Short summary:

**Background:** Small for gestational age (SGA) is commonly defined by an estimated fetal weight below 10th centile. These fetuses were long considered to be constitutionally small babies with a good perinatal outcome. Clinical studies over the last decade have demonstrated that on average SGA have poorer perinatal results, suboptimal neurodevelopment and higher postnatal cardiovascular risks compared with adequate for gestational age (AGA) newborns. These data have led to the notion that a proportion of SGA fetuses are in reality forms of late-onset fetal growth restriction (FGR) where placental insufficiency is not reflected in the UA Doppler. Consequently, the clinical need has emerged to develop additional markers of poor perinatal outcome allowing identify late-onset FGR among SGA fetuses.

Newer findings suggest that FGR induces primary cardiac and vascular changes that could explain the increased predisposition to cardiovascular disease in adult life even in the FGR subgroups with normal fetal Doppler.

**Objective:**

2.4.2. Objectives

a) **Primary aim of the study:**
To develop and evaluate a prognostic model for mean RR at one year of age using parameters of cardiac function

b) **Secondary aims of the study:**
Evaluate the correlation between diagnostic antenatal parameters and other secondary short- and intermediate-term adverse outcomes; adverse birth outcome [pH <7.15, operative delivery for fetal distress (fetal scalp blood analysis pH < 7.20 or abnormal fetal heart rate tracing)], abnormal child growth pattern and abnormal metabolic profile. Abnormal cardiovascular outcome at birth and at 12 months of age.

c) **Main study endpoints**
- Prediction of cardiovascular outcome at 12 months of age. Regarding fetal cardiac function parameter an analysis calculating z-scores for cases will be performed for using z-scores in the SGA comparing with AGA group.

d) **Secondary study parameters/endpoints**
Obstetrical endpoints:
- Mortality defined as intra-uterine death or death before hospital discharge
- Acidosis defined as pH<7.15
- Apgar at 5 minutes <7
- Admission to NICU
- Operative delivery for suspected fetal distress (fetal scalp blood analysis pH < 7.20 or abnormal fetal heart rate tracing)

Metabolic endpoints:
- Ponderal index, for describing body proportionality at birth
- Catch up growth. To assess the growth patterns in the first year.
- Metabolic markers, to assess the neonatal metabolic profile

Cardiovascular endpoints:
- Cardiovascular outcome at birth and at 12 months of age
- Changes in autonomic nervous system

Study design: Prospective longitudinal observational study

Study population: 150 fetuses >32 weeks gestational age suspected of growth restriction defined as an estimated fetal weight or fetal abdominal circumference below the 10th population percentile, and born at term age (>37 weeks gestational age). 150 GA matched controls.

Study procedures:

- Maternal characteristics:
  - First visit: Evaluation of clinical history
  - Each visit: RR/ urine examination

- Ultrasound parameters:
  - Each follow up: Fetal biometry, feto-maternal Doppler, 3 D sweep brain, placenta, AFI (GE, Voluson E8).
  - Fetal functional echocardiography
  - Data will be analyzed by Echopac software.

- Fetal ECG/CTG
  - Computerized CTG will be conducted, at the same time the fetal ECG will be conducted for 40 minutes
  - Data will be stored to perform a PRSA analysis.

- Postpartum:
Background information  CURIOSA-Study

- Cord blood markers for metabolic profile.
- Birth outcome data
- Placenta pathology
- Cardiovascular evaluation
- Evaluation of baroreflex sensitivity

- After 1 year:
  - 12 months of life: Cardiovascular examination, evaluation of baroreflex sensitivity and obtain growth charts