PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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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VERSION 1 – REVIEW

REVIEWER	Stephanie Blankenship Northwestern University Feinberg School of Medicine, Obstetrics and Gynecology
REVIEW RETURNED	18-Dec-2022

GENERAL COMMENTS	• Page 3, line 8. Can this retrospective review really reduce neonatal morbidity and mortality? As stated, this phrase is misleading. I suggest rephrasing to something along the lines of, “Data gleaned from this retrospective cohort study can help to inform management of future FGR pregnancies, specifically timing of antenatal CCS management, with the goal to reduce morbidity and mortality.” • Page 4, line 8. Removed the clarifier “most” often preterm and leave it as “often preterm.” Many early onset FGR cases do carry to term/early term, particularly if due to other causes of FGR that are not placentally-mediated (structural/chromosomal anomalies, constitutional, etc.) • Page 8, Lines 6-8: Recommend rephrasing the primary objective. Again, the authors should ask themselves if they really have the capability to optimize the timing of antenatal CCS administration, and reduce morbidity/mortality, via a retrospective review. This retrospective methodology cannot accomplish this aim. This retrospective review can really only aim to compare neonatal outcomes associated with two different strategies for CCS administration in pregnancies affected by early-onset FGR, in order to inform optimal management of antenatal CCS administration with the goal to reduce perinatal morbidity/mortality in future pregnancies. • Please define perinatal mortality – if this includes intrauterine fetal demise (IUFD), what is the mechanism for CCS reducing IUFD? Data suggests CCS reduces neonatal morbidity/mortality related to prematurity, but CCS are not administered to prevent IUFD. Consider only assessing neonatal mortality and in-hospital mortality in the composite primary outcome. Neonatal mortality (within 28 days or 7 days of life) should also be clearly defined. • Consider having an English-language reviewer. There are certain grammatical and vocabulary errors that require revising throughout.

	For example, on page 9 (line 20), do the authors mean “warrant” or “warn” physicians? Warrant does not make sense. Another example is “Objective 1) Comparison main timing strategies” should be either “1) Comparing main timing strategies” or “1) Comparison of main timing strategies”. • Page 10, Line 25: Why was the subgroup analysis determined to be > or < 34 weeks? Consider evaluating based on > or < 37 weeks, 34 weeks, 32weeks at delivery to align with other studies. • Page 10, Table 2: Are the authors tracking initial and repeat/rescue course of betamethasone timing in fetal characteristics for the prediction tool? • Use of a prediction model is innovative in this study design. Use of existing statistics from TRUFFLE trial for the sample size calculation is appropriate. • Page 12, line 37—why reference only CCS for the indication of spontaneous preterm labor, and not data on CCS in the broader FGR population which would be more applicable here, to then distinguish the particular subgroup of early-onset FGR of interest (example, meta-analysis of 16 observational studies of FGR fetuses delivered preterm, PubMed ID PMC8237697)? An AGA fetus born preterm (due to preterm labor, for example) likely has a different physiology than an FGR fetus born preterm. FGR fetuses exposed to chronic intrauterine stress related to placental dysfunction are exposed to higher concentrations of endogenous steroids, and thus additional exogenous steroids may have a lesser impact on changing outcomes in FGR fetuses. This is an important reason for why steroid administration in FGR pregnancies, especially early-onset FGR pregnancies (particularly those with abnormal dopplers, reflective of the greatest placental dysfunction), is an interesting area of study and raises questions about biologic plausibility that requires further study. • Figure 2: Suggest a different term than “termination of pregnancy” (as this denotes abortion, which doesn’t seem appropriate here) or just remove this Termination of Pregnancy box completely and keep the Delivery box (and include “Decision for delivery based on fetal or maternal factors, or a combination of both conditions” as a caption under the baby symbol in the Delivery box.

REVIEWER	Abimbola Ayorinde University of Warwick Warwick Medical School, Population Evidence and Technologies
REVIEW RETURNED	23-Jan-2023

GENERAL COMMENTS	The proposed study addresses important issues in the use of antenatal corticosteroids in pregnancies complicated by early-onset fetal growth restriction. I have a few comments: The study analyses routinely collected data/medical records. It may be useful to update the title and abstract to more accurately reflect this. Is it clear that each hospital entirely practiced one strategy? Could there be cases where a hospital practice both strategies? That is, some patients in the same hospital may receive strategy A and others strategy B? How will you check and account for this? Although you stated that ethical approval was not required, there are probably other approvals needed to be able to access the data for research purposes. Please clarify. Should the pre-existent disorders be listed under maternal characteristics (Table 1)? Is there any risk of missing data? How do you plan to deal with it?

	Not sure how the six hospitals were selected or why the remaining three hospitals are not included. Are there systematic differences between those included and those that are not? Samples size calculation section is not very clear. You mentioned that you expect to include about 1800 patients, is it possible to give an indication of how much power that sample size would provide?

VERSION 1 – AUTHOR RESPONSE

Comments from Reviewer 1:

• Page 3, line 8. Can this retrospective review really reduce neonatal morbidity and mortality? As stated, this phrase is misleading. I suggest rephrasing to something along the lines of, "Data gleaned from this retrospective cohort study can help to inform management of future FGR pregnancies, specifically timing of antenatal CCS management, with the goal to reduce morbidity and mortality."
Thank you for this suggestion. We rephrased our primary objective in the abstract on page 3 (lines 27-30):

"This study aims to 1) use practice variation to compare CCS timing strategies in early-onset FGR on fetal and neonatal outcomes."

To add, we rephrased this in the manuscript on page 6 (lines 35-46):

"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."

• Page 4, line 8. Removed the clarifier "most" often preterm and leave it as "often preterm." Many early onset FGR cases do carry to term/early term, particularly if due to other causes of FGR that are not placentally-mediated (structural/chromosomal anomalies, constitutional, etc.)
We removed the word 'most' on page 5 (line 25), thank you for the suggestion:

"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."

• Page 8, Lines 6-8: Recommend rephrasing the primary objective. Again, the authors should ask themselves if they really have the capability to optimize the timing of antenatal CCS administration, and reduce morbidity/mortality, via a retrospective review. This retrospective methodology cannot accomplish this aim. This retrospective review can really only aim to compare neonatal outcomes associated with two different strategies for CCS administration in pregnancies affected by early-onset FGR, in order to inform optimal management of antenatal CCS administration with the goal to reduce perinatal morbidity/mortality in future pregnancies.
We rephrased our primary objective throughout the manuscript e.g. on page 6 (lines 35-46):

"This study aims to compare these two timing strategies of antenatal CCS administration in early-onset FGR on a composite 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 added the definitions of perinatal, neonatal and in-hospital mortality on page 10 (lines 3-11):

“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.”, thank you for both suggestions.

• Please define perinatal mortality – if this includes intrauterine fetal demise (IUFD), what is the mechanism for CCS reducing IUFD? Data suggests CCS reduces neonatal morbidity/mortality related to prematurity, but CCS are not administered to prevent IUFD. Consider only assessing neonatal mortality and in-hospital mortality in the composite primary outcome. Neonatal mortality (within 28 days or 7 days of life) should also be clearly defined.
We thank the reviewer for this suggestion. In strategy B, defined as administration of CCS when the umbilical artery shows an absent or reversed flow, there might be an increased risk of stillbirth in case physicians are tempted to prolong pregnancy to complete the course of CCS before initiating delivery (by inducing labor or performing a C-section). Therefore, to take this theoretical risk into account, we chose to include stillbirth in our composite primary outcome.

• Consider having an English-language reviewer. There are certain grammatical and vocabulary errors that require revising throughout. For example, on page 9 (line 20), do the authors mean “warrant” or “warn” physicians? Warrant does not make sense. Another example is “Objective 1) Comparison main timing strategies” should be either “1) Comparing main timing strategies” or “1) Comparison of main timing strategies”.
We asked a native-English speaker to read the paper to correct grammatical and vocabulary errors throughout the manuscript.

• Page 10, Line 25: Why was the subgroup analysis determined to be > or < 34 weeks? Consider evaluating based on > or < 37 weeks, 34 weeks, 32weeks at delivery to align with other studies.
We thank the reviewer for this suggestion and critically reviewed the subgroup definitions of landmark FGR trials. The initial threshold of 34 weeks gestational age for the subgroup analysis in the OPTICORE study is based on the fact that CCS are generally withheld in case of late preterm birth (> 34 weeks) in the Netherlands. We added this explanation to our manuscript on page 11 (line 42-47):

“The decision for this subgroup analysis was due to the fact that antenatal CCS are administered up to 34 weeks of gestational age in the Netherlands.”

We agree that alignment of subgroup definitions and their cut-offs with other studies is of major importance. However, landmark trials in early-onset FGR patients (e.g. STRIDER, TRUFFLE, GRIT) used different cut-offs of gestational age in their subgroup analysis on study outcomes (i.e. STRIDER used 26 weeks of gestation at randomisation as cut-off, TRUFFLE used three cut-offs (26-27 weeks, 28-29 weeks and 30-31 weeks of gestation at study entry) and GRIT used 30 weeks of gestation at recruitment as cut-off). In addition, creating more than two subgroups (i.e. more than one cut-off for gestational age) as suggested by the reviewer would result in a decrease in statistical power to show statistical interaction (if present) between the timing strategies and gestational age at birth on study outcomes. We therefore chose to stick to the cut-off of 34 weeks of gestational age.

• Page 10, Table 2: Are the authors tracking initial and repeat/rescue course of betamethasone timing in fetal characteristics for the prediction tool?
We understand the comment of the reviewer, as physicians might be more inclined to initiate delivery (e.g. by performing a caesarean section) shortly after CCS administration and we do track this characteristic in our dataset. Nevertheless, we did not add this characteristic to the prediction tool, as this tool is designed to be used as a possible timing strategy for CCS administration (neither fetal nor

neonatal outcomes), and therefore, adding the timing of initial/rescue courses does not suit the intended use of the model.

• Use of a prediction model is innovative in this study design. Use of existing statistics from TRUFFLE trial for the sample size calculation is appropriate.
Thank you.

• Page 12, line 37—why reference only CCS for the indication of spontaneous preterm labor, and not data on CCS in the broader FGR population which would be more applicable here, to then distinguish the particular subgroup of early-onset FGR of interest (example, meta-analysis of 16 observational studies of FGR fetuses delivered preterm, PubMed ID PMC8237697)? An AGA fetus born preterm (due to preterm labor, for example) likely has a different physiology than an FGR fetus born preterm. FGR fetuses exposed to chronic intrauterine stress related to placental dysfunction are exposed to higher concentrations of endogenous steroids, and thus additional exogenous steroids may have a lesser impact on changing outcomes in FGR fetuses. This is an important reason for why steroid administration in FGR pregnancies, especially early-onset FGR pregnancies (particularly those with abnormal dopplers, reflective of the greatest placental dysfunction), is an interesting area of study and raises questions about biologic plausibility that requires further study.
Thank you for your suggestion, we added this to our discussion on page 14 (lines 25-33):

“In addition, in a meta-analysis of sixteen observational studies including mainly small-for-gestational age infants (i.e. birthweight <10th 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) (31).”

• Figure 2: Suggest a different term than “termination of pregnancy” (as this denotes abortion, which doesn’t seem appropriate here) or just remove this Termination of Pregnancy box completely and keep the Delivery box (and include “Decision for delivery based on fetal or maternal factors, or a combination of both conditions” as a caption under the baby symbol in the Delivery box.
We changed this in our Figure, thank you for the suggestion.

Comments from Reviewer 2:
• The study analyses routinely collected data/medical records. It may be useful to update the title and abstract to more accurately reflect this.
We have stated this more clearly in the abstract on (page 3, lines 49-55), thank you for the suggestion:

“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.”

• Is it clear that each hospital entirely practiced one strategy? Could there be cases where a hospital practice both strategies? That is, some patients in the same hospital may receive strategy A and others strategy B? How will you check and account for this?
Hospitals have a high adherence rate regarding their ‘clinical management of FGR’ guidelines. There is no within-hospital practice variation between physicians on this matter. We added this to our manuscript on page 7 (line 23-29):

“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.”

It is however possible, that cross-over occurred, as CCS could have been given on maternal instead of fetal indication or reversed flow is measured at first presentation with FGR. In our database we

include the indication for CCS administration as well, so we will be able to distinguish between CCS administration on maternal and fetal indication when analyzing the data. Also, we will use an intention-to-treat approach for the comparison of timing strategies on study outcomes, as our study design (and thus analysis) mimics a cluster randomized controlled trial.

• Although you stated that ethical approval was not required, there are probably other approvals needed to be able to access the data for research purposes. Please clarify.
Thank you for the comment, we described it more extensively now on page 7 (line 38-60) and page 8 (line 3):

“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).”

• Should the pre-existent disorders be listed under maternal characteristics (Table 1)?
Agree, thank you for the suggestion. We changed this in the Table on page 9.

• Is there any risk of missing data? How do you plan to deal with it?
We thank the reviewer for this question. Indeed, there is a risk of missing data, especially for secondary neonatal outcomes (e.g. BPD), 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 complete the data on study outcomes, we will use discharge letters of the referral hospitals. This is described in our manuscript on page 8 (lines 47-52) using the following text:

“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, if data regarding our candidate predictors is missing we will use multiple imputation to impute missing data for these variables. This is added to our manuscript on page 12 (lines 28-33):

“Missing data regarding possible predictors will be imputed by multiple imputation.”

Nevertheless, for the primary outcome, our data collection is safeguarded by a national registration of pregnancy outcomes (PERIDOS). This information is described in our manuscript on page 8 (lines 52-58):

“In addition, data collection regarding the primary outcome is safeguarded by a national registration on pregnancy outcomes (PERIDOS).”

• Not sure how the six hospitals were selected or why the remaining three hospitals are not included. Are there systematic differences between those included and those that are not?
There are no systematic differences between the participating six and remaining three hospitals. We chose to include these hospitals to have a similar amount of centers for strategy A and B, as was

required for the design of our study. Hopefully, we explained this more clearly now in the manuscript on page 7 (lines 13-24):

“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).”

• Samples size calculation section is not very clear. You mentioned that you expect to include about 1800 patients, is it possible to give an indication of how much power that sample size would provide? Thank you for the comment. The power of our cohort will be 80% with three clusters per timing strategy, we explained this on page 13 (line 17-23):

“Including patient data from six participating hospitals (three per 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% (3,28).” We hope to have clarified our sample size calculation.

VERSION 2 – REVIEW

REVIEWER	Stephanie Blankenship Northwestern University Feinberg School of Medicine, Obstetrics and Gynecology
REVIEW RETURNED	25-Feb-2023

GENERAL COMMENTS	Thank you for addressing the relevant comments.

REVIEWER	Abimbola Ayorinde University of Warwick Warwick Medical School, Population Evidence and Technologies
REVIEW RETURNED	28-Feb-2023

GENERAL COMMENTS	Thank you for addressing my comments. I have no further comments. However, I suggest proofreading the manuscript more carefully for the use of language/terminologies, as well as punctuation and grammar. For example, you said “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”. It is unusual to use “production levels” for hospitals. Should this be “We expect that inclusion of six hospitals over a ten-year time period will result in a total sample of approximately 1800 patients, based on the birth rates at the hospitals”?