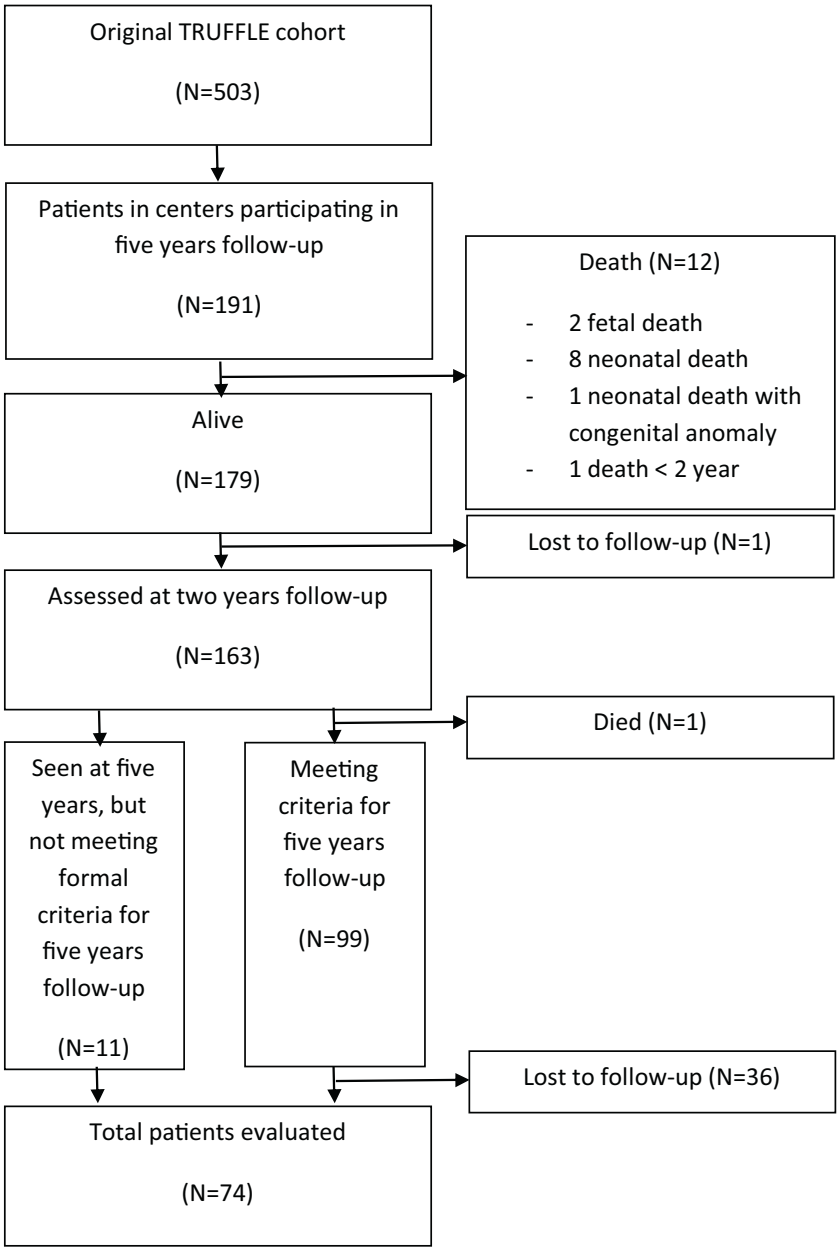

Fig. 1. Flowchart patients TRUFFLE study.

Table 1
Comparison of perinatal, maternal and neonatal characteristics of surviving TRUFFLE children in the three Dutch centers between those assessed and not assessed at age five.

Variables	Children assessed at five year follow up (n = 74)	Children alive and not assessed (n = 105)	P-value (95% CI)
Maternal age, mean ± SD in years	29.4 ± 5.1	30.3 ± 5.9	0.300 (−0.787 to 2.537)
BMI, median (IQR)	23.5 (21.4–27.5)	24.2 (21.3–28.4)	0.612
Caucasian ethnicity, n (%)	58 (78.4%)	85 (81.0%)	0.672
Nulliparous, n (%)	44 (59.5%)	72 (68.6%)	0.209
Smoking during pregnancy, n (%)	10 (13.5%)	22 (21.0%)	0.201
Gestational hypertensive morbidity, n (%)	61 (82.4%)	86 (81.9%)	0.928
PE/HELLP, n (%)	46 (62.2%)	64 (61.0%)	0.870
Allocation group			0.509
CTG STV, n (%)	26 (35.1%)	33 (31.4%)	
DV p95, n (%)	20 (27.0%)	37 (35.2%)	
DV no A, n (%)	28 (37.8%)	35 (33.3%)	
Antihypertensive medication, n (%)	48 (64.9%)	67 (63.8%)	0.885
Magnesium treatment, n (%)	15 (20.3%)	22 (21.0%)	0.912
Antenatal corticosteroid, n (%)			0.055
0 courses	1 (1.4%)	0 (0%)	
1 course	70 (94.6%)	105 (100%)	
2 courses	3 (4.1%)	0 (0%)	
End diastolic flow prior to delivery			
Positive	32 (43.2%)	50 (47.6%)	0.338
Absent	36 (48.6%)	41 (39.0%)	
Reversed	6 (8.1%)	14 (13.3%)	
Interval to delivery, median (IQR) in days	4.5 (2.2–8.5)	6.9 (2.7–17.2)	0.017 *
Gestational age at delivery, mean ± SD (weeks)	29.7 ± 1.5	31.2 ± 2.0	<0.001 * (0.92–2.0)
Birthweight, mean ± SD (grams)	910 ± 194	1097 ± 280	<0.001 * (118–258)
Birthweight P50 ratio, mean ± SD	59.9 ± 9.4	60.5 ± 9.3	0.719 (−2.289 to 3.313)
Male sex, n (%)	34 (45.9%)	56 (53.3%)	0.330
Apgar score < 7 at 5 min, n (%)	4 (5.4%)	6 (5.7%)	1.000
Umbilical artery pH	n = 61	n = 90	
Median (IQR)	7.26 (7.2–7.29)	7.26 (7.21–7.30)	0.714
<7.0, n (%)	2 (3.3%)	1 (1.1%)	0.566
Severe neonatal morbidity, n (%)	23 (31.1%)	27 (25.7%)	0.431
NEC, n (%)	2 (2.7%)	2 (1.9%)	1.000
GMH ≥ grade III, n (%)	3 (4.1%)	2 (1.9%)	0.650
BPD > 36 weeks, n (%)	13 (17.6%)	6 (5.7%)	0.011 *
Proven sepsis, n (%)	9 (12.2%)	21 (20.0%)	0.167
PVL ≥ grade II, n (%)	0 (0%)	2 (1.9%)	0.512
NDI at 2 years of age[a]	5 / 74 (6.8%)	11 / 89 (12.4%)	0.231
Abnormal Bayley at 2 years of age[b], n (%)	5 / 74 (6.8%)	11 / 89 (12.4%)	0.231

SD = standard deviation. IQR = inter quartile range. CI = confidence interval. BMI = Body mass index. PE = preeclampsia. HELLP = hemolysis elevated liver enzymes low platelets. CTG = cardiotocography. STV = short term variation. DV = ductus venosus. NEC = necrotizing enterocolitis. GMH = germinal matrix cerebral haemorrhage. BPD = bronchopulmonary dysplasia. PVL = periventricular leukomalacia. NDI = neurodevelopmental impairment.
[a] NDI: defined as a bayley score <85, CP with a GMFCS ≥ 1, hearing loss requiring a hearing aid or severe visual loss (partially sighted or legally certifiable as blind).
[b] Bayley III score or corrected Bayley II mental development index score of less than 85 or an estimated cognitive delay of more than three 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).

Bayley score below 85 (and thus NDI) compared 11 out of 89 (12.4%) in the group seen at age two but not seen at age five (p = 0.23).

The mean Bayley score at two years of age of the 74 included patients was 99.4 ± 12.1 and of the 36 patients with five years' follow up indication but who were lost to follow-up, 93.3 (±15.7, p = 0.047). Perinatal outcomes did not differ between children seen and those lost to follow-up.

Table 2 presents the scores on the neurodevelopmental tests. Neurodevelopmental impairment (NDI) occurred in 11 of 73 patients (15.1%), all of whom had an FSIQ < 85. Of one patient FSIQ could not be calculated, due to missing PSIQ. One or more IQ scale score <85 occurred in 26 of 74 patients (35.1%).

Table 3A presents variables associated with FSIQ < 85. FSIQ < 85 was associated with a lower GA at delivery, a lower birth weight, absent or reversed end-diastolic flow prior to delivery and severe neonatal morbidity.

Table 3B presents variables associated with any IQ scale <85. Birth weight, male sex, and birth weight ratio were associated with any IQ scale <85. A trend towards absent or reversed end-diastolic flow prior to delivery was seen. Maternal education was not associated with IQ outcomes.

Motor outcomes are presented in Table 2. An abnormal M-ABC-II-NL (≤ 7) was found in 27 of 71 patients that completed the M-ABC-II-NL or M-ABC-I (38.0%). Male sex and BPD were significantly associated with abnormal M-ABC-II-NL (p = 0.01) (Table 3C).

On the behavioural test five (8.6%) children scored in the clinical (=abnormal) range.

When combining the cognitive, motor and behavioural outcomes, there were 64 children with known outcomes of all tests. Of these children, there were 34 (53.1%) with FSIQ < 85 and/or CP and/or M-ABC-II-NL ≤ 7 and/or with a CBCL score > 60. This overall outcome measure was similar for children born below and beyond 30 weeks gestational age.

Table 4 compares the neurodevelopmental outcome at two and five years of age. On a group level, outcomes remained fairly stable.

Table 2
Neurodevelopmental outcome at five years of age corrected for prematurity.

Developmental domain	Value N = 74
Age at follow-up in months	
Calendar, median (IQR)	62 (61–65)
Corrected, median (IQR)	60 (59–62)
WPPSI-III score, median (IQR)[a]	
FSIQ	97.0 (91.0 – 107.0)
VIQ	101.0 (91.0 – 108.5)
PIQ	97.0 (88.8 – 107.0)
PSQ	94.0 (79.0 – 103.0)
WPPSI-III score <85, n (%)[b]	
FSIQ	11 (15.1%)
VIQ	9 (12.2%)
PIQ	9 (12.2%)
PSQ	20 (27.4%)
All IQ scores normal, n (%)	48 (64.9%)
Cerebral palsy, n (%)	2 (2.7%)
Mild vision problems, n (%)	5 (6.8%)
Mild hearing problems, n (%)	1 (1.4%)
Motor development: M-ABC-II-NL n = 71[c]	
Total score; median (IQR)	8.0 (6.0 – 10.0)
Manual dexterity; median (IQR)	8.0 (6.0 – 9.0)
Ball skills; median (IQR)	9.0 (6.0 – 10.0)
Balance skills; median (IQR)	9.0 (6.0 – 10.0)
Number of children with motor score ≤7 [d], n (%)	27 (38.0%)
Behavior (CBCL) [e] n = 58	
Total score, median (IQR)	43.0 (40.0 – 53.0)
Borderline n (%)	1 (1.7%)
Clinical score n (%)	5 (8.6%)
FSIQ < 85 or M-ABC-II-NLM-ABC ≤7 (or M-ABC-I < 16th percentile) or CBCL > 60 or CP, n=64	34 (53.1%)

SD = standard deviation. IQR = inter quartile range. WPPSI = Wechsler Preschool and Primary Scale of Intelligence. FSIQ = full scale intelligence quotient. VIQ = verbal intelligence quotient. PIQ = performance intelligence quotient. PSQ = processing speed quotient. IQ = intelligence quotient. M-ABC-II-NL = movement assessment battery for children. CBCL = child behavior checklist. CP = cerebral palsy, defined as GMFCS ≥ 1.

[a] At age corrected for prematurity.
[b] Of one child the PSQ (and therefore the FSIQ could not be calculated.
[c] Six children underwent M-ABC I, for those only the total motor score is reported.
[d] M-ABC-II-NL score ≤7 = impaired, ≥8 = normal.
[e] CBCL score total score: 60–63 = borderline (mildly impaired), > 63 = clinical (severely impaired).

Comment

The outcomes of the Dutch children participating in TRUFFLE, antenatally diagnosed with FGR, born at a mean GA of 30 weeks and a mean birth weight of 910 g, was fairly good, as illustrated by the median IQ score within normal range. The rates of children with IQ scores <85 was also comparable to the normed population. However, NDI rates increased from 6.8% at age two to 15.1% at age five. Moreover, 35% of the children had any IQ score 85, which is substantially higher than found in a control group [34]. Of the studied population, about half of the children scores positive on a composite outcome measure of FSIQ < 85 and/or CP and/or M-ABC-II-NL in the abnormal range and/or CBCL score > 60. M-ABC-II-NL in the abnormal range contributes most in this composite measure. Severe impairments were scarce in our study group. IQ and motor problems were related to GA, birthweight, male sex and neonatal morbidities, in particular BPD for the motor problems. Children with a FSIQ below 85 had more often reversed or absent flow prior to birth in comparison to children with a normal IQ score. GA, birthweight, male sex, and BPD are known risk factors for adverse outcomes in such patient groups. Overall rates of impairments were similar for the whole study group and those born growth restricted below 30 weeks' gestation. We hypothesize that BPD is found to be associated with long-term outcomes as being the expression of the more vulnerable children among this sample

The strength of this study is the relatively large and homogeneous study population, and the clear antenatal diagnosis of FGR from placental insufficiency (in contrast with SGA), as much as possible with respect to the lack of consensus on the definition of FGR. Children were assessed systematically in outpatient clinics according to a standardized program, using a well validated test battery and the corrected ages to score test outcomes [35].

Limitations can be found in the restriction of the selection. Data were collected retrospectively, because the extended follow-up period was not part of the initial trial protocol. Although we studied a relatively vulnerable sample with lower GA and birthweight compared to the sample not seen at follow up, NDI at age two in our sample was lower than in the total sample. Also in the lost to follow up group, NDI at age two occurred more often than in the 74 children seen at age five. Outcome can therefore not be extrapolated to the whole TRUFFLE sample, since we cannot be certain about the direction of possible bias. Another limitation is the number of children evaluated which resulted in lack of power to figure out which of these risk factors were most related to our outcome measures in a multivariate analysis. Therefore, we decided to only show univariate relations with possible factors related to the different outcome measures.

A systematic review by Murray et al. [36] demonstrated that children with FGR, especially those who are also born preterm, have an increased risk of NDI later in childhood. In other studies investigating cognitive outcomes around five years of age in very preterm FGR or SGA children, there is a large variation in definition of FGR, primary aim, study design and type of tests used [37–46].

In a systematic review performed by Levine et al. [47], 16 studies on neurodevelopmental outcomes among very preterm FGR in comparison with normally grown children were identified and 11 of these reported poorer neurodevelopmental outcome.

Our cognitive results best correspond to those found by Walker et al. [43] and Schreuder et al. [40].

The studies that have reported poorer cognitive outcomes in study populations comparable to our study [39,41,42], were limited by very small numbers of patients.

We observed impairments in processing speed in one quarter of our study group. This has previously been reported in studies in very preterm born children [48,49]. However, these studies did not focus on FGR in particular, but included all patients born below 32 weeks' gestation and all patients born below 30 weeks' gestation or below 1000 g respectively.

The study of Korzeniewski et al. [50] compared the cognitive and behavioural outcomes at ten years of age between normally grown and growth restricted premature born fetuses. The results indicate that children with severe FGR experienced more problems on multiple domains of the cognitive and neurobehavioral development.

In the present study 35.1% of the children had any abnormal IQ scale score, which is lower than in the 46% found in the preterm and higher than the 15% in the term population in the study of Potharst et al, using the same instruments [34]. Also, when comparing the median FSIQ, VIQ, PIQ and PSIQ scores of our study group to the preterm born children [34], the scores of our group is slightly higher [34].

The current study shows a relatively high incidence of motor impairment (M-ABC score ≤ 7). Within the M-ABC-II-NL the section with the lowest score is manual dexterity with a median score of 8.0 (6.0–10.0). We hypothesize that processing speed problems may in part underpin these manual dexterity problems [51].

Our study cannot provide new evidence that ductus venosus measurements might improve long-term outcome as was done in

Table 3A
Analysis of factors associated with FSIQ < 85.

Associated variable, n (%), mean ± SD or median (IQR)	FSIQ ≥ 85 (n = 62)	FSIQ < 85 (n = 11)	P-value
Maternal age in years	30.0 (26–33)	25.0 (24–32)	0.157
Nulliparous	35 (56.5%)	9 (81.8%)	0.182
Maternal smoking	9 (14.5%)	1 (9.1%)	>0.999
Preeclampsia/ HELLP	36 (58.1%)	9 (81.8%)	0.135
Antenatal corticosteroid treatment	61 (98.4%)	11 (100%)	>0.999
Allocation group			0.466
CTG STV	23 (37.1%)	2 (18.2%)	
DV p95	16 (25.8%)	4 (36.4%)	
DV no A	23 (37.1%)	5 (45.5%)	
End diastolic flow prior to delivery			0.020*
Positive	30 (48.4%)	2 (18.2%)	
Absent	29 (46.8%)	6 (54.5%)	
Reversed	3 (4.8%)	3 (27.3%)	
GA at delivery in weeks	29.6 (28.8–30.9)	28.9 (28.3–29.3)	0.024*
Birthweight in grams	915 (794–1043)	800 (660–920)	0.029*
Birthweight P50 ratio	58.9 (54.5–66.4)	59.3 (55.7–62.5)	0.677
Sex			0.057
Boys	25 (40.3%)	8 (72.7%)	
Girls	37 (59.7%)	3 (27.3%)	
Severe neonatal morbidity	15 (24.2%)	7 (63.6%)	0.014*
BPD	8 (12.9%)	5 (45.5%)	0.009*
NDI at 2 years of age	4 (6.5%)	0 (0%)	>0.999
Low maternal education	13 (22%)	2 (20%)	>0.999

FSIQ = full scale intelligence quotient. SD = standard deviation. IQR = interquartile range. BPD = Bronchopulmonary dysplasia. NDI = neurodevelopmental impairment = WPPSI FSIQ score <85, CP with a GMFCS ≥ 1, hearing loss requiring a hearing aid or severe visual loss (partially sighted or legally certifiable as blind. CTG = cardiotocography. STV = short term variation. DV = ductus venosus. GA = gestational age.
* $p < 0.05$ a n = 70.

Table 3B
Analysis of factors associated with any IQ scale < 85 (FSIQ, VIQ, PIQ or PSIQ).

Associated variable, n (%), mean ± SD or median (IQR)	Normal (n = 48)	Any IQ scale score <85 (n = 26)	P-value
Maternal age	30 (26–33)	27 (24–30.3)	0.059
Nulliparous	27 (56.3%)	17 (65.4%)	0.445
Maternal smoking	6 (12.5%)	4 (15.4%)	0.734
Preeclampsia/ HELLP	30 (62.5%)	18 (37.5%)	0.900
Antenatal corticosteroid treatment	47 (97.9%)	26 (100%)	>0.999
Allocation group			0.429
CTG STV	18 (37.5%)	8 (30.8%)	
DV p95	12 (25.0%)	8 (30.8%)	
DV no A	18 (37.5%)	10 (38.5%)	
End diastolic flow prior to delivery[a]			0.052
Positive	24 (50.0%)	8 (32.0%)	
Absent	23 (47.9%)	13 (52.0%)	
Reversed	1 (2.1%)	4 (16.0%)	
GA at delivery	29.5 (28.8–30.5)	29.2 (28.7–31.3)	0.973
Birthweight	930 (781–1050)	850 (735–928)	0.042*
Birthweight P50 ratio	62.3 (56.6–67.4)	56.6 (48.5–61.4)	0.003#
Sex			0.048*
Boys	18 (37.5%)	16 (61.5%)	
Girls	30 (62.5%)	10 (38.5%)	
Severe neonatal morbidity	13 (27.1%)	10 (38.5%)	0.313
BPD	7 (14.6%)	6 / 25 (24.0%)	0.318
NDI at 2 years of age	2 (4.2%)	3 (11.5%)	0.337
Low maternal education	10 (21.7%)	6 (25.0%)	0.758

IQ = intelligence quotient. SD = standard deviation. IQR = interquartile range. NDI = neurodevelopmental impairment = a WPPSI-III score <85, CP with a GMFCS ≥ 1, hearing loss requiring a hearing aid or severe visual loss (partially sighted or legally certifiable as blind. CTG = cardiotocography. STV = short term variation. DV = ductus venosus. GA = gestational age.
Severe neonatal morbidity: NEC ≥ grade II, GMH ≥ grade III, BPD ≥ 36 weeks, proven sepsis, PVL ≥ grade II. *$p < 0.05$, # $p < 0.01$.
[a] Of one patient the last EDF before delivery is missing.

Table 3C
Analysis of factors associated with a total M-ABC-II-NL ≤ 7 or M-ABC-I below 16th percentile.

Associated variable, n (%), mean ± SD or median (IQR)	Normal (n = 44)	Abnormal (n = 27)	P-value
Maternal age	30 (26.5–33.5)	28 (25–31)	0.098
Nulliparous	27 (61.4%)	14 (51.9%)	0.555
Maternal smoking	6 (13.6%)	4 (14.8%)	0.692
Preeclampsia/ HELLP	31 (70.5%)	13 (29.5%)	0.114
Antenatal corticosteroid treatment	43 (97.7%)	27 (100%)	0.382
Allocation group			0.252
CTG STV	14 (31.8%)	11 (40.7%)	
DV p95	10 (22.7%)	9 (33.3%)	
DV no A	20 (45.5%)	7 (25.9%)	
End diastolic flow prior to delivery[a]			0.987
Positive	19 (43.2%)	12 (44.4%)	
Absent	22 (50.0%)	13 (48.1%)	
Reversed	3 (6.8%)	2 (7.4%)	
GA at delivery	29.6 (28.5–30.6)	29.1 (28.3–30)	0.319
Birthweight	910 (798–1023)	820 (675–965)	0.115
Birthweight P50 ratio	63.1 (57.3–68.9)	57.7 (53.4–62.1)	0.127
Sex			0.010*
Boys	14 (31.8%)	17 (63.0%)	
Girls	30 (68.2%)	10 (37.0%)	
Severe neonatal morbidity	11 (25.0%)	12 (44.4%)	0.089
BPD	4 (9.1%)	9 (33.3%)	0.010*
NDI at 2 years of age	2 (4.5%)	3 (11.1%)	0.294
Low maternal education[b]	8 (18.2%)	6 (30.0%)	0.520

m-ABC-II-NL = movement assessment battery for children. SD = standard deviation. IQR = interquartile range. NDI = neurodevelopmental impairment = WPPSI-III scale score <85, CP with a GMFCS ≥ 1, hearing loss requiring a hearing aid or severe visual loss (partially sighted or legally certifiable as blind. CTG = cardiotocography. STV = short term variation. DV = ductus venosus. GA = gestational age.
Severe neonatal morbidity: NEC ≥ grade II, GMH ≥ grade III, BPD ≥ 36 weeks, proven sepsis, PVL ≥ grade II. *p < 0.05.
[a] Of one patient the last EDF before delivery is missing.
[b] Of 8 patients in the normal motor score group and of 7 patients in the abnormal motor score group the maternal educational level is missing.

Table 4
Neurodevelopmental outcome at two and five years of age.

Outcome variable	2 years	5 years
DQ/IQ (median (IQR))	100.0 (90.0 – 110.0)	97.0 (91.0 – 107.0)
Cerebral palsy, n (%)	0 / 74 (0%)	2 / 74 (2.7%)[a]
Mild vision problems, n (%)	2 / 72 (2.8%)	5 / 74 (6.8%)
Mild hearing problems, n (%)	0 / 73 (0%)	1 / 74 (1.4%)

DQ = developmental quotient. IQ = intelligence quotient. SD = standard deviation. The same patients were assessed at both two and five years of age.
[a] Both children with CP had a GMFCS score of 1. One child had an one-sided hemiplegia and one child a spastic diplegia.

the original TRUFFLE publication at age two. However, it does provide evidence of fairly low rates of severe disabilities in children participating in TRUFFLE. It is important that future management trials in FGR plan follow-up until and beyond the age of five years follow from the start. At and after the age of five, the different developmental domains can be assessed much better than at age two, when motor and mental development are more intertwined. Also, at age five and up there is much greater predictive strength towards academic achievement later on in life.

Conclusion

In general, in a neurodevelopmental follow-up study after early-onset FGR, the FSIQ of these five-year-old children was within normal limits. Nevertheless, the rate of IQ score in the abnormal range increased from 6.8% at age two to 15.1% at age five and a high rate of motor problems was seen. GA at delivery, birthweight (ratio), EDF prior to delivery and neonatal morbidity were the most important risk factors for cognitive outcomes.

Conflicts of interests

No conflicts of interests to report

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