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The SAVE FGR study: Short term variation Analysis versus Visual Evaluation of cardiotocography in early-onset Fetal Growth Restriction to trigger expedited birth - study protocol for a stepped wedge cluster randomized trial

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Abstract

Background Early-onset fetal growth restriction (eoFGR) is associated with high risks of adverse outcomes and a key dilemma in clinical obstetrical practice in determining the optimal timing of birth. Cardiotocography (CTG) is an important tool for antepartum fetal surveillance and typically assessed visually. Computerised CTG including short term variation (STV) analysis offers an objective analysis by quantifying the beat-to-beat variation in the fetal heart rate. Currently, there is a lack of randomized studies of sufficient power that examine whether birth intervention based on such quantified STV improves outcomes by ensuring timely intervention. The aim of this study is to compare perinatal and long-term outcomes up to two years of corrected age, from birth based on monitoring the fetal condition using visual evaluation of the CTG only versus CTG supported by computerised STV analysis.

Methods This study is a multicenter stepped wedge cluster randomized trial including women with singleton pregnancies between 24 and 32 weeks of gestation with eoFGR (abdominal circumference or estimated fetal weight below p10 AND umbilical artery pulsatility index above p95) with an indication for fetal CTG monitoring. In the control period, CTG monitoring is performed through visual evaluation and birth is expedited when the CTG exhibits signs of hypoxia, such as a reduced heart rate variability or repetitive, unprovoked decelerations. In the intervention period, visual evaluation of the CTG is supported by STV analysis, with birth expedited if the STV is below 3.5 ms (below 29 weeks' gestation) or 4.0 ms (between 29 and 32 weeks' gestation), or if other signs of hypoxia are observed visually. The intended sample size is at least 16 clusters and 800 participants. Coprimary outcomes are perinatal death and neurodevelopmental impairment at two years of corrected age based on the Ages and Stages Questionnaire.

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Secondary outcomes include mode of birth, neonatal morbidity, maternal health and infant health outcomes until two years CA. Analysis will be intention-to-treat and per-protocol.

Discussion This study will provide insight if STV-analysis in the timing of birth in pregnancies complicated by eoFGR improves perinatal outcomes and neurodevelopmental outcomes until two years of corrected age.

Trial registration Prospectively registered at August 24, 2023. ClinicalTrials.gov: NCT06010238.

Keywords Fetal growth restriction, Placental insufficiency, Cardiotocography, Computerised cardiotocography, Short-Term variation, Fetal hypoxia, Perinatal mortality, Fetal death, Infant development

Introduction

Early-onset fetal growth restriction (eoFGR) is a rare condition, affecting 0.5–1.5% of pregnancies [1]. eoFGR is defined as the inability of a fetus to reach its biological growth potential, diagnosed before 32 weeks of gestation [2]. The most common pathophysiological mechanism is uteroplacental insufficiency, mainly caused by placental maternal vascular malperfusion due to suboptimal trophoblast invasion in the spiral arteries [3]. Fetuses with eoFGR have increased risks of perinatal mortality, preterm birth, neonatal morbidity, poor neurodevelopmental outcomes, as well as other adverse long-term health effects [4–7]. Such pregnancies can impose a substantial burden on parental well-being [8–12]. As no therapeutic interventions are available, management involves close monitoring of the fetal and maternal condition (as hypertensive disorders often co-exist), until expedited birth is indicated. The optimal timing of birth is a fine balance between the risks of prematurity and the risks of hypoxia due to remaining in a hostile intrauterine environment [13].

Fetal heart rate monitoring is essential for detection of progressive fetal hypoxia, which causes measurable pathophysiological adaptations [14–16]. While repetitive decelerations are typically obvious when assessing the cardiotocogram (CTG), the visual evaluation of reduced heart rate variability is subject to significant variation between clinicians [17]. This subjectivity could be overcome by quantification of the short term variation (STV) using the Dawes-Redman algorithm. This method is commonly referred to as computerised or computer-assisted CTG analysis [18–20]. STV analysis is believed by many to be valuable in facilitating timely intervention due to its objective measurement [21]. It is even described as the gold standard for antenatal monitoring of eoFGR in some countries due to its face value. The pitfall is that such assessment may falsely reassure observers, who may subsequently ignore important other signals in the CTG from visual evaluation. However, it is unknown if the use of quantified STV to trigger expedited birth results in better outcomes.

Previously, systematic reviews have investigated the use of antenatal computerised CTG in comparison to visual evaluation. Grivell et al. [22, 23] found that the use of computerised CTG significantly reduced perinatal mortality [22, 23], whereas Baker et al. [24] reported a non-significant reduction using this method for high-risk pregnancies. For eoFGR, Pels et al. [25] found no association between the use of STV and short term outcomes. Two randomized controlled trials, GRIT [26] and TRUFFLE [14], have studied the timing of birth in eoFGR, respectively comparing immediate to delayed birth and comparing triggers for expediting birth based on fetal ductus venosus Doppler changes and STV cutoffs or STV-values alone. In a post-hoc analysis, visual and computerized CTG were indirectly compared using individual participant data form both trials, suggesting better outcomes with computerized CTG, although not significant [16]. A retrospective cohort study in eoFGR indicated that highly abnormal computerised CTG was associated with fetal death and neonatal hypoxia but not with major neonatal morbidity or two-year neurodevelopmental outcomes [27]. In conclusion, there is a lack of randomized controlled trials directly comparing CTG evaluation supported by STV analysis with visual interpretation of CTG in eoFGR.

Objectives

The objectives of the SAVE FGR study are as follows:

1. To investigate if, in pregnancies complicated by severe eoFGR fetuses, the use of CTG supported by STV analysis to trigger expedited birth in comparison to visual evaluation of the CTG improves perinatal and two years' neurodevelopmental outcomes (hypothesis testing).
2. To explore the predictive value of available prognostic markers including characteristics from fetal electrocardiography and (experimental) placental biomarkers in combination and as stand-alone, for the primary and secondary outcomes (hypothesis-generating).
3. To explore the impact of eoFGR on parental mental health and wellbeing.

Through comprehensive data collection and biobanking, we aim to advance understanding of the most appropriate timing of birth in eoFGR and to ultimately develop a multimodal clinical decision support tool (FGR Perinatal Outcome Decision Support project).

Hypothesis

Visually undetectable CTG changes that indicate hypoxia can be detected by computer assisted CTG analyses by a subtle lower STV. In those cases, birth is indicated earlier than when visual CTG abnormalities would occur, thereby preventing progressive hypoxia. In other cases, births may be expedited at a later gestational age when hypoxia is suspected based on visual assessment, but this is negated by STV analysis. Overall, we anticipate that the timing of birth is improved by standardizing CTG evaluation with the support of STV analysis to trigger expedited birth, resulting in less severe hypoxia with milder symptoms. As a result, the rates of perinatal mortality, neonatal morbidity and long-term neurodevelopmental impairment are hypothesized to decrease and healthy survival to increase in comparison to visual CTG evaluation.

Methods

Study design and setting

The study is a multicenter stepped wedge cluster-randomized trial. The design is to test for superiority, with 1:1 allocation. The study will be conducted in at least 16 clusters, with each cluster consisting of one or multiple tertiary care centers. Smaller centers or satellite sites affiliated with a larger overarching center may be grouped to form a single cluster. Ethical approval was obtained by the Central Committee on Research Involving Human Subjects (NL84591.000.24) in the Netherlands. The study is anticipated to also being conducted in Denmark, Belgium and Poland, after obtaining ethical approval from respective the competent authorities. Amendments to the study protocol, if deemed necessary, will be initiated by the sponsor and submitted to the responsible ethics committee for approval. Modifications will only be implemented after receiving approval from the ethics committee. A list of study sites can be obtained from www.fetalgrowthrestriction.com.

Participants characteristics

In order to be eligible for inclusion, a patient must meet all of the following criteria:

- Singleton pregnancy;
- Gestational age from 24 + 0 to 31 + 6 weeks;
- Identified FGR (abdominal circumference (AC) and/or estimated fetal weight (EFW) < p10 AND umbilical artery Doppler pulsatility index (PI) > p95) based on local reference charts;
- Indication for fetal monitoring by CTG (admitted to hospital or frequent ambulatory according to local protocol);
- Maternal age ≥ 16 years;
- Written informed consent.

The EFW will be calculated with the Hadlock 3 formula [28]. For central analysis, the percentile values of AC and EFW will be based on the INTERGROWTH-21st reference curves [29, 30].

A patient who meets any of the following criteria will be excluded from participation in this study:

- Known fetal congenital or chromosomal anomalies influencing perinatal outcome;
- Imminent labor or expected maternal indication for birth within 48 hours;
- Lack of proficiency in Dutch, Polish, French, Danish or English.

Recruitment and consent

Recruitment and consent procedures will proceed according to national law and regulations. Eligible patients will be informed about the study by a trained and authorized member of the local study team (e.g. attending physician, obstetrician or research associate of the obstetrics department). Eligible patients will receive written information and an animated video is available to support the oral and written information The patients are informed that participation is voluntary, and that withdrawal will not affect the right to the most appropriate medical treatment or her relationship with the doctor. Furthermore, patients are given as much time as they need for consideration and are given the opportunity to ask questions. Written informed consent is required to be included in the study. Participants can withdraw at any time for any reason. The website www.fetalgrowthrestriction.com provides information in lay language about FGR and the study itself, including updates on its progress and results. When available, approximately two years after the study closure, participants will be informed of the key findings.

Informed consent will be asked for:

- Collection of data of the mother and fetus/infant, including ethnicity and educational level;
- Questionnaires on maternal wellbeing;
- In centers with biobanking facility: the collection of maternal and umbilical cord blood samples and placenta tissue; and to store the remaining biomaterials after analysis in a biobank for 50 year.
- The use of data by specialized institutions, to develop a decision support tool for timing of birth in eoFGR and to improve the Nemo Fetal Monitoring System;

- Contacting of the mother and co-parent or legal guardian for follow-up, including the SAVE FGR follow up study.

If applicable, the other legal guardian of the infant will be asked for consent for collection of the data on the infant, in accordance with European laws. Since the trial has a stepped wedge design, patients will not need to provide informed consent for the intervention, as that will be incorporated in daily practice.

Intervention description

The STV value can be obtained using software implementing the Dawes-Redman algorithm [20]. Previously, our team collaborated in the development of STV analysis freeware (STVcalc), which has been validated to provide the same calculation as the original Oxford Sonicaid system [31]. Clinical monitoring requires a 40–60 min CTG tracing that allows for reliable STV calculation. Intervention decisions based on STV calculations should not be based on short-term recordings. In the intervention period, it is advised to expedite birth if STV is below 3.5 ms (below 29 weeks of gestation) or below 4.0 ms (at 29 weeks of gestation and onwards), regardless of whether the CTG is normal with visual evaluation. If the treating physician interprets the CTG as abnormal based on visual evaluation, but the STV is above the cut-off value, it is also recommended that the birth is expedited. In the control period, the decision for expedited birth is based on visual CTG signs of hypoxia, including a reduction in baseline heart rate or variability, and repetitive unprovoked decelerations [32]. At all times during the study, the treating physician determines whether there is an indication for birth, weighing all available factors, both fetal and maternal. When the participant has reached 32 weeks of gestation, the study intervention stops and the timing of birth will be according to local protocol, with continued data collection for study purposes.

CTG monitoring will preferably be performed using the Nemo Fetal Monitoring System, which additionally allows for the non-invasive collection of the fetal electrocardiogram. In case of machine unavailability, unsatisfactory signal quality or any contra-indication, the classic Doppler-based CTG can be used. Training programs for the use of the Nemo Fetal Monitoring System, as well as training in application of STV-software are installed and required before the start of a study site. The adherence to the allocated intervention is monitored by the study monitor through the electronic database.

Relevant concomitant care

Most of the procedures and assessments required for data collection are routinely embedded in eoFGR protocols in the participating centers. After an antenatal diagnosis of eoFGR, the neonatologist and fetal medicine expert will counsel the mother and the co-parent regarding survival and morbidity chances and together they decide when to initiate active fetal monitoring and active management. The indication for fetal monitoring will follow the decision for active management, in which it is intended to expedite delivery when antenatal risks are deemed too high, in order to prevent fetal death. The SAVE FGR protocol allows for routine FGR care according to local protocol with all clinical interventions deemed necessary. Use of therapeutics and interventions will be recorded in the study database.

A few of these standard operating procedures are as follows [21]:

- Maternal hypertensive disorders are treated per local protocol. Preeclampsia without severe features is not a solitary reason for expedited birth.
- Magnesium sulphate can be administered for fetal neuroprotection. The timing and gestational age limit is determined by local protocol.
- Corticosteroids for acceleration fetal lung maturation are advised when expedited birth is likely to arise within 7–14 days.

The recommended procedures and clinical assessments are outlined below. While not mandatory, they are highly recommended for data collection, which is crucial for the ultimate objective to develop a decision support tool.

1. Ultrasound investigation: performing a weekly scan as minimum;

   a. Fetal biometry (every 7–14 days): head circumference, femur length, AC, and EFW [28];
   b. Fetal and maternal Doppler measurements (at least weekly): at each ultrasound [33];

      - PI and end-diastolic flow of umbilical artery: measured in a free loop of the umbilical cord [33];
      - PI of middle cerebral artery: identified with color flow mapping and measured at the proximal third of the middle cerebral artery, close to its origin in the internal carotid artery [33];
      - PI and notching of uterine artery: measured 1 cm downstream from the crossover point with the external iliac artery [33]. The presence of notching is defined as reduced early diastolic velocities before the maximum diastolic velocity in the Doppler waveform [33, 34];
      - PI of ductus venosus: identified with color flow mapping, showing the umbilical vein,

the ductus venosus (with typical aliasing area) and the fetal heart. Decisions based on an abnormal ductus venosus should be according to local protocol.

c. Amniotic fluid measurements: amniotic fluid index and deepest vertical pocket should be measured when Doppler measurements are done;

2. Maternal surveillance: routine maternal surveillance usually includes blood pressure measurement and, if abnormal, a check for proteinuria;
3. Maternal blood sampling (at study entry, weekly thereafter and at birth; preferably taken in addition to routine blood sampling): serum and plasma for placental growth factor (PIGF), soluble FMS-like tyrosine kinase-1 (sFlt-1) and experimental markers such as miRNA expression profiles that reflect placental function (in centers with biobanking facilities);
4. Placental histopathologic investigation and classification according to the Amsterdam Criteria [35] by using a synoptic reporting tool that implemented the criteria [36]. From a selection of centers, parenchymal biopsies will be collected for biomarker validation [35];
5. Umbilical cord blood sampling for biomarker analyses from the umbilical vein (in centers with biobanking facilities) in addition to umbilical artery pH measurement, preferably sampled within 15 min after birth [37];
6. Questionnaire contacts to assess maternal health and wellbeing at inclusion and term age;
7. The SAVE FGR follow-up study includes questionnaire assessments for both the mother and the co-parent at 2, 6, 12 and 24 months of corrected age (CA). In addition, the co-parent is asked to complete questionnaires at two extra time points: study entry and term age. Questionnaires gather data on the infant's health, physical growth parameters, and (neuro)development, as well as the wellbeing of both the mother and co-parent (psychological health and quality of life) (see Table 1).

Outcomes

The coprimary outcomes are perinatal death (defined as antenatal, intrapartum or neonatal death before discharge from the Neonatal Intensive Care Unit) and neurodevelopmental impairment (defined as a score on the Ages and Stages Questionnaire [38] (ASQ) at two years CA of more than two standard deviations (SD) below the mean on the total scale or below − 1SD on two or more scales). These outcomes will be assessed by the clinical trial and the follow-up study, respectively.

The following secondary outcomes will be analyzed in the trial:

Table 1 Time scheme of the SAVE FGR follow-up study

	Study Entry Trial	Term age	Corrected age			
			2 months	6 months	12 months	24 months
Infant (completed by mother)						
General questionnaire on infant health and physical growth parameters			X	X	X	X
ASQ-III (or IV, if available)				X		X
CBCL 1,5–5						X
Lexilijst (only for Dutch-speaking)						X
Bayley Scales of Infant and Toddler Development-IV						X
Both parents						
WHO-QOL-BREF			X	X	X	X
EPDS-9			X	X	X	X
PCL-5			X		X	X
HADS-A			X	X	X	X
Open questions			X			
Only co- parent						
WHO-QOL-BREF	X	X				
Lifetime EPDS	X					
EPDS-9	X	X				
PCL-5	X	X				
HADS-A	X	X				

ASQ Ages and Stages Questionnaire, *CBCL* Child Behavior Checklist, *WHO-QOL-BREV* World Health Organization Quality of Life-BREF, *EPDS* Edinburgh Postnatal Depression Scale, *PCL* Posttraumatic Stress Disorder Checklist, *HADS-A* Hospital Anxiety and Depression Scale – Anxiety subscale

1. Composite of major neonatal morbidity until discharge home. Major neonatal morbidity is defined as intraventricular hemorrhage grade 3 or more [39], periventricular leukomalacia grade 2 or more [40], bronchopulmonary dysplasia [41, 42], necrotizing enterocolitis Bell stage 2 or more [43], sepsis, or retinopathy of prematurity requiring therapy.
2. Individual neonatal morbidities of the composite outcome and additionally persisting ductus arteriosus, solitary intestinal perforation, persistent pulmonary hypertension of the newborn, respiratory distress syndrome, duration of mechanical ventilation in days, medication need, tube feeding, hypoglycemia, hyperbilirubinemia expressed as neonatal jaundice, retinopathy of prematurity, duration of hospitalization and the use of inotropic agents.
3. Maternal parameters, including (severity of) hypertensive disease and hemorrhage, ability to breastfeed.
4. Birth parameters, including gestational age at birth, birth weight, mode of birth, low Apgar score at 5 min and umbilical cord pH.
5. Maternal mental health and quality of life, including outcomes of World Health Organization Quality of Life-BREF (WHO-QOL-BREF) [44], Quality of Life-Gravidity (QOL-GRAV) [45], (lifetime) Edinburgh Postnatal Depression Scale (EPDS-9) [46, 47], Posttraumatic Stress Disorder Checklist (PCL-5) [48], Wijma Delivery Expectancy/Experience Questionnaire (WDEQ-A/B) [49] and Hospital Anxiety and Depression Scale - Anxiety (HADS-A) [50] at inclusion and term age.

The following secondary outcomes will be analyzed in the follow-up study:

1. General health of the infant, including biometrical values (such as as height SD, corrected for gestational age at birth and for mid-parental SD, weight SD for CA, head circumference and Body Mass Inde SD for CA, neurodevelopment (including Ages and Stages questionnaire [38]), the use of therapies, medication and need for surgeries and aids, at 2, 6, 12 and 24 months CA; CBCL [51] and Lexilijst [52] at 24 months CA.
2. Neurodevelopmental impairment, defined as an abnormal test on Bayley Scales of Infant and Toddler Development IV [53] (composite cognitive score < 85, or composite motor score < 85), cerebral palsy (based on maternal reporting), hearing loss needing hearing aids, or severe visual loss (legally certifiable as blind or partially sighted) assessed at two years CA.
3. All individual components of neurodevelopmental impairment, including Bayley Scales of Infant and Toddler Development IV [53] composite cognitive score, composite motor score, cerebral palsy, ASQ [38].
4. Mental health of the mother and the co-parent (WHO-QOL-BREF [44], EPDS-9 [46], PCL-5 [48], HADS-A [50] and open questions) at 2, 6, 12 and 24 months CA of the infant.

All remaining outcomes required by the core outcome sets for FGR [54] and preeclampsia [55] will also be collected.

Other outcomes are as follows:

- Postnatal growth markers (height, weight and head circumference) and the ability to breastfeed;
- Costs, direct and indirect, calculated of the maternal and neonatal/infant health care consumption.

Participant timeline

For pregnant women, participation extends from inclusion until birth, with data collection until term age. Data from the fetus/infant will be collected until neonatal discharge home. If enrolled in the SAVE FGR follow-up study, participation for both parents and the infant lasts until 2 years CA. A schematic overview of the clinical trial is shown in Fig. 1 and an overview of the follow-up study in Table 1.

Allocation and randomization

In accordance with the stepped wedge study design, all centers will start with the control period. Following a cluster randomization sequence, centers will be allocated to switch at a certain time to the intervention period. At the end of the study, all centers will have switched, resulting in an equal number of participants in the control and intervention arms. Centers will be randomized to switch either early or late, defined as after approximately one third or two thirds of their anticipated total inclusions, respectively. To allow classification of clusters according to actual size and to balance clusters accordingly, randomization will be performed after sufficient information is available on recruitment rates from all centers within each country. This is estimated to be at eight months after the start of recruitment or after 30% of anticipated inclusions. Decisions regarding the timing of randomization will be made by the central study team (including a methodologist (HG)), after consultation with the Data Safety Monitoring Board (DSMB) and the Trial Advisory Committee. The randomization will be performed

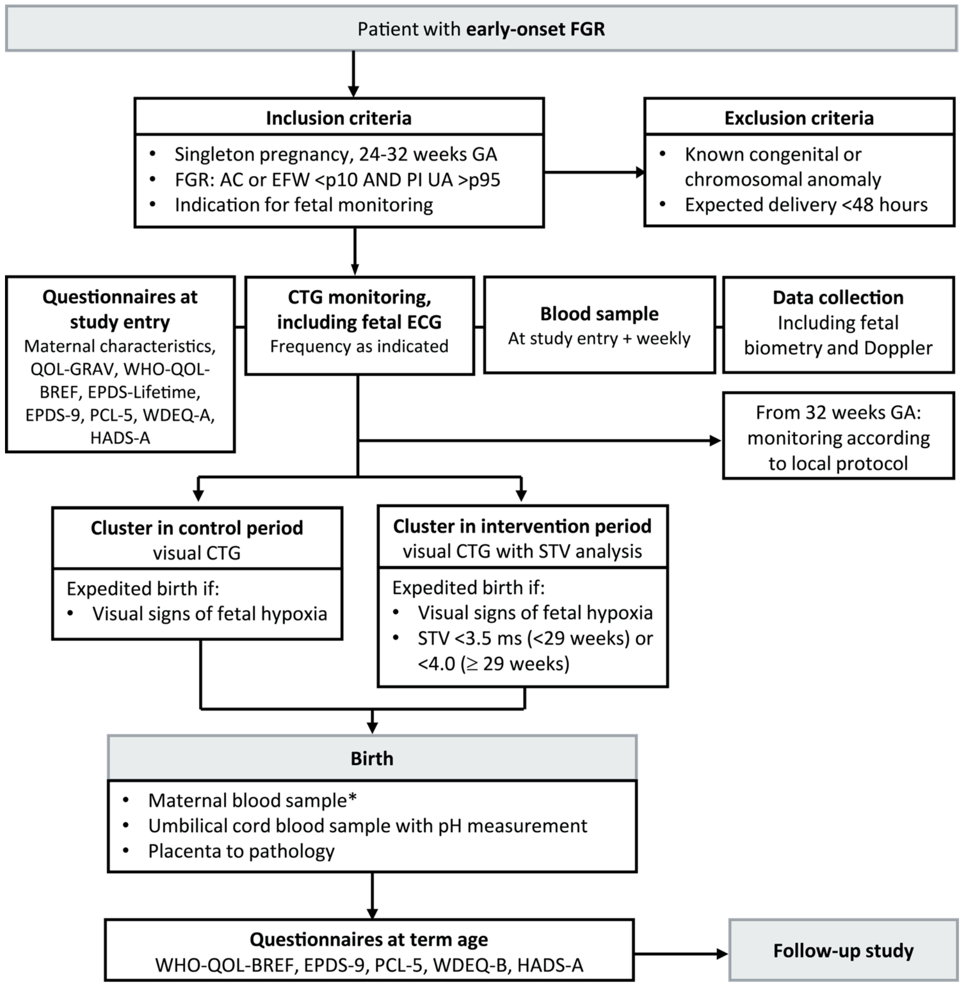

Fig. 1 Flowchart of the SAVE FGR study design.
AC: Fetal Abdominal Circumference; ASQ: Ages and Stages Questionnaire; CBCL: Child Behaviour Checklist; CTG: Cardiotocography; EFW: Estimated Fetal Weight; EPDS: Edinburgh Postnatal Depression Score; FGR: Fetal Growth Restriction; GA: Gestational Age; HADS-A: Hospital Anxiety and Depression Scale – Anxiety subscale; PCL: Posttraumatic Stress Disorder Checklist; PI: Pulsatility Index; QOL-GRAV: Quality of Life-Gravidity; UA: Umbilical Artery; WDEQ-A: Wijma Delivery Expectancy/Experience Questionnaire – Version A; WDEQ-B: Wijma Delivery Expectancy/Experience Questionnaire – Version B; WHO-QOL-BREF: World Health Organization Quality of Life – BREF. * Drawing of blood sample needs to be performed when decision for birth has been reached

according to a computer-generated algorithm and cannot be influenced by personnel involved in the execution of the study.

Blinding

Due to the open label design of the trial, blinding of the intervention is not possible. Data analysts are blinded by referring to period A and B.

Data and biomaterials collection and management

Data will be collected in Castor Electronic Data Capture (EDC), a secured web-based electronic case record form that meets Good Clinical Practice (GCP) Guidelines [56]. Trained and authorized members of each local study team will collect and enter data in Castor EDC, from which questionnaires will also be sent. Built-in validation checks will be used to minimize data entry errors. Data handling will be done with pseudonymized data using study codes, with the key code to personal information linkage only available to authorized members of the local study team. Persons with access to the study data include investigators, research staff, monitoring and quality assurance personnel, and members of the DSMB. To implement quality control of the data and monitoring, the sponsor, authorized representatives of the sponsor and local authorities may review original patient medical records. In case of withdrawal, any results collected up to the point of withdrawal will be analyzed, unless the participant requests their collected data to be deleted.

Results from neurodevelopmental tests conducted by healthcare providers, including the Bayley Scales of Infant and Toddler Development [53], and data from routine follow-up visits will be collected. The availability of these data will primarily depend on the local and national routine follow-up protocols. When feasible, a local follow-up specialist will be included in the study team to facilitate data collection through routine local procedures.

Signals from the Nemo Fetal Monitoring System are extracted by the centers regularly and securely stored on a server at Amsterdam University Medical Centers (Amsterdam UMC). In the centers with a biobanking facility, maternal blood samples will be taken from all participants at multiple time points starting at inclusion and umbilical cord blood just after birth. Biomarker analysis will be performed centrally at the University Medical Center Groningen (UMCG). Histopathological evaluation of the placenta will initially be performed in participating centers, and will be reviewed at the Erasmus Medical Center and the UMCG by two perinatal pathologists using placenta slides (digitally, if feasible). Fresh placenta parenchymal biopsies in RNAlater solution will be obtained from consenting participants at Amsterdam UMC and UMCG. Only the principal investigator, researchers and central laboratory staff who help process the material and measurements will have access to the material. All biomaterials will be kept confidential and stored pseudonymized. After analysis, all biomaterials will be stored at the Amsterdam UMC according to local hospital protocol for a maximum of 5 years after termination of the study. Biomaterials will be retained for use in the SAVE FGR study or, with participant consent, for future research. If additional consent is provided, residual biomaterials will be stored in a separate biobank for up to 50 years.

Reported data of the participants are subject to medical confidentiality, local data protection laws and General Data Protection Regulation (GDPR) (EU). All study-related information will be stored securely at the study site, with Amsterdam UMC remaining the owner of the data. External parties will only be allowed to use coded data. Agreements regarding data and biomaterial sharing are defined in a signed Clinical Trial Agreement, to which GDPR and Dutch privacy regulation by the Algemene Verordening Gegevensbescherming apply. All data will be stored for 15 years in a secured database, accessible only to the investigators. The data storage period corresponds with each country's legal requirements. Trial data is assessed by the monitoring and quality assurance board of the Amsterdam UMC.

Statistical methods and sample size calculation

Sample size

We anticipate an 11% difference in the primary outcome of perinatal death, based on the prevalence of the primary outcome in analysis of the GRIT [26], STRIDER [57] and TRUFFLE-cohort [58]. In a cross-sectional stepped wedge cluster randomized design with 16 clusters, intraclass correlation coefficient of 0.05 and with beta of 0.80 and alpha of 0.05, 704 patients need to be evaluated to allow the detection of a difference of 11%. Considering the slightly higher chance of loss to follow-up in a cluster-randomized clinical trial, at least 800 participants will be included in the study. If additional centers participate, resulting in more clusters, this may allow for a larger sample size. Given the uncertainty of assumptions and the freedom allowed by the stepped wedge cluster randomized design, this flexibility allows for increased robustness of the findings. The sample size is sufficient to achieve the necessary statistical power for examining the primary long-term outcome.

Statistical methods and analysis

Principal analyses will be by intention-to-treat, including all participants. Participants who discontinue the intervention will be analyzed in the group that they were allocated to and will be excluded in the per protocol analysis. Of participants who remain pregnant beyond 32 weeks of gestation, data will be continued to be collected and analyzed in the intention-to-treat analysis and in the per-protocol analysis. Interim analysis for formal efficacy testing will not be performed. However, a safety analysis will be conducted for the DSMB after 50% of participants have been enrolled in the Netherlands.

Primary analysis will be undertaken separately for the primary outcome of perinatal death and for the coprimary outcome of survival without neurodevelopmental impairment at two years CA using logistic regression. To account for clustering of observations and possible period effects, a marginal model based on generalized estimating equations (GEE) will be used [59]. Repeated measurements, such as ultrasound measurements, per individual center will be identified by period (in time) and control/intervention period as fixed effects. This approach will quantify the treatment effect adjusted for any period effect. If the treatment effect is statistically significant in accordance with our hypothesis, it will be concluded that timely birth based on the use of CTG supported by STV analysis is beneficial.

Additionally, prespecified sensitivity analyses for the primary outcomes using the same analytical framework will be performed:

1. adjusting for gestational age, socioeconomic status (by parental educational level) and EFW percentile at randomization, and (development) of hypertensive disease;
2. selection of participants without any offspring congenital anomaly that could either explain the small fetal size in hindsight or would have a likely effect on the primary outcome;

3. a per-protocol analysis for the primary outcome; selection of participants with the decision for expedited birth being supported by STV analysis (the intervention period) or without (control period);
4. decision for birth based on a safety net criterium.

Secondary outcomes will be analyzed as odds ratio or differences in means with 95% confidence intervals. Prudence in interpretation and correction for multiple testing will be applied. Odds ratios will be calculated using generalized linear models (log link function), and continuous outcomes will be analyzed using linear regression. Open-ended responses will be analyzed by coding analysis.

P-values will be two-sided and statistical significance will be set at a p-value below 0.05. Two researchers will independently perform the statistical analyses using the latest version of R, Stata or SPSS. The results of the analyses will be discussed with a third researcher to find the most reliable results in consensus.

Subgroup analyses

Subgroup analysis will be performed to evaluate the effect of assisted STV on the abovementioned outcome measures in subgroups defined by (a) gestational age at study entry (< 28 weeks and ≥ 28 weeks of gestation), (b) EFW at study entry (< 800 g, 800–999 g, ≥ 1000 g) and (c) gestational age at birth (< 32 weeks and ≥ 32 weeks).

Non-adherence and missing data

In case of missing data, the principles described by Jakobsen et al. will be followed to decide how to handle missing data based on the type of variable or outcome, type of missingness, and proportion of missing data [60]. Either complete case analysis or single or multiple imputation are possible solutions for missing data. As some missing data is expected regarding neurodevelopmental outcomes, imputation on these outcomes is anticipated. Imputation will not be performed for baseline criteria. Women who withdraw from the study will remain in their control/intervention group for the intention-to-treat analysis and their data will be used for analysis.

Oversight and monitoring

The sponsor has established a working group to oversee the trial and its procedures. The Trial Advisory Committee consists of two independent members (ATP and FF) with ample expertise in FGR research. The committee will provide independent oversight on the progress of the trial and advise the trial team on significant matters wherever applicable, including any recommendations based on interim findings. Unlike the DSMB, which focuses primarily on participant safety and criteria for trial continuation, the Trial Advisory Committee contributes to the overall quality, methodology, and feasibility of the study.

The sponsor has established an independent DSMB to perform ongoing safety surveillance. The DSMB will monitor progress and compliance of the trial according to GCP regulations and other local rules and regulations and review any unexpected serious adverse events (SAEs). The DSMB has the right to review any data that may impact the trial. The composition, the meeting schedule, the criteria on which the DSMB may advise to terminate the trial prematurely and the conflicts of interest with the sponsor are described in the DSMB charter. Any advice(s) of the DSMB will only be communicated to the sponsor. If the sponsor decides not to fully implement the advice, the sponsor will submit the advice to the reviewing Medical Research Ethics Committee (METC), including a note of explanation.

Results will be reported to the DSMB after the outcomes for the first 50 included patients, then after every 100 inclusions. An interim safety review will be conducted after completing 50% of the total intended inclusions in the Netherlands. The safety analysis is of limited value due to the stepped wedge design, which results in most patients being from the control group for 50% of the inclusions. An additional endpoint adjudication committee consisting of neonatologists will assess the causes of neonatal mortality by each report to the DSMB. Based on the first meeting, the DSMB will communicate at what frequency further additional safety reviews are advised. If any safety concerns arise among the trial staff before the completion of the first 50% of Dutch cases, the first meeting may be called sooner.

Adverse event reporting

All adverse events (AEs) reported by the participant or observed by the investigator or other staff members will be reported for all participants, from the time of study entry until the conclusion of study treatment. SAEs will be reported from the first study-related procedure until the end of the trial per participant-infant couple. All (S)AEs will be followed until they have abated, or until a stable situation has been reached. Participants withdrawn from the study due to any (S)AE will be followed at least until the outcome is determined even if it implies that the follow-up continues after the patient has left the trial. The study population has a high risk of serious complications inherent to the vulnerable condition under study. The protocol-specific SAEs include perinatal death and maternal hospital admission during pregnancy for fetal monitoring, antenatal blood loss, (threatened) preterm labor or maternal hypertensive disorders. These complications are included in the primary and secondary outcomes and are recorded in the case record form.

Protocol-specific SAEs will be reported to the MREC by line listing yearly.

Monitoring

For this study, minimal intensive remote monitoring is required, and on-site monitoring is only performed within Amsterdam UMC. Monitoring will be conducted in compliance with GCP and local rules and regulations. The monitor will have access to the data and source documents of the trial to assess quality.

Ancillary and post-trial care

The sponsor/investigator needs to have a liability insurance which is in accordance with article 7 of the Medical Research Involving Human Subjects Act (WMO). As only data, blood samples and placenta tissue will be collected, no additional risks are expected from participation and therefore no insurance for the participants is necessary.

Dissemination plan

Results will be published as open access or free-to view scientific articles in peer-reviewed international scientific journals and will be presented at (inter)national conferences. The results of the two years' follow-up will be analyzed and published separately to prevent delay of publication of the short-term outcomes. If the results offer new insights and modification for the standard treatment guidelines on FGR is applicable, an amendment of the national guideline will be initiated. Original data will be made available upon request for re-use in future studies after the publication of the results. Biomaterial is only made available if participants have given consent for further use.

Discussion

Various tools are used to monitor fetal health, aiding the timing of expedited birth of fetuses with eoFGR. The timing of birth should be when the risk of ill-effects of the fetus remaining in the unfavorable hypoxic intrauterine environment exceeds the risk of prematurity related effect [18, 61]. For antenatal day-to-day monitoring, CTG is the most important tool. Evaluation of the heart rate variability can be performed visually or by computerised STV analysis. This study compares those two types of CTG analysis. Based on previous literature, we hypothesize that the main purpose of STV analysis is to function as a more objective marker that detects early signs of fetal hypoxia.

Severe hypoxia is a critical factor influencing offspring outcome, and its timely detection is essential in perinatal care. Accurate identification can guide clinical decision-making and improve neonatal prognosis. In this study, we hypothesize that the support of STV analysis in CTG evaluation more accurately identifies chronic hypoxia and the imminent risk of acute increased severity of hypoxia, allowing for some fetuses to be born earlier and some later. Ultimately, we hypothesize that this approach will reduce severe adverse outcomes through timely intervention. To assess its impact, perinatal death and neurodevelopment at two years have been selected as primary outcome measures. To study the effects of hypoxia as a mediator of long-term outcomes, umbilical arterial cord blood pH and high grade placental lesions are potential proxies.

Several factors are known to influence STV, which are also subject to practice variation. Corticosteroids, often administered for fetal lung maturation, were observed to result in a statistically significant, but clinically non-significant decrease in the fetal heart rate variation after 48–71 h [62]. Magnesium sulphate, often provided if birth is imminent, was also associated with minor decreases in variability [63, 64].

Strengths and challenges

A strength of this study is its multicenter nature, conducted across multiple European centers. This enables a large and diverse study population for this clinical trial. It is rare to undertake such large trials in this patient group, as they are difficult to conduct due to the high risk of adverse pregnancy outcomes. The stepped wedge design allows for comparison both across all clusters and within each cluster and reduces the effect of practice variation between clusters as each cluster serves as its own control over time. Additionally, the inclusion of sequential maternal blood sampling is a promising aspect, considering the predictive value of (serial) maternal biomarkers to detect placental insufficiency is currently unknown.

The cluster randomized stepped wedge design also has limitations, including the risks of cluster effects and time effects. Both effects will be adjusted for in the analysis using a generalized estimating equations (GEE) model [65]. Randomization of the monitoring strategies per center is crucial for effective intervention implementation. Some participating centers currently use STV analysis as a standard clinical practice. Switching to visual evaluation during the control period would deviate from their established clinical protocols, potentially confounding the intervention effects. Additionally, differences in regional FGR protocols (monitoring parameters and frequency, co-medication and management of comorbidities) may influence outcomes. Consequently, the results of our study are strongly influenced by clinical management practices. Although this reflects actual practice, this will be accounted for in the design, crucial management practices will be reported and also corrected for in the analysis. Furthermore, as blinding of the intervention is not possible, the risk of contamination bias exists. A final limitation of this study and future research is the challenge of determining causality, specifically if the support of STV analysis directly would influence the outcome. Several factors hamper causal determination including the interval between the CTG trigger leading to the expedited birth and the actual birth, potential insults to the fetus during this period, intrapartum interventions (or lack thereof), mode and timing of birth, use of epidural/spinal or general anesthesia during birth interventions, and neonatal interventions after birth. These factors can independently affect trial outcomes, independent of the trial arm.

For the follow-up study, questionnaires are used for logistic, financial and feasibility reasons. Currently, the Bayley Scales of Infant and Toddler Development assessment is the most commonly used diagnostic assessment for infant neurodevelopment, often referred to as the gold standard [66]. However, this tool is complex, must be performed by trained professionals and is not part of the standard follow-up in all participating countries. To avoid a high missing rate for this primary outcome, we chose to use the ASQ as tool to identify neurodevelopmental impairment for the primary outcome. The ASQ is a simple, valid and cost-effective questionnaire [67]. However, the aim is to collect information from the available formal assessments performed according to local follow-up standards.

This study is the first prospective randomized study to evaluate whether the use of CTG supported by STV analysis is an effective trigger for expedited birth in eoFGR to improve outcomes. The results will fill a clear knowledge hiatus and inform evidence-based guidelines.

Trial Status

Protocol version: V5.0, 28/07/2025

Recruitment started: June 2025

Approximate date recruitment completed: September, 2027

Abbreviations

AC	Abdominal Circumference
AE	Adverse Events
AFI	Amniotic Fluid Index
Amsterdam UMC	Amsterdam University Medical Center
ASQ	Ages and Stages Questionnaire
CA	Corrected Age
CBCL	Child Behavior Checklist
CTG	Cardiotocography
DSMB	Data Safety Monitoring Board
EDC	Electronic Data Capture
EFW	Estimated Fetal Weight
eoFGR	early-onset Fetal Growth Restriction
EPDS	Edinburgh Perinatal Depression Scale
ERC	European Research Council
FGR	Fetal Growth Restriction
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GEE	Generalized Estimating Equations
HADS-A	Hospital Anxiety and Depression Scale – Anxiety subscale
MREC	Medical Research Ethics Committee
PI	Pulsatility Index
PCL	Posttraumatic Stress Disorder Checklist
PlGF	Placental Growth Fcator
QOL-GRAV	Quality of Life-Gravidity
SAE	Serious Adverse Event
SAVE FGR	Short term variation Analysis versus Visual Evaluation of cardiotocography in Fetal Growth Restriction
SD	Standard Deviation
sFlt-1	Soluble FMS-like tyrosine kinase-1
STV	Short Term Variation
UA	Umbilical Artery
UMCG	University Medical Center Groningen
WHO-QOL-BREF	World Health Organization Quality of Life – BREf
WDEQ-A	Wijma Delivery Expectancy/Experience Questionnaire – Version A
WDEQ-B	Wijma Delivery Expectancy/Experience Questionnaire – Version B
WMO	Medical Research Involving Human Subjects Act

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Authors' contributions

WG and SJG were involved in the conception and design of the study. ECL, YJ and AS helped with the design of the protocol and are involved with the implementation as coordinators for the Danish, Belgian and Polish centers, respectively. WG applied for funding. HG helped with the design and provided statistical expertise. MEB drafted the first version of manuscript. All authors contributed to refinement of the study protocol and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Ethical board approval for the execution of this trial was obtained from the Central Committee on Research Involving Human Subjects on 14th October 2024 (protocol version 3.0 dated 19th July 2024, NL84591.000.24). Written, informed consent to participate will be obtained from all participants. Ethical approval for the follow-up study was obtained from the MREC Amsterdam UMC on 5th December 2025 (protocol version 2.0 dated 7th October 2025, 2025.0840).

Consent for publication
Not applicable - no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results.

Role of sponsor and funder
The sponsor has the final role in the study design; collection, management, analysis,interpretation of the data; writing of the report; and the decision to submit the report forpublication. The sponsor will have ultimate authority over any of these activities. Thefunding agency has provided funds to perform the study according to the predefined plan.It has no role or authority in any of these activities.

Competing interests
The authors declare no competing interests.

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