Term planned delivery based on fetal growth assessment with or without the cerebroplacental ratio in low-risk pregnancies (RATIO37): an international, multicentre, open-label, randomised controlled trial

Marta Rial-Crestelo, Marek Lubusky, Mauro Parra-Cordero, Ladislav Krofta, Anna Kajdy, Eyal Zohav, Elena Ferriols-Perez, Rogelio Cruz-Martinez, Marian Kacerovsky, Elena Scazzocchio, Lucie Roubalova, Pamela Socias, Lubomir Hašlík, Jan Modzelewski, Eran Ashwal, Julia Castellá-Cesari, Monica Cruz-Lemini, Eduard Gratacos, Francesc Figueras*, on behalf of the RATIO37 Study Group†*

Summary

Background The cerebroplacental ratio is associated with perinatal mortality and morbidity, but it is unknown whether routine measurement improves pregnancy outcomes. We aimed to evaluate whether the addition of cerebroplacental ratio measurement to the standard ultrasound growth assessment near term reduces perinatal mortality and severe neonatal morbidity, compared with growth assessment alone.

Methods RATIO37 was a randomised, open-label, multicentre, pragmatic trial, conducted in low-risk pregnant women, recruited from nine hospitals over six countries. The eligibility criteria were designed to be broad; participants were required to be 18 years or older, with an ultrasound-dated confirmed singleton pregnancy in the first trimester, an alive fetus with no congenital malformations at the routine second-trimester ultrasound, an absence of adverse medical or obstetric history, and the capacity to give informed consent. Women were randomly assigned in a 1:1 ratio (block size 100) using a web-based system to either the concealed group or revealed group. In the revealed group, the cerebroplacental ratio value was known by clinicians, and if below the fifth centile, a planned delivery after 37 weeks was recommended. In the concealed group, women and clinicians were blinded to the cerebroplacental ratio value. All participants underwent ultrasound at 36+0 to 37+6 weeks of gestation with growth assessment and Doppler evaluation. In both groups, planned delivery was recommended when the estimated fetal weight was below the tenth centile. The primary outcome was perinatal mortality from 24 weeks' gestation to infant discharge. The study is registered at ClinicalTrials.gov (NCT02907242) and is now closed.

Findings Between July 29, 2016, and Aug 3, 2021, we enrolled 11 214 women, of whom 9492 (84·6%) completed the trial and were eligible for analysis (4774 in the concealed group and 4718 in the revealed group). Perinatal mortality occurred in 13 (0·3%) of 4774 pregnancies in the concealed group and 13 (0·3%) of 4718 in the revealed group (OR 1·45 [95% CI 0·76–2·76]; p=0·262). Overall, severe neonatal morbidity occurred in 35 (0·73%) newborns in the concealed group and 18 (0·38%) in the revealed group (OR 0·58 [95% CI 0·40–0·83]; p=0·003). Severe neurological morbidity occurred in 13 (0·27%) newborns in the concealed group and nine (0·19%) in the revealed group (OR 0·56 [95% CI 0·25–1·24]; p=0·153). Severe non-neurological morbidity occurred in 23 (0·48%) newborns in the concealed group and nine (0·19%) in the revealed group (0·58 [95% CI 0·39–0·87]; p=0·009). Maternal adverse events were not collected.

Interpretation Planned delivery at term based on ultrasound fetal growth assessment and cerebroplacental ratio at term was not followed by a reduction of perinatal mortality although significantly reduced severe neonatal morbidity compared with fetal growth assessment alone.

Funding La Caixa foundation, Cerebra Foundation for the Brain Injured Child, Agència per la Gestió d'Ajuts Universitaris i de Recerca, and Instituto de Salud Carlos III.

Lancet 2024; 403: 545–53

Published **Online** January 11, 2024 https://doi.org/10.1016/S0140-6736(23)02228-6

See **Comment** page 506

*Both equally contributed as senior authors

†The ratio37 Study Group are listed in the appendix (p 2)

BCNatal–Barcelona Center for Maternal-Fetal and Neonatal Medicine, Hospital Clínic and Hospital San Joan de Deu, Barcelona, Spain (M Rial-Crestelo PhD, Prof E Gratacos PhD, Prof F Figueras PhD); **The Fetal Medicine Center, Department of Obstetrics and Gynecology Palacky University Hospital, Olomouc, Czech Republic** (Prof M Lubusky PhD, L Roubalova MD); **Maternal Fetal Medicine Unit, Department of Obstetrics and Gynecology, University of Chile Hospital, Santiago, Chile** (Prof M Parra-Cordero PhD, P Socias MD); **Institute for the Care of Mother and Child, the Third Faculty of Medicine, Charles University, Prague, Czech Republic** (Prof L Krofta PhD, L Hašlík PhD); **First Department of Obstetrics and Gynecology, Centre of Postgraduate Medical Education, Warsaw, Poland** (Prof A Kajdy PhD, J Modzelewski PhD); **Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel** (E Zohav MD, E Ashwal MD); **Department of Obstetrics and Gynecology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel** (E Zohav, E Ashwal); **Obstetrics and Gynecology Consorci Parc de Salut Mar, Hospital del Mar, Barcelona, Spain** (E Ferriols-Perez PhD, J Castellá-Cesari MD); **Fetal**

Introduction

Adverse perinatal outcomes, including perinatal death and severe neonatal morbidity, affect 2–3% of all pregnancies at term, and a large proportion is caused by placental insufficiency.[1] Placental failure results in a decreased fetal oxygen reserve, predisposing fetuses to severe hypoxia during labour. Detection of placental insufficiency has been recognised as a key measure to prevent adverse perinatal outcomes.[2] This is of particular importance after 37 weeks, when a pronounced increase in preventable stillbirths occurs,[3] and planned delivery is not associated with an increase in adverse neonatal outcomes.[4,5]

Currently, the best clinical surrogate for placental insufficiency is fetal smallness for gestational age (SGA),

Medicine Department, Instituto Medicina Fetal México, Children and Women's Specialty Hospital of Querétaro, Querétaro, Mexico (Prof R Cruz-Martinez PhD); **University Hospital Hradec Kralove, Charles University, Faculty of Medicine, Hradec Kralove, Czech Republic** (Prof M Kacerovsky PhD); **Maternal Fetal Medicine Department, Hospital de Especialidades del Niño y la Mujer, Dr Felipe Nuñez Lara, Querétaro, Mexico** (Prof M Cruz-Lemini PhD); **Atencio a la Salut Sexual i Reproductiva (ASSIR) de Barcelona, Primary Care Center, Catalan Institut of Health, Barcelona, Spain** (E Scazzocchio PhD)

Correspondence to: Prof Francesc Figueras, BCNatal–Barcelona Center for Maternal-Fetal and Neonatal Medicine, Hospital Clínic and Hospital San Joan de Deu, 08028 Barcelona, Spain
ffiguera@clinic.cat

See Online for appendix

Research in context

Evidence before this study

Antenatal detection of fetal growth restriction has been identified as a key measure in the prevention of stillbirth. The clinical surrogate for placental insufficiency is fetal smallness (defined by an ultrasound-estimated fetal size below the tenth centile). We searched PubMed and MEDLINE from database inception to Feb 28, 2023, to review the available evidence on the association between cerebroplacental ratio and adverse perinatal outcome. One study has shown that, compared to selective ultrasound, universal third-trimester ultrasound at term triples the detection of small-for-gestational-age (SGA) babies. However, detection of SGA still fails to detect a large proportion of adverse perinatal outcomes. The Doppler cerebroplacental ratio detects fetal hypoxia, and a low cerebroplacental ratio is associated with a 3·7-fold increased risk of perinatal mortality and neurological problems. For the past 15 years, there has been an ongoing debate in the literature as to whether the cerebroplacental ratio index should be added to routine ultrasound screening in pregnancies at term to improve detection and help prevent adverse perinatal outcomes. However, no randomised trials have evaluated whether routine use of the cerebroplacental ratio improves perinatal outcomes in the low-risk obstetric population.

Added value of this study

RATIO37 was a randomised controlled trial conducted in a low-risk population that provides evidence that the addition of the cerebroplacental ratio, a Doppler measurement of the cerebral-umbilical fetal circulation, to a routine 36 week ultrasound growth assessment does not reduce perinatal mortality, although it reduces severe neonatal morbidity compared with ultrasound alone, albeit without impact on perinatal mortality. This strategy has the potential to reduce severe morbidity by approximately 17%.

Implications of all the available evidence

Our results add to the increasing awareness of prenatal subclinical placental insufficiency in shaping the health of neonates, and the opportunity of prenatal detection to prevent adverse outcomes. To our knowledge, this study represents the highest-quality data available on the effect of using cerebroplacental ratio measurements alongside standard ultrasound on perinatal outcomes, and might influence the design of future protocols and guidelines for pregnancy care. Specific implications could vary from a population-wide use of the cerebroplacental ratio measure where routine ultrasound is already in use, to contingent indications in settings where ultrasound is used according to risk criteria.

which is usually defined by ultrasound as an estimated fetal weight below the tenth centile.[6] Antenatal detection of SGA is associated with a reduction in adverse outcomes.[7,8] However, definitions of suboptimal growth, based on the tenth centile cut-off, fail to detect approximately two thirds of stillbirths and severe neonatal complications secondary to hypoxia at term.[1,9] This has prompted research aiming to identify additional markers for placental insufficiency. The Doppler cerebroplacental ratio detects the presence of fetal brain vasodilation secondary to chronic hypoxia combined with increased placental impedance. In fetuses with suspected SGA, a low cerebroplacental ratio is associated with a 3·7-fold increased risk of perinatal mortality[10] and is associated with long-term neurological problems.[11] Recent observational evidence from large studies suggests that the cerebroplacental ratio is associated with perinatal mortality and neonatal morbidity, independent of birthweight,[10,12,13] supporting the concept that the cerebroplacental ratio can detect latent placental insufficiency among fetuses with weights above the tenth centile. However, no randomised trials have evaluated whether routine use of the cerebroplacental ratio improves perinatal outcomes in the low-risk obstetric population.

In this study, we report the results of the RATIO37 study, a large international multicentre pragmatic trial that aimed to evaluate whether planned delivery at term based on ultrasound fetal growth assessment and cerebroplacental ratio determination can reduce stillbirths and severe neonatal morbidity compared with a strategy based solely on fetal growth assessment.

Methods

Study design and participants

RATIO37 was a randomised, controlled, open-label, multicentre study conducted in nine hospitals in six countries (Spain, Israel, Poland, the Czech Republic, Chile, and Mexico; appendix p 2). It was designed as a pragmatic trial[14] to evaluate the real-world effectiveness of Doppler evaluation at 36–37 weeks gestation. The inclusion criteria were broad; participants were required to be 18 years or older, with an ultrasound-dated confirmed singleton pregnancy[15] in the first trimester, an alive fetus with no congenital malformations at the routine second-trimester ultrasound, an absence of adverse medical or obstetric history, and the capacity to give informed consent. Exclusion criteria were fetal congenital malformations (including chromosomal abnormalities), congenital infections, and subsequent obstetric complications requiring delivery before the scheduled 37-week scan. The study protocol[16] was approved by the ethics committee of the coordinating

centre (HCB/2016/0108), and ancillary approval was obtained from each participating centre.

Randomisation and masking

Women were approached at routine antenatal scans at the participating hospitals. Upon agreement to participate in the study and after obtaining written consent, women were randomly assigned in a 1:1 ratio using a web-based system. The block size of 100 was generated using an online number randomisation tool, and was stratified for participating site to ensure a balanced distribution between the study group within each site. Patients were allocated to either the revealed group (37-week cerebroplacental ratio available for clinical management) or concealed group (37-week cerebroplacental ratio unavailable for clinical management).

Due to the nature of the intervention, it was not possible to mask participants or health professionals from the obstetric department to the study group; however, obstetric management followed similar protocols in each of the participating centres that were agreed upon before the study onset and were available throughout the study conduction as Standard Operating Procedures.

Procedures

An ultrasound examination was performed at 36+0 to 37+6 weeks of gestation for all patients, and included fetal weight estimation[17] and Doppler evaluation. Doppler measures were obtained in the absence of fetal movements and with voluntarily suspended maternal breathing. Doppler parameters were measured automatically from three or more consecutively similar waveforms, with the angle of insonation as close to 0° as possible. The umbilical artery pulsatility index was measured using a free-floating cord loop. The middle cerebral artery pulsatility index was measured in a transversal view of the fetal head at the level of its origin from the circle of Willis. The latter two parameters were used to derive the cerebroplacental ratio, ie, the middle cerebral artery pulsatility index divided by the umbilical artery pulsatility index. A cerebroplacental ratio below the fifth centile was considered abnormal.[18] Management was performed according to the group allocation. In the revealed group, the cerebroplacental ratio value was known by managing clinicians, and if it was abnormal a planned delivery after 37 weeks was recommended (labour induction or elective caesarean section as per obstetric indications). In the concealed group, women and clinicians were masked to the cerebroplacental ratio value. In both groups, planned delivery was recommended when the estimated fetal weight was below the tenth centile, according to the standard of care.[6]

Outcomes

The primary outcome was perinatal mortality (from 24 weeks gestational age to neonatal discharge). This was a planned change from the published protcol to prevent measurement bias. Secondary outcomes were, first, severe neurological morbidity (defined as a composite of intraventricular haemorrhage grade III/IV,[19] periventricular leukomalacia,[20] or hypoxic-ischaemic encephalopathy[21]); second, severe non-neurological morbidity (necrotising enterocolitis requiring surgery, renal failure [serum creatinine greater than 1·5 mg/dL], and cardiac failure requiring ionotropic agents or the need to stay in the NICU for 10 or more days for non-neurological conditions); and third, diagnostic performance of estimated fetal weight and cerebroplacental at the 37 week ultrasound for birthweight less than the third centile, a change from the planned protocol to provide higher clinical relevance.

The tertiary outcomes were mild adverse perinatal outcome, defined as a composite of the following: emergent caesarean section for fetal distress, umbilical artery pH less than 7·10 and base excess of less than –12 mEq/L, 5 min Apgar score less than 7, and admission to the neonatal unit; and second, diagnostic performance of estimated fetal weight and cerebroplacental ratio for low birthweight.

Statistical analysis

The across-country expected perinatal mortality in the concealed (control) group was estimated as 0·5%. The minimum clinically important difference (relative risk of

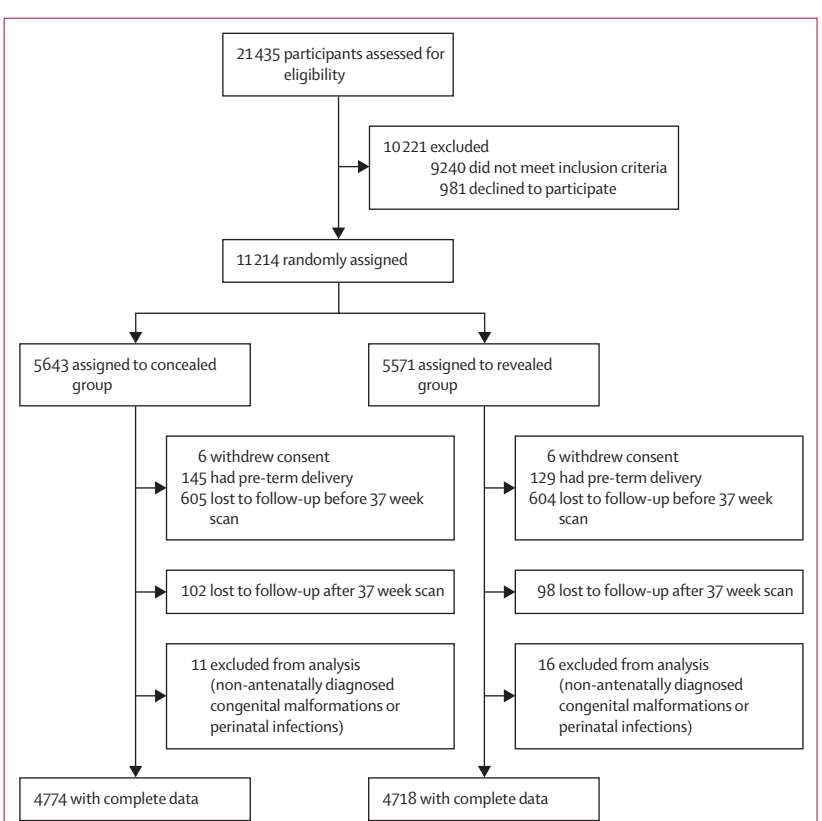

Figure 1: **Study profile**

the intervention) was set at 0·4 (from 0·5% to 0·2%) according to previous discussion among all principal investigators at each site. A simulation was performed using a mixed logistic model with fixed effects of the intercept and the study group (concealed *vs* revealed), and random effects of the intercept for countries (based on the Green and MacLeod procedure)[22] show that a sample size of 9500 participants would achieve a power of 82% (95% CI 73–89). The country-weighted rate of exclusions because of preterm delivery before the intervention was estimated to be 4·5%. Additionally, 1·0% of women were expected to withdraw consent, and 0·5% were expected to be excluded because of fetal malformations or perinatal infections. Finally, the loss-to-follow-up was estimated as 15% (10% from the point of random allocation to the 37-week evaluation, and 5% from the 37-week evaluation to delivery). The resulting sample size for recruitment was 11 582.

	Concealed group (n=5643)	Revealed group (n=5571)
Maternal age at recruitment, years	32·3 (5·3)	32·4 (5·2)
Weight at enrolment, kg	65·8 (12·4)	65·5 (12·3)
Height, cm	164·3 (7·2)	164·1 (7·1)
BMI at enrolment, kg/m²	24·02 (4·4)	24·01 (4·4)
Smoking at recruitment	147 (2·6%)	148 (2·7%)
Alcohol use during pregnancy	28 (0·5%)	34 (0·6%)
Use of recreational drugs during pregnancy	25 (0·4%)	38 (0·7%)
Education level		
No education	50 (0·9%)	35 (0·6%)
Primary	245 (4·3%)	238 (4·3%)
Secondary	3008 (53·3%)	2960 (53·1%)
Higher education	2340 (41·5%)	2338 (42·0%)
Low socioeconomic status	1040 (18·4%)	1009 (18·1%)
Ethnic origin		
White	4405 (78·1%)	4379 (78·6%)
Latin American	1034 (18·3%)	1009 (18·1%)
Asian	129 (2·3%)	109 (2·0%)
Black	11 (0·2%)	9 (0·2%)
Other	64 (1·1%)	65 (1·2%)
Nulliparity	3128 (55·4%)	3142 (56·4%)
Assisted reproductive technique	168 (3·0%)	181 (3·2%)
Second trimester abdominal circumference, Z-value*	0·33 (1·4)	0·34 (1·4)
Gestational age at 37-week scan, weeks†	36·8 (0·93)	36·7 (0·97)
Estimated fetal weight at 37-week scan, g†	2903 (346)	2898 (352)
Estimated fetal weight centile at 37-week scan†	59·5 (26·9)	59·7 (26·9)
Estimated fetal weight <10th centile	201/4887 (4·1%)	199/4832 (4·1%)
Estimated fetal weight <3rd centile	64/4887 (1·3%)	53/4832 (1·1%)
Umbilical artery pulsatility index†	0·87 (0·15)	0·87 (0·15)
Middle cerebral artery pulsatility index†	1·71 (0·31)	1·71 (0·31)
Cerebroplacental ratio†	2·00 (0·45)	2·02 (0·45)
Cerebroplacental ratio <5th centile†	330 (6·8%)	270 (5·6%)

Data are mean (SD) or n (%). *Denominator includes 9726 non-missing values (4908 in the concealed group and 4818 in the revealed group) †Denominator includes ultrasound data from 9719 participants (4887 in the concealed group and 4832 in the revealed group; not including losses-to-follow-up before scanning [n=1209], due to preterm delivery [n=274], and due to consent withdrawal [n=12]).

Table 1: **Baseline characteristics of the population**

The efficacy variables were analysed and compared between groups by odds ratios (ORs) and 95% CIs. This value was computed using the generalised linear mixed model for binary responses (logit link function). In these mixed logistic effects models we defined the study group as a fixed effect and country as an intercept random effect (enrolled patients from the population of possible patients). The Wald test was used for the main analysis. No inferential analysis was performed for baseline comparability. For the remaining inferential analysis, due to the exploratory purpose, statistical tests were applied with 0·05 two-sided significance without α correction.

We prespecified certain subgroups as being of special interest: age (≤35 years *vs* >35 years); ethnicity (White *vs* non-White [patient self-definition]); socio-economic status (low—no education or primary education only, unemployed, or both; and non-low—secondary education or above, or in employment); and BMI at enrolment (<30 kg/m² *vs* ≥30 kg/m²). The same logistic mixed regression model used for the main analysis was applied to examine the study group and subgroup interactions. Subgroup interactions were considered statistically significant at a significance level of 10%.

Handling of missing data followed the principles specified in the ICHE9 and the CPMP/EWP/1776/99 Rev1 Guideline on Missing Data in confirmatory trials. Missingness was assumed to follow a non-random pattern. Formal imputations were performed for the outcome variables by multiple imputation separately by randomisation group. A sensitivity analysis of complete cases was secondarily performed.

The primary analysis for all outcomes was performed by intention-to-treat analysis (all randomly allocated participants regardless of whether they remained in the same group at the study end). Subsequently, outcome analysis was performed per-protocol to assess the robustness of the results. The protocol deviation considered in this study was no compliance with the intervention. Predefined non-compliance criteria included women who did not carry out the planned research scan (for both groups) or the rejection of planned delivery if recommended (only in the revealed group).

Three post hoc analyses were selected: first, overall severe neonatal morbidity; second, for women with complete data and a cerebroplacental ratio less than the fifth centile, the frequency of the predefined outcomes was analysed by each study group; and third, for women with complete data in the concealed group, the frequency of the predefined outcomes was analysed according to the cerebroplacental ratio.

Central monitoring audits were performed every 3 months on the central database by site, systematically including checks for missing and invalid data, and procedural auditing with prespecified quality targets—the rate of randomly allocated women attending the planned 37-week scan (target >75%), the rate of abnormal cerebroplacental ratio results (target 2–10%), and the rate of women with abnormal cerebroplacental ratio results in the revealed group with planned delivery (target >75%).

The quality of the Doppler measurements was audited annually, stratified by centre, by random selection of images for quality assessment using a validated scoring system.[23] The procedure and results of the first quality assessment have been published previously.[24] Sample size estimation was done using the lme4 and simr v1.0 packages of R version 3.2.5; all other analyses were done with STATA verson 17.0.

This study was registered at ClinicalTrials.gov, NCT02907242.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 3, 2016, and Aug 29, 2021, 21435 women were assessed for eligibility. Of them, 11214 (52·3%) fulfilled the inclusion criteria and consented to participate. After random allocation at a median gestational age of 21·6 weeks (SD 5·4), 5643 women were allocated to the concealed group and 5571 were allocated to the revealed group (figure 1). Table 1 shows the baseline characteristics by study group.

Primary and secondary efficacy analyses were checked for all randomly allocated participants who did not withdraw consent, and who did not have a preterm delivery, congenital malformations, or perinatal infections. A total of 9492 women had complete data (4774 in the concealed group and 4718 in the revealed group).

The baseline and clinical differences among included patients (n=10901) between patients with complete and incomplete data (losses-to-follow-up) are shown in the appendix (p 3). Of note, there were differences in epidemiological baseline characteristics secondary to different patterns of losses-to-follow-up among participating countries. However, the ultrasound and Doppler characteristics did not differ between women with complete and those with incomplete data.

Table 2 shows the endpoints according to the study group, and table 3 details the overall perinatal outcomes by study group in patients with complete data. Adverse events for the pregnant women were not collected. Regarding the primary outcome, the primary analysis showed no significant effect of the intervention on perinatal mortality. Perinatal mortality occurred in 13 (0·3%) pregnancies in the concealed group and 13 (0·3%) in the revealed group (OR 1·45 [95% CI 0·76–2·76]; p=0·262; appendix p 4). For the secondary outcomes, no difference between the study groups was found for severe neurological morbidity (0·56 [0·25–1·24]; p=0·153; appendix p 4), but significant reductions were found in severe non-neurological morbidity (0·58 [0·39–0·87]; p=0·0086). Overall, severe neonatal morbidity (neurological or non-neurological) was found to be reduced in the revealed group (0·58 [0·40–0·83]; p=0·0033). Figure 2 shows the primary efficacy analysis.

The sensitivity analysis of the 9492 women with complete data also indicated similar associations, with ORs of 1·00 (95% CI 0·46–2·16; p=0·998), 0·71 (0·30–1·66; p=0·425), 0·39 (0·18–0·85; p=0·018), and 0·52 (0·29–0·92; p=0·024) for perinatal mortality, severe neurologic morbidity, severe non-neurologic morbidity, and overall severe morbidity, respectively.

Among included women, 4876 (88·9%) of 5481 in the concealed group and 4736 (87·4%) of 5420 in the revealed group were managed as per protocol. The per protocol efficacy analysis (both with multiple imputation and restricted to cases with complete data, appendix p 4) supports the robustness of the intention-to-treat approach.

	Concealed group (n=4774)	Revealed group (n=4718)	Risk difference* (95%CI)	p value
Perinatal death, n (%)	13 (0·3%)	13 (0·3%)	0·01 (–0·21 to 0·24)	0·98
Fetal deaths	11	8	..	..
Neonatal deaths	2	5	..	..
Severe neurological morbidity, n (%)	13 (0·3‰)	9 (0·2%)	–0·08 (–0·29 to 0·13)	0·55
IVH grade III/IV	2	0	..	..
PVL	1	0	..	..
HIE	12	9	..	..
Severe non-neurological morbidity, n (%)	23 (0·5%)	9 (0·2%)	–0·29 (–0·55 to –0·056)	0·014
Necrotising enterocolitis	1	0	..	..
Renal failure	1	0	..	..
Cardiac failure	1	0	..	..
NICU admission ≥10 days†	21	9	..	..
Overall severe morbidity, n (%)	35 (0·7%)	18 (0·4%)	–0·35 (–0·67 to –0·05)	0·022

IVH=intraventricular haemorrhage. PVL=periventricular leukomalacia. HIE=hypoxic-ischemic encephalopathy. NICU=neonatal intensive care unit. *Corresponding odds ratios are shown in the appendix (p 4) †For non-neurological reasons.

Table 2: **Study endpoints by randomisation group in patients with complete data**

In the subgroup of women in the revealed group with complete data and an abnormal cerebroplacental ratio, 70 (27%) of 261 declined planned delivery.

Figure 3 shows the subgroup analyses. Because there were no primary or secondary events in the prespecified subgroup of women with low socioeconomic status, this subgroup analysis was not performed. Similarly, because there were no cases of severe neurological morbidity among women with a BMI greater than or equal to 35, this interaction could not be evaluated. None of the other prespecified interaction terms (maternal age ≤35 *vs* >35 years, enrolment BMI ≤30 *vs* >30, and White *vs* non-White ethnicity) were found to significantly modify the effect of the intervention.

Table 3 displays the effect of the intervention on the predefined tertiary outcomes (birthweight under the tenth and under the third centiles, and mild adverse outcome) in women with complete data. No significant effects were found. The intention-to-treat analysis of 10 901 included women (5481 in the concealed group and 5420 in the revealed group) also failed to show any significant effect for birthweight less than the tenth centile (OR 1·00, 95% CI 0·84–1·19), birthweight less than the third centile (0·92, 0·61–1·37), or mild adverse outcome (1·06, 0·95–1·19).

The diagnostic performance (95% CI) of estimated fetal weight under the tenth centile, cerebroplacental ratio less than the fifth centile, both criteria, and any of the criteria for low birthweight (ie, <10th and <3rd centile) at birth in patients with complete data is shown in the appendix (p 5). The efficacy of revealed versus concealed management (intention-to-treat) in the subgroup of women with elective caesarean section (n=1244) is shown in the appendix (p 6). Statistical significance was not reached for any of the outcomes.

For severe neonatal morbidity, the first prespecified post hoc analysis revealed that cerebroplacental ratio was associated with a significant reduction in overall severe morbidity (OR 0·58 [95% CI 0·40–0·83]; p=0·0033). In women with complete data and a cerebroplacental ratio less than the fifth centile (n=581), there was one fetal death (in the concealed group), two neurological adverse outcomes (one in each group), and seven non-neurological adverse outcomes (all in the concealed group; appendix p 7). The distribution of the time interval between the scan and delivery in cases with abnormal ratio by study group is shown in the appendix (p 11).

For the third post hoc analysis in women in the concealed group with complete data (n=4774), those with a cerebroplacental ratio less than the fifth centile had a significantly higher risk of a non-neurological adverse outcome (OR 6·2, 95% CI 2·5–15·2), overall severe outcome (4·2, 1·9–9·3), birthweight less than the tenth centile (4·3, 3·1–6·0), and birthweight less than the third centile (OR 4·5, 95% CI 2·4–8·7). Supplementary table 6 shows this analysis.

	Missing data, n (%; n=9492)	Concealed group (n=4774)	Revealed group (n=4718)	p value
Gestational age at delivery, weeks	408 (4·3%)	39·5 (1·18)	39·5 (1·21)	0·074
Birthweight, g	135 (1·4%)	3366 (434)	3361 (440)	0·537
Birthweight centile	481 (5·1%)	55·9 (27·6)	55·7 (27·6)	0·768
Birthweight <10th centile	481 (5·1%)	256 (5·7%)	256 (5·7%)	0·932
Birthweight <3rd centile	481 (5·1%)	50 (1·1%)	45 (1%)	0·631
Neonatal sex	137 (1·4%)	NA	NA	0·839
Male	NA	2392/4693 (51·0%)	2386/4662 (51·2%)	..
Female	NA	2301/4693 (49·0%)	2276/4662 (48·8%)	..
Labour onset	1 (<0·1%)	NA	NA	0·384
Spontaneous	NA	2989 (62·6%)	2904 (61·6%)	..
Labour induction	NA	1155 (24·2%)	1199 (25·4%)	..
Elective caesarean section	NA	630 (13·2%)	614 (13·0%)	..
Method of induction	573 (6%)	NA	NA	0·278
No induction	NA	3342/4461 (74·9%)	3271/4458 (73·4%)	..
Prostaglandins	NA	820/4461 (18·4%)	863/4458 (19·4%)	..
Oxytocin	NA	85/4461 (1·9%)	104/4458 (2·3%)	..
Mechanical methods	NA	214/4461 (4·8%)	220/4458 (4·9%)	..
Mode of delivery	132 (1·4%)	NA	NA	0·044
Spontaneous	NA	3180/4695 (67·7%)	3134/4665 (67·2%)	..
Instrumental	NA	231/4695 (4·9%)	284/4665 (6·1%)	..
Caesarean section	NA	1284/4695 (27·3%)	1247/4665 (26·7%)	..
Instrumental delivery for non-reassuring fetal status	275 (2·9%)	120/4629 (2·6%)	152/4588 (3·3%)	0·124
Caesarean section for non-reassuring fetal status	275 (2·9%)	310/4629 (6·7%)	305/4588 (6·6%)	..
5-minute Apgar score <7	229 (2·4%)	34/4647 (0·7%)	27/4616 (0·6%)	0·383
Neonatal acidosis	227 (2·4%)	240/4657 (5·2%)	273/4608 (5·9%)	0·105
Hypoglycaemia	93 (1%)	30 (0·6%)	10 (0·2%)	0·002
Admission to the neonatal unit	0	507 (10·6%)	490 (10·4%)	0·768
Mild adverse outcome	374 (3·9%)	799/4592 (17·4%)	827/4526 (18·3%)	0·277

Data are mean (SD) or n (%). NA=not applicable.

Table 3: **Perinatal outcomes of both groups among patients with complete data**

Discussion

This randomised controlled trial conducted in a low-risk obstetric population provides evidence that addition of the cerebroplacental ratio to a routine 36-week ultrasound growth assessment does not reduce perinatal mortality, but reduces severe neonatal morbidity compared with ultrasound alone. This strategy has an effect on severe neonatal morbidity that ranges from a 17% to a 60% reduction, according to our 95% CI.

The value of cerebroplacental ratio to predict or prevent adverse perinatal outcomes has shown conflicting results in previous observational studies[25,26] and one randomised controlled trial.[27] Recently, a systematic review that included 21 studies, 13 observational prospective studies, and eight retrospective studies concluded that the cerebroplacental ratio was strongly associated with adverse perinatal outcomes, suggesting the need for

randomised controlled trials to evaluate the benefits and risks of its clinical application.[28] In a single-site randomised controlled trial, Sherrell and colleagues[27] allocated 501 unselected pregnancies to the standard of care (no screening) or screening at 37 to 38 weeks gestation by the cerebroplacental ratio and placental growth factor, as markers of placental insufficiency. There was no difference in the rate of perinatal adverse outcomes between screened and non-screened pregnancies (25·3% *vs* 22·2%). A substantially larger sample size and a more stringent definition of neonatal morbidity may explain the positive findings in the present trial compared with this previous study.

Since the publication of our study protocol[16] in 2016, other randomised controlled trial protocols have been published,[29,30] including the CEPRA study, which aimed to evaluate a delivery strategy based on the cerebroplacental ratio in pregnancies affected by reduced fetal movements, and the PROMISE study, which aimed to determine whether the introduction of a pre-labour screening test at term combining the cerebroplacental ratio and maternal placental growth factor level would reduce a composite of adverse outcomes.

In term low-risk pregnancies, the identification of fetuses at risk for neonatal morbidity and mortality is challenging due to the scarcity of diagnostic tools. The use of routine ultrasound for fetal growth assessment is still subject to controversy because of conflicting results,[31] and because two thirds of severe adverse outcomes occur in fetuses with a fetal weight above the tenth centile.[1,9] The potential use of the cerebroplacental ratio as a high-risk marker that is independent of fetal weight has raised considerable interest in recent years, but the evidence to date has been inconclusive. The results of this multicentre randomised trial support that the combination of the cerebroplacental ratio and ultrasound fetal growth assessment in low-risk pregnant women near term could improve perinatal outcomes compared with ultrasound use alone. According to an expected event rate of 0·7% for overall severe morbidity (as found in the concealed group), an OR of 0·58 could be translated into a need to screen 342 patients to prevent one event. Assuming a screening-positive rate of 5%, 17 women would be recommended for planned delivery. Cerebroplacental ratio measurement is technically easy, and can be implemented in clinical practice without the need for highly specialised training. This Doppler measurement has been used for the management of fetal growth restriction for decades, and has been shown to be feasible and reproducible across a wide range of settings, equipment, and operators.[24] The recommendation of elective delivery is part of current protocols in the management of fetal growth restriction and is perceived by women as a procedure that meets their expectations and experiences of personal control during childbirth.[4]

This pragmatic trial measured the efficacy of the intervention in routine clinical practice in a real setting

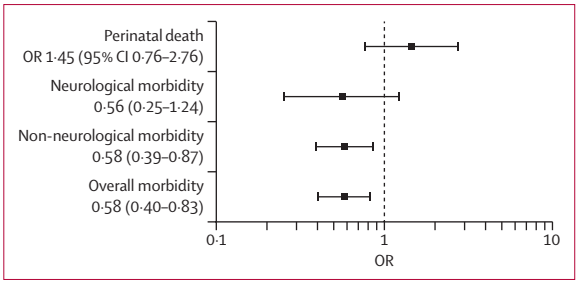

Figure 2: **Primary analysis of the efficacy of revealed versus concealed management**
OR=odds ratio.

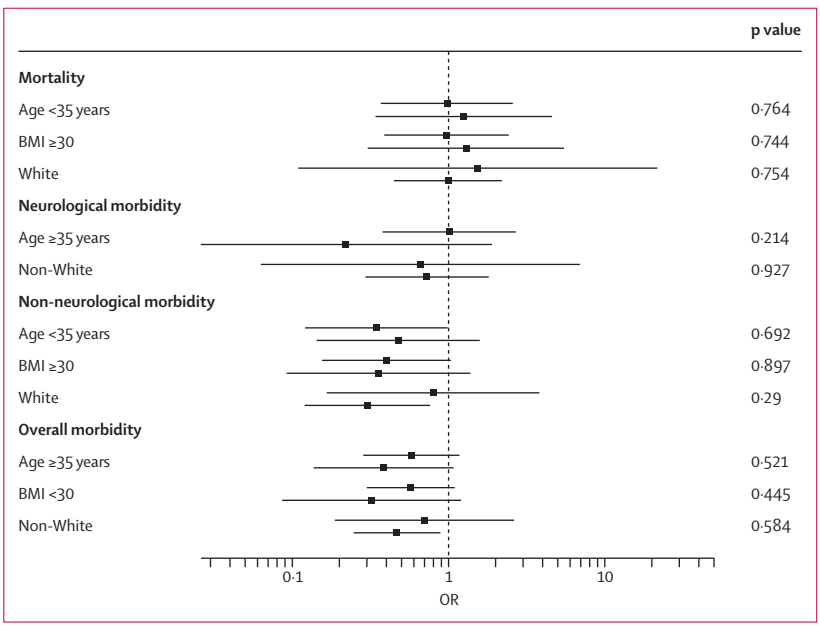

Figure 3: **Forest plot for subgroup analysis comparing revealed *vs* concealed management**
p values compare the odds ratios across the different subgroups for each factor. BMI, kg/m². OR=odds ratio.

and not under ideal conditions as in explanatory trials. Furthermore, the population characteristics of the six participating centres markedly differed in terms of maternal characteristics (age, socioeconomic level, BMI, and ethnicity) and obstetric practices, as reflected by elective caesarean rates. This heterogeneity increases the external validity, and makes conclusions generalisable to a wide range of clinical settings and populations. Although the mean gestational age at delivery did not differ between the study groups, among women with abnormal cerebroplacental ratio mean gestational age at delivery occurred 1 week earlier in the revealed than in the concealed group (268 *vs* 275 days). It could be speculated that this longer exposure to hypoxic conditions in the concealed group may explain the higher incidence of severe morbidity.

Our trial has some limitations. First, the study failed to demonstrate a reduction in the primary outcome. The observed prevalence of perinatal mortality (2·4 per 1000)

was substantially lower than the 5·0 per 1000 expected from estimates reported in 2000 by WHO. This rendered our study underpowered for moderate effects on the primary outcome. Second, the rate of loss to follow-up was relatively large: 1409 (13%) of 11 214 randomly allocated women. A relatively early randomisation strategy was adopted because it reflects clinical practice in many settings, where women are allocated to low-risk or high-risk pathways in the second trimester. This resulted in a proportion of women dropping from the study for subsequent findings. Third, because of the nature of the study design, caregivers were not masked to the cerebroplacental ratio-revealed group. We argue that this might have resulted in a conservative bias, because the knowledge of an abnormal cerebroplacental ratio was more likely to result in overdiagnosis of neonatal morbidity rather than underdiagnosis. Inherent to the open-label design it is impossible to know how the effect of the intervention (revealed *vs* concealed) was mediated. Fourth, adherence to the intended intervention (planned delivery for an abnormal cerebroplacental ratio) in the revealed group was approximately 70%. Whereas this reflects real-life clinical practice, we speculate that if the adherence in the revealed group had been higher than 70%, the effect of the intervention would have been greater. Fifth, as with any antenatal Doppler measurement, the cerebroplacental ratio is subject to reproducibility issues. However, this measurement is included in some international guidelines in the management of SGA.[32,33] Sixth, we acknowledge that it is plausible that the cerebroplacental ratio could be more effective for management of what are known as sub-small fetuses, those with estimated fetal weight slightly above the tenth centile (with subtle placental insufficiency), rather than **of** larger fetuses. However, this study was not designed to address this question. Finally, long-term follow-up is needed to evaluate whether the intervention has delayed consequences into childhood. Population-based studies show that uncomplicated early-term delivery is associated with a lower school performance at 12 years across the spectrum of birthweight centiles.[34]

In conclusion, in this multicentre randomised trial, the combined use of the cerebroplacental ratio and ultrasound fetal growth assessment as diagnostic tools to indicate planned delivery failed to show any reduction in perinatal mortality, but did reduce adverse neonatal outcomes in third-trimester pregnant women at term compared with ultrasound alone. Further randomised trials are required to confirm the results of the present study and to help determine whether the cerebroplacental ratio is beneficial in all pregnancies or in selected groups.

Contributors

EG and FF conceived and designed the protocol of the study, evaluated the results, and wrote and reviewed the manuscript. They both contributed as senior authors. MR-C recruited the patients and collected the data in the primary center, evaluated the results, wrote the manuscript, and coordinated the study between centers. ML, LR, MP-C, PS, LK, LH, AK, JM, EZ, EA, EF-P, JC-C, RC-M, MC-L, MK, and ES recruited the patients and collected the data in their respective centers and reviewed the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

EG declares payment to their institution in support of the present study from La Caixa Foundation (LCF/PR/ GN18/10310003); Cerebra Foundation for the Brain Injured Child (Carmarthen, Wales, UK); AGAUR (grant 2017 SGR number 1531); and Instituto de Salud Carlos III (PI15/00903). EG declares payment to their institution outside the present study from Roche Diagnostic International; and book royalties from Comumna Edicions and Editorial Médica Panamericana. FF declares payment to their institution outside the present study from Roche Diagnostic International; book royalties from Editorial Médica Panamericana; and consulting fees and payments for lectures from Roche Diagnostic International, outside the present study.

Data sharing

Anonymised individual participant data, the study protocol, statistical analysis plan, and informed consent form will be available after publication via email after approval of a proposal with a signed data access agreement.

Acknowledgments

MR-C participated in the study under a non-scholarship grant of the European Erasmus Mundus International Joint Doctorate. The project was partially funded by grants: from the La Caixa Foundation (LCF/PR/ GN18/10310003); Cerebra Foundation for the Brain Injured Child (Carmarthen, Wales, UK); AGAUR (grant 2017 SGR number 1531), and Instituto de Salud Carlos III (PI15/00903) co-funded by the European Union. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain and Centre for Biomedical Research on Rare Diseases (CIBERER), Barcelona, Spain.

References

1 Chauhan SP, Rice MM, Grobman WA, et al. Neonatal morbidity of small- and large-for-gestational-age neonates born at term in uncomplicated pregnancies. *Obstet Gynecol* 2017; **130:** 511–19.
2 Flenady V, Wojcieszek AM, Middleton P, et al. Stillbirths: recall to action in high-income countries. *Lancet* 2016; **387:** 691–702.
3 Pilliod RA, Cheng YW, Snowden JM, Doss AE, Caughey AB. The risk of intrauterine fetal death in the small-for-gestational-age fetus. *Am J Obstet Gynecol* 2012; **207:** 318.e1–e6.
4 Grobman WA, Rice MM, Reddy UM, et al. Labor Induction versus expectant management in low-risk nulliparous women. *N Engl J Med* 2018; **379:** 513–23.
5 Middleton P, Shepherd E, Morris J, Crowther CA, Gomersall JC. Induction of labour at or beyond 37 weeks' gestation. *Cochrane Database Syst Rev* 2020; **7:** CD004945.
6 Lees CC, Stampalija T, Baschat A, et al. ISUOG practice guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol* 2020; **56:** 298–312.
7 Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. *BMJ* 2013; **346:** f108.
8 Lindqvist PG, Molin J. Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? *Ultrasound Obstet Gynecol* 2005; **25:** 258–64.
9 Poon LCY, Tan MY, Yerlikaya G, Syngelaki A, Nicolaides KH. Birth weight in live births and stillbirths. *Ultrasound Obstet Gynecol* 2016; **48:** 602–06.
10 Conde-Agudelo A, Villar J, Kennedy SH, Papageorghiou AT. Predictive accuracy of cerebroplacental ratio for adverse perinatal and neurodevelopmental outcomes in suspected fetal growth restriction: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2018; **52:** 430–41.
11 Dunn L, Sherrell H, Kumar S. Review: systematic review of the utility of the fetal cerebroplacental ratio measured at term for the prediction of adverse perinatal outcome. *Placenta* 2017; **54:** 68–75.
12 Khalil A, Morales-Roselló J, Townsend R, et al. Value of third-trimester cerebroplacental ratio and uterine artery Doppler indices as predictors of stillbirth and perinatal loss. *Ultrasound Obstet Gynecol* 2016; **47:** 74–80.

13 Prior T, Mullins E, Bennett P, Kumar S. Prediction of intrapartum fetal compromise using the cerebroumbilical ratio: a prospective observational study. *Am J Obstet Gynecol* 2013; **208:** 124.e1–6.

14 Roland M, Torgerson DJ. Understanding controlled trials: what are pragmatic trials? *BMJ* 1998; **316:** 285.

15 Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. *Br J Obstet Gynaecol* 1975; **82:** 702–10.

16 Figueras F, Gratacos E, Rial M, et al. Revealed versus concealed criteria for placental insufficiency in an unselected obstetric population in late pregnancy (RATIO37): randomised controlled trial study protocol. *BMJ Open* 2017; 7: e014835.

17 Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements—a prospective study. *Am J Obstet Gynecol* 1985; **151:** 333–37.

18 Baschat AA, Gembruch U. The cerebroplacental Doppler ratio revisited. *Ultrasound Obstet Gynecol* 2003; **21:** 124–27.

19 Volpe JJ. Volpe's Neurology of the Newborn 5th edn. 2008. https://www.sciencedirect.com/book/9781416039952/neurology-of-the-newborn (accessed Dec 5, 2015).

20 de Vries LS, Eken P, Dubowitz LMS. The spectrum of leukomalacia using cranial ultrasound. *Behav Brain Res* 1992; **49:** 1–6.

21 D'Alton ME, Hankins GDV, Berkoqitz RL, et al. Executive summary: neonatal encephalopathy and neurologic outcome, second edition. *Obstet Gynecol* 2014; **123:** 896–901.

22 Green P, Macleod CJ. SIMR: an R package for power analysis of generalized linear mixed models by simulation. *Methods Ecol Evol* 2016; **7:** 493–98.

23 Molloholli M, Napolitano R, Ohuma EO, et al. OP15.05: image scoring system for quality control of umbilical and uterine artery Doppler measurement. *Ultrasound Obstet Gynecol* 2016; **48:** 98.

24 Rial-Crestelo M, Morales-Roselló J, Hernández-Andrade E, et al. Quality assessment of fetal middle cerebral and umbilical artery Doppler images using an objective scale within an international randomized controlled trial. *Ultrasound Obstet Gynecol* 2020; **56:** 182–86.

25 Khalil AA, Morales-Rosello J, Morlando M, et al. Is fetal cerebroplacental ratio an independent predictor of intrapartum fetal compromise and neonatal unit admission? *Am J Obstet Gynecol* 2015; **213:** 54.e1–10.

26 Bligh LN, Alsolai AA, Greer RM, Kumar S. Prelabor screening for intrapartum fetal compromise in low-risk pregnancies at term: cerebroplacental ratio and placental growth factor. *Ultrasound Obstet Gynecol* 2018; **52:** 750–56.

27 Sherrell HC, Clifton VL, Kumar S. Prelabor screening at term using the cerebroplacental ratio and placental growth factor: a pragmatic randomized open-label phase 2 trial. *Am J Obstet Gynecol* 2020; **223:** 429.e1–9.

28 Dunn L, Sherrell H, Kumar S. Review: systematic review of the utility of the fetal cerebroplacental ratio measured at term for the prediction of adverse perinatal outcome. *Placenta* 2017; **54:** 68–75.

29 Damhuis SE, Ganzevoort W, Duijnhoven RG, et al. The cerebro placental ratio as indicator for delivery following perception of reduced fetal movements, protocol for an international cluster randomised clinical trial; the CEPRA study. *BMC Pregnancy Childbirth* 2021; **21:** 285.

30 Sherrell H, Clifton V, Kumar S. Predicting intrapartum fetal compromise at term using the cerebroplacental ratio and placental growth factor levels (PROMISE) study: randomised controlled trial protocol. *BMJ Open* 2018; **8:** e022567.

31 Henrichs J, Verfaille V, Jellema P, et al. Effectiveness of routine third trimester ultrasonography to reduce adverse perinatal outcomes in low-risk pregnancy (the IRIS study): nationwide, pragmatic, multicentre, stepped wedge cluster randomised trial. *BMJ* 2019; **367:** l5517.

32 Lees CC, Stampalija T, Baschat A, et al. ISUOG practice guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. *Ultrasound Obstet Gynecol* 2020; **56:** 298–312.

33 Melamed N, Baschat A, Yinon Y, et al. FIGO (international federation of gynecology and obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. *Int J Gynaecol Obstet* 2021; **152** (suppl 1)**:** 3–57.

34 Burger RJ, Mol BW, Ganzevoort W, et al. Offspring school performance at age 12 after induction of labor *vs* non-intervention at term: a linked cohort study. *Acta Obstet Gynecol Scand* 2023; **102:** 486–95.