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CLINICAL ARTICLE

Obstetrics

Effect of delayed versus immediate umbilical cord clamping in vaginal delivery at term: A randomized clinical trial

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Abstract

Objective: To compare maternal blood loss with immediate cord clamping versus delayed cord clamping in women undergoing spontaneous vaginal delivery at term.

Methods: Parallel group non-blinded randomized trial conducted at a single center in Italy. Women with singleton gestations who underwent spontaneous vaginal delivery at term were eligible and were randomized in a 1:1 ratio to either immediate or delayed cord clamping. In the immediate cord clamping group, cord clamping was within 15 s after birth. In the delayed cord clamping group, cord clamping was after more than 60 s, or when the cord had stopped pulsing. The primary outcome was change in maternal hemoglobin level from the day of delivery to day one after delivery.

Results: A total of 122 participants were enrolled in the trial. There were no significant differences in maternal blood loss as assessed by comparing the decrease in maternal hemoglobin level (mean difference − 0.10 g/dl, 95% confidence interval − 0.28 to 0.08) between the two groups. The mean hemoglobin level at postdelivery day 1 was 11.0 ± 1.5 g/dl in the delayed group and 11.3 ± 1.6 g/dl in the immediate group.

Conclusions: Delayed umbilical cord clamping, compared with immediate umbilical cord clamping, resulted in no significant change in maternal hemoglobin level 1 day after delivery.

Trial Registration: Clinicaltrials.gov NCT04353544.

KEYWORDS
cord clamping, hemoglobin, umbilical cord, vaginal delivery

1 | INTRODUCTION

The third stage of labor commences with the delivery of the baby and ends with the delivery of the placenta and its membranes.[1] Routine active management of the third stage of labor, including removal of the placenta by controlled cord traction, using uterotonics after delivery to stimulate contraction of the uterus and uterine massage, reduces the risk of postpartum hemorrhage (PPH).[2–10] PPH is the leading cause of maternal death worldwide, with 127 000 deaths annually.[11,12]

In the third stage of labor, delayed, rather than early, cord clamping reduces the risk of death before discharge for babies born

preterm.[13] Delayed cord clamping is defined as the prolongation of the time between the delivery of a newborn and the clamping of the umbilical cord. Delayed umbilical cord clamping is usually performed 25 s to 5 min after giving birth.[13]

Benefits of delayed umbilical cord clamping include improved transitional circulation, better establishment of red blood cell volume, decreased need for blood transfusion, and lower incidence of necrotizing enterocolitis and intraventricular hemorrhage.[14]

A more liberal approach to delaying clamping of the umbilical cord also in term infants appears to be warranted, particularly in light of growing evidence that delayed cord clamping increases early hemoglobin concentrations.[15] However, data are lacking regarding maternal outcomes associated with delayed cord clamping, with concerns associated with an increased risk of PPH.[16] In a recent randomized trial including 113 participants, Purisch et al.[17] showed that among women undergoing cesarean delivery at term, delayed umbilical cord clamping did not result in significantly increased risk of PPH.

The hypothesis of this trial was that in women with singleton pregnancy who underwent spontaneous vaginal delivery at term, delayed cord clamping would increase maternal blood loss.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This was a single-center parallel group randomized trial of women with singleton pregnancies who underwent spontaneous vaginal delivery at a single center in Italy (Casa di Cura Accreditata Fabia Mater) from April 16, 2020 to February 25, 2021. The trial was approved by the local IRB (Casa di Cura Accreditata Fabia Mater). #CE 04-18OST (1 February, 2018). All participants in the trial provided written informed consent.

Inclusion criteria were: 18–50 years of age, singleton pregnancy, cephalic presentation, pregnancy duration at randomization between 37^{+0} and 41^{+6} weeks, and spontaneous onset of labor.

Exclusion criteria were: multiple pregnancies, preterm deliveries, induced labor, operative deliveries, women with hypertension, abnormal placentation, maternal bleeding disorders, and planned cord blood banking.

2.2 | Intervention and control group

As was standard practice for all spontaneous vaginal deliveries, women received active management of the third stage of labor, with removal of the placenta by controlled cord traction after cord clamping, along with uterine massage and uterotonics after delivery, including oxytocin 10 IU given intramuscularly.

In the immediate cord clamping group, cord clamping was within 15 s after delivery. In the delayed cord clamping group, cord clamping was more than 60 s after delivery, or when the cord had stopped pulsing (up to 5 min).

2.3 | Outcomes

The primary outcome was the change in maternal hemoglobin level on day 1 after delivery compared with the predelivery hemoglobin level obtained at the time of the active stage of labor. The secondary outcomes were PPH, defined as an estimated blood loss more than 500 ml, administration of additional uterotonics, and need for maternal blood transfusion.

2.4 | Randomization and masking

Eligible participants were randomly allocated in a 1:1 ratio to either immediate or delayed cord clamping. Women were randomized by a web-based system, and the randomization sequence was prepared by an independent statistician. The recruiters and the trial coordinator did not have access to the randomization sequence. The trial was open-label given the nature of the interventions.

Women were approached by the research staff and counseled about the trial at the time of active stage of labor in case of spontaneous onset of labor. At that time eligible women received a complete blood count with hemoglobin level assessment. Eligible women who agreed to take part in the study were randomized at the time of delivery of the baby in case of spontaneous vaginal delivery.

2.5 | Sample size calculation

Calculation of the sample size was based on the following consideration: a mean ± standard deviation change in hemoglobin level for spontaneous vaginal delivery of −0.9 ± 1.0 g/dl with immediate cord clamping[18] and of 1.5 g/dl with delayed cord clamping group,[14] and an anticipated 20% crossover rate from delayed to immediate cord clamping.[16] Based on these considerations, setting a power of 80% to detect a significant greater drop in postdelivery day 1 maternal hemoglobin level, with a two-sided type 1 error of 5%, a sample size of 122 participants was planned.

2.6 | Statistical analysis

Data are shown as means, or as number (percentage). Univariate comparisons of dichotomous data were performed with the use of the χ^2 test with continuity correction. Comparisons between groups were performed with the use of the *t* test to test group means by assuming equal within-group variances.

The primary analysis was an intention-to-treat comparison of the treatment assigned at randomization. The effect of immediate

or delayed cord clamping on each outcome was quantified as relative risk or as mean difference (MD) with 95% confidence interval (CI).

A two-sided *P* value less than 0.05 was considered significant.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 19.0 (IBM Inc.,).

3 | RESULTS

3.1 | Trial population

During the study period, 122 women met the inclusion criteria and were included in the study. Sixty-two were randomized into the delayed cord clamping group and 60 into the immediate cord clamping group. All women randomized into the immediate cord clamping group received the assigned treatment, but five women randomized into the delayed cord clamping group received cord clamping within 15 s after birth and four received cord clamping between 1 and 2 min before the cord stopped pulsing. No women were excluded after randomization or lost to follow up (Figure 1).

Table 1 shows the baseline demographic and clinical characteristics for each group. Mean maternal age was 30 years in both groups and mean birth weight was about 3300 g.

3.2 | Primary and secondary outcomes

Primary outcome data were available for all participants (Table 2). There were no significant differences in maternal blood loss as assessed by comparing the decrease in maternal hemoglobin level (MD −0.10 g/dl, 95% CI −0.28 to 0.08 g/dl) between the two groups. The mean hemoglobin level at postdelivery day 1 was 11.0 ± 1.5 g/dl in the delayed cord clamping group and 11.3 ± 1.6 g/dl in the immediate cord clamping group (MD −0.30 g/dl, 95% CI −0.85 to 0.25 g.dl). There were three cases of PPH in the delayed cord clamping group and four in the immediate cord clamping group. Additional uterotonics were required in 17.7% of the women randomized in the delayed

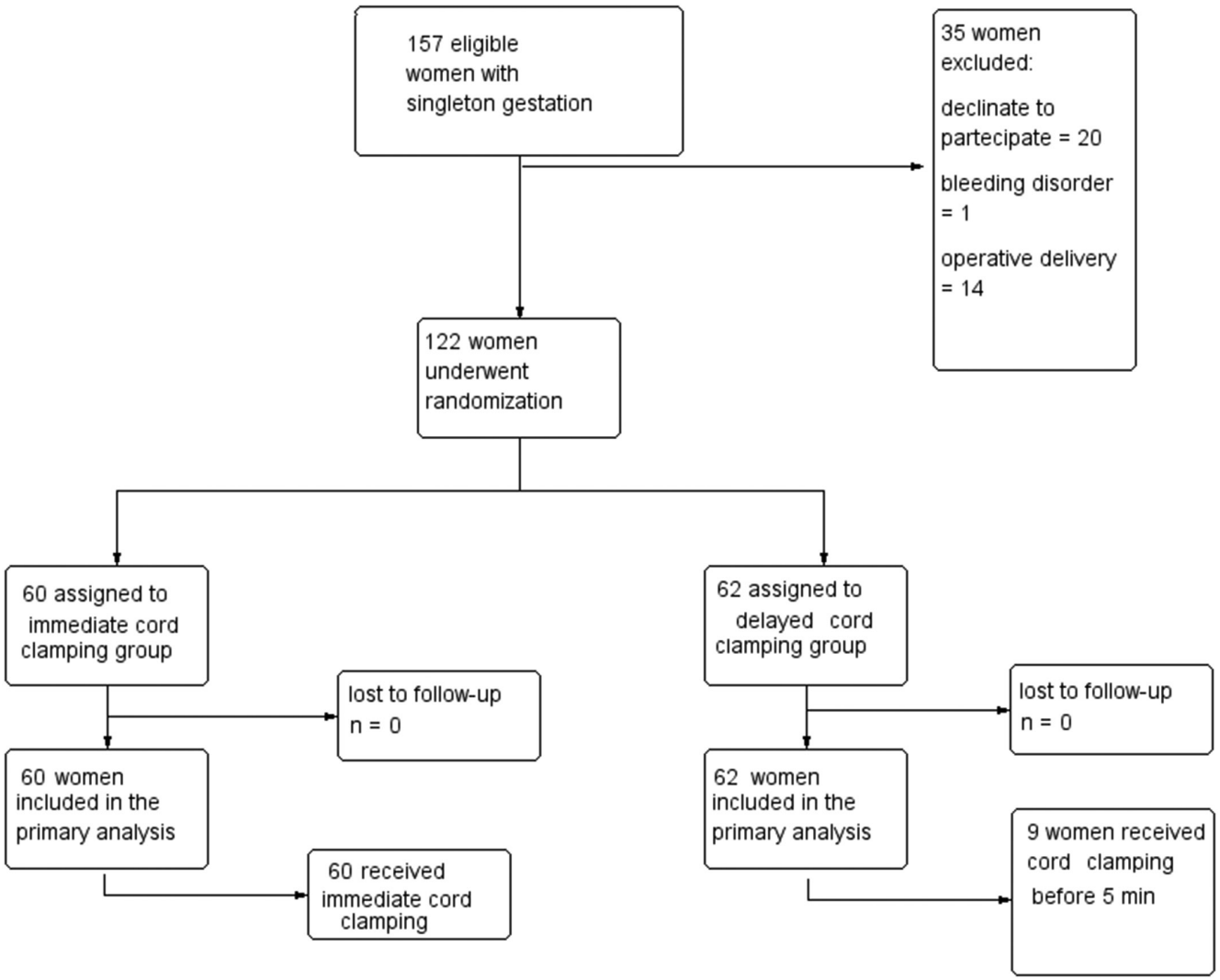

FIGURE 1 Study flow chart

cord clamping group and in 15.0% of the women randomized in the immediate cord clamping group (relative risk 1.18, 95% CI 0.53–2.65). No women underwent hysterectomy and no women received blood transfusions.

4 | DISCUSSION

This randomized trial aimed to compare maternal blood loss with immediate cord clamping versus delayed cord clamping. The study showed that among women undergoing spontaneous vaginal delivery at term, delayed umbilical cord clamping, compared with immediate umbilical cord clamping, resulted in no significant change in maternal hemoglobin level 1 day after delivery.

The major limitations of the trial were the small sample size and the single-center study design. Moreover, the unblinded study design limited the generalizability of our findings. In the delayed cord clamping group, there was a 14.5% crossover rate with 9 of 62 women receiving cord clamping before 5 min. However, this rate was lower than expected. The mean decrease in hemoglobin level at postdelivery day 1 was lower than the mean expected in the sample size calculation. This may have affected our results and made the primary outcome underpowered. The trial was underpowered for uncommon but important outcomes, such as maternal transfusions. The study included only spontaneous vaginal deliveries of singleton pregnancies, and therefore results cannot be generalizable to multiple gestations and operative vaginal delivery. Almost all included participants were Caucasian, limiting the findings to this population.

Delayed cord clamping has been associated with several neonatal benefits in both term and preterm pregnancies.[13–15] Concern about the risk of PPH associated with delayed cord clamping has been identified as a barrier to implementation of this procedure in term pregnancies.[17] Among low- and middle-income countries, several have maternal mortality rates in excess of 1000 women per 100 000 live births, and World Health Organization statistics suggest that 60% of maternal deaths in low- and middle-income countries are due to PPH, accounting for more than 100 000 maternal deaths per year.[19,20]

In a recent Cochrane review, McDonald et al.[15] included 15 trials involving a total of 3911 women undergoing term delivery. Participants generally had low-risk pregnancies and underwent vaginal delivery. Few included trials reported data on maternal outcomes.[13] The timing of cord clamping was not shown to be associated with PPH or increased mean blood loss. Only three trials reported data on maternal postpartum hemoglobin. Pooled data showed that maternal hemoglobin values were not significantly different between the women in the early and late cord clamping groups with an MD of −0.12 g/dl.

TABLE 1 Characteristics of the included women[a]

Characteristic	Delayed cord clamping ($n = 62$)	Immediate cord clamping ($n = 60$)
Age, years	29.9 ± 5.3	30.2 ± 5.0
Advanced maternal age[b]	6 (9.7%)	8 (13.3%)
Smoking	3 (4.8%)	5 (8.3%)
Nulliparous	50 (80.6%)	44 (73.3%)
Birthweight, g	3372 ± 421	3392 ± 487
BMI ≥ 30	7 (11.3%)	8 (13.3%)
Prenatal iron supplements	36 (58.1%)	33 (55.0%)
Chronic hypertension	1 (1.6%)	2 (3.3%)
GH	6 (9.7%)	5 (8.3%)
Diabetes mellitus or GDM	8 (12.9%)	7 (11.7%)
Maternal race		
Caucasian	61 (98.4%)	60 (100%)
Other	1 (1.6%)	0
Fetal birth weight, g	3150 ± 455	3270 ± 580

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); GDM, gestational diabetes mellitus; GH, gestational hypertension.

[a]Data are presented as mean ± standard deviation or as number (percentage).

[b]Older than 35 years.

TABLE 2 Primary and secondary outcomes[a]

Outcome	Delayed cord clamping ($n = 62$)	Immediate cord clamping ($n = 60$)	Mean difference or relative risk (95% CI)	*P* value
Decrease in Hb level 24 h after delivery, g/dl	1.1 ± 0.4	1.2 ± 0.6	−0.10 (−0.28 to 0.08)	NS
PPH	3 (4.8%)	4 (6.7%)	0.73 (0.17–3.11)	NS
Need for additional uterotonics	11 (17.7%)	9 (15.0%)	1.18 (0.53–2.65)	NS
Admission to NICU	2 (3.2%)	1 (1.7%)	1.94 (0.18–20.79)	NS
Clinical jaundice	12 (19.4%)	10 (16.7%)	1.16 (0.54–2.48)	NS
Phototherapy	9 (14.5%)	6 (10.0%)	1.45 (0.55–3.83)	NS
Neonatal death	0	0	–	–
Polycythemia	0	0	–	–

Abbreviations: CI, confidence interval; Hb, hemoglobin; NICU, neonatal intensive care unit; NS, non significant; PPH, postpartum hemorrhage.

[a]Data are presented as mean ± standard deviation or as number (percentage).

Among women undergoing spontaneous vaginal delivery at term, delayed umbilical cord clamping, compared with immediate umbilical cord clamping, resulted in no significant difference in change in maternal hemoglobin level 1 day after delivery. Our study supports the routine use of delayed umbilical cord in spontaneous vaginal delivery at term. Further multicenter studies were needed to confirm our findings.

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[Correction added on 08-May-2022, after first online publication: CRUI-CARE funding statement has been added.]

CONFLICTS OF INTEREST

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

CD: substantial contribution to design and conception. GS: involved in statistical analysis and interpretation of data. ES: contribution to design and conception. MA: revised critically for important intellectual content. BZ: involved in drafting the manuscript. EG: involved in drafting the manuscript. AL: involved in interpretation of data. ADS: had given final approval of the version.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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