Doppler Modifications in Intrauterine Growth Restricted Fetuses

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Primary Objective: To assess the hemodynamical effects of administration of AS in FGR fetuses and to compare these effects with those that occur in appropriate for gestational age (AGA) fetuses. Secondary Objective(s): To investigate the effect of...

Ethical review	Not approved
Status	Will not start
Health condition type	Foetal complications
Study type	Observational non invasive

Summary

ID

NL-OMON43435

Source
ToetsingOnline

Brief title
DOMINO

Condition

- Foetal complications

Synonym
function of the heart, small for gestational age

Research involving
Fetus in utero

Sponsors and support

Primary sponsor: Obstetrie & Gynaecologie
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cardiac remodeling, Corticosteroids, Doppler assesment, Fetal growth restriction

Outcome measures

Primary outcome

Detecting changes in the fetal hemodynamic system before and after admistration of antenatal corticosteroids in the growth restricted fetus (FGR) compared with the appropriate for gestational age (AGA) fetus.

Data about Doppler parameters will be expressed as the number of standard deviations from the respective normal means for gestation (* value). The measurements will be analyzed for each fetus and compared before and after treatment; each fetus will be considered as its own control. The data obtained on the control day (baseline examination) will be considered for significant difference with the measurements acquired in the subsequent ultrasounds.

Secondary outcome

Changes in the methylation of the HSD11B2 gene after administration of corticosteroids in the growth restricted fetus (FGR) compared with the appropriate for gestational age (AGA) fetus.

Methylation analysis will be performed by pyrosequencing. These results are calculated by a computer program and shown as a percentage. Immune parameters will be analyzed by multicolor flowcytometry, rtPCR analysis of RNA, and immunohistologic stainings.

Study description

Background summary

The fetal heart is the central organ in fetal adaptive response to placental insufficiency in prenatal life. Fetal growth restriction (FGR) is associated with several cardiovascular changes involving preload, afterload, ventricular compliance and myocardial contractility and it is well known that in the growth restricted fetus cardiac output is redistributed from right to left ventricle * the so-called *Left dominance* of the FGR fetus. These functional and morphological changes (*Cardiac Remodeling*) can be assessed using echocardiographic parameters. In fact, several studies demonstrated an impairment of these parameters in FGR fetuses . Despite that, while several studies have been published about the modification of Doppler parameters of the peripheral circulation in FGR fetuses following antenatal steroids (AS), to the best of our knowledge no study has been published about the modification of fetal functional echocardiographic parameters after corticosteroids in these fetuses.
Steroids have to pass the placenta to reach the fetus. The placenta regulates high cortisol levels in the fetus. Several genes are involved in fetal growth and may be affected by AS. The HSD11B2 gene for example codes for the 11-* hydroxysteroid dehydrogenase type 2 enzyme. This enzyme converts active cortisol into inactive cortisone in the human placenta. It is a regulatory mechanism to prevent the fetus from high intra-uterine cortisol levels. DNA methylation is an epigenetic change of the DNA; a methyl group is coupled to a cytosine molecule followed by a guanine molecule (CpG island). DNA methylation might have impact on transcription of genes and cellular function. DNA methylation is the best studied epigenetic process in relation to pregnancy outcomes and fetal programming.In a recent study methylation of the HSD11B2 gene is related to lower birth weight and has impact on neurobehavioral outcome. In another recent study, methylation of the HSD11B2 gene is related to social economic adversity. In FGR fetuses receiving AS, methylation of the HSD11B2 gene and other genes might have impact on the extent to which the modification of fetal hemodynamical parameters change.

As altered methylation of the HSD11B2 gene will result in altered levels of steroids in the fetal circulation, altered methylation most likely also influences fetal immune characteristics. Higher levels of cortisol could cause fetal immune activation and inflammation. This immune activation of a vulnerable and developing fetal immune system could cause skewing of the fetal immune system, and could for example cause a more allergy prone immune phenotype. It could furthermore be hypothesized that in an immune associated pregnancy complication as FGR, the fetus is more prone to immune modulation. Besides the effects the steroids have on the fetal immune system it is reasonable to expect effects on the maternal immune system. As the maternal immune system is already challenged during pregnancy by the tolerance of the semi-allogenic fetus, steroids will most likely also skew the maternal immune system.

Our hypothesis is that fetal hemodynamical parameters change in FGR fetuses after AS, and this process is influenced by methylation of the HSD11B2 gene in the placenta.
We furthermore hypothesize that the degree of methylation of the HSD11B2 gene influences the effect of maternal steroid administration on fetal immune responses. This will be furthermore influenced by maternal immune parameters.

Study objective

Primary Objective: To assess the hemodynamical effects of administration of AS in FGR fetuses and to compare these effects with those that occur in appropriate for gestational age (AGA) fetuses.

Secondary Objective(s):
To investigate the effect of methylation of the HSD11B2 gene and other genes in relation to hemodynamical changes in FGR fetuses after AS compared to AGA fetuses.

To investigate the effects of methylation of the HSD11B2 gene to fetal immune characteristics.

To determine the intra- and interobserver reliability of the myocardial performance index (MPI) on the Voluson E8 (GE Medical Systems, Zipf, Austria).

Study design

Prospective cohort study design

Study burden and risks

All patients are already admitted on the Obsterical department because of the fetal growth restriction or other reason to administer antenatal steroids.
Ultrasound investigation will be devided in four sessions of 30 minutes. No invasive procedures will take place.
Ultrasoud investigation is considered to be without risks for the pregnant woman or her fetus.

Contacts

Public
Selecteer

Hanzeplein 1
Groningen 9700RB

NL
Scientific
Selecteer

Hanzeplein 1
Groningen 9700RB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

- Singleton pregnancies between 24 and 34 weeks gestation diagnosed with FGR (AC * 10th percentile/ decline in growth pattern * 40 percentiles) undergoing antenatal steroids (AS) (betamethasone 12 mg i.m. 2 doses 24 hours apart) for medical indication.
- Singleton pregnancies between 24 and 34 weeks gestation with AGA fetuses (EFW * 10th percentile, AC* 10th percentile, normal growth pattern, normal umbilical artery (UA) and uterine arteries (AAUt) Dopplers) undergoing AS for medical indication.

Exclusion criteria

Maternal age under 18 years
Not capable of speaking and reading the Dutch language
Multiple pregnancies
Congenital abnormalities
Abnormal fetal karyotype

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Generic name:	Ultrasound
Registration:	Yes - CE intended use

Ethics review

Not approved

Date:	31-05-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL55700.042.16