DRIGITAT: Doppler Ratio In fetal Growth restriction Intervention Trial At (near) Term

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Does, in late preterm fetuses identified as small-for-gestational-age (SGA), timing of delivery based on abnormal umbilicocerebral ratio (UCR) improve neurodevelopmental outcome?

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Foetal complications
Study type	Interventional

Summary

ID

NL-OMON55736

Source
ToetsingOnline

Brief title
DRIGITAT

Condition

- Foetal complications

Synonym
Fetal growth restriction, fetal growth retardation

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: Fetal growth restriction, Placental insufficiency, Umbilicocerebral ratio

Outcome measures

Primary outcome

7-point average difference MDI/PDI Bayley-3 at 2 years

Secondary outcome

Composite outcome of neonatal morbidity appropriate for late preterm

gestations, perinatal mortality, mode of delivery, maternal quality of life,

costs.

Study description

Background summary

Fetal Growth Restriction (FGR) is often defined as small for gestational age (SGA), a definition based on size, usually the 10th percentile on growth centiles, and thus affects 10% of all fetuses. Among SGA fetuses is a considerable group of fetuses that is constitutionally small and healthy and among the appropriate for gestational age (AGA) fetuses is a group of fetuses that are growth restricted despite a *normal* weight. The pathophysiological mechanism in FGR is uteroplacental insufficiency that leads to failure of the placental exchange unit to serve the fetal needs. When the growth restricted fetus remains undelivered the insufficiency progresses and the prolonged placental restraints put the fetus at risk for fetal demise.Also, whilst remaining in utero, permanent alterations in fetal physiology increases the fetus* chances of disease in adulthood. On the other hand, when delivered timely, usually in the late preterm period, the baby is at risk for neonatal transitional disease and gross morbidity.

Because of the diagnostic substitution of SGA with FGR, the effect of any approach is diluted by the inability to identify fetuses with true placental growth restriction and identify the fetuses that may benefit from timely interventions by avoiding fetal risks that surpass the neonatal disadvantages. A major challenge is to find the FGR fetus in the SGA group.

Functional parameters, such as Doppler ultrasound and serum biomarkers can help

distinguish the FGR fetuses from healthy SGA fetuses. Redistribution of the fetal circulation, signalled by an increased umbilicocerebral ratio (UCR) caused by a decrease in resistance in the middle cerebral artery (MCA, reflecting cerebral flow) and an increased resistance in the umbilical artery (UmbA reflecting placental flow) is an adaptation to scarcity with long-term adverse consequences in survivors. Serum biomarkers, including sFlt and PlGF, have received attention as markers for placental function, as they have considerable association with relevant outcomes. This also holds true for the clear associations of late prematurity and significant adverse neurodevelopmental outcomes. Even in the absence of severe neonatal morbidity, uncommon in late prematurity, there are significant effects from gestational age. These may be related to a simple effect from gestational age, but are more likely due to the underlying reason for premature delivery.

The dilemma is obvious: previous studies clearly show diagnostic accuracy, resulting in many (doctors) to believe in an *obvious* effective test-treatment combination in SGA fetuses. Intuitively, physicians balance the effect on outcomes from cohort evidence of associations of the diagnostic tools with the cohort evidence of the effect of gestational age. This leads to practice variation due to different perceptions of risk. However, prospective comparative evidence is lacking. There is international consensus that a RCT on intervention on abnormal UCR is now opportune, and that serum biomarkers should be further investigated for their potential added value in guiding timing of delivery. This study is embedded in an international initiative.

For references, see chapter 1 of the study protocol.

Study objective

Does, in late preterm fetuses identified as small-for-gestational-age (SGA), timing of delivery based on abnormal umbilicocerebral ratio (UCR) improve neurodevelopmental outcome?

Study design

Cohort of women with identified SGA pregnancies (EFW/FAC < p10) with a nested RCT in fetuses with abnormal UCR (> 0.8)

Intervention

Delivery at 36 weeks when UCR is abnormal and fetal growth is mildly abnormal (EFW/FAC p3-p10) and delivery at 34 weeks when UCR is abnormal and fetal growth is severely abnormal (EFW/FAC below p3).

Study burden and risks

Patients participating in the cohort and in the non-interventional arm of the RCT do not incur additional risks compared to patients not participating in this study. They receive standard care and follow-up according to local protocol. The additional study-related procedures patients undergo in these groups (blood sampling, fill out questionnaires) do not oppose additional risks and the burden of these procedures are considered minimal.
In case of an abnormal UCR, patients could be randomized for timely delivery. In previously conducted cohort studies the relevance (diagnostic accuracy) of abnormal UCR has been signalled extensively and there is general consensus that an abnormal UCR is a signal of FGR with strong association with poor outcomes: stillbirth, inability to withstand uterine contractions, neonatal morbidity and long-term neurodevelopmental
delay.[5-9] Patients in the interventional arm of the RCT are therefor likely to have a benefit from early delivery with less exposure to the placental insufficiency.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

Inclusion criteria for the cohort:
- Singleton pregnancies with identified SGA fetus (EFW/FAC < p10)
- Gestational age from 32+0 up to and including 36+6 weeks

Inclusion criteria for the nested RCT:
- Singleton pregnancies with identified SGA-fetus (EFW/FAC < p10)
AND
- UCR (UmbilicoCerebral Ratio) > 0.8 on at least 2 occasions with an interval of at least 15 hours (or - when measurement of PI in the middle cerebral artery is impossible - the PI of the umbilical artery is > p90 on at least 2 occasions with an interval of at least 15 hours)
AND
- EFW/FAC < p3 AND 34+0 up to and including 36+6 weeks of gestation
OR
- EFW/FAC < p10 AND 36+0 up to and including 36+6 weeks of gestation

Exclusion criteria

- Maternal age <18 years
- Inability to give informed consent
- Uncertainty about the expected due date
- Suspicion of congenital anomalies which can influence the prognosis of the pregnancy or health of the fetus
- Proven chromosomal abnormalities
- Maternal or fetal indication for short-term delivery

Study design

Design

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

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-09-2018
Enrollment:	939
Type:	Actual

Ethics review

Approved WMO Date:	18-01-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL62923.018.17