# Timing of umbilical cord clamping during an elective caesarean delivery and its association with neonatal gut microbiome

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Primary Objective: To compare the composition and functionality of neonatal microbiome arising from mothers receiving antibiotic prophylaxis before skin incision with the microbiome of neonates born when antibiotics are given after umbilical cord...

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

# Summary

### ID

NL-OMON47498

**Source** ToetsingOnline

**Brief title** 

Cesarean delivery and neonatal gut microbiome

# Condition

- Other condition
- Autoimmune disorders
- Obstetric and gynaecological therapeutic procedures

#### Synonym

disturbance in the mcirobiota of the gut, Gut microbiome dysbiosis

#### **Health condition**

#### Microbiome

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# Research involving

Human

### **Sponsors and support**

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

### Intervention

Keyword: Elective cesarean delivery, gut microbiome, neonates

### **Outcome measures**

#### **Primary outcome**

The composition and functionality of neonatal gut microbiome of the neonate is

the main endpoint of the project.

The following compositional outcomes will be used:

- Alpha diversity (Shannon Diversity Index)

- Beta diversity (Bray-Curtis dissimilarity)

The following functional outcome will be used:

- Metacyclin Pathways

#### Secondary outcome

The secondary outcomes for the study are: maternal endometritis and wound

infection. Maternal endometritis will be diagnosed when maternal temperature is

above 38°C on two separate occasions, accompanied by uterine tenderness,

tachycardia or leucocytosis. Wound infection is defined as purulent discharge,

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erythema and induration of surgical incision site.

# **Study description**

#### **Background summary**

During a caesarean delivery, umbilical cord clamping can be carried out before or after providing the mother with a perioperative prophylactic antibiotic. If the cord is clamped prior to giving the mother a prophylactic antibiotic, then this antibiotic cannot pass on to the infant. However, if the cord is clamped after giving the mother antibiotics these maternal antibiotics crosses the placenta and reaches the circulation of the infant. In this study it is hypothesized that such antibiotics alter the composition and functionality of the neonatal gut microbiome. A modification of neonatal microbiome has been associated with the development of asthma, allergies, type 1 diabetes and obesity later in life. This small intervention thus could have important consequences for the future health of the infant.

In the Netherlands, most of these elective CS are carried out primarily based medical indications such as breech presentation. The most common complications for the mother after C-sections include infectious morbidities like endometritis and wound infection. The 2008 meta-analysis carried out by Costantine et al. identified strong evidence that antibiotic prophylaxis for caesarean delivery that is given before skin incision, rather than after umbilical cord clamping, decreases the incidence of postpartum endometritis and total infectious morbidities, without affecting neonatal outcomes. This meta-analysis has been the basis for current protocols in the procedure for CS in some hospitals in The Netherlands, including the UMCG. In 2014, results from the systematic review of Mackeen et al. in The Cochrane Library, showed that intravenous prophylactic antibiotics for all types of CS administered preoperatively significantly decreases the incidence of composite maternal postpartum infectious morbidity as compared with administration after cord clamping. Such a review would indicate that, for the mother, antibiotics given prior to skin incision would be a better choice in preventing post-operative infections. An important point to note however is that, in all these studies, the short and long term effects of antibiotic exposure on neonatal health has been widely neglected. In their systematic review Mackeen et al. stressed the need to elucidate short- and long-term adverse effects of antibiotics for neonates. In 2015, in their randomized controlled trial and meta-analysis Zhang et al. using the end points of postpartum endometritis and total infectious morbidities, concluded that for an elective caesarean delivery, the effects of antibiotic prophylaxis before skin incision and after umbilical cord clamping were equal.

In studies that investigate the effect of giving antibiotics pre and post cord clamping on mother and neonate, the effect of the antibiotics on neonatal gut microbiome is ignored. The concerns regarding the administration of antibiotics before cord clamping has traditionally been about unnecessary foetal exposure that might mask foetal infections and increase need for sepsis work up in infants. Recent studies, however, have focused more on the change in neonatal microbiome as a result of pre cord clamping antibiotics. The antibiotics given to the mother prior to skin incision rapidly cross the placenta and reach the circulation of the neonate before birth, with an inevitable but not yet fully characterized influence on newborn microbial colonization. Previous guidelines advised cord clamping prior to giving mothers antibiotics to prevent such collateral neonatal antibiotic exposure. There is increasing evidence for a functional role of gut microbiota in driving immune development in the newborn and the development of chronic conditions later in life. The human gut microbiome plays an extremely important role in early neonatal development (10), but also possible in later health and adult onset of disease. The establishment of stable microbial communities within the gastrointestinal tract closely parallels growth and immune development in early life. Antibiotic exposure in children has been associated with increased risk of diabetes, obesity, inflammatory bowel disease, asthma and allergies. Recent studies by Yossour et al. and Bokulish et al. have noted the role of antibiotic exposure in microbial community instability. Gut microbiome immaturity in infants has been associated with malnutrition and reduced diversity has been observed in infants who later develop type 1 diabetes. Furthermore, development of childhood obesity has been linked with distinct microbial composition changes. Disturbances in the intestinal microbiome in early life has been associated with the development of immune-mediated disorders like allergy, asthma and atopic eczema later in life. Thus, there is sufficient need to investigate this possible source of microbiome disruption in early life that can result in grave future consequences.

It is thus of extreme important that high quality evidence of immediate benefits to the mother should be weighed against equally good evidence about any potential risks of long-term harm to the infant. However, so far, no RCTs have measured the effects on infants receiving intrapartum antibiotics. Such studies are unlikely to be undertaken because of the long duration of follow up required to measure health outcomes that might not present until years later. Evidence suggesting an adverse effect of early antibiotic exposure on the infant gut currently comes from observational studies but the limitations in such studies mean they are less likely to be included in systematic reviews. This RCT therefore seeks to explore the effect of antibiotics given before skin incision on the composition and functionality of neonatal microbiome up to 1 year of life. Should this study reveal important changes in the neonatal microbiome composition, this would be a strong indication to set up larger studies, that follow infants for a longer period of time. Therefore, this study is of crucial importance and seeks answer an important guestion regarding the reproductive origins of adult disease.

#### Study objective

#### **Primary Objective:**

To compare the composition and functionality of neonatal microbiome arising from mothers receiving antibiotic prophylaxis before skin incision with the microbiome of neonates born when antibiotics are given after umbilical cord clamping in caesarean delivery.

#### Secondary Objective(s):

To compare the rates of endometritis, wound infection and Urinary Tract Infection (UTI) between the group of women receiving antibiotics prophylaxis before skin incision and after umbilical cord clamping.

#### Study design

This randomized control trial will be carried out at the University Medical Centrum Groningen (UMCG). All pregnant women undergoing elective CS at the UMCG will be asked to participate when they come for their appointment at 36 weeks of pregnancy. Participation will be noted only after asking a fully informed consent.

Randomization will be carried out without involvement of investigator in trial conducting. Fifty participants will be randomly assigned to receiving antibiotics before skin incisions or after cord clamping in a 1:1 ratio. Females scheduled for planned CS will be admitted to the hospital 4 hours prior to their surgery. In case of the group having umbilical cord clamping cord clamping after giving the antibiotic, the antibiotic (1 gram of Cefazolin) will be administered 30 minutes prior to surgical incision by the anaesthesiologist. In the group receiving the antibiotics after cord clamping, 1 gram of Cefazolin (once, intravenous) will be administered by the anaesthesiologist as soon as the umbilical cord has been clamped. Level of cephazolin in cord blood will be measured by collecting 60 mL of cord blood.

One day before the caesarean section vaginal and blood samples will be collected by obstetrician at the ward and the stool samples of the mother will be collected on the day itself.

The stool of the neonate will be collected on days 1, 2 and 3 by the nurses at the nursery ward. These samples will be stored at -80°C. At the time of discharge from the hospital after day 3, the parents of the infant will be provided with 6 labelled stool collection kits for collection of stool samples. The stool of the infant will be collected each week from week 1 to week 6. The mother/father will be instructed to collect the samples and store them in her own refrigerator in the freezer, after labelling them. On week 6 the parents with the infant will return to the UMCG, bring the plastics bags with the collected samples. These samples will be collected from the parents and stored at -80°C.

In addition to collecting the faecal samples, the parents will also be asked to fill in a written questionnaire every week, answering questions related to the diet, vaccinations, medication and general health of the infant during these weeks.

The stool samples and questionnaires of the neonates at time points 6 months and one year will be collected from the homes of the patients.

#### Intervention

This study is a Phase 4 study with the intervention in this study being the timing of umbilical cord clamping. It is either done 1) After giving the mother the prophylactic antibiotic 2) Prior to giving the mother the prophylactic antibiotic. Practically this will be done as follows:

One gram of Cefazolin (once, intravenous) will be administered 30 minutes before CS by the anaesthesiologist in the group of women receiving antibiotics before skin incision. In the other group, the same antibiotics will be administered after umbilical cord clamping. Usage of 1g cefazolin as prophylaxis in CS in line with the indications of the standard protocol.

#### Study burden and risks

The burden associated with the study can be divided into 2 parts 1) During the length of stay in the UMCG and 2) After discharge from the UMCG. During the length of the stay in the hospital the mother and the neonate face minimal burden and no invasive tests. Stool samples from the mother will be collected shortly before CS. The first stool of the neonate will be collected shortly after the CS. After discharge of the mother and neonate, parents will be asked to collect the stool of the infant in provided plastic bags, every week for a period of 6 weeks and freeze this. The samples will be brought to the UMCG at the regular check-up at 6 weeks. In addition to the stool sample, the parents will have fill in a written questionnaire every week regarding diet, medications and vaccinations of the neonates. The stool samples and questionnaires will again be collected at 6 months and 1 year form the houses of the mother and infant.

The risks associated with cord clamping before giving antibiotics to the mother is the possible occurrence of post-operative infections like endometritis and wound site infections. As mentioned previously, however, these studies have not been limited women undergoing elective CS. Thus, the true increased risk of these women, by exposing them to antibiotics post cord clamping cannot be truly estimated based on these reviews. In the trail carried out by Zhang et al., taking into account only elective CS, the effects of antibiotic prophylaxis before skin incision and after umbilical cord clamping were equal.Even though the estimated risk is small we have kept in mind certain elements that can minimize this risk further. In the UMCG, women undergoing elective CS stay in the ward for 3 days after surgery and are under the supervision of nurses and doctors, who can detect post-operative infections should they occur. These women will immediately be treated, in case of signs of infection

The effects of the pre- incisional antibiotics on neonatal gut microbiome has not been greatly studied. A number of studies implicate neonatal antibiotic exposure in altering neonatal metabolism and the development of obesity in later life. Furthermore, studies also associate early gut microbiome disruptions with the development of obesity, allergy and insulin dependent diabetes. Thus this study offers the tools to investigate this matter is of great importance.

# Contacts

#### Public

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# **Trial sites**

### **Listed location countries**

Netherlands

# **Eligibility criteria**

#### Age

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

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## **Inclusion criteria**

Healthy pregnant women at >38 weeks of pregnancy undergoing elective cesarean section (CS) at the UMCG

### **Exclusion criteria**

Emergency cesarean section Temperature >37.5 degrees celcius Premature rupture of membranes Cephalosporin allergy Exposure to antibiotic agent 2 weeks before CS

# Study design

### Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Prevention

### Recruitment

NL	
Recruitment status:	Recruitment stopped
Start date (anticipated):	22-03-2019
Enrollment:	100
Туре:	Actual

# **Ethics review**

#### Approved WMO

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Date:	05-02-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-10-2018
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** CCMO

ID NL61493.042.17