Statistical Analysis Plan

Official title

The Effect of Time Window for Umbilical Cord Clamping During Cesarean Section on the Health Outcomes of Offspring Hemoglobin and Maternal Blood Loss.

NCT number

Not yet assigned.

Document date

08/01/2022

Objectives

To evaluate the effects of umbilical cord clamping at different time after cesarean section on the health outcomes of offspring hemoglobin, maternal blood loss, as well as children's growth and development.

Primary outcomes

The neonatal hemoglobin and the change in maternal hemoglobin.

Secondary outcomes

The incidence rate of neonatal anemia and jaundice, Apgar score, the incidence rate of neonatal intensive care unit (NICU) admission, placental weight, maternal hemoglobin after the cesarean, estimated maternal blood loss, the incidence rate of maternal blood transfusion.

Exploratory secondary outcomes

The children's hemoglobin, anemia, growth, and development.

Statistical Analysis

The primary analysis will be conducted following the intention-to-treat principle. All tests will be two-sided with alpha set at 0.05. No adjustment will be made for multiple testing for multiple outcomes.

Baseline characteristics and outcomes will be summarized using appropriate descriptive statistics: mean (standard deviation) or median (P_{25}~P_{75}) for continuous variables, counts (%) for categorical variables. For continuous variables, Analysis of Variance (ANOVA) or Kruskal-Wallis test will be used to examine the differences among the three intervention groups and the control group as appropriate. For categorical variables, $\chi^{\wedge 2}$ or Fisher exact test will be carried out as appropriate.

Given an anticipated low rate of loss-to-follow up concerning the primary outcomes, the primary analyses will be conducted following a complete case strategy. Specifically, the neonatal hemoglobin and the change in maternal hemoglobin will be analyzed using mixed linear regression model (with necessary transformation for better normality) or mixed median regression model, where study center will be modelled as

a random effect. Potential confounding factors that differ among groups at baseline will be adjusted. Non-inferiority test will be employed with respect to the effect of delayed cord clamping on the change in maternal hemoglobin, in which the margin of non-inferiority is set at 0.87 g/dL, an expected clinically significant difference of the change in maternal hemoglobin. Non-inferiority would be concluded if the lower limit of the confidence interval was greater than -0.87 g/dL. If significant differences are observed in neonatal hemoglobin between groups, appropriate methods (such as trend test) will be used to further explore the association between different time of umbilical cord clamping and neonatal hemoglobin level. Center-stratified analysis will be carried out with generalized linear regression model to determine whether the effect on primary outcomes varies across centers.

Secondary analyses will also be conducted only among complete cases. Mixed linear regression model (with necessary transformation for better normality) or mixed median regression model will be used to evaluate the effects of delayed cord clamping on the Apgar score, placental weight, maternal hemoglobin after the cesarean, and estimated maternal blood loss. Mixed logistic regression model will be fitted to assess the effects on the incidence rate of neonatal anemia, neonatal jaundice, neonatal intensive care unit (NICU) admission, and maternal blood transfusion. Center effects will be modeled by including a random effect. Potential confounding factors that differ among groups at baseline will be adjusted.

Multiple imputation method will be applied to deal with missing values before the analysis of exploratory secondary outcomes, if needed, and the results based on imputed data will be compared with those based on complete cases. Mixed linear regression model (with necessary transformation for better normality), mixed median regression model and mixed logistic regression model will be constructed as appropriate to estimate the effect on follow-up outcomes of children. These outcomes primarily include the hemoglobin and anemia at 6, 12, 18 months, the Z-score of length and weight at 3, 6, 12, 18 months, and the results of Denver Developmental Screening Test (DDST) at 3, 6, 12, 18 months. Random effects of centers and months of follow up will be set in models for the dependencies among observations nested within individuals and centers. Length and weight at birth are the pre-specified covariates for the models of follow-up length and weight, respectively. Baby sex is the pre-specified covariate for the model of the DDST result. Other confounding factors that differ among groups at baseline will be adjusted.

Sensitivity analysis will be performed on the basis of per-protocol dataset to confirm the robustness of the main result of two primary outcomes. Participants will be considered as compliant with the protocol if the time of cord clamping is as follows:

Arms	**Anticipated procedure**	**Permissible time range**
Control group	Immediately clamp	< 15s
Experimental group1	Clamp at 30s after delivery	⩾15s and < 45s
Experimental group2	Clamp at 60s after delivery	⩾45s and < 75s
Experimental group3	Clamp at 90s after delivery	⩾75s and < 105s