Mild induced labour prior to planned caesarean delivery to improve neonatal outcome - a randomized trial (Lacarus)

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The primary outcome is the occurrence of neonatal respiratory morbidity within 24 hours after birth. Painful contractions. Progression of labour after stopping OCT. Nonreassuring fetal heart rate pattern during OCT.

Ethical review	Not approved
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON51769

Source
ToetsingOnline

Brief title
Lacarus

Condition

- Other condition

Synonym
cesarean section

Health condition

gezonde zwangerschap met sectio indicatie (electief)

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Family Larsson Rosenquist Foundation

Intervention

Keyword: cesarean section, copeptin, oxytocin, stress

Outcome measures

Primary outcome

The primary endpoint will be the rate of respiratory morbidity between infants in the study group (OCT prior ECS) and the control group (no OCT prior ECS).

Neonatal respiratory morbidity is characterized by one or more of the following criteria, tachypnea (more than 60 breaths per minute), expiratory grunting, chest wall retractions, flaring of the nostrils, cyanosis, need for oxygen or any positive pressure support present for at least two hours within the first 48 hours after birth. Corresponding diagnoses of neonatal respiratory morbidity are usually but not exclusively respiratory distress syndrome (RDS) or transient tachypnea of the newborn (TTN).

Positive pressure support includes continuous positive airway pressure (CPAP) or high-flow nasal cannula or mechanical ventilation.

Neonatal death within 48 hours after delivery are also included in the composite outcome as competing events.

Secondary outcome

* Any admission of the infant to a NICU within 48 hours irrespective of diagnosis

* Fetal stress parameters:

* Copeptin and pH in arterial umbilical cord blood (serum tubes * stability

24-48h at room temperature

* Course of postnatal weight change and maximal postnatal weight loss

* Bilirubin at least one measurement including time point during postnatal

hospital stay (TCB, blood)

* Maternal total blood loss

* Duration of exclusive breastfeeding (up to 10 isolated formula feedings are

included)

* Duration of total breastfeeding (day of last breastfeeding)

* Retrospectively, antibiotics during pregnancy: when and how long

* Prospectively, antibiotics postpartum: when and what

* Basel, Zürich, St. Gallen: For microbiom analysis collection of infant*s

stool and mother*s milk * biobanking until end of study,

* Basel: Total nucleated cell count (TNC) and CD34+ cells in the umbilical cord

blood (The pregnant woman must agree to donate umbilical cord blood.

* All: Weight, length, BMI until 1 year (parent parameters as well)

* Any antibiotics during pregnancy and in childhood

Study description

Background summary

Caesarean section is a life-saving obstetrical operation for birth complications and high risk deliveries. However, caesarean delivery rates are rising worldwide and exceed in many countries by far the medical need 1. Every pregnant woman should be informed about the benefits and risks of a caesarean section and vaginal birth. Some women give more weight to the risks of vaginal delivery than to those of a caesarean section. On the other hand, there are

pregnancies where vaginal delivery is not recommended but contractions are not contraindicated. For this reason, the caesarean section rate will remain significant even if no caesarean sections are performed without a medical indication. High caesarean rates are associated with increased maternal and neonatal morbidity, such as neonatal respiratory disorders 2*4, a significant increase in the predisposition to allergic and autoimmune diseases 5,6 and obesity 7.
Conversely, the process of vaginal birth prepares the fetus for the extra-uterine environment and confers respiratory, cardiovascular and homeostatic advantages to the newborn8, and is considered to play a critical role in preparing the mother to bond with and breastfeed her infant9*11.
Vaginal delivery of a healthy infant provokes a unique surge in stress hormones of the infant incommensurable with levels in children or adults measured in any other situation, best described when measuring the stable by-product of arginine vasopressin (AVP), copeptin8. In contrast, newborns delivered by caesarean section performed before the onset of labour and rupture of the membranes, also known as elective caesarean section (ECS), have low copeptin concentrations at birth unless other stressors are present, including chorioamnionitis or intrauterine growth restriction (IUGR)12,13. In newborns delivered by caesarean section after a trial of labour, copeptin concentrations rise between these two extremes14.
Copeptin is a nonspecific but highly sensitive plasma indicator of stress, and a more sensitive marker than cortisol 15. It derives from the prohormone of AVP and is secreted in equimolar ratio to AVP. Pulsatile secretion, platelet binding and a short half-life make direct measurement of AVP unfeasible in the clinical setting. Copeptin, however, remains stable in blood collection tubes and is readily measured by sandwich immunoassay15. Animal studies suggest that AVP regulates lung fluid secretion and reabsorption during transition from an uterine to an air-breathing environment and that fetal AVP release is triggered by uterine contractions8.
In a randomized, placebo-controlled trial, in women with singleton pregnancies who were scheduled to undergo ECS, we found that a brief oxytocin challenge test, also referred to as trial of labour, to mimic natural labour before caesarean delivery triggered a mild fetal stress response16. We concluded that the excellent acceptance of the induced labour and the absence of any safety issues favour the project of a larger trial geared to clinical endpoints such as neonatal respiratory morbidity and breastfeeding success.

Study objective

The primary outcome is the occurrence of neonatal respiratory morbidity within 24 hours after birth.

Painful contractions. Progression of labour after stopping OCT. Nonreassuring fetal heart rate pattern during OCT.

Study design

This is a multicentre, prospective, open label randomised controlled trial where pregnant women receive either oxytocin or the standard used ringers lactate.
The effect of oxytocin is obvious, so blinding is not useful.

Intervention

OCT group: Oxytocin 5 IU/500 ml Ringer® lactate or NaCl will be infused at a rate of 12 ml/h and doubled every 10 min until it induced five uterine contractions per 15-min interval at which point it will stopped. The infusion is stopped if no contractions develop after 40 minutes and the maximum infusion rate of 96ml/h is given.

Control group: standard procedure prior ECS. Infusion with Ringer® lactate

Study burden and risks

The burden is low. We do not ask additional tests, but only data related from standard of care and potentially a few additional questions. Mothers will have labour related pain.
Risks are low, oxytocine is used in this group of patients to induce vaginal delivery as standard of care.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Newborns

Inclusion criteria

* singleton pregnancy
* ECS without preceding contractions or rupture of the membranes
* Absence of a contraindication to oxytocin.
* Informed Consent as documented by signature.

Exclusion criteria

Non-inclusion criteria mother:
* Known or suspected unwillingness to follow the protocol
* Substance abuse (for example heroin, cocaine, amphetamine)
* Placenta praevia
* Clinical signs of infection
* Treated hypertension
* Preeclampsia
* Diabetes type I or II
* Steroid therapy during pregnancy
* Betablocker intake at inclusion
* Antenatal steroid administration for lung maturation
* A history of more than one previous caesarean section

Non-inclusion criteria fetus:
* Chromosomal aberration
* Malformation
* IUGR
* Nonreassuring fetal heart rate pattern

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	200
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Oxytocin
Generic name:	Oxytocin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	22-02-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Not approved

Date:	17-06-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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
EudraCT	EUCTR2021-003660-26-NL
ClinicalTrials.gov	NCT03693885
CCMO	NL79417.000.21