TWIN Longitudinal Investigation of FEtal discordance

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Myocardial disorders
Study type	Observational non invasive

Summary

ID

NL-OMON52625

Source
ToetsingOnline

Brief title
TwinLife

Condition

- Myocardial disorders
- Foetal complications
- Cognitive and attention disorders and disturbances

Synonym
Selective intrauterine growth restriction (sIUGR); prenatal growth restriction

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Dutch Heart Foundation

Intervention

Keyword: Epigenomics, Health, Monozygotic, Pregnancy Complications, Twins

Outcome measures

Primary outcome

1. Change in percentage DNA methylation in MSCs at birth within MC twin pairs in relation to measures of intra-uterine discordance: percentage of birthweight difference and percentage of placenta share difference. 2. Within twin pair differences at follow-up in childhood (2, 5, 8 years) with respect to risk of CVD and NDI as explained by the DNA methylation differences at birth. Study parameters of CVD at follow-up: cardiac load reflected by left-ventricular mass, vascular stiffness reflected by aortic pulse-wave velocity (aPWV) and remodelling of the arterial wall (carotid intima-media thickness (cIMT). Study parameters of neurodevelopment: cognitive, language and motor developmental test scores (with a normed mean of 100 and a standard deviation of 15).

Secondary outcome

Prenatal

Within twin-pair differences in fetal growth and cardiovascular parameters (ultrasound scans every 2 weeks)

• Head- and abdominal circumference, femur length

• Cardiac measurements: Tricuspid/mitral regurgitation, cardiothoracic ratio, subjective assessment of (bi-) ventricular hypertrophy

• Pulsed wave Doppler measurements: ductus venosus (DV), umbilical vein (VU), umbilical artery (AU), middle cerebral artery (ACM), tricuspid valve (TV), mitral valve (MV), aortic valve (AoV) and pulmonary valve (PV)

• Myocardial perfusion imaging (MPI)

• Speckle tracking strain analysis of the left and right ventricle

• Color Tissue Doppler Imaging (cTDI) of the myocardium

Birth

Functional read-outs of epigenetic differences in MSCs

• Gene expression (gene-specific (qPCR) and whole-transcriptome (RNA-seq).

• Cellular metabolism (e.g. using Seahorse Biosciences XF96 Analyzer).

Neonatal evaluation (for each twin)

• Gestational age at birth

• Gender

• Apgar score at 1, 5 and 10 minutes

• Birth order of twins

• Status of the twins: donor versus recipient in TTTS or TAPS; growth restricted versus normal grown co-twin in sIUGR

• Differences in brain maturation, myelination, global brain abnormality score and specific types of brain lesions (using the Kidokoro score), cortical thickness and folding and quantitative measures of brain connectivity, and volumetric brain growth

• Within-twin pair differences in placental cortisol and scalp hair cortisol

• Neonatal mortality: up to 28 days of life

• Neonatal morbidity including

• Respiratory distress syndrome

• Proven early onset neonatal sepsis

• Retinopathy of prematurity

• Necrotizing enterocolitis[8]

• Patent ductus arteriosus

• Severe cerebral injury, including at least one of the following

• intraventricular hemorrhage >=grade 3[9]

• cystic periventricular leukomalacia >=grade 2[10]

• ventricular dilatation >p97[11]

• porencephalic or parenchymal cysts

• severe cerebral lesions associated with adverse neurological outcome[12]

Follow-up

Within-pair epigenetic differences in peripheral tissues at 2, 5, 8 years

• Dynamic DNA methylation changes as measured in buccal swab DNA.

Study description

Background summary

Lifelong health is in part set during intrauterine life. An adverse intrauterine environment can induce persistent epigenetic changes that are thought to cause long-term health effects. There is an urgent need for human studies that can identify the epigenetic alterations that underlie the impact of intrauterine adversity on disease, in particular cardiovascular disease (CVD) and neurodevelopmental impairment (NDI). This study will focus on identical twin pairs who shared a single placenta i.e., monochorionic (MC) twins. Every year, over 600 MC twins are born in The Netherlands and they are at high risk of experiencing an adverse intrauterine environment. In one third of pairs, one fetus has significantly less access to nutrients and resources during pregnancy than its co-twin, conditions known to be linked to increased CVD risk and impaired neurodevelopment in adults. Thus, although genetically

identical, great differences in intrauterine exposure exist within twin pairs, providing an unique natural experiment allowing a robust assessment of the development of cardiac- and neurodevelopmental risk factors in childhood and probe the underlying epigenetic mechanisms. Instead of relying on commonly used blood samples, this study will examine altered epigenetic regulation in mesenchymal stromal cells (MSCs), an enhanced proxy for other tissues involved in CVD and NDI. These multipotent cells are known to display metabolic changes in newborns exposed to an adverse intrauterine environment and can be differentiated into other cell types. The hypothesis is that twins discordant for pregnancy complications display a distinct epigenetic signature in MSCs. This signature contributes to cellular metabolic alterations and is associated with future cardiovascular and neurodevelopmental outcome in childhood and beyond. Our results will not only address an unmet clinical need in the high-risk group of MC twins, but may also advance early-life CVD prevention strategies and underpin their efficacy in the general population.

Study objective

The main objective is to pinpoint the biological pathways that set long-term risk of CVD and NDI when epigenetically disturbed during fetal development by (1) establishing a longitudinal cohort of MC twins, (2) defining epigenetic alterations induced by an adverse intrauterine environment by comparing genome-wide DNA methylation of MC twins in MSCs, and (3) evaluating the role of these epigenetic alterations in mediating the effects of intrauterine adversity on cardiovascular and neurodevelopmental risk factors at birth and at the age of 2, 5 and 8 years.

Study design

A longitudinal observational study.

Study burden and risks

MC twins are at high risk of experiencing adverse prenatal conditions. The focus in current research, however, has been on the resulting acute complications during pregnancy. In this study, we will focus on the postnatal period as a first and essential step to understand and address the long-term health consequences of complicated MC pregnancies. The LUMC is the national referral center for the management, treatment and follow-up of complicated MC twin pregnancies, and therefore has ample experience in performing (clinical) assessments of MC twins and their parents with minimal burden and risk. The majority of assessments already is part of standard clinical care for specific sub-groups of MC twins and without risk. In this study, we will perform these assessments to the whole population of MC twins born in the LUMC. Antenatal, a burden for the pregnant mother during routine ultrasound might be prolonged examination time (~10 minutes) for the additional cardiac

measurements. At birth, placenta, cord and cord blood is easy to collect with no risk to the mother or new-borns. Postnatally (between day 0-3), cranial and cardiac ultrasound and, at 2, 5 and 8 years, neurodevelopmental evaluation are standard of care for all MC twins complicated by Twin-Twin Transfusion Syndrome (TTTS), Twin Anemia-Polycythemia Sequence (TAPS), prematurity (gestational age at birth <30 weeks or birth weight <1000 grams), severe growth restriction (birth weight are assessed as part of standard care at our outpatient clinic. After informed consent from both parents, a control group of uncomplicated twins (N~35) will be assessed (from prenatal to birth to follow-up at 2, 5 and 8 years) specifically for the purpose of this study. These assessments are not associated with any risk and the burden is minimal (e.g. 120 minutes at 2 and 5 years and 150 minutes at 8 year follow-up). Neurodevelopmental assessment at 2, 5 and 8 years is generally experienced as enjoyable for children. A mouth swab and a few scalp hairs will be taken postnatally and at follow-up which is without risk. In addition to routine cranial ultrasound scan in the first postnatal week, the infants will undergo neuro-imaging, consisting of a cranial ultrasound and MRI-examination around TEA. Cranial ultrasound is a safe and non-burdening bedside procedure. MRI is also considered a low-risk and minimally invasive procedure (CCMO) and we will follow the standard precautions for neonatal MRI examinations in our hospital. For extremely preterm born infants (<28 weeks), infants with TAPS, TTTS and those with brain lesions already detected on routine cranial ultrasound, the MRI scan at TEA is part of standard clinical care. Infants with a clinical indication for an MRI scan will receive a light oral sedative (chloral hydrate) according to our current NICU guideline to achieve optimal diagnostic scan quality. We will scan all other infants, where MRI is not part of routine clinical care, during natural sleep using the *feed and wrap* method.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

- MC twin pregnancies.
- Parents aged >=18 years, who are able to consent.
- Written informed consent from both parents to participate in this longitudinal study, form being approved by the Ethic Committee.

Exclusion criteria

- The presence of major anatomical abnormalities.
- Genetic disorders
- Triplet pregnancies or higher order multiple pregnancies.
- Twin reversed arterial perfusion (TRAP)
- MC twins with single or double fetal demise

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-01-2019
Enrollment:	400
Type:	Actual

Ethics review

Approved WMO

Date:	09-01-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	10-10-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	04-12-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	27-08-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	24-10-2022

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	NL67331.058.18