Development of the cardiac autonomic nervous system in utero

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The primary aim of this pilot study is to gain insight in the normal development of the cANS in utero with HRV-analysis, in order to calculate sample size required for future research.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON46618

Source
ToetsingOnline

Brief title
FoCUS - Foetal Cardiac aUtonomic nervous System

Condition

- Other condition

Synonym
cardiac autonomic nervous system

Health condition

cardiale autonome zenuwstelsel

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Canon Medical

Systems Nederland

Intervention

Keyword: Autonomic nervous system, Development, Fetus, Heart

Outcome measures

Primary outcome

HRV measurements (representing cANS):

o SDNN (standard deviation of all normal-to-normal (N-N) beats (ms) *

representing total variability

o RMSSD (root mean square of successive differences between N-N beats (ms) *

displays vagal control

o SDNN/RMSSD ratio * sympatho-vagal balance in time domain

o pNN50 * proportion of N-N intervals differing more than 50 ms

Secondary outcome

Factors possibly influencing HRV:

o mHR * mean fetal heart rate during investigation

o Gestational age at time of ultrasound examination

o Fetal Gender

o Fetal behavior (e.g. (breathing) movements)

Study description

Background summary

Improvements in surgery and intensive care strategies result in a survival of more than 90% of children with congenital heart disease (CHD) into adulthood nowadays. With these higher survival rates, comorbidity becomes more apparent. The most common comorbidity in CHD is arrhythmia, a major cause of

hospitalization and use of medication. Although frequently occurring, the origin of these rhythm disturbances is still unclear.
It has been shown that the cardiac autonomic nervous system (cANS) affects the arrhythmogynesis. In adults with various non-congenital heart diseases an altered cANS, expressed by decreased heart rate variability, has been found. Also, fetuses with CHD have a different cANS compared with healthy fetuses. These findings led to the hypothesis that maldevelopment of the cANS could play a role in arrhythmias. However, until now little is known about the normal development of cANS in utero.

The ANS can be subdivided into two branches: the sympathetic and parasympathetic branch. Sympathetic stimulation increases heart rate, force of contraction and conduction velocity, mainly through norepinephrine. Parasympathetic stimulation with acetylcholine results in the opposite effect. Under normal conditions these branches are balanced. The developmental pathway of the cANS branches is a complex process under influence of genes, cells and their interactions. Following the anatomical findings in mice embryos, cANS development starts after 10 weeks of gestation. The establishment of innervation occurs at different moments in development, as it is known that signs of the sympathetic innervations are observed later in pregnancy then those of the parasympathetic branch. Yet, the exact timeline of innervation in utero remains unclear.

A non-invasive tool to assess the human cANS in vivo is the analysis of heart rate variability (HRV), a variation in the interval between consecutive heartbeats, since alterations in HRV reflects autonomic tone. HRV-analysis is widely used in adult cardiology, but still not common in fetal echocardiography. Most fetal data are derived from cardiotocography (CTG) registrations, yet CTG does not have the temporal accuracy to assess beat-to-beat variability. Fetal magnetocardiography (MCG) and electrocardiography (ECG) are also used in research setting, where the former is not suitable for daily clinical use and the latter not reliable due to signal loss. The new ultrasonographic technique color Tissue Doppler Imaging (cTDI) could provide HRV-analysis more accurately and is an easy, non-invasive tool for daily use in fetal medicine. Fetal HRV-analysis with cTDI has never been studied before.

The assessment of the normal development of the cANS may help to understand the pathophysiology of arrhythmias. Since many features are unclear, we will first conduct a pilot study.

Study objective

The primary aim of this pilot study is to gain insight in the normal development of the cANS in utero with HRV-analysis, in order to calculate sample size required for future research.

Study design

We will conduct a observational pilot study of 16 pregnant women. We will invite the participants from 10 weeks of gestation onwards, since mice show a present cANS from that point. Subjects will be assigned for a specific week of gestation to have the first examination in order of admission. The first participant will have the first ultrasound examination at 10 weeks of gestation, the second participant at 11 weeks of gestation, the third participant at 12 weeks of gestation and so on, and then the ninth participant again at 10 weeks of gestation, and so on. This examination will be repeated every 8 weeks until the estimated due date, which is maximal 4 investigations during the pregnancy. All ultrasound examinations are conducted by an experienced ultrasonographer (F.Zwanenburg, primary investigator) at Leiden University Medical Center (LUMC), under supervision of M.C. Haak, consultant in fetal medicine.

Study burden and risks

Ultrasound is a safe and non-invasive technique, which means that participators are not exposed to additional risks in their pregnancy. However, imaging examinations always carries the risk of unexpected findings, which have to be communicated to the women. The women are examined in a tertiary care level, so immediate counseling of a fetal medicine expert is available. Therefore, the following steps will be executed immediately if an unexpected finding occurs:
1. The primary investigator will communicate the finding to the participator
2. The primary investigator will contact the supervisor of the day (which is a fetal medicine expert) to evaluate the finding
3. The supervisor of the day will have a conversation with the participator in which the finding and (if necessary) following procedures will be explained
4. The current obstetric health care provider of the participator (midwife/gynaecologist) will be informed
The burden to participate is extra time and travel expenses, but with a maximum of four ultrasound examinations this is mild. Participators do not have benefit of the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Pregnant women with:
- Age * 18 years
- Singleton pregnancy
- Low-risk pregnancy

Exclusion criteria

Detected fetal congenital abnormalities
Fetal chromosomal abnormalities identified by diagnostic testing
Fetal rhythm disturbances during current pregnancy
Pre-eclampsia in current pregnancy
Fetal growth <2.3 percentile
Currently using medication with cardiac side effects

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-06-2018
Enrollment:	16
Type:	Actual

Ethics review

Approved WMO

Date:	07-06-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	02-10-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL65087.058.18

Study results

Date completed:	30-11-2019
Actual enrolment:	18