PRACTICAL PROTOCOL | SAVE FGR

Short term variation Analysis versus Visual Evaluation of cardiotocography in Fetal Growth Restriction

CONTACT

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Study website: https://fetalgrowthrestriction.com

BACKGROUND

Early-onset fetal growth restriction (eoFGR) is a condition in which a fetus cannot reach its intrinsic growth potential, often due to placental insufiffiency. eoFGr is associated with increased risks of adverse outcomes, including stillbirth, perinatal mortality and morbidity and poor long-term outcomes. In clinical practice, a dilemma is experienced in determining the optimal timing of delivery. A balance exists between delivering the fetus too prematurely for preventing further failure to thrive from the intrauterine environment with the consequences associated with preterm birth, and delivering the fetus too late with risk for progressive hypoxia. For this optimal timing, guidelines with clear evidence have not been established yet and current clinical practice often relies on a (subjective) interpretation of prognosticators and possible outcomes.

In obstetric care for eoFGR, cardiotocography (CTG) is used for fetal monitoring and if this becomes abnormal, birth (usually with caesarean section) is expedited. CTG can be either assessed visually by the caregiver or computer analyzed by calculating the short term variation (STV). STV analysis offers an objective analysis by quantifying the fetal heart rate variability. Reduced STV has been showed to be a predictor of poor perinatal and long-term outcomes.

This multicenter stepped-wedge cluster randomized trial investigates which approach of CTG analysis leads to better outcomes for fetuses with eoFGR. In the control period of the study, all CTG recordings will be evaluated visually. In the intervention period, visual evaluation is supported by STV analysis of the CTG. The aim of this study is to compare the perinatal and long-term outcomes of monitoring the fetal condition supported with STV by computerized CTG compared with visual interpretation of the CTG. The end goal is to develop advanced and integrated decision support for the clinicians, by the FGR PODS project.

STUDY DESIGN

- 16 recruiting clusters (of 16 up to 21 hospitals) in the Netherlands, Belgium and Denmark
- Intended sample size: 800 participants

<u>Cluster randomized</u>

All centers will start with the control period. When 30% of patients (240) have been recruited, all centers will be evaluated for recruitment rates in order to determine which centers are ‘small’ centers and which centers are ‘large’ centers. At that point, centers will be randomized to ‘early’ switch to intervention period (at 33% of patients) or to ‘late’ switch to intervention period (at 66% of patients). In this randomization, small and large centers will be balanced to ensure equal distributions.

Coprimary outcomes	Secondary outcomes
1. Perinatal death 2. Neurodevelopmental impairment at two years of corrected age (CA) (Ages and Stage Questionnaire)	1. Composite of major neonatal morbidity until discharge home. Major neonatal morbidity is defined as intraventricular hemorrhage grade 3, periventricular leukomalacia grade 2 or more, moderate or severe bronchopulmonary dysplasia, necrotizing enterocolitis according to Bell stage 2 or more, or retinopathy of prematurity requiring therapy. 2. Individual neonatal morbidities of the composite outcome and additionally persisting ductus arteriosus, persistent pulmonary hypertension of the neonate, respiratory distress syndrome, duration of invasive mechanical ventilation in days, medication need, hypoglycaemia, neonatal jaundice, sepsis, retinopathy and cardiovascular function. 3. Delivery characteristics including low Apgar score at 5 minutes, umbilical cord pH, and (severity of) hypertensive disease. 4. Maternal physical and mental health parameters, including outcomes of WHO-QOL-BREF, QOL-GRAV, (lifetime) EPDS, PCL-5, WDEQ-A/B and HADS-A at inclusion and term age. 5. Long-term follow-up until two-years of corrected age on health of the infant: general health and neurodevelopment (questionnaire on development and physical growth, including height SD, corrected for gestational age at delivery and for mid-parental SD, weight SD for CA, head circumference and BMI SD for CA, the use of therapies, medication and need for surgeries and aids, ASQ) at 2, 6, 12 and 24 months CA; CBCL and Lexilijst at 24 months CA, where available. 6. Neurodevelopmental impairment, defined as an abnormal test result on Bayley III (or Bayley IV, if available) (composite cognitive score <85, or composite motor score <85), cerebral palsy, hearing loss needing hearing aids, or severe visual loss (legally certifiable as blind or partially sighted) assessed at two years CA, where available. 7. Long-term follow-up on the mental health of the mother and the co-parent (WHO-QOL-BREF, EPDS, PCL-5, HADS-A and open questions; on multiple time points until 2 years after term age) 8. All remaining outcomes required by the core outcome set for fetal growth restriction will also be collected.

INCLUSION PROCEDURE

Inclusion criteria

- Singleton pregnancy
- Gestational age from 24 + 0 to 31 +6 weeks
- Identified FGR (abdominal circumference OR estimated fetal weight <p10 AND umbilical artery Doppler >p95)
- Indication for fetal monitoring (i.e. active management) by CTG (admitted to hospital or frequently ambulatory)
- Maternal age ≥16 years
- Written informed consent

Notes:

- Hospitals can use their own references for EFW, FAC, below is used in the central analysis and recommended:
  - EFW is calculated with the Hadlock 3 formula.
  - Percentile value of the estimated fetal weight is based on the Hadlock reference curve.
  - Percentile value of the abdominal circumference is based on the Intergrowth-21st reference curve.
- An indication for fetal motoring is determined following counseling by healthcare providers and after agreement upon active management.

Exclusion criteria

- Known congenital anomalies or chromosomal anomalies influencing perinatal outcome
- Imminent labour or expected maternal indication for delivery <48 hours

Informed consent procedure

Inform the eligible woman, with verbal information, animation video and the patient information form. The patient information form can be found in your hospital's research folder and a generic version can be found on the study website. Also inform the patient about the study website which will provide information for patients about eoFGR and the study project. Ask patient if they want to the receive quarterly newsletter from the study team.

Summarize for patients, the informed consent is for:

- Use of data for analysis
- Participation in questionnaires
- Translational research / Biobanking

A trained and authorized member of the local study team will counsel the patient and take informed consent
Formal authorization (degelation log) by the local principal investigator. Scan the written informed consent, as well as the additional informed consent, into the hospital server. The original is stored in a secure environment and a copy is provided to the participant. After inclusion, create a new patientID and inform participants of their unique studyID, prepare them for prompted questionnaires (distributed by central team). Report patientID in medical file.

The following informed consents must be provided:

1. SAVE FGR Trial, including informed consent to be approached for the follow-up study
2. If applicable: biobanking of remaining materal blood samples (50 year storage)

If applicable, the other legal guardian of the neonate will be asked for consent for collection of the data on the infant, in accordance with European laws, and also to be approached for participating in the follow-up study.

STUDY PROCEDURES

BEFORE THE STUDY

- Stand-alone MOSOS CTG for STV evaluation and NEMO hardware will be provided and installed.
- Training for the use of the Nemo Fetal Monitoring System and in STV-software will be given before the start of a site.
- Arrange lab logistics and local biobanking logistics.
- Arrange with Pathology about options for storage of paraffine blocks, scanning of histologic slides, use of free-of-charge Synoptic Reporting Tool for reporting of histology findings.
- Castor CRF will be created by central study team
- Create the Investigator Site File (provided by the central study team)
- Fill in the Delegation log

DATA COLLECTION

- Use the secure trial data platform Castor (link on study website)
- After inclusion, send directly the first questionnaire and enter the first pseudomized data
- Questionnaires will be sent by central study team at future timepoints using Castor
- Most clinical data will be exported from EPD or manual CASTOR entry supported.

BLOOD SAMPLING

- At study entry, weekly thereafter and at delivery: 1 tube 10 mL EDTA, 1 tube 10 mL serum tube
- Send tubes to lab for processing and -70/80°C storage of plasma and serum. In batch transportation to central facility (Amsterdam UMC)
- Blood samples will be analyzed centrally in batch after the end of the study.

FETAL ECG

- Apply the Nemo patch morning to evening, or as long as possible
- Fallback method is standard Doppler ultrasound method
- The CTG is evaluated and acted upon as per standard clinical protocol and as frequently as clinically indicated, in the intervention period supported by STV analysis (40-60 minutes of tracing needed to allow for calculation of the STV, with delivery indicated if the STV is <3.5 ms at <29 weeks gestation or <4.0 ms at 29-32 weeks gestation)
- Document STV in intervention period in chart
- When not evaluated clinically, disengage NEMO machine from central network
- At 32 weeks of gestation, the study intervention stops → data will still be collected, but the decision when to deliver the fetus will be according to local protocol.
- Signals sent to the central data hub in Amsterdam UMC on a regular basis, instructions available

FETAL BIOMETRY AND DOPPLER

- Weekly ultrasound scans on all participants as minimum, performed by trained personnel.
  - Fetal biometry (every 7-14 days): HC, AC, FL and EFW according to Hadlock-3 formula.
  - Fetal Doppler measurements: pulsatility index (PI) and end-diastolic flow of umbilical artery, PI of middle cerebral artery, PI of ductus venosus, and PI and PI of uterine artery
  - Amniotic fluid index
- All parameters exported from ultrasound software in batch on a regular basis.

DELIVERY

- Draw maternal blood samples if the decision for delivery has been reached
- Collect umbilical cord blood sample for pH measurement within 15 minutes after delivery
- Collect umbilical cord blood sampling for biobank. Use venous blood in plasma tube and store under the same conditions as the other blood samples.
- Send placenta to pathology

NEONATAL DISCHARGE HOME

- Collect data on the neonatal outcomes
- Use discharge letter

N.B.: In case of fetal death, only send the questionnaires on parental health in the follow-up.

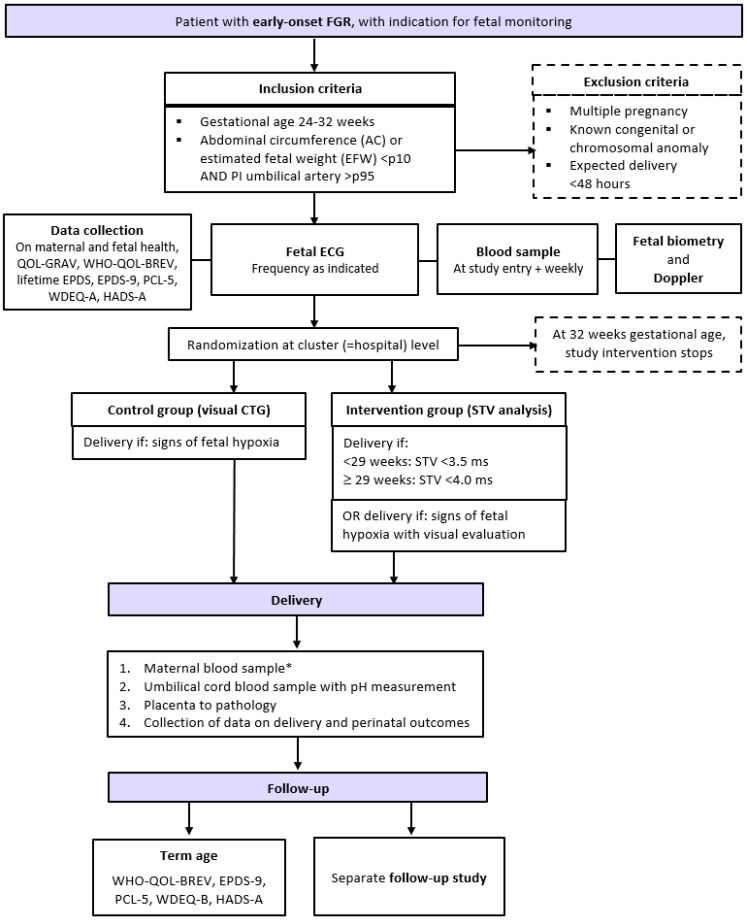

Figure 1. Flowchart of the SAVE FGR study design and interventions.
FGR: Fetal growth restriction, CTG: cardiotocography; EPDS: Edinburgh Postnatal Depression Score; QOL-GRAV: Quality of Life Gravidity Questionnaire; ASQ: Ages and Stages Questionnaire;
** Drawing of blood sample needs to be performed when decision for delivery has been reached*

FOLLOW UP

The follow-up study is a monocenter study and conducted from the Amsterdam UMC. Therefore, all questionnaires will be sent by the central study team.

- The woman will be approached for questionnaire contacts at 2, 6, 12, and 24 months after term age on both the health of the mother and the infant
- The co-parent will be approached questionnaire contacts at study entry, term age, and 2, 6, 12 and 24 months after term age
- At two years of corrected age (CA), additional non-questionnaire assessments include the Bayley Scales of Infant and Toddler Development score (Bayley-III, or Bayley-IV if available). Depending on the local protocol, infants follow the standard follow-up protocol. This data will be used as much as is feasible.

TIME SCHEME	Study Entry Trial	Term age	After term age			
			2 months	6 months	12 months	24 months
Infant						
General questionnaire on infant health and physical growth parameters			X	X	X	X
ASQ-III (of IV, if available)			X	X	X	X
CBCL 1,5-5						X
Lexilijst						X
Bayley Scale-III (of IV, if available)						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-BREV	X	X				
Lifetime EPDS	X					
EPDS-9	X	X				
PCL-5	X	X				
HADS-A	X	X				

Table 1. Overview of the follow-up study.
Abbreviations: 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