The Cerebro Placental Ratio as indicator for delivery in perception of reduced fetal movements.

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To assess if prompt start of labour (<16 hours) of a fetus with RFM, based on CPR <1.1 in term pregnancy will improve the neonatal outcome (including perinatal mortality and long-term (neurodevelopmental) outcome) and maternal outcome...

Ethical review	Approved WMO
Status	Completed
Health condition type	Pregnancy, labour, delivery and postpartum conditions
Study type	Interventional

Summary

ID

NL-OMON54778

Source
ToetsingOnline

Brief title
CEPRA study

Condition

- Pregnancy, labour, delivery and postpartum conditions

Synonym
Decreased fetal movements, Reduced fetal movements

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,Roche (in kind)

Intervention

Keyword: cerebro placental ratio, placental insufficiency, reduced fetal movements

Outcome measures

Primary outcome

Composite severe adverse neonatal outcome of morbidity and mortality.

Secondary outcome

1. Mild neonatal morbidity

2. Long-term outcome

3. Maternal morbidity and health related quality of life anxiety ante- and

postpartum

4. Cost effectiveness

5. Serum biomarkers

6. Standard placental immunohistochemistry

Study description

Background summary

Maternal perception of reduced fetal movements (RFM) occurs in 6-15% of pregnancies. Perceived RFM can result from harmless causes, such as altered fetal position or maternal distraction due to other activities or stress. In some cases however, RFM is an important sign of placental insufficiency (PI). PI is usually a chronic process of impaired exchange at the placental surface, leading to reduction in nutrition and oxygen transport towards the fetus. If long-lasting and/or severe, the fetus can be shown to have inadequate fetal growth. However, in case of PI onset in late gestation fetal size may be within normal ranges and PI is not picked up. In these cases, RFM may be the first sign of PI and fetal compromise, especially without maternal hypertension/preeclampsia pointing towards placental problems. RFM has a 2.4-5-fold increase in stillbirth (SB) and other adverse outcomes such as asphyxia, neurodevelopmental impairment in the offspring and maternal hypertensive disease. Although the SB rate (>28 weeks gestation) in the Netherlands has declined to 2.3/1000 in 2015, a large proportion of SB remains unexplained and in 20-30% substandard care factors are identified, such as inadequate action after RFM. The fear of SB in case of perceived RFM

leads to substantial 'overtreatment' of patients who experience RFM. Prediction of SB is difficult and CPR (combined with RFM) may aid prediction. SB is an unequivocal outcome but is considered the tip of the iceberg. The major challenge for management of RFM lies in its high incidence and the low but disastrous risk of SB, which constitutes a major obstetric, societal, and political issue. In terms of societal impact, the complete spectrum of adverse fetal and maternal outcomes related to PI is more important than mortality alone, because of the higher incidence of these -more or less subtle- long-term consequences. As an example: a liveborn child that develops cerebral palsy will require lifelong care at huge financial and emotional expenses; but also subtle childhood adverse outcomes such as lower IQ and increased cardiovascular risk profile of both the mother and child are important to consider as a societal burden. Functional parameters, that reflect placental function, such as Doppler ultrasound and serum biomarkers can help distinguish the compromised fetuses from healthy fetuses. A low cerebroplacental ratio (CPR) on Doppler ultrasound indicates a decrease in resistance in the middle cerebral artery (cerebral flow) and/or an increased resistance in the umbilical artery (placental flow) indicating redistribution of the fetal circulation: a compensatory adaptation to nutrient and oxygen deprivation. A low CPR can identify a compromised fetus, also with normal fetal size. It is unclear whether timed delivery in RFM based on CPR achieves better outcomes than expectant management, balancing risks of prolonged PI and adverse short-term and long-term (neurodevelopmental) outcomes including death versus risks of immediate delivery (relative prematurity, intensified care; no further midwifery care/home deliveries). This uncertainty translates into considerable practice variation regarding the use of CPR for management of RFM, as we observed in a nationwide survey. Serum markers for placental function, such as serum soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PLGF,) have also been shown to have considerable association with the proposed adverse outcomes related to PI. Their value has also not been established yet in RFM management.

Study objective

To assess if prompt start of labour (<16 hours) of a fetus with RFM, based on CPR <1.1 in term pregnancy will improve the neonatal outcome (including perinatal mortality and long-term (neurodevelopmental) outcome) and maternal outcome. Furthermore it results in savings in healthcare resources.

Study design

A multicentre, cluster randomized controlled clinical trial with randomization at cluster level. Randomization per cluster level includes hospitals are either blinded or unblinded for CPR results throughout the entire study period. A hospital is finished at the moment a total of 141 participants are included into the cluster of which the hospital is part. Once finished a hospital cannot be randomized again. Seen the study design there are two patient information sheets, one for hospitals randomized into a blinded cluster and one for hospitals randomized into an unblinded cluster.

Intervention

Unblinded arm: in case the CPR is abnormal start of labour within 16 hours is pursued. If the CPR in the unblinded arm is normal monitoring and management according to local protocol will follow, usually expectant, women can return to their original (primary) care giver.
Comparison:
Blinded arm; the CPR value is unknown, treatment decisions and intervention is not based on the CPR measurement. Monitoring and management is continued according to local protocol. Usually referral back to routine (primary) care.

Study burden and risks

Nature and extent of the burden Open arm: CPR< 1.1, prompt start of delivery (<16 hours) CPR> 1.1, monitoring and management according to local protocol Blind arm: CPR unknown, monitoring and management according to local protocol - Single blood sample (venipuncture) at moment of participation in: - All participants in the blinded arm - Participants with an abnormal CPR in the open arm - Filling out questionnaires at 4 different moments: at moment of inclusion, and 6 weeks, 12 months and 24 months postpartum. - The questionnaire 24 months postpartum is an extended survey. Risk analysis: Prompt start of delivery in case of reduced fetal movements and an abnormal CPR may have benefits for the foetus as it is no longer exposed to the consequences of PI consisting of hypoxia and lack of nutritions. Induction of labour can potentially prevent the development of placental related disorders of the mother such as pregnancy induced hypertension and preeclampsia. Disadvantages may include the inability to deliver at home or in first line care. No extra risks are to be expected by participation in the study.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9700RB
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9700RB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

- Singleton pregnancies with reduced fetal movements
- Gestational age 37+0 up to and including 40+6 weeks
- Cephalic presentation
- Normal CTG

Exclusion criteria

- Small for gestational age
- Other indications for immediate delivery
- Incomplete CPR measurement

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	01-07-2020
Enrollment:	1260
Type:	Actual

Ethics review

Approved WMO Date:	17-12-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-02-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-03-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-06-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	21-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-11-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-02-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-03-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-08-2021

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-12-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-07-2023
Application type:	Amendment
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	NL68768.042.19
Other	NL7557