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CLINICAL ARTICLE

Obstetrics

Effect of delayed cord clamping on jaundice and hypoglycemia in the neonates of mothers with gestational diabetes mellitus

Hailing Shao[1] | Yiyu Qian[1] | Shichu Gao[1] | Dongru Dai[2] | Ying Hua[1]

[1]Department of Obstetrics and Gynecology, the Second Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

[2]Department of Obstetrics and Gynecology, Wenzhou People Hospital, Wenzhou, China

Correspondence
Ying Hua, Department of Obstetrics and Gynecology, the Second Affiliated Hospital of Wenzhou Medical University, Wenzhou 325027, China.
Email: wzfeyhy1015@126.com

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Abstract

Objective: To study the effect of delayed cord clamping (DCC) on the bilirubin levels and hypoglycemia in neonates with diabetic mothers (NDMs).

Methods: This is a comparison between a prospective cohort and a historical control cohort. Women with gestational diabetes mellitus who performed DCC were enrolled into the prospective cohort (n = 156), and those who performed early cord clamping (ECC) were enrolled into the historical control cohort (n = 161).

Results: NDMs who received DCC had higher transcutaneous bilirubin than those in the ECC group whether maternal glycemic control was good or poor. DCC increased the rate of neonatal hyperbilirubinemia and phototherapy when maternal blood glucose was well controlled but not when it was poorly controlled. No differences were found in initial blood glucose levels on days 1 to 3 of life between the two groups.

Conclusion: Delayed cord clamping increased bilirubin levels, the risk of neonatal hyperbilirubinemia, and phototherapy in IDMs without improved initial blood glucose levels. Therefore, DCC was not recommended in NDMs.

KEYWORDS
delayed cord clamping, gestational diabetes mellitus, neonatal jaundice

1 | INTRODUCTION

The American College of Obstetricians and Gynecologists recommends a delay of at least 30–60 s in cord clamping in term and preterm neonates, as delayed cord clamping (DCC) increases hemoglobin and hematocrit, improves iron store, and reduces the incidence of blood transfusion and intraventricular hemorrhage.[1–3] However, more placental transfusion can result in potential disadvantage, it could increase the rate of phototherapy and hyperbilirubinemia in neonates.[1]

Gestational diabetes mellitus (GDM) affects approximately 14% of pregnancies worldwide[4]; it is a condition of glucose intolerance.[5] Its prevalence ranges from 4.5% to 15.2% worldwide with an increasing trend.[6] GDM poses considerable persistent risks to both mothers and infants.[7,8] The Hyperglycemia and Adverse Pregnancy Outcome study (HAPO) revealed that the neonates of diabetic mothers NDMs were at increased risk of neonatal hypoglycemia and hyperbilirubinemia.[7] However, direct evidence is absent on the adverse effect of DCC in NDMs.

To investigate whether DCC would worsen jaundice and hyperbilirubinemia in the neonates of mothers with GDM, the present study assessed the effect of DCC on neonatal bilirubin, hyperbilirubinemia, and the rate of phototherapy, as well as hypoglycemia in NDMs. We predicted that performing DCC in NDMs would increase the risk of neonatal jaundice and the level of blood glucose at birth.

2 | MATERIALS AND METHODS

This is a comparison between a prospective cohort and a historical control cohort. Ethics approval was obtained from the

Research Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University (approval number: L-2019–13). This prospective cohort study began on July 1, 2017, 6 months after the introduction of DCC in our hospital to mitigate confounders of mothers, and ended on May 30, 2018. Pregnant women all signed written informed consent when they were admitted to hospital for delivery and neonates received umbilical cord clamping more than 30 seconds after birth. Recruitment was consecutive. The historical control cohort was collected from December 1, 2015 to September 30, 2016 because ECC was the standard method in our hospital before 2017, in which neonates received cord clamping immediately after birth. The enrolled controls were matched with the mothers of the DCC group for age, body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters), and gestational age.

All women who received all prenatal examinations and delivered in our hospital were screened. All participants were systematically screened for eligibility during the study period both in the prospective cohort and the historical control cohort. Pregnant women without any risk factors for GDM were screened with oral glucose tolerance test (OGTT) at 24–28 weeks or the first prenatal examination after 28 weeks, and those with high-risk factors were screened with fasting plasma glucose or OGTT at the first prenatal examination. The OGTT screening protocol was the same for both cohorts. In the present study, the standard of well-controlled maternal glycemia was 120-minute glucose levels less than 6.7 mmol/L and glycated hemoglobin (HbA1c) levels less than 6.0% in the third trimester.[8] Failure to meet this standard was considered as poor maternal glucose control. Women with GDM were eligible if they were 18–45 years old, were expecting a singleton pregnancy scheduled for a vaginal delivery at term (37–41$^{6/7}$ weeks), and their pregnancy was not complicated with amniotic fluid abnormality, preterm labor, or placenta previa. Pregnant women with clinical diseases such as hypertension disorder or abnormal liver function, or with Rhesus-negative blood were excluded. Neonates were included if their birth weight was between 2.5 and 4.0 kg. Neonates with major congenital malformations such as congenital heart disease, congenital biliary atresia, and congenital anal atresia, as well as neonatal septicemia, hemolytic disease, or other diseases affecting bilirubin metabolism, were excluded.

Baseline clinical data including maternal age, gestational age, BMI, gestational age, neonatal birth weight, and Apgar scores at 1 and 5 min were recorded. The therapeutic methods and effectiveness for GDM were also documented. The primary outcomes were transcutaneous bilirubin levels at 1–3 days of age, the rate of phototherapy, the incidence of hyperbilirubinemia, and initial blood glucose levels in neonates.

Pregnant women received the standardized labor and delivery management for our hospital. The percutaneous bilirubin was measured using a uniform TCB device (JM-103, Konica Minolta, Japan) by the physician with similar skill. The attending neonatologist administered phototherapy when neonates were considered hyperbilirubinemic or at risk for hyperbilirubinemia based on the transcutaneous bilirubin and serum bilirubin levels. Hyperbilirubinemia was defined as bilirubin level exceeding the 95th centile of bilirubin for age in hours.[9] Initial blood glucose was measured within 30 minutes after birth and before breastfeeding. The standard for hypoglycemia was less than 2.2 mmol/L (40 mg/dl).

We used SPSS 18.0 software (SPSS, Chicago, IL, USA) to analyze the data. Normally distributed variables were presented as mean ± standard deviation and analyzed by Student's *t* test. Non-normally distributed variables were expressed as median and interquartile range and analyzed by Mann-Whitney *U* test. Categorical variables were presented as number (%) and analyzed by Pearson's χ^2 test. The participants were stratified according to the degree of maternal glycemic control. A p value <0.05 was considered statistically significant.

3 | RESULTS

As shown in Figure 1, a total of 318 pregnant women met the inclusion criteria during the study period of July 1, 2017 to May 30, 2018. According to the exclusion criteria, 156 cases were finally admitted to the DCC group. There were 161 cases in the ECC group, which was a historical control group during the study period of December 1, 2015 to September 30, 2016. Baseline characteristics are presented in Table 1. No significant differences were found between the ECC group and the DCC group concerning maternal and neonatal demographic variables such as BMI of pregnant women and 1-min and 5-min Apgar scores of newborns ($P > 0.05$).

As shown in Table 2, NDMs who received DCC had higher transcutaneous bilirubin on days 1 to 3 of life and higher incidence of hyperbilirubinemia ($P < 0.05$). The requirement for phototherapy increased markedly from 8.7% (14/161) in the ECC group to 16.7% (26/156) in the DCC group ($P = 0.029$). However, there was no difference in neonatal blood glucose at birth between the two groups ($P = 0.162$) (Table 2). Three neonates in the ECC group and two neonates in the DCC group were diagnosed with hypoglycemia (data not shown).

The levels of transcutaneous bilirubin and initial blood glucose were further analyzed based on the degree of maternal glycemic control, including the poorly-controlled or untreated group and

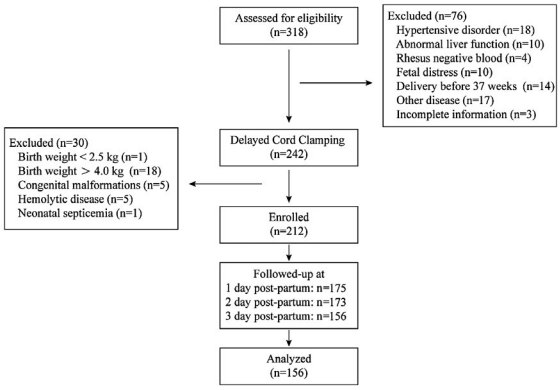

FIGURE 1 Study flowchart

TABLE 1 The maternal and child demographic characteristics[a]

	ECC group (*n* = 161)	DCC group (*n* = 156)	*P* value
Mother's age, years	29.85 ± 4.04	30.77 ± 4.52	0.057
Primipara	84 (52.2)	92 (59.0)	0.223
Maternal BMI	25.79 ± 2.92	25.66 ± 2.89	0.679
Gestational age, days	275.06 ± 6.88	275.44 ± 6.53	0.614
Fetal sex, male	100 (52.6)	90 (47.4)	0.422
Newborn weight, g	3336.89 ± 335.05	3282.18 ± 307.23	0.131
Newborn height, cm	49.90 ± 1.13	50.02 ± 1.13	0.352
Apgar scores at 1 min	9.68 ± 0.63	9.74 ± 0.55	0.365
Apgar scores at 5 min	9.99 ± 0.11	10.00 ± 0.00	0.158

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DCC, delayed cord clamping; ECC, early cord clamping.

[a]Values are given as mean ± standard deviation or as number (percentage).

TABLE 2 Neonatal bilirubin status within 3 days of life and initial blood glucose[a]

Variable	ECC group (*n* = 161)	DCC group (*n* = 156)	*P* value
Bilirubin at day 1 of age, mg/dl	4.96 ± 2.22	6.08 ± 2.18[b]	0.001
Bilirubin at day 2 of age, mg/dl	8.72 ± 2.45	10.12 ± 2.80[b]	0.001
Bilirubin at day 3 of age, mg/dl	11.11 ± 3.17	12.12 ± 3.12[b]	0.004
Neonates needing phototherapy	14 (8.7)	26 (16.7)[b]	0.029
Hyperbilirubinemia	10 (6.2)	21 (13.5)[b]	0.044
Initial blood glucose, mmol/L	4.05 ± 0.87	4.20 ± 1.00	0.162

Abbreviations: DCC, delayed cord clamping; ECC, early cord clamping.

[a]Values are given as mean ± standard deviation, or as number (percentage).

[b]A statistically significant difference compared with ECC group: $P < 0.05$.

the well-controlled group (Table 3). Stratified analysis showed that the transcutaneous bilirubin levels of newborns who received DCC were generally higher than those who received ECC regardless of the degree of maternal glycemic control. Compared with the well-controlled group, neonatal bilirubin levels showed a further increase in the combined poorly-controlled and untreated group whether in the ECC group or the DCC group.

TABLE 3 Stratification of neonatal outcomes based on the degree of maternal glycemia control[a]

Degree of glycemia control	ECC group	DCC group	*P* value
Well-controlled	(*n* = 114)	(*n* = 130)	
Bilirubin in day 1 of age (mg/dl) (<6 mg/dl)	4.94 ± 2.27	6.06 ± 2.28[b]	0.001
Bilirubin in day 2 of age (mg/dl) (<9 mg/dl)	8.54 ± 2.33	9.97 ± 2.98[b]	0.001
Bilirubin in day 3 of age (mg/dl) (<12 mg/dl)	10.99 ± 3.20	12.09 ± 3.21[b]	0.008
Jaundice requiring phototherapy (%)	7 (6.1)	22 (16.9)[b]	0.009
Hyperbilirubinemia (%)	4 (3.5)	17 (13.1)[b]	0.008
Initial blood glucose (mmol/L)	4.11 ± 0.90	4.24 ± 1.03	0.286
Poorly-controlled or untreated	(n = 47)	(n = 26)	
Bilirubin at day 1 of age, <6 mg/dl	5.00 ± 2.11	6.20 ± 1.64[b]	0.014
Bilirubin at day 2 of age, <9 mg/dL	9.17 ± 2.68	10.02 ± 1.66[b]	0.045
Bilirubin at day 3 of age <12 mg/dl	11.41 ± 3.11	12.30 ± 2.69	0.386
Jaundice requiring phototherapy	7 (14.9)	4 (15.4)	1.000
Hyperbilirubinemia	6 (12.8)	4 (15.4)	1.000
Initial blood glucose, mmol/L	3.92 ± 0.79	3.95 ± 0.82	0.890

Abbreviations: DCC, delayed cord clamping; ECC, early cord clamping.

[a]Values are given as mean ± standard deviation, or as number (percentage).

[b]A statistically significant difference compared with ECC group: $P < 0.05$.

When the blood glucose of pregnant women was well controlled, the rates of neonatal hyperbilirubinemia and phototherapy in the DCC group were significantly higher than those in the ECC group. But the differences disappeared when the blood glucose of pregnant women was untreated or poorly-controlled. Among neonates that received ECC, the incidence of hyperbilirubinemia and phototherapy in the neonates whose mothers had poor blood glucose control during pregnancy (12.8%, 14.9%, respectively) was higher than that in neonates whose mothers had good blood glucose control (3.5%, 6.1%, respectively). Besides, there was no significant difference in neonatal blood glucose levels at birth between the DCC group and ECC group either in the well-controlled group or in the combined untreated and poorly-controlled group.

4 | DISCUSSION

In the present study, we demonstrated that DCC in NDMs would increase neonatal bilirubin levels and the risk of neonatal

hyperbilirubinemia and jaundice requiring phototherapy on days 1 to 3 of life compared with NDMs in an ECC group. The transcutaneous bilirubin levels of newborns in the DCC group were generally higher than those in the ECC group regardless of the degree of maternal glycemic control, whereas poor maternal glycemic control was associated with a further increase in neonatal bilirubin levels in both groups. Unexpectedly, the rates of neonatal hyperbilirubinemia and jaundice requiring phototherapy in the DCC group were significantly higher than those in the ECC group when the blood glucose of pregnant women was well controlled rather than when the blood glucose was untreated or poorly-controlled. Besides, DCC did not increase the level of blood glucose at birth in NDMs.

Delayed cord clamping provides extra blood volume and red cell volume for neonates through physiologic placental transfusion,[10] which results in neonatal hyperbilirubinemia and jaundice, theoretically. As reported in clinical studies, healthy neonates with DCC had higher bilirubin levels and required a longer duration of phototherapy compared with those who did not receive DCC.[11,12] However, a few studies, including our previous study, reported that DCC did not influence the bilirubin or phototherapy needs of healthy neonates, which was contrary to the results of the present study.[10,13] The object of studies may be the principal element for the discrepant results. Most of the previous studies involved normal pregnant women without complications, including gestational diabetes mellitus, gestational hypertension, intrahepatic cholestasis of pregnancy; but our study focused on pregnant women with GDM.

Gestational diabetes mellitus is characterized by progressive insulin resistance and compensatory hyperinsulinemia with advancing gestation, which would disorder the fetal energy metabolism, resulting in an increase in bilirubin synthesis and the incidence of jaundice.[6,7,14] The high state of glucose uptake and metabolic rate in pregnant women with diabetes were related to an increase in erythropoietin secretion, thereby resulting in the increased fetal erythropoiesis. A hematocrit value that is too high, like polycythemia, used to be considered as one of the causes of hyperbilirubinemia.[15] As shown in a randomized controlled trial study, the risk of hyperbilirubinemia was significantly higher in NDMs compared with neonates of normal pregnant mothers.[14] In the present study, we found that DCC in NDMs increased the incidence of neonatal hyperbilirubinemia and jaundice requiring phototherapy with a relatively adequate sample size. This may be because the extra blood volume from DCC could further enhance hematocrit levels, resulting in polycythemia[11] and increased bilirubin production. However, a recent study observed that DCC in NDMs was not associated with a higher rate of neonatal jaundice requiring phototherapy, although performing DCC led to an increased polycythemia ratio, which may be the result of the insufficient sample size.[16]

Treatments, whether dietary modification or pharmacological therapies, have been proven to reduce immediate adverse outcomes for neonates—improving some pregnancy outcomes by reducing fetal overgrowth, maternal adiposity, and pregnancy-related hypertension—so a consensus has been reached.[6,17] There are, however, conflicting findings with regard to other outcomes, such as neonatal hyperbilirubinemia and jaundice requiring phototherapy, and neonatal hypoglycemia.[17–22] Although neonatal hyperbilirubinemia was significantly related to the 1-hour and 2-hour plasma glucose levels,[7] there was no difference in the proportion of neonatal phototherapy between the specific treatment (dietary advice and insulin) group and the routine care group.[17,22] Likewise, both in the ECC group and the DCC group, poorly-controlled maternal glycemia was associated with a further non-significant increase in neonatal bilirubin levels. We found that the transcutaneous bilirubin levels of newborns in the DCC group were generally higher than those in newborns in the ECC group, especially when the maternal glucose was well controlled. Moreover, the rates of neonatal hyperbilirubinemia and jaundice requiring phototherapy in the DCC group were significantly higher than in the ECC group when maternal blood glucose was well controlled but not when it was poorly controlled, which was less expected. This could be due to the small sample sizes in the ECC and DCC groups (ECC: 47, DCC: 26) and the small numbers of newborns diagnosed with hyperbilirubinemia (ECC: 6/47, DCC: 4/26) and requiring phototherapy (ECC: 7/47, DCC: 4/26). Further studies including larger sample sizes are needed to verify the reliability of these results. But we also speculated that maternal glycemic control is an important risk factor for neonatal jaundice, which could hide the effect of DCC on the bilirubin levels in NDMs.

Hypoglycemia is another common short-term complication in NDMs, which is the result of neonatal hyperinsulinism disturbing the normal activation of glucose and ketone generating metabolic pathways.[23] In view of the relationship of restrictive blood transfusion practices with the increasing risk of hypoglycemia,[24] the extra blood from placental transfusion supplied by DCC may be a protective factor for hypoglycemia in NDMs. In the present study, however, DCC was unable to increase the initial blood glucose levels and decrease the rate of hypoglycemia in NDMs. Similar results were reported by Korkut et al.[16] One possible reason was that fetal macrosomia was excluded from the present study, being prone to hypoglycemia.[25]

Additionally, maternal glycemic control status was weakly positively associated with neonatal hypoglycemia.[25] However, some available evidence showed that tight glucose management in women with GDM could not improve initial neonatal glucose concentrations and was not related to neonatal hypoglycemia.[18–22] Inconsistently, we found that no significant difference was observed in neonatal blood glucose levels at birth between the DCC group and ECC group, whether maternal glycemic control was good or poor. Furthermore, the neonates in the combined untreated and poor glycemic control group did not have hypoglycemia.

Collectively, all these aspects reinforce that the variations in the study design, the sample size and the heterogeneous study population contributed to the conflicting results. There is a need for prospective, multicenter, large-scale trials to elucidate the impact of DCC on neonatal hypoglycemia and neonatal jaundice in NDMs where the mothers have different maternal glycemic control statuses. The limitation of the present study was that we failed to conduct a randomized controlled trial because DCC was a mandatory operation after 2017 in our hospital. For this reason,

we selected a historical control cohort as the ECC group. The strengths of the present study were focusing on the neonates with diabetic mothers and the repeated measurement of the bilirubin levels to ensure a comprehensive assessment of the effect of DCC on bilirubin levels.

Given that poor maternal glycemic control was associated with higher neonatal bilirubin levels, increased incidence of neonatal hyperbilirubinemia, and a higher rate of phototherapy, well-controlled maternal glycemia is more beneficial for the reduction of immediate neonatal complications. Regardless of maternal glucose control levels, DCC increased bilirubin levels without improving blood glucose levels. However, NDMs receiving DCC had a higher risk of hyperbilirubinemia and phototherapy when maternal blood glucose was well controlled but not when it was poorly controlled. Therefore, DCC was not recommended in NDMs.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the present study. HS analyzed and interpreted the data, and drafted the article; YQ, SG, and DD acquired the data; YH made substantial contributions to conception and design, and revised the manuscript critically for important intellectual content and gave final approval of the version to be published.

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