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# OPtimal TIming of antenatal COrticosteroid administration in pregnancies complicated by early-onset fetal growth REstriction (OPTICORE): study protocol of a multicentre, retrospective cohort study



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# OPtimal TIming of antenatal COrticosteroid administration in pregnancies complicated by early-onset fetal growth REstriction (OPTICORE): study protocol of a multicentre, retrospective cohort study

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## ABSTRACT

### Introduction

Early-onset fetal growth restriction (FGR) requires timely and therefore often preterm delivery to prevent fetal hypoxia leading to stillbirth or neurologic impairment. To reduce neonatal morbidity and mortality following this preterm birth, antenatal corticosteroids (CCS) are administered. The efficacy of CCS is likely to be highest when delivery takes place within one to seven days after the last dose. Optimal timing of CCS administration is challenging in the setting of early-onset FGR, as the exact onset and course of fetal hypoxia is unpredictable. Of note, international guidelines do not provide directives on this topic. In the Netherlands, two timing strategies are commonly practiced: administration of CCS when the umbilical artery A) shows a pulsatility index above the 95$^{th}$ centile; B) shows absent or reversed end-diastolic velocity (a more progressed disease state). This study aims to 1) use practice variation to compare these two CCS timing strategies in early-onset FGR on fetal and neonatal outcomes, and 2) develop a dynamic tool to predict the time interval in days until delivery, which could be used as an additional timing strategy for antenatal CCS treatment in early-onset FGR.

### Methods and analysis

A multicentre, retrospective cohort study will be performed including patients treated between 2012 and 2021 in six of the nine tertiary perinatal hospitals in the Netherlands (estimated sample size n=1800). Primary outcome for the comparison of the two CCS timing strategies is a composite of perinatal, neonatal and in-hospital mortality. Secondary outcomes are in line with the COSGROVE core outcome set for FGR including long-term follow-up. For the dynamic prediction tool, the primary endpoint is defined as days until birth.

## Ethics and dissemination

The need for ethical approval was waived by the Ethics Committee of the University Medical Center Utrecht (METC NedMec, registration number 22/613).

## Trial registration

ClinicalTrials.gov registration number: NCT05606497.

## Strengths and limitations of this study

- This large cohort study will provide important information on the ideal momentum for antenatal CCS treatment in pregnancies complicated by early-onset fetal growth restriction (FGR). With that, we aim to reduce neonatal morbidity and mortality for future FGR pregnancies.
- Practice variation will be used to study two commonly practiced timing strategies of antenatal CCS therapy in early-onset FGR.
- Second, a dynamic prediction tool will be developed to forecast the time interval until birth, a novel technique in prediction research.
- A possible limitation of our observational study is reflected by other differences in obstetric and neonatal routine care (other than antenatal CCS timing strategies) that might influence study outcome measures.

## BACKGROUND

Early-onset fetal growth restriction (FGR) is defined as failure of a fetus to meet its growth potential, with its detection before 32 weeks of pregnancy. Early-onset FGR occurs in approximately 0.5-1% of all pregnancies and is a notable cause of stillbirth (2%), neonatal morbidity (24%) and mortality (8-19%) (1–5). In developed countries, early-onset FGR is most commonly caused by placental dysfunction leading to unmet fetal metabolic and gaseous demands (6,7). In a prolonged and increasing hypoxic state, the anticipated risks of stillbirth rise. Active fetal surveillance of early-onset FGR pregnancies is therefore warranted and consists of ultrasound (fetal Doppler sonography) and analyses of the fetal heart rate pattern (cardiotocography) to detect critical fetal hypoxia and instigate timely, most often preterm, delivery. Alternatively, maternal health issues can warrant for pre-term termination of pregnancy as early-onset FGR frequently coincides with (pre-)eclampsia (8).

Antenatal corticosteroids (CCS) lower the risks of neonatal morbidity and mortality following spontaneous preterm birth (9,10). Literature suggests that antenatal CCS treatment may be most beneficial in reducing adverse neonatal outcome when a completed course of CCS (i.e. two doses of betamethasone or dexamethasone at an 24 hours interval) is administered one to seven days prior birth (adjusted odds ratio 1.46, 95% confidence interval (CI) 1.20-1.77 as compared to an time span longer than 7 days prior to birth) (11). Although the clinical benefit and possible harms of antenatal CCS therapy are subject of debate in early-onset FGR, it is one of the very few antenatal treatments that can possibly improve neonatal health. Repeated courses of CCS should be avoided, as they have been associated with decreased birthweight, length, head circumference and higher rates of cerebral palsy (12,13). Therefore, adequate timing of CCS administration is likely to be important, also in the setting of early-onset FGR pregnancies when preterm birth is anticipated.

There is consensus that repetitive decelerations on the cardiotocography registration reflect fetal distress and an increased risk of fetal death (13). They are thus an important trigger to initiate birth. Unfortunately, it is difficult to predict when these repetitive decelerations will occur during the period of active fetal surveillance, which makes it challenging to administer CCS within the ideal timeframe of 7 days prior to birth. International guidelines do not provide directives regarding the timing of CCS treatment in early-onset FGR (1,14–16). In the Netherlands, two timing strategies regarding antenatal CCS administration in early-onset FGR are currently being practiced (Figure 1 (17)):

- Strategy "A": administration of CCS when the pulsatility index (PI) of the umbilical artery (UA) becomes abnormal (i.e. > 95th percentile), irrespective of its end-diastolic waveform.
- Strategy "B": administration of CCS when absent or reversed end-diastolic velocity of the UA is detected, thus in a more progressed disease state as compared to strategy A.

This study aims to compare these two timing strategies regarding CCS administration in early-onset FGR on the composite outcome of perinatal, neonatal and in-hospital mortality. In addition, we aim to develop a dynamic, prediction tool to regularly assess the time interval until birth during the period of active fetal surveillance. Ultimately, the use of such a dynamic risk tool could be used as an additional timing strategy for CCS treatment in early-onset FGR to improve neonatal outcome.

## METHODS

### Objective

The primary objective of this study is to optimize the timing of antenatal CCS administration in pregnancies complicated by early-onset FGR. With that, we aim to reduce perinatal, neonatal and in-hospital mortality. To do so, we will 1) compare two timing strategies regarding CCS administration in early-onset FGR; 2) develop a dynamic, prediction tool with the outcome "days until birth". This dynamic prediction model could serve as an additional strategy to plan for CCS treatment.

**Study design and setting**

A multicentre, retrospective cohort study will be performed. Patients will be included from six tertiary teaching hospitals in the Netherlands if diagnosed with early-onset FGR between 2012 and 2021. Neonates were actively managed at 24 weeks since 2010 in the Netherlands. Therefore, and considering the learning curve neonatologists experienced in the first two years of this new policy, patients will be included from 2012 onwards. Each CCS timing strategy (as described in the introduction) is practiced by three of six participating hospitals. By using this practice variation between hospitals, our cohort study mimics the design of a cluster randomized controlled trial (RCT). This study protocol was submitted to the Ethics Committee of the University Medical Center Utrecht (METC NedMec, registration number 22/613), which confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply to this study. Therefore, an official approval was not required under the WMO (18). In addition, the need for informed consent was waived as an exception was made in accordance with the General Data Protection Regulation (19). Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this study.

**Study population**

To be eligible for inclusion, a patient must meet all of the following criteria: 1) Early-onset FGR in accordance with the consensus-based definition of Gordijn *et al.* (20); 2) Singleton pregnancy; 3) Age ≥ 18 years; 4) Installed active, neonatal management after counselling (thus having an indication for CCS administration in case of birth < 34 weeks of gestational age). Exclusion criteria are 1) Multiple pregnancies; 2) Fetal congenital abnormalities or antenatal diagnosed genetic disorders; 3) Patients who stated that their patient or offspring data may not be used for scientific research.

**Data collection**

Patients will be identified using parturition books. Data will be captured in a CASTOR electronic case report form, a Good Clinical Practice compliant Electronic Data Capture system (21). Medical records will be scrutinized for patient characteristics of mothers as well as the neonates. Neonates are often transferred to a level II referral hospital after being treated in the level III NICU of the participating hospitals. To complete information on neonatal study outcomes, admission or discharge letters of these patient transfers will be traced to ensure complete follow-up assessment. In addition, follow-up on our primary outcome is safeguarded by a national registration on pregnancy outcomes (PERIDOS). Information on neurodevelopment will be obtained from follow-up assessments in the participating perinatal centers of from letters of the local paediatricians. All variables and outcomes that will be collected are summarized in Table 1.

**Table 1.** Maternal and neonatal patient characteristics

| Maternal characteristics | Pregnancy characteristics | Neonatal characteristics |
|---|---|---|
| Age | Gestational age at time of diagnosis | Sex |
| Ethnic background | Gravidity | Gestational age at birth |
| Smoking status | Parity | Birth weight |
| Drug use | Time between corticosteroid administration and birth (days) | Birth weight centile (Hoftiezer) |
| Body Mass Index | Mode of delivery (caesarean or vaginal) | Apgar scores at 5 minutes |

| | | |
|---|---|---|
| Transfer to other perinatal centers before delivery | Pre-existent disorders<br>Chronic kidney disease; Systemic Lupus Erythematosus; Inflammatory Bowel Disease; Antiphospholipid Syndrome; Diabetes; Chronic Hypertension; Other medical disease affecting maternal or neonatal outcome | Arterial and venous pH with base excess |
| | Obstetric history<br>Previous pregnancy affected by fetal growth restriction, pre-eclampsia, (iatrogenic) preterm birth or diabetes gravidarum. | Mechanical ventilation<br>Need for mechanical ventilation during admission, whether this was <72 hours after birth and the duration (days). |
| | Hypertensive disorders of pregnancy<br>Pregnancy-Induced Hypertension; Pre-eclampsia | Duration supplemental oxygen during admission |
| | Ultrasound-based markers (of each performed ultrasound examination)<br>Pulsatility ndex of umbilical artery; End-diastolic velocity waveform umbilical artery; Estimated fetal weight; Pulsatility index of middle cerebral artery; Cerebroplacental Ratio; Pulsatility index of veins ductus venosus; Atrial systolic velocity of ductus venosus; Presence of echodense fetal bowel | Perinatal, neonatal and in-hospital death |
| | Cardiotocography registration<br>Short-term variation (if available); Presence of repetitive decelerations | Adverse outcome measures<br>Respiratory Distress Syndrome; Necrotizing Enterocolitis ≥ 2 according to the Bell's stages; Bronchopulmonary Dysplasia, moderate and severe; Intraventricular Hemorrhage grade 3, venous infarction, posthemorrhagic ventricular dilatation; Cystic Periventricular Leukomalacia; Retinopathy of prematurity with plus disease to which treatment is needed ; Early and delayed neonatal sepsis, culture-proven or clinically suspected; Persistent pulmonary hypertension of the newborn |
| | Other pregnancy-related disorders<br>Pregnancy cholestasis; Gestational diabetes | Long-term follow-up |
| | Fetal death | |

## Outcomes

*Objective 1) Comparison main timing strategies of CCS in early-onset FGR*

Primary endpoint is defined as a composite of perinatal, neonatal and in-hospital mortality. Follow-up for this endpoint is defined as time between diagnosis of early-onset FGR and perinatal, neonatal and in-hospital mortality, or to discharge to home. Secondary outcomes for this study objective are defined in accordance with the Core Outcome Set for FGR (COSGROVE)-study supplemented with other relevant maternal outcomes (22), see Supplementary file 1. Follow-up on offspring outcomes is extended until 2-years of corrected

age. Outcome measures regarding long-term follow up will be collected if available (i.e. for children born before 30 weeks gestational age, for children born after a longer pregnancy duration follow-up management varies between clinics). Follow-up on secondary maternal outcomes ends after six weeks post-partum (Figure 2 (17)).

*Objective 2) Development of a dynamic prediction tool of days until birth*

We will develop a dynamic prediction model to regularly assess the time interval until birth during the period of active fetal surveillance. Such a dynamic prediction model could warrant physicians on the upcoming pre-term delivery and can therefore serve as a trigger for CCS administration. Traditionally, prognostic models are based on 'statistic' information, not considering the vast amount of new information that becomes available on a daily basis. To better align with clinical care, dynamic prediction could be used, a novel technique in the risk assessment research field (23). Daily updates can be generated on the outcome of "days until birth" by adding new information about maternal or fetal health, e.g. retrieved by ultrasonography and CTG-registration routinely used in FGR pregnancies, to the dynamic equation. This provides the physician with an up-to-date time interval assessment.

**Statistical analyses**

*Objective 1) Comparison main timing strategies of CCS in early-onset FGR*

As our study design mimics a cluster-RCT, we will align our statistical analysis with the methods practiced by such trials. Intra-cluster correlation should thus be considered. Primary and secondary outcomes will be compared between the two timing strategies by use of the practice variation between the participating centers using a multivariable, mixed-effects model, taking hierarchy of the data into account. Important differences in routine care between the

participating centers, other than the timing strategy, and between participants across the timing strategies are considered to be important confounding variables, and will be adjusted for in the analyses. These differences in routine care will be identified by studying local, management protocols and by scheduling research meetings to discuss routine care in the participating centers. Adjusted odds ratios with 95% confidence intervals will be calculated for dichotomous outcome measures and mean with standard deviations will be calculated for continuous outcome measures (and median with interquartile range for continuous non-parametric outcomes). Timing strategy "A" will be held as reference group. For secondary outcome measures similar analyses will be performed. Exploratory subgroup analyses will be performed based on gestational age at birth (below versus above 34 weeks). Heterogeneous treatment effects will be assessed by introducing an interaction term between the subgroup variable and the CCS treatment timing strategy to the mixed-effects model for the primary outcome. A formal test of interaction will be performed. Afterwards, the primary analysis will be repeated within each stratum of the subgroup.

*Objective 2) Development of a dynamic prediction tool of days until birth*

**Table 2.** Candidate predictors dynamic, prediction tool

| Fetal | Maternal |
|---|---|
| Estimated fetal weight | Presence of hypertensive disorders of pregnancy |
| Gestational age | Use of anti-hypertensive drugs |
| Pulsatiliy index umbilical artery | Use of intravenous anti-hypertensive medication |
| Pulsatility index cerebral middle artery | Use of magnesium sulphate |
| Cerebroplacental ratio | Number of hypertensive crises |
| Pulsatility index of veins ductus venosus | Presence of lung edema |
| Absence of interval growth | Progression of organ dysfunction |
| Repetitive decelerations on CTG | |
| Short-term variability | |
| Subjective fetal movements | |

To allow dynamic prediction, information known at baseline as well as subsequent clinical and ultrasonographic information that becomes available will be used in a proportional baselines landmark supermodel, with days until birth as the outcome (24).

Candidate predictors were selected based on literature and clinical practice, summarized in Table 2. For these candidate predictors, repeated measures will be gathered on the day of every follow-up ultrasonography (i.e. once or twice a week). The final set of predictors will be selected using backward stepwise elimination based on the Akaike Information Criterion. Internal validation using bootstrapping and subsequent shrinkage will be performed to account for potential overfitting. Model performance will be reported by assessing discrimination based on the c-statistic, and calibration both visually using calibration plots and quantitatively using the calibration-in-the-large and calibration slope. The c-statistic, calibration-in-the-large, and calibration slope will be determined at each time point, and we will report this series of model performances in a graph. Statistical analyses will be conducted using the latest version of R at the time of analysis (current version 4.0.3.1.32) (25).

**Sample size calculation**

*Objective 1) Comparison main timing strategies of CCS in early-onset FGR*

We performed a power calculation based on the fact that our study design mimics a cluster-RCT. As such, intra-cluster correlation of study outcomes needs to be considered when performing sample size calculations using an intra-cluster correlation coefficient. We used three clusters (i.e. hospitals) per CCS timing strategy, an expected incidence of 6.8% on our primary outcome (based on the TRUFFLE trial) and an intra-cluster correlation coefficient varying between 0.001-0.0091 for calculations (3,26). Including patient data from six participating hospitals will allow us to detect a range in minimal difference on the primary outcome of 1.7-4.6% (3,27). We expect that inclusion in six hospitals over a ten year time period will result in a total sample of approximately 1800 patients.

*Objective 2) Development of a dynamic prediction tool of days until birth*

Currently, no formal sample size calculation requirements are available for dynamic prediction model development. We will use the same sample size as for objective 1. Number of candidate predictors will be based on Riley *et al.*, using a margin of error of 5%, expected shrinkage factor of 0.9, and Cox-Snell R squared statistic of 0.099 (28).

## DISCUSSION

The OPtimal TIming of antenatal COrticosteroids in early-onset fetal growth REstriction (OPTICORE)-study will provide a large cohort of early-onset FGR pregnancies, including patient data of six participating hospitals in the Netherlands. The results derived from this study will likely provide the clinician with guidance on the optimal time window for antenatal CCS administration in this patient population. With that, we aim to improve the neonatal and overall outcome for future early-onset FGR pregnancies.

There is an abundance of literature about the efficacy of antenatal CCS administration in women undergoing spontaneous preterm labour. Optimal timing of antenatal CCS administration – with a completed course between one and seven days before delivery – shows the largest risk reduction for infant mortality compared to no administration of antenatal CCS (adjusted risk ratio 0.5, 95%CI 0.4-0.6) versus a time interval of more than seven days till birth (adjusted risk ratio 0.7, 95%CI 0.6-0.9) (29). Similar results were found for the outcome of severe neonatal brain injury and a composite outcome measure of mortality and/or severe neonatal morbidity (29). However, strong evidence for the efficacy (or the absence of it) of antenatal CCS treatment in the setting of early-onset FGR is lacking, as no subgroup analysis has been performed on this specific population in previously performed RCTs (9). The relative hypoxic and starved intra-uterine environment in early-onset FGR likely results in higher levels of fetal

endogenous corticosteroids. It remains uncertain whether antenatal CCS administration on top of this increased fetal endogenous corticosteroid release is still of benefit (30). Nevertheless, international guidelines on FGR advise to administer antenatal CCS in pregnancies at risk for preterm birth.

Adequate timing of CCS treatment is challenging as the time interval until delivery in early-onset FGR pregnancies is difficult to forecast. Risks of stillbirth or neurological impairment due to acute (on top of chronic) hypoxia have to be balanced against the risks of neonatal morbidity and mortality due to prematurity. The landmark TRUFFLE and GRIT trials, that assessed CTG and ultrasound parameters as triggers for timely delivery in FGR pregnancies, have not resulted in clear uniform recommendations on how to time delivery (3,31). In an observational study, Hecher *et al*. described the time sequence pattern in the development of abnormalities in fetal Doppler patterns and CTG-registration, the latter ultimately demanding delivery. They included 110 cases of FGR in a prospective, longitudinal study. However, not all pregnancies complicated by early-onset FGR follow this pattern in daily practice and especially the time line of changes in Doppler pattern until delivery varies between patients. Additionally, maternal factors (such as concomitant (pre-)eclampsia warranting birth) were ignored in the time sequence monitoring-management summary. Consequently, due to the heterogeneity in time sequence patterns and the continuous trade-off between fetal, neonatal, and maternal health, the optimal timing of delivery remains a major clinical challenge in early-onset FGR.

The ideal design to compare the two strategies for CCS administration would be a RCT. However, a sample size for such a trial would be challenging given the low incidence of both early onset-FGR and our primary outcome. We thus chose to perform a retrospective cohort study over a timespan of a decade, using practice variation as an instrument to mimic a cluster-

RCT. Follow-up on our primary outcome is safeguarded by a national registration on pregnancy outcomes (PERIDOS). However, achieving complete follow-up on the various other neonatal outcomes can be challenging, especially for the secondary outcome of bronchopulmonary dysplasia, as neonates will be transferred to a level II referral hospital when they are well enough to be discharged from the neonatal intensive care unit. To overcome this limitation, we will use discharge letters from the level II referral hospitals to complete follow-up information. Another challenge will be the patient transfers between tertiary care centers for delivery (e.g. because of unavailability of care on the neonatal intensive care unit), as patients in our study are allocated to the center where they give birth while their CCS strategy was installed elsewhere. This results in cross-over between the treatment strategies in our intention-to-treat analysis. Other differences in obstetric and neonatal routine care (other than antenatal CCS timing strategies) might influence the primary and secondary outcome measures regarding perinatal and neonatal mortality and morbidity. Analyses will be corrected for confounding factors, yet residual confounding could remain an issue of our study design.

Strengths of this study comprise the large sample size that will be included in the study, the use of a consensus-based definition of early-onset FGR and the collection of outcome measures according to the COSGROVE-study with core outcomes for FGR (22). Also, we will use a novel and promising technique in prediction research, namely dynamic prediction (23,24). A multivariable and dynamic tool for initiation of CCS therapy might very well be superior to the use of a single-variable trigger (as used by strategies A and B) in terms of predicting the interval until birth. We will use this technique to develop an additional strategy to define the optimal time window for antenatal CCS therapy.

In summary, this large cohort of early-onset FGR pregnancies will provide important insights in the timing of antenatal CCS in pregnancies complicated by early-onset FGR. With that, we aim to reduce perinatal, neonatal and in-hospital mortality.

## LIST OF ABBREVIATIONS

CCS – Corticosteroids

CI – Confidence Interval

COSGROVE - Core Outcome Set for Fetal Growth Restriction

FGR – Fetal Growth Restriction

PI – Pulsatility Index

RCT – Randomized Controlled Trial

UA – Umbilical Artery

WMO – Medical Research Involving Human Subjects Act

## DECLARATIONS

### Ethics and dissemination

This study was submitted to the Ethics Committee of the University Medical Center Utrecht (METC NedMec, registration number 22/613), which confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply to this study. Therefore, an official approval was not required under the WMO (18). In addition, the need for informed consent was waived as an exception was made in accordance with the General Data Protection Regulation (19). Results of this study will be presented at conferences and published in peer-reviewed journals.

### Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this study.

## Competing interests

The authors declare no conflict of interest.

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Not applicable.

## Author's contributions

JK, TL, WG, SG, FG, WO, EK, ES, and MM contributed to the overall design of the study and JK is the principal investigator of the study. All authors read and approved the final version for submission.

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## TITLES AND LEGENDS FIGURES

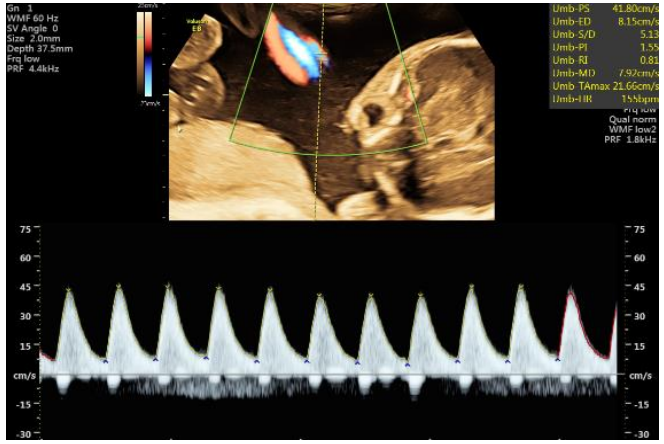
**Figure 1.** Timing strategies regarding antenatal CCS administration in early-onset FGR in the Netherlands

Abbreviations: CCS, corticosteroids; PI, pulsatility index; UA, umbilical artery. Reference image strategy "B": (17)

**Figure 2.** Study design and duration of follow-up

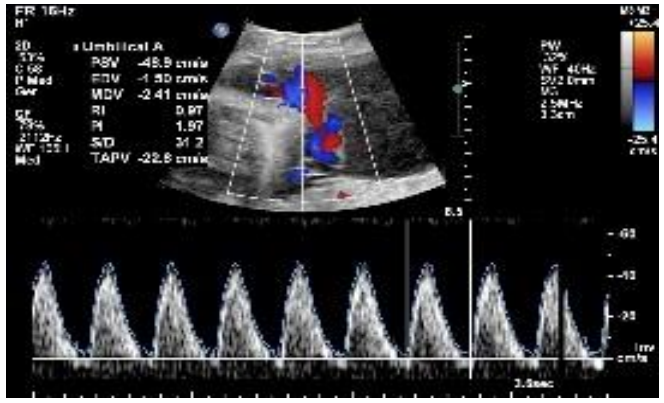
Abbreviations: FGR, fetal growth restriction; CCS, corticosteroids; PI, pulsatility index; UA, umbilical artery; AEDV, absent end-diastolic velocity; REDV, reversed end-diastolic velocity; FU, follow-up; CA, corrected age. Reference image strategy "B": (17)

# Strategy “A”

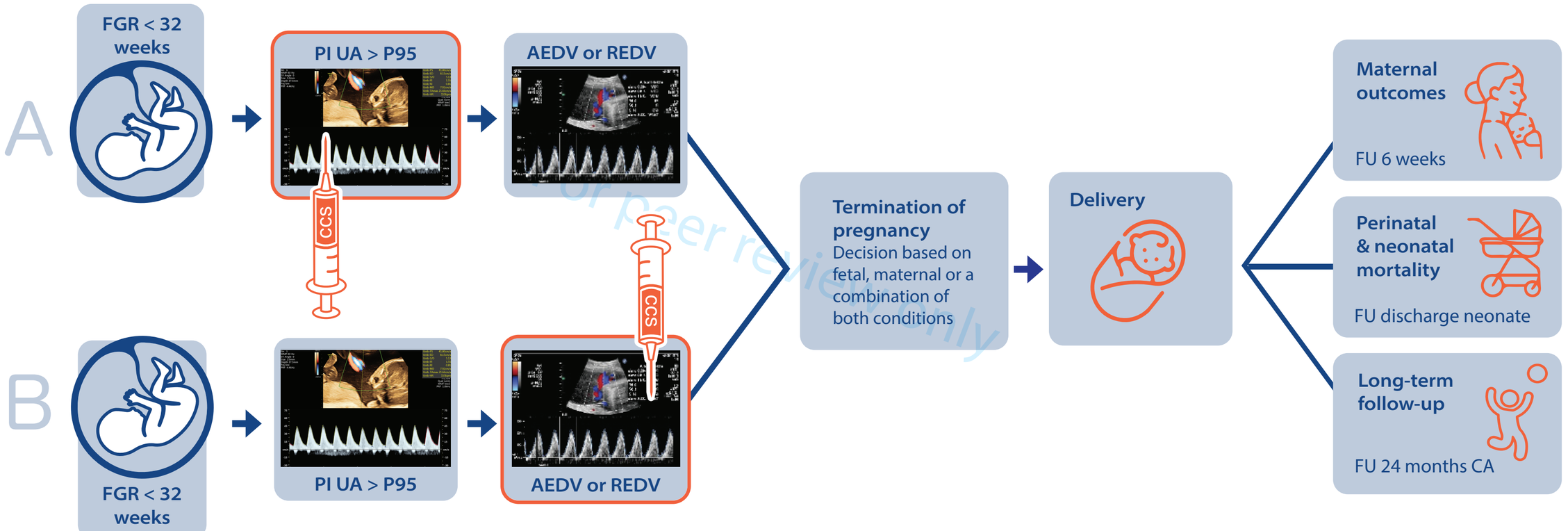


Administration of CCS when the PI of the UA becomes abnormal (i.e. > p95), irrespective of its end-diastolic waveform.

# Strategy “B”



Administration of CCS when an absent or reversed end-diastolic velocity (EDV) of the UA is detected.



## Supplementary file 1

**COSGROVE: Core Outcome Set for FGR supplemented with other relevant endpoi**

| Domain | Outcome |
|---|---|
| **Maternal** | Pre-eclampsia |
| | Eclampsia |
| | Maternal death |
| | Mode of birth |
| **Fetal** | Stillbirth/livebirth |
| **Neonatal** | Gestational age at birth |
| | Preterm birth |
| | Extremely preterm birth |
| | Birthweight |
| | Birthweight <10$^{th}$ percentile |
| | Birthweight <3$^{rd}$ percentile |
| | Need for mechanical ventilation |
| | Bronchopulmonary dysplasia, moderate and severe |

| | |
|---|---|
| | |
| | Necrotizing enterocolitis ≥ 2 according to the Bell's stages |
| | Neonatal seizures |
| | Hypoxic-ischemic encephalopathy |
| | Neonatal death |
| | In-hospital death |
| | Respiratory distress syndrome |
| | Intraventricular hemorrhage |
| | Cystic periventricular leukomalacia |
| | Retinopathy of prematurity |

| | |
|---|---|
| | Neonatal sepsis |
| | Persistent pulmonary hypertension of the newborn |
| | Duration of supplemental oxygen therapy during admission |
| | Need for mechanical ventilation < 72 hours post-partum |
| **Childhood (Long-term follow-up)** | Cognitive impairment (available for children born before 30 weeks gestational age, for children born after a longer pregnancy duration follow-up management varies between clinics) |
| | Motor impairment (available for children born before 30 weeks gestational age, for children born after a longer pregnancy duration follow-up management varies between clinics) |
| | Cerebral palsy |
| | Hearing impairment |
| | Visual impairment |

**ints with definitions (20)**

| Definition |
|---|
| Gestational hypertension accompanied by one or more of the following new-onset conditions at or after 20 weeks' gestation:<br>1. Proteinuria;<br>2. Other maternal organ dysfunction, including: Acute kidney injury (creatinine ≥90 µmol/L; 1 mg/dL); liver involvement (elevated transaminases e.g. ALT or AST >40 IU/L) with or without right upper quadrant or epigastric abdominal pain); neurological complications (examples include eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomata); haematological complications (thrombocytopenia – platelet count below 150,000/µL, diffuse intravasal coagulation, hemolysis);<br>3. Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth) (30) |
| Eclampsia refers to the occurrence of new-onset, generalized, tonic-clonic seizures or coma in a woman with preeclampsia (31) |
| Death of mother during pregnancy or the first six weeks after delivery (postpartum). |
| Defined as either vaginal or caesarean section. |
| Stillbirth: death of fetus ante- or intrapartum (20)<br>Livebirth: birth of a living neonate |
| Time in weeks and days |
| Delivery at <37.0 weeks gestation |
| Delivery at <28.0 weeks gestation |
| Weight at time of birth in grams (g) |
| Presence of birthweight below the 10 $^{th}$ percentile according to Hoftiezer *et al.* (32) |
| Presence of birthweight below the 3 $^{rd}$ percentile according to Hoftiezer *et al.* (32) |
| Need for intubation and mechanical ventilation to support gas exchange |
| Bronchopulmonary dysplasia is diagnosed if gestational age <32 weeks: at a postmenstrual age of 36 weeks, >21% oxygen has been administered cumulatively for 28 or more days (33) |

| |
|---|
| ○ Moderate: Need for <30% oxygen at 36 weeks postmenstrual age<br>○ Severe: Need for ≥30% oxygen and/or positive pressure (positive pressure ventilation or continuous positive airway pressure) at 36 weeks postmenstrual age |
| Definitive medical necrotising enterocolitis:<br>• Abdominal distention with pneumatosis intestinalis, portal venous gas, or both.<br>• Other radiographic signs such as fixed, dilated loops of intestine and ileus patterns are not pathognomonic but should be treated as such.<br>Surgical necrotising enterocolitis:<br>• Free intraperitoneal air on abdominal radiograph after initial medical signs and symptoms.<br>• Persistent ileus pattern, abdominal distension, and radiographs that show an absence of bowel gas, coupled with deteriorating clinical and laboratory values. (34) |
| Transient electrographic change in the brain due to an abnormal, excessive or synchronous neuronal activity either with the occurrence of clinical signs (electro-clinical) or without them (electrographic only) in preterm infants up to 44 weeks of post menstrual age (35) |
| Clinical syndrome that results from a severe or prolonged hypoxic-ischemic episode before or during birth (36) |
| Death of the neonate within 28 days after birth |
| Death of the neonate until hospital-discharge |
| Neonatal respiratory distress syndrome, characterized by extensive lung inflammation and surfactant catabolism leading to lung dysfunction, with need for surfactant (37) |
| Intraventricular hemorrhage grade 3 according to Papile *et al*., venous infarction, posthemorrhagic ventricular dilatation needing treatment (38) |
| Cystic periventricular leukomalacia characterized by diffuse injury of the white matter, which possibly leads to cerebral palsy (39) |
| Retinopathy of prematurity with plus disease for which treatment is needed |

| |
|---|
| • Early-onset: neonatal sepsis in the first 72 hours of age<br>• Late-onset: neonatal sepsis after the first 72 hours of age<br>• Clinical: based on clinical condition<br>• Culture-proven |
| Persistent pulmonary hypertension of the newborn occurs in case of persistent abnormally, elevated pulmonary vascular resistance after birth, leading to severe hypoxemia |
| Duration of supplemental oxygen therapy during admission (in days) |
| Need for intubation and mechanical strategies to support gas exchange within 72 hours after birth |
| A decreased ability of cognitive function using the Dutch Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III-NL) at a corrected age of 24 months,. Severe disability will be defined as a Bayley Mental Development Index score more than 2SD below the mean score (i.e. ≤70). Moderate disability will be defined as a Bayley Mental Development Index score 1 to 2 SD below the mean score (i.e. 71-85) (40,41) |
| A decreased ability of fine and gross motor function using part of the Dutch Bayley Scales and Infant and Toddler Development, Third Edition (BSID-III-NL) at corrected age of 24 months. Severe disability will be defined as a score of more than 2 SD below the mean score (i.e. ≤70). Moderate disability will be defined as a score 1 to 2SD below the mean score (i.e. 71-85) (40,41) |
| A group of disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain (42) |
| A decreased ability of the auditory system requiring hearing aids or deafness |
| A decreased ability of the visual system requiring aids or blindness |

BMJ Open

# OPtimal TIming of antenatal COrticosteroid administration in pregnancies complicated by early-onset fetal growth REstriction (OPTICORE): study protocol of a multicentre, retrospective cohort study

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# OPtimal TIming of antenatal COrticosteroid administration in pregnancies complicated by early-onset fetal growth REstriction (OPTICORE): study protocol of a multicentre, retrospective cohort study

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## ABSTRACT

### Introduction

Early-onset fetal growth restriction (FGR) requires timely, often preterm, delivery to prevent fetal hypoxia causing stillbirth or neurologic impairment. Antenatal corticosteroids (CCS) administration reduces neonatal morbidity and mortality following preterm birth, most effectively when administered within one week preceding delivery. Optimal timing of CCS administration is challenging in early-onset FGR, as the exact onset and course of fetal hypoxia is unpredictable. International guidelines do not provide a directive on this topic. In the Netherlands two timing strategies are commonly practiced: administration of CCS when the umbilical artery shows A) a pulsatility index above the 95$^{th}$ centile; B) absent or reversed end-diastolic velocity (a more progressed disease state). This study aims to 1) use practice variation to compare CCS timing strategies in early-onset FGR on fetal and neonatal outcomes; 2) develop a dynamic tool to predict the time interval in days until delivery, as a novel timing strategy for antenatal CCS in early-onset FGR.

### Methods and analysis

A multicentre, retrospective cohort study will be performed including pregnancies complicated by early-onset FGR in six tertiary hospitals in the Netherlands in the period between 2012-2021 (estimated sample size n=1800). Main exclusion criteria are multiple pregnancies and fetal congenital or genetic abnormalities. Routinely collected data will be extracted from medical charts. Primary outcome for the comparison of the two CCS timing strategies is a composite of perinatal, neonatal and in-hospital mortality. Secondary outcomes include the COSGROVE core outcomes set for FGR. A multivariable, mixed-effects model will be used to compare timing

strategies on study outcomes. Primary outcome for the dynamic prediction tool is 'days until birth'.

## Ethics and dissemination

The need for ethical approval was waived by the Ethics Committee (University Medical Center Utrecht). Results will be published in open-access, peer-reviewed journals and disseminated by presentations at scientific conferences.

## Trial registration

ClinicalTrials.gov: NCT05606497.

## Strengths and limitations of this study

- This study includes a large sample of early-onset FGR patients using a consensus-based and internationally accepted FGR definition.
- This study uses novel techniques in prediction research to develop a dynamic prediction tool to forecast the time interval in days until birth.
- The outcomes of our study are in line with landmark trials in FGR and a core outcomes set for this specific patients population (COSGROVE).
- Residual confounding could be a possible limitation of our observational study, caused by other (unaccounted) differences in obstetric and neonatal routine care (other than antenatal CCS timing strategies) between participating hospitals that might influence study outcome measures.
- Follow-up on secondary outcomes of the offspring, including long-term follow-up, might not be complete in all patients.

## BACKGROUND

Early-onset fetal growth restriction (FGR) is defined as failure of a fetus to meet its growth potential, with its detection before 32 weeks of pregnancy. Early-onset FGR occurs in approximately 0.5-1% of all pregnancies and is a notable cause of stillbirth (2%), neonatal morbidity (24%) and mortality (8-19%) (1–5). In developed countries, early-onset FGR is most commonly caused by placental dysfunction leading to unmet fetal metabolic and gaseous demands (6,7). In a prolonged and increasing hypoxic state, the anticipated risks of stillbirth rise. Active fetal surveillance of early-onset FGR pregnancies is therefore warranted and consists of ultrasound (fetal Doppler sonography) and analysis of the fetal heart rate pattern (cardiotocography) to detect critical fetal hypoxia and instigate timely, often preterm, delivery. Alternatively, maternal health issues can necessitate pre-term delivery as early-onset FGR frequently coincides with (pre-)eclampsia (8).

Antenatal corticosteroids (CCS) lower the risks of neonatal morbidity and mortality following spontaneous preterm birth (9,10). Literature suggests that antenatal CCS treatment may be most beneficial in reducing adverse neonatal outcome when a completed course of CCS (i.e. two doses of betamethasone or dexamethasone at an 24 hours interval) is administered one to seven days prior to birth (adjusted odds ratio 1.46, 95% confidence interval (CI) 1.20-1.77 in comparison to a time span longer than 7 days prior to birth) (11). Although the clinical benefit and possible harms of antenatal CCS therapy are subject of debate in early-onset FGR, it is one of the very few antenatal treatments that can possibly improve neonatal health. Repeated courses of CCS should be avoided, as they have been associated with decreased birthweight, length, head circumference and higher rates of cerebral palsy (12,13). Therefore, adequate timing of CCS administration is likely to be important, also in the setting of early-onset FGR pregnancies when preterm birth is anticipated.

There is consensus that repetitive decelerations on the cardiotocography registration reflect fetal distress and an increased risk of fetal death (13). They are thus an important trigger to initiate birth. Unfortunately, it is difficult to predict when these repetitive decelerations will occur during the period of active fetal surveillance, which makes it challenging to administer CCS within the ideal timeframe of 7 days prior to birth. International guidelines do not provide a clear directive regarding the timing of CCS treatment in early-onset FGR (1,14–16). In the Netherlands, two timing strategies regarding antenatal CCS administration in early-onset FGR are currently being practiced (Figure 1 (17)):

- Strategy "A": administration of CCS when the pulsatility index (PI) of the umbilical artery (UA) becomes abnormal (i.e. > 95th percentile), irrespective of its end-diastolic waveform.
- Strategy "B": administration of CCS when absent or reversed end-diastolic velocity of the UA is detected, thus in a more progressed disease state as compared to strategy A.

This study aims to compare these two timing strategies of antenatal CCS administration in early-onset FGR on a composite outcome of perinatal, neonatal and in-hospital mortality (definitions listed in 'methods' section below). With that, we aim to inform clinicians about the optimal timing management of antenatal CCS administration to improve outcomes of pregnancies complicated by early-onset FGR. In addition, we aim to develop a dynamic, prediction tool to regularly determine the time interval until birth in days during the period of active fetal surveillance. Ultimately, the use of such a dynamic risk tool could be used as an additional timing strategy for CCS treatment in early-onset FGR with the aim to improve neonatal outcome.

## METHODS

### Study design and setting

This multicentre, retrospective cohort study is designed to mimic a cluster randomized controlled trial (RCT). The study will be performed in six tertiary teaching hospitals in the Netherlands, all equipped with a level III neonatal intensive care unit. These hospitals were selected based on their local guidelines for FGR management (i.e. CCS timing strategy in early-onset FGR). The selection of these six hospitals resulted in an even distribution of the hospitals over the two CCS timing strategies (as is custom in a cluster-RCT) and a sufficient sample size of our study (see power calculation). To add, hospitals have a high adherence rate regarding the guidelines for the management of FGR pregnancies and, therefore, there is no within-hospital variation between physicians on this matter.

Patients will be included when diagnosed with early-onset FGR between 2012 and 2021. Neonates were actively managed at 24 weeks of gestational age since 2010 in the Netherlands. Therefore, and considering the learning curve neonatologists experienced in the first two years of this new policy, patients will be included from 2012 onwards. This study protocol was assessed by the Ethics Committee of the University Medical Center Utrecht (METC NedMec, registration number 22/613), which confirmed that the Medical Research Involving Human Subjects Act (WMO) does not apply to this study (18). In addition, the need for informed consent was waived as an exception was made in accordance with the General Data Protection Regulation as A) processing the data is necessary with a view to scientific research; B) the research is of public interest; C) requesting consent requires disproportionate effort (i.e. the number of patients is too high); D) the research embodies such assurances that the privacy of the data subject will not be disproportionally harmed (19). A Data Management Plan has been drawn up and participating centers had to be rewarded with a ISO27001/NEN7510 certificate

to meet the General Data Protection Regulation requirements (19). Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

**Study population**

To be eligible for inclusion, a patient must meet all of the following criteria: 1) Early-onset FGR in accordance with the consensus-based definition of Gordijn *et al.* (20); 2) Singleton pregnancy; 3) Age ≥ 18 years; 4) Consented active, neonatal management after counselling (thus having an indication for CCS administration in case of birth < 34 weeks of gestational age). Exclusion criteria are 1) Multiple pregnancies; 2) Fetal congenital abnormalities or antenatal diagnosed genetic disorders; 3) Patients who stated that their patient or offspring data may not be used for scientific research.

**Data collection**

Patients will be identified using parturition records. Data will be captured in a CASTOR electronic case report form, a Good Clinical Practice compliant Electronic Data Capture system (21).

Medical records will be scrutinized to extract the patient characteristics of mothers as well as the offspring. The offspring is often transferred to a level II neonatology unit after being treated in the level III neonatal intensive care unit of the participating hospitals. To complete information on neonatal study outcomes, admission and discharge letters of these patient transfers will be used to ensure complete follow-up assessment. In addition, data collection regarding the primary outcome is safeguarded by a national registration on pregnancy outcomes (PERIDOS). Information on neurodevelopment will be obtained from follow-up

assessments in the participating perinatal centers or from letters of the local paediatricians. All variables and outcomes that will be collected are summarized in Table 1.

**Table 1.** Patient characteristics of the mother and the offspring

| Maternal characteristics | Pregnancy characteristics | Characteristics of the offspring |
|---|---|---|
| Age | Gestational age at time of diagnosis | Sex |
| Ethnic background | Gravidity | Gestational age at birth |
| Smoking status | Parity | Birth weight |
| Drug use | Time between corticosteroid administration and birth (days) | Birth weight centile (Hoftiezer) |
| Body Mass Index | Mode of delivery (caesarean or vaginal) | Apgar scores at 5 minutes |
| Transfer to other perinatal centers before delivery | Obstetric history<br>Previous pregnancy affected by fetal growth restriction, pre-eclampsia, (iatrogenic) preterm birth or diabetes gravidarum. | Arterial and venous pH with base excess |
| Pre-existent disorders<br>Chronic kidney disease; Systemic Lupus Erythematosus; Inflammatory Bowel Disease; Antiphospholipid Syndrome; Diabetes; Chronic Hypertension; Other medical disease affecting maternal or neonatal outcome | Hypertensive disorders of pregnancy<br>Pregnancy-Induced Hypertension; Pre-eclampsia | Mechanical ventilation<br>Need for mechanical ventilation during admission, whether this was <72 hours after birth and the duration (days). |
| | Other pregnancy-related disorders<br>Pregnancy cholestasis; Gestational diabetes | Perinatal, neonatal and in-hospital mortality |
| | Ultrasound-based markers (of each performed ultrasound examination)<br>Pulsatility ndex of umbilical artery; End-diastolic velocity waveform umbilical artery; Estimated fetal weight; Pulsatility index of middle cerebral artery; Cerebroplacental Ratio; Pulsatility index of veins ductus venosus; Atrial systolic velocity of ductus venosus; Presence of echodense fetal bowel | Adverse outcome measures<br>Respiratory Distress Syndrome; Necrotizing Enterocolitis ≥ 2 according to the Bell's stages; Bronchopulmonary Dysplasia, moderate and severe; Intraventricular Hemorrhage grade 3, venous infarction, posthemorrhagic ventricular dilatation; Cystic Periventricular Leukomalacia; Retinopathy of prematurity with plus disease to which treatment is needed ; Early and delayed neonatal sepsis, culture-proven or clinically suspected; Persistent pulmonary hypertension of the newborn |
| | Cardiotocography registration<br>Short-term variation (if available); Presence of repetitive decelerations | Duration supplemental oxygen during admission |
| | Fetal death | Long-term follow-up |

## Outcomes

*Objective 1) Comparison of two main timing strategies of CCS in early-onset FGR*

The primary outcome is defined as a composite of perinatal, neonatal and in-hospital mortality. Follow-up for this endpoint is defined as time between diagnosis of early-onset FGR and

perinatal, neonatal and in-hospital mortality, or to discharge to home. Perinatal mortality will be defined as death from 22 completed weeks of gestation up to seven days following birth, neonatal mortality as death within 28 days following birth and in-hospital mortality as death from birth up to hospital discharge of the infant (22). Secondary outcomes for this study objective are defined in accordance with the Core Outcomes Set for FGR (COSGROVE)-study supplemented with other relevant maternal outcomes (23), see Supplementary file 1 (24-36). Follow-up on secondary maternal outcomes ends after six weeks post-partum. Follow-up on offspring outcomes is extended until two-years of corrected age (Figure 2 (17)). Data regarding the long-term follow up will be collected if available (i.e. at least for children born before 30 weeks of gestational age or with a birth weight <1000 grams). Follow-up management for children born after a longer pregnancy duration varies between hospitals.

*Objective 2) Development of a dynamic prediction tool of days until birth*

We will develop a dynamic prediction model to regularly determine the time interval until birth during the period of active fetal surveillance. Such a dynamic prediction model could alert physicians about the upcoming pre-term delivery and can therefore serve as a trigger for CCS administration. Traditionally, prediction models are based on 'static' information, not considering the vast amount of new information that becomes available on a daily basis. To better align with clinical care, dynamic prediction could be used, a novel technique in the risk assessment research field (37). Daily updates can be generated on the outcome of "days until birth" by adding new information about maternal or fetal health, e.g. retrieved by ultrasonography and CTG-registration routinely used in FGR pregnancies, to the dynamic model. This provides the physician with an up-to-date time interval assessment.

**Statistical analyses**

*Objective 1) Comparison of two main timing strategies of CCS in early-onset FGR*

As our study design mimics a cluster-RCT, we will align our statistical analysis with the methods adopted by such trials. Intra-cluster correlation should thus be considered. Primary and secondary outcomes will be compared between the two timing strategies by use of the practice variation between the participating centers using a multivariable, mixed-effects model, taking hierarchy of the data into account. Important differences in routine care between the participating centers, other than the timing strategy, and between participants across the timing strategies are considered to be important confounding variables, and will be adjusted for in the analyses. These differences in routine care will be identified by studying local, management protocols and by scheduling research meetings to discuss routine care in the participating centers. Adjusted odds ratios with 95% confidence intervals will be calculated for dichotomous outcome measures and mean with standard deviations will be calculated for continuous outcome measures (and median with interquartile range for continuous non-parametric outcomes). Timing strategy "A" will be held as reference group. For secondary outcome measures similar analyses will be performed. Exploratory subgroup analyses will be performed based on gestational age at birth (below versus above 34 weeks). The decision for this subgroup analysis was due to the fact that antenatal CCS are administered up to 34 weeks of gestation in the Netherlands. Heterogeneous treatment effects will be assessed by introducing an interaction term between the subgroup variable and the CCS treatment timing strategy to the mixed-effects model for the primary outcome. A formal test of interaction will be performed. Afterwards, the primary analysis will be repeated within each stratum of the subgroup.

*Objective 2) Development of a dynamic prediction tool of days until birth*

To allow for dynamic prediction, information known at baseline as well as subsequent clinical and ultrasonographic information that becomes available will be used in a proportional baselines landmark supermodel, with days until birth as the outcome (38). Candidate predictors were selected based on literature and clinical practice, summarized in Table 2. For these candidate predictors, repeated measures will be gathered on the day of every follow-up ultrasonography (i.e. once or twice a week). Missing data regarding possible predictors will be imputed by multiple imputation. The final set of predictors will be selected using backward stepwise elimination based on the Akaike Information Criterion. Internal validation using bootstrapping and subsequent shrinkage will be performed to account for potential overfitting. Model performance will be reported by assessing discrimination based on the c-statistic, and the calibration both visually using calibration plots and quantitatively using the calibration-in-the-large and calibration slope. The c-statistic, calibration-in-the-large, and calibration slope will be determined at each time point, and will be reported in a graph as a series. Statistical analyses will be conducted using the latest version of R at the time of analysis (current version 4.0.3.1.32) (39).

**Table 2.** Candidate predictors dynamic, prediction tool

| Fetal | Maternal |
|---|---|
| Estimated fetal weight | Presence of hypertensive disorders of pregnancy |
| Gestational age | Use of anti-hypertensive drugs |
| Pulsatiliy index umbilical artery | Use of intravenous anti-hypertensive medication |
| Pulsatility index cerebral middle artery | Use of magnesium sulphate |
| Cerebroplacental ratio | Number of hypertensive crises |
| Pulsatility index of veins ductus venosus | Presence of lung edema |
| Absence of interval growth | Progression of organ dysfunction |
| Repetitive decelerations on CTG | |
| Short-term variability | |
| Subjective fetal movements | |

## Sample size calculation

*Objective 1) Comparison of two main timing strategies of CCS in early-onset FGR*

We performed a power calculation based on the fact that our study design mimics a cluster-RCT. In a cluster-RCT, the statistical power of a study is determined by amongst others the amount of clusters (i.e. hospitals) to be included (not patients), the intra-cluster correlation of study outcomes and expected incidence of the primary outcome. We performed a power calculation using three clusters (i.e. hospitals) per CCS timing strategy, an expected incidence of 6.8% on our primary outcome (based on the TRUFFLE trial) and an intra-cluster correlation coefficient varying between 0.001-0.0091 (3,40). Including patient data from six participating hospitals (three per timing strategy) will allow us to detect a range in minimal difference on the primary outcome of 1.7-4.6% with an alpha (α) of 5% and a power (1-β) of 80% (3,41). We expect that inclusion in six hospitals over a ten year time period will result in a total sample of approximately 1800 patients, based on the production levels of the hospitals.

*Objective 2) Development of a dynamic prediction tool of days until birth*

Currently, no formal sample size calculation requirements are available for dynamic prediction model development. We will use the same sample size as for objective 1. The number of candidate predictors will be based on Riley *et al.*, using a margin of error of 5%, expected shrinkage factor of 0.9, and Cox-Snell R squared statistic of 0.099 (42).

## DISCUSSION

The OPtimal TIming of antenatal COrticosteroids in early-onset fetal growth REstriction (OPTICORE)-study will provide a large cohort of early-onset FGR pregnancies, including patient data of six participating, tertiary hospitals in the Netherlands. The results derived from this study will likely provide the clinician with guidance on the optimal time frame for antenatal

CCS administration in this patient population. With that, we aim to improve the neonatal and overall outcome for future early-onset FGR pregnancies.

There is an abundance of literature about the efficacy of antenatal CCS administration in women undergoing spontaneous preterm labor. Optimal timing of antenatal CCS administration – with a completed course between one and seven days before delivery – shows the largest risk reduction for infant mortality compared to no administration of antenatal CCS (adjusted risk ratio 0.5, 95%CI 0.4-0.6) versus a time interval of more than seven days till birth (adjusted risk ratio 0.7, 95%CI 0.6-0.9) (43). Similar results were found for the outcome of severe neonatal brain injury and a composite outcome measure of mortality and/or severe neonatal morbidity (43). In addition, in a meta-analysis of sixteen observational studies including mainly small-for-gestational age infants (i.e. birthweight <10$^{th}$ centile), a significant lower neonatal mortality rate was found for infants exposed to antenatal CCS versus unexposed infants (pooled odds ratio 0.63, 95%CI 0.46-0.86) (44). However, strong evidence for the efficacy (or the absence of it) of antenatal CCS treatment in the setting of early-onset FGR is lacking, as no subgroup analysis has been performed on this specific population in previously performed RCTs, which would provide more robust information (9). The relative hypoxic and starved intra-uterine environment in early-onset FGR likely results in higher levels of fetal endogenous steroids. It remains uncertain whether antenatal CCS administration on top of this increased fetal endogenous corticosteroid release is still of benefit (45). Nevertheless, international guidelines on FGR advise to administer antenatal CCS in pregnancies at risk for preterm birth.

Adequate timing of CCS treatment is challenging as the time interval until delivery in early-onset FGR pregnancies is difficult to predict. Risks of stillbirth or neurological impairment due to acute, on top of chronic, hypoxia have to be balanced against the risks of neonatal morbidity and mortality due to prematurity. The landmark TRUFFLE and GRIT trials, that

assessed CTG and ultrasound parameters as triggers for timely delivery in FGR pregnancies, have not resulted in clear uniform recommendations on how to time delivery (3,46). In an observational study, Hecher *et al*. described the time sequence pattern in the development of abnormalities in fetal Doppler patterns and CTG-registration (13). They included 110 cases of FGR in a prospective, longitudinal study. However, not all pregnancies complicated by early-onset FGR follow this pattern in daily practice and notably, the time line of changes in Doppler patterns until delivery especially varies between patients. Additionally, maternal factors (such as concomitant (pre-)eclampsia warranting birth) were ignored in the time sequence monitoring-management summary. Consequently, due to the heterogeneity in time sequence patterns and the continuous trade-off between fetal, neonatal, and maternal health, the optimal timing of delivery remains a major clinical challenge in early-onset FGR.

The ideal design to compare the two strategies for CCS administration would be a RCT. However, gathering a large enough sample for such a trial would be challenging given the low incidence of both early onset-FGR and our primary outcome. We thus chose to perform a retrospective cohort study over a timespan of a decade, using practice variation as an instrument to mimic a cluster-RCT. Follow-up on our primary outcome is safeguarded by a national registration on pregnancy outcomes (PERIDOS). However, achieving complete follow-up on the various other neonatal outcomes can be challenging, especially for the secondary outcome of bronchopulmonary dysplasia, as infants will be transferred from a level III neonatal intensive care unit to a level II neonatology unit when they are well enough to be discharged from the neonatal intensive care unit. To overcome this limitation, we will use discharge letters from the level II referral hospitals to complete follow-up information. Another challenge will be the patient transfers between tertiary care centers for delivery (e.g. because of unavailability of capacity on the neonatal intensive care unit), as patients in our study are allocated to the

center where they give birth while their CCS were administered elsewhere. This results in cross-over between the treatment strategies in our intention-to-treat analysis. Other differences in obstetric and neonatal routine care (other than antenatal CCS timing strategies) might influence the primary and secondary outcome measures namely perinatal and neonatal mortality and morbidity. Analyses will be corrected for confounding factors, yet residual confounding could remain an issue of our study design.

Strengths of this study comprise the large sample size that will be included in the study, the use of a consensus-based definition of early-onset FGR and the collection of outcome measures according to the COSGROVE-study with core outcomes for FGR (23). Also, we will use a novel and promising technique in prediction research, namely dynamic prediction (37,38). A multivariable and dynamic tool for initiation of CCS therapy might very well be superior to the use of a single-variable trigger (as used by strategies A and B) in terms of predicting the interval until birth. We will use this technique to develop an additional strategy to define the optimal time window for antenatal CCS therapy.

In summary, this large cohort of early-onset FGR pregnancies will provide important insights into the timing of antenatal CCS in pregnancies complicated by early-onset FGR. With that, we aim to reduce perinatal, neonatal and in-hospital mortality.

**LIST OF ABBREVIATIONS**

CCS – Corticosteroids

CI – Confidence Interval

COSGROVE - Core Outcome Set for Fetal Growth Restriction

FGR – Fetal Growth Restriction

PI – Pulsatility Index

RCT – Randomized Controlled Trial

UA – Umbilical Artery

WMO – Medical Research Involving Human Subjects Act

## DECLARATIONS

### Ethics and dissemination

This study was submitted to the Ethics Committee of the University Medical Center Utrecht (METC NedMec, registration number 22/613), which confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply to this study. Therefore, an official approval was not required under the WMO (18). In addition, the need for informed consent was waived as an exception was made in accordance with the General Data Protection Regulation (19). A Data Management Plan has been drawn up and participating centers had to be rewarded with a ISO27001/NEN7510 certificate to meet General Data Protection Regulation requirements (19). Results will be published in open-access, peer-reviewed journals and disseminated by presentations at scientific conferences. Data will be made available by requesting the corresponding author.

### Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

### Competing interests

The authors declare no conflict of interest.

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**Author's contributions**

JK, TL, WG, SG, FG, WO, EK, ES, and MM contributed to the overall design of the study and JK is the principal investigator of the study. All authors (JK, TL, WG, SG, FG, WO, EK, ES, MM, DK, MB, JD, SM, GM, HK, RJ, SA, RK, JJ, BR) read and approved the final version for submission.



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## TITLES AND LEGENDS FIGURES

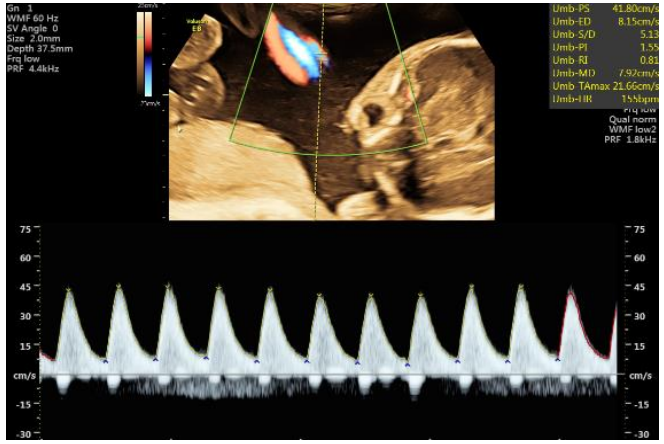
**Figure 1.** Timing strategies regarding antenatal CCS administration in early-onset FGR in the Netherlands

Abbreviations: CCS, corticosteroids; PI, pulsatility index; UA, umbilical artery. Reference image strategy "B": (17)

**Figure 2.** Study design and duration of follow-up

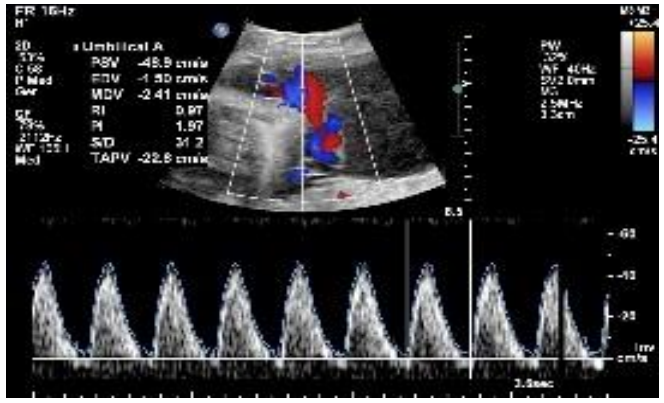
Abbreviations: FGR, fetal growth restriction; CCS, corticosteroids; PI, pulsatility index; UA, umbilical artery; AEDV, absent end-diastolic velocity; REDV, reversed end-diastolic velocity; FU, follow-up; CA, corrected age. Reference image strategy "B": (17)

# Strategy “A”

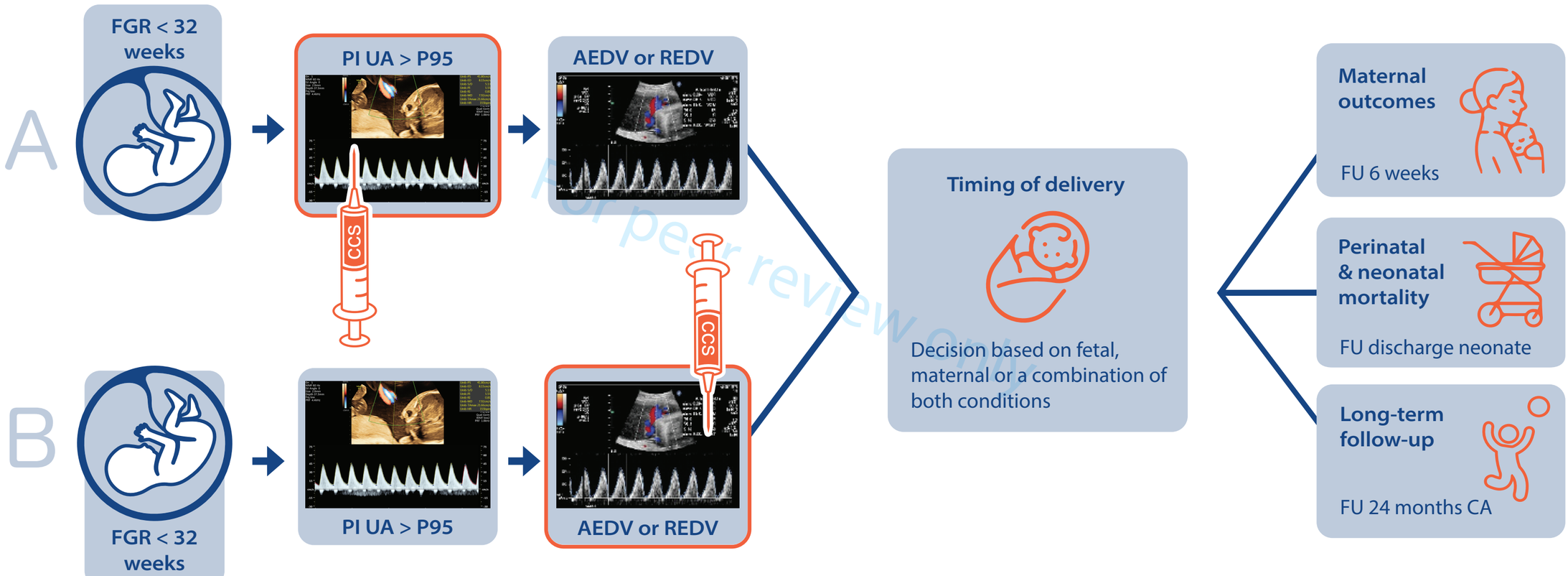


Administration of CCS when the PI of the UA becomes abnormal (i.e. > p95), irrespective of its end-diastolic waveform.

# Strategy “B”



Administration of CCS when an absent or reversed end-diastolic velocity (EDV) of the UA is detected.



**Supplementary file 1**

**COSGROVE: Core Outcome Set for FGR supplemented with other relevant endpoi**

| Domain | Outcome |
|---|---|
| **Maternal** | Pre-eclampsia |
| | Eclampsia |
| | Maternal death |
| | Mode of birth |
| **Fetal** | Stillbirth/livebirth |
| **Neonatal** | Gestational age at birth |
| | Preterm birth |
| | Extremely preterm birth |
| | Birthweight |
| | Birthweight <10$^{th}$ percentile |
| | Birthweight <3$^{rd}$ percentile |
| | Need for mechanical ventilation |
| | Bronchopulmonary dysplasia, moderate and severe |

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| | Necrotizing enterocolitis ≥ 2 according to the Bell's stages |
| | Neonatal seizures |
| | Hypoxic-ischemic encephalopathy |
| | Neonatal death |
| | In-hospital death |
| | Respiratory distress syndrome |
| | Intraventricular hemorrhage |
| | Cystic periventricular leukomalacia |
| | Retinopathy of prematurity |

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| | Neonatal sepsis |
| | Persistent pulmonary hypertension of the newborn |
| | Duration of supplemental oxygen therapy during admission |
| | Need for mechanical ventilation < 72 hours post-partum |
| **Childhood (Long-term follow-up)** | Cognitive impairment (available for children born before 30 weeks gestational age, for children born after a longer pregnancy duration follow-up management varies between clinics) |
| | Motor impairment (available for children born before 30 weeks gestational age, for children born after a longer pregnancy duration follow-up management varies between clinics) |
| | Cerebral palsy |
| | Hearing impairment |
| | Visual impairment |

**nts with definitions (20)**

| Definition |
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| Gestational hypertension accompanied by one or more of the following new-onset conditions at or after 20 weeks' gestation:<br>1. Proteinuria;<br>2. Other maternal organ dysfunction, including: Acute kidney injury (creatinine ≥90 µmol/L; 1 mg/dL); liver involvement (elevated transaminases e.g. ALT or AST >40 IU/L) with or without right upper quadrant or epigastric abdominal pain); neurological complications (examples include eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomata); haematological complications (thrombocytopenia – platelet count below 150,000/µL, diffuse intravasal coagulation, hemolysis);<br>3. Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler wave form analysis, or stillbirth) (24) |
| Eclampsia refers to the occurrence of new-onset, generalized, tonic-clonic seizures or coma in a woman with preeclampsia (25) |
| Death of mother during pregnancy or the first six weeks after delivery (postpartum). |
| Defined as either vaginal or caesarean section. |
| Stillbirth: death of fetus ante- or intrapartum (22)<br>Livebirth: birth of a living neonate |
| Time in weeks and days |
| Delivery at <37.0 weeks gestation |
| Delivery at <28.0 weeks gestation |
| Weight at time of birth in grams (g) |
| Presence of birthweight below the 10 $^{th}$ percentile according to Hoftiezer *et al.* (26) |
| Presence of birthweight below the 3 $^{rd}$ percentile according to Hoftiezer *et al.* (26) |
| Need for intubation and mechanical ventilation to support gas exchange |
| Bronchopulmonary dysplasia is diagnosed if gestational age <32 weeks: at a postmenstrual age of 36 weeks, >21% oxygen has been administered cumulatively for 28 or more days (27) |

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| ○ Moderate: Need for <30% oxygen at 36 weeks postmenstrual age<br>○ Severe: Need for ≥30% oxygen and/or positive pressure (positive pressure ventilation or continuous positive airway pressure) at 36 weeks postmenstrual age |
| Definitive medical necrotising enterocolitis:<br>• Abdominal distention with pneumatosis intestinalis, portal venous gas, or both.<br>• Other radiographic signs such as fixed, dilated loops of intestine and ileus patterns are not pathognomonic but should be treated as such.<br>Surgical necrotising enterocolitis:<br>• Free intraperitoneal air on abdominal radiograph after initial medical signs and symptoms.<br>• Persistent ileus pattern, abdominal distension, and radiographs that show an absence of bowel gas, coupled with deteriorating clinical and laboratory values. (28) |
| Transient electrographic change in the brain due to an abnormal, excessive or synchronous neuronal activity either with the occurrence of clinical signs (electro-clinical) or without them (electrographic only) in preterm infants up to 44 weeks of post menstrual age (29) |
| Clinical syndrome that results from a severe or prolonged hypoxic-ischemic episode before or during birth (30) |
| Death of the neonate within 28 days after birth |
| Death of the neonate until hospital-discharge |
| Neonatal respiratory distress syndrome, characterized by extensive lung inflammation and surfactant catabolism leading to lung dysfunction, with need for surfactant (31) |
| Intraventricular hemorrhage grade 3 according to Papile *et al*., venous infarction, posthemorrhagic ventricular dilatation needing treatment (32) |
| Cystic periventricular leukomalacia characterized by diffuse injury of the white matter, which possibly leads to cerebral palsy (33) |
| Retinopathy of prematurity with plus disease for which treatment is needed |

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| • Early-onset: neonatal sepsis in the first 72 hours of age<br>• Late-onset: neonatal sepsis after the first 72 hours of age<br>• Clinical: based on clinical condition<br>• Culture-proven |
| Persistent pulmonary hypertension of the newborn occurs in case of persistent abnormally, elevated pulmonary vascular resistance after birth, leading to severe hypoxemia |
| Duration of supplemental oxygen therapy during admission (in days) |
| Need for intubation and mechanical strategies to support gas exchange within 72 hours after birth |
| A decreased ability of cognitive function using the Dutch Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III-NL) at a corrected age of 24 months,. Severe disability will be defined as a Bayley Mental Development Index score more than 2SD below the mean score (i.e. ≤70). Moderate disability will be defined as a Bayley Mental Development Index score 1 to 2 SD below the mean score (i.e. 71-85) (34,35) |
| A decreased ability of fine and gross motor function using part of the Dutch Bayley Scales and Infant and Toddler Development, Third Edition (BSID-III-NL) at corrected age of 24 months. Severe disability will be defined as a score of more than 2 SD below the mean score (i.e. ≤70). Moderate disability will be defined as a score 1 to 2SD below the mean score (i.e. 71-85) (34,35) |
| A group of disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain (36) |
| A decreased ability of the auditory system requiring hearing aids or deafness |
| A decreased ability of the visual system requiring aids or blindness |