ORIGINAL ARTICLE

Neonatal Outcomes in Delayed Umbilical Cord Clamping Neonate of Mothers with Gestational Diabetes Mellitus

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Background: Delayed umbilical cord clamping (DCC) in neonates who do not require immediate postnatal resuscitation had benefit for both preterm and term infants by enhancing blood volume and iron storage. However, neonatal outcomes in mothers with gestational diabetes mellitus (GDM) remain limited.

Objective: To investigate neonatal outcomes in DCC infants of GDM mothers.

Materials and Methods: The present study was a prospective cohort comparison with a historical control cohort. The data were gathered at Kuchinarai Crown Prince Hospital, Kalasin, Thailand from between July 2022 and June 2023. The study group comprised of newborns delivered to mothers with GDM who underwent DCC and immediate cord clamping (ICC) as study and control cohort groups, respectively. Demographic and clinical data were collected and analyzed.

Results: One hundred fifty subjects were recruited and divided equally. Both groups had parity in their respective cohorts. DCC group had significantly higher hemoglobin (Hb) levels and hematocrit (Hct) than ICC group at 18.8/17.5 g/dL and 59.5%/55.4%, respectively. DCC in GDM pregnant women treated with diet control alone or diet control with medication had significant higher in Hb level and Hct than ICC group at 18.7/17.4 g/dL and 59.3%/55.1%, and 19.0/17.7 g/dL and 59.9%/56.3%, respectively. Other characteristics of both groups were comparable. After birth, glucose level, hypoglycemia risk, micro-bilirubin levels at 48 hours, Agar score at 1 and 5 minutes and length of stay were comparable among both groups.

Conclusion: The present study indicated that delayed cord clamping in neonates born to mothers with GDM can increase Hb levels without causing any complications. It is recommended for all infants who do not require immediate resuscitation.

Keywords: Delayed umbilical cord clamping; Gestational diabetes mellitus; Neonatal outcome

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Delayed umbilical cord clamping (DCC) is recommended for all infants who do not require immediate resuscitation for better outcomes of both mothers and infants[1]. The recommended duration for DCC varies among medical organizations. The American Heart Association (AHA), the American Academy of Pediatrics (AAP) and the American College Obstetricians and Gynecologists (ACOG) recommend DCC after 30 to 60 seconds[2,3]. The World Health Organization (WHO) recommends DCC after at least one minute[1].

From current evidence, it is shown that DCC is beneficial to both preterm and term infants[3]. DCC results in increased hemoglobin (Hb) levels, iron storage, and enhanced long term development outcomes in newborns[3]. For preterm infants who receive DCC, increased hematocrit (Hct) is observed in the first week[4]. Blood volume and red blood cell count are increased in DCC infants compared to those receiving immediate cord clamping (ICC)[3]. Additionally, DCC reduces the need for blood transfusions, decreases the risk of necrotizing enterocolitis (NEC), and lowers the incidence of intraventricular hemorrhage (IVH) among newborns. However, DCC might lead to neonatal jaundice and therefore, increased phototherapy treatment[3].

Gestational diabetes mellitus (GDM) is a

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common condition worldwide. In the United States the incidence of GDM, medicated and non-medicated, is approximately 7%[5]. In Thailand, a survey in Siriraj Hospital found the incidence of GDM at 20%[6]. GDM is known to cause various complications in infants, such as respiratory distress at birth, low blood sugar (BS) after birth, and infant mortality[7,8]. However, there were limited studies and clear guidelines on the effects of DCC in infants born to GDM mothers. The aim of the present study was to investigate the outcomes of DCC and ICC infants of GDM mothers.

Materials and Methods

The present study was a prospective cohort comparison with a historical control cohort in infants born from GDM mothers delivered at Kuchinarai Crown Prince Hospital (KCPH), Kalasin, Thailand between July 2022 and June 2023. The research protocol was approved by the Ethics Committee of Kalasin Provincial Public Health Office (KLS. REC26/2565). The inclusion criteria were singleton term pregnant women, at 37 to 42 weeks of gestation, as documented by their last menstruation periods or antenatal ultrasonography during their first trimesters, who were diagnosed of GDM and delivered at KCPH during the specified period.

Diagnosis of GDM was performed by a two-step screening process with diagnosis criteria based on Carpenter & Coustan's criteria as recommended by ACOG[5,9] in both cohorts. Pregnant women with high-risk factors for GDM were screened at the first prenatal examination. Risk factors for GDM included severe obesity, strong family history of type 2 diabetes and previous history of GDM, impaired glucose metabolism, or glucosuria[7]. Those without any risk factors for GDM were screened at 24 to 28 weeks of gestation. Informed consent was obtained from all pregnant women on admittance to hospital for delivery. Data from the historical control cohort were collected from records between December 2019 and May 2021 before DCC introduction in KCPH. ICC groups were matched with the DCC group by maternal age, gestational age (GA) and body mass index (BMI). Infants with any abnormalities during pregnancy, and/or after birth, or diagnosed with fetal distress and hemolytic disease were excluded.

In the present study, infants in the study group underwent 45 seconds DCC after birth and technique of DDC of all physicians was performed according to ACOG recommendation. The control group underwent ICC. Blood samples for both methods were taken according to the standard care guidelines for infants born to mothers with GDM at KCPH. Data collection composed of demographic data, neonatal Hb, Hct, and BS within two hours after birth, micro-bilirubin (MB) at 48 hours after birth, length of stay in hospital (LOS). The BS level was evaluated using a glucometer device (Accu-Chek, Roche, BKK, Thailand), which is a routine diagnostic practice in rural hospital under the Ministry of Public Health of Thailand. Additionally, both groups' general information, such as the mother's age, BMI, route of delivery, GA at birth, treatment, birth body weight (BW), and Apgar scores at 1 and 5 minutes were recorded. All collected data were analyzed using the IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA). Quantitative data was reported as means and standard deviations. Differences between groups were compared using unpaired t-test. Qualitative data were reported as frequencies and percentages. Statistical significance was determined at p-value of less than 0.05 with a confidence interval of 95%.

The sample size was calculated based on Shao et al.'s study[10]. The study revealed a mean ± standard deviation (SD) of bilirubin level at second day of age among the neonates in DCC and ICC arm were 10.12±2.80 and 8.72±2.45 mg/dl, respectively. Two independent proportions with a two -tailed test with an α error of 5% and power of 90% and ratio at 1:1 were used. The minimum sample size in the present study and control groups were at least 75 cases in each group.

Results

During the period of study, 80 pregnant women diagnosed with GDM were included. In the study group, two infants were diagnosed with fetal distress, two infants were referred to other hospitals, and one infant was diagnosed with congenital heart disease. Those were excluded from the study. One hundred and fifty cases were included for further analysis. Seventy-five cases from a historical control group matched with the study group were included as shown in Figure 1. The mean age of participants was 31.5 years old. Average BMI of participants was 27.7 kg/m^2. One quarter (39 out of 150) of all subjects were nulliparous. Half of all cases delivered by vaginal route. Demographic characteristics of both groups, namely maternal age, BMI, parity, route of delivery, GA, BW, and GDM treatment revealed no significant differences as shown in Table 1. Hb and Hct of DCC group were significantly higher than the ICC group at 18.8/17.5 g/dL and 59.5%/55.4%,

Table 1. Demographic and clinical characters of DCC (n=75) and ICC groups (n=75)

	DCC	ICC	p-value	MD	95% CI
Age (years); mean±SD	30.9±4.8	32.0±4.9	0.164	–1.1	–2.7 to 0.5
BMI (kg/m^2); mean±SD	27.2±4.9	28.1±5.1	0.271	–0.9	–2.5 to 0.7
Nulliparity; n (%)	18 (24.0)	21 (28.0)	0.577		
Vaginal delivery**	38 (50.7)	34 (45.3)	0.513		
GA (weeks); mean±SD	38.2±1.0	38.2±0.7	0.985	–0.0	–0.3 to 0.3
Birth weight (g); mean±SD	3,184±507.5	3,203±471.4	0.814	–18.9	–176.9 to 139.1
Diet control; n (%)	55 (73.3)	54 (72.0)	0.855		
PP D1; mean±SD					
Hb (g/dL)	18.8±2.4	17.5±1.8	<0.001	1.3	0.6 to 2.0
Hct (%)	59.5±6.1	55.4±4.7	<0.001	4.1	2.3 to 5.8
BS (mg/dL)	67.7±17.2	68.3±15.9	0.814	–0.6	-0.6 to 4.7
Apgar 1 minute	8.0±0.1	8.0±0.2	0.566	0.0	-0.0 to 0.1
Apgar 5 minutes	10.0±0.0	10.0±0.2	0.441	0.0	-0.0 to 0.1
Neonatal hypoglycemia; n (%)	5 (6.7)	6 (8.0)	0.754		
PP D2; mean±SD					
MB (mg/dL)	9.1±2.3	9.2±2.1	0.758	–0.1	-0.8 to 0.6
LOS (days); mean±SD	3.7±3.2	3.9±5.4	0.840	–0.1	–1.6 to 1.3

SD=standard deviation; DCC=delayed umbilical cord clamps; ICC=immediate umbilical cord clamping; MD=mean difference; CI=confidence interval of difference; BMI=body mass index; GA=gestational age; PP D1=immediate postpartum; PP D2=postpartum 48 hours; Hb=hemoglobin; Hct=hematocrit; BS=blood sugar; MB=micro-bilirubin; LOS=length of stay

Table 2. Comparison of diet control and medication treatment among DCC (n=109) and ICC (n=42)

	Diet; mean±SD		p-value	MD	95% CI	Diet & Med; mean±SD		p-value	MD	95% CI
	DCC (55)	ICC (54)				DCC (20)	ICC (21)			
PP D1										
Hb (g/dL)	18.7±2.4	17.4±1.9	0.002	1.3	0.5 to 2.2	19.0±2.3	17.7±1.3	0.034	1.3	0.1 to 2.5
Hct (%)	59.3±6.1	55.1±4.8	<0.001	4.2	2.2 to 6.3	59.9±6.0	56.3±4.6	0.035	3.6	0.3 to 7.0
BS (mg/dL)	63.5±11.9	68.3±14.3	0.056	–4.9	–9.9 to 0.1	79.3±23.7	68.3±19.9	0.116	11.0	–2.8 to 24.8
PP D2										
MB (mg/dL)	8.8±2.3	9.1±2.1	0.413	–0.3	–1.2 to 0.5	9.8±2.3	9.3±2.2	0.447	0.5	–0.9 to 2.0

SD=standard deviation; DCC=delayed umbilical cord clamping; ICC=immediate umbilical cord clamping; MD=mean difference; CI=confidence interval of difference; Diet=diet control only; Diet & Med=diet control with hypoglycemic agent; Hb=hemoglobin; Hct=hematocrit; BS=blood sugar; PP D1=immediate postpartum; PP D2=postpartum 48 hours; MB=micro-bilirubin

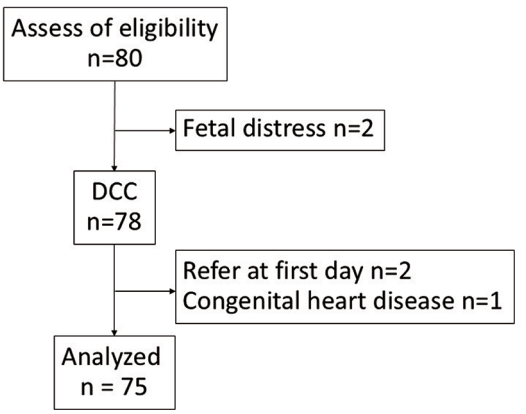

Figure 1. Flow diagram of study.

DCC: delayed umbilical cord clamping

respectively. However, BS, neonatal hypoglycemia, MB, LOS, and Apgar scores of DCC and ICC groups were comparable as depicted in Table 1.

Subgroup analysis between only dietary control and combined dietary and medication controls were performed to examine neonatal outcomes between DCC and ICC groups as shown in Table 2. Hb and Hct of infants with DCC group were significantly higher than those in ICC group born to mothers with only dietary control or dietary with medication control at 18.7/17.4 g/dL and 59.3%/55.1%, and 19.0/17.7 g/dL and 59.9%/56.3%, respectively. There was no statistically significant difference of BS and MB among infants with DCC and ICC in both only dietary control and combined dietary control with medication groups.

Discussion

The present study was prospectively conducted in conjunction with a historical control cohort in a sub provincial hospital in northeastern Thailand. Before 2022, the hospital used ICC as standard protocol for infants of GDM pregnant women. Many recommendations supported the DCC as a routine practice in newborns not requiring immediate resuscitation[1-3].

In the current study, Hb and Hct of infants in the DCC group were significantly higher than those from ICC group without any increased neonatal complication such as hypoglycemia and BS. It implied that the amount of red blood cells in infants of DCC group was higher than those of the ICC group. This finding supported the recommendation of ACOG, WHO, AHA, and AAP[1-3]. DCC protocol did not affect the incidence of neonatal hypoglycemia and BS among GDM pregnant women. The current finding aligned with Bennett et al.'s study from 2022 that utilizing both management methods, which is diet control and combined diet control with medication, resulted in similar outcomes among pregnant women with pre-existing DM[11]. Additionally, Korkut et al. from Türkiye reported no difference in the incidence of neonatal hypoglycemia between infants of the two groups[12].

According to ACOG recommendations, DCC in preterm and term infants might increase the likelihood of neonatal jaundice[3]. Neonatal red blood cells contain HbF that is suitable for intrauterine fetuses surviving in hypoxic conditions. The oxygen supply for intrauterine fetuses comes from the maternal umbilical vein. The average oxygen dissociation curve of intrauterine fetus was found shifted to the left from normal, which gives red blood cells higher capacity for transferring oxygen from low oxygen conditions to the fetus[7]. After the delivery, physiologic jaundice of the neonate is a consequence of fetal red blood cells degeneration. Neonatal jaundice monitoring and prompt phototherapy are needed for the prevention of neurological damage from severe neonatal jaundice. Nevertheless, ACOG recommends performing DCC in healthy infants who do not require immediate resuscitation after birth, as the overall benefits outweigh the risks[3].

In the present study, infants of mothers with GDM in both DCC and ICC groups showed no significant difference in MB level. The current study was in lieu of the findings by Qian et al.'s study from China from 2020[13]. Bilirubin level in Qian's study was measured by transcutaneous methods. Bilirubin measurement in the study utilized capillary blood sampling from the neonatal heel for measurement. In Qian's study neonatal jaundice occurrence among those with DCC at 30 to 60 seconds, and at 60 to 90 seconds were comparable, however infants with DCC of 91 to 120 seconds or longer required phototherapy to treat jaundice[13]. Bilirubin levels measured by transcutaneous or venous routes between infants of DCC and ICC groups in pregestational DM from Bennett's study showed no significant difference[11]. Furthermore, in Bennett's study, the need for phototherapy for jaundice treatment did not differ between these groups. In the present study, contrasting to Shao's findings in which neonate from GDM mother that received DCC for more than 30 seconds had higher level of bilirubin from transcutaneous measurement during the period between the first to third day compared to those who received ICC, required significantly more often phototherapy for infants than those in ICC[10]. In the present study there was no significant difference between neonates of DCC and ICC groups in regard to Apgar scores at 1 and 5 minutes, and LOS. The results were consistent with Shao's and Bennett's studies[10,11]. Comparison of the present to the previous studies are summarized and presented in Table 3.

Table 3. Comparison from the previous to the present studies among DCC and ICC in pregnant women with GDM

	Korkut[12]	Bennett[11]	Shao[10]	Present study
Year	2019	2021	2021	2024
Country	Türkiye	USA	China	Thailand
GA (weeks)	38.0/38.2	38.0/38.1	39.3/39.3	38.2/38.2
BW (Kg)	3.4/3.4	3.4/3.63	3.3/ 3.3	3.2/3.2
Hb (g/dL)		19.1/17.4		18.8/17.5*
Hct (%)	60.6/54.5*	55.6/52.4		59.5/55.4*
Bilirubin (mg/dL)		10.2/10.5	10.12/8.72*	9.1/9.2
BS (mg/dL)			75.6/72.9	67.7/68.3
Hypoglycemia (%)	12.5/20	19.2/30.6		6.7/8.0
LOS		3.0/3.0		3.7/3.9

GDM=gestational diabetes mellitus; DCC=delayed umbilical cord clamps; ICC=immediate umbilical cord clamping; GA=gestational age; BW=birth weight; Hb=hemoglobin; Hct=hematocrit; BS=blood sugar; LOS=length of stay

* Statistical significance at $p<0.05$

In the present study infants born to GDM mothers who were treated solely with diet control or diet control combined with medication, the Hb and Hct levels of the DCC group were significantly higher than those in the ICC group. There was no difference between BS and MB among infants in DCC and ICC groups.

As shown in existing literature, DCC results

in the increase of Hb and Hct levels in infants born to GDM mothers. This did not increase the rate of neonatal hypoglycemia. The MB in infants that received DCC was higher than those that received ICC, though without statistical significance. In the present study, infants with DCC did not show an increased rate of neonatal hypoglycemia and MB levels at 48 hours postpartum.

However, bias of historical control group form medical record, single-center design, limited number of sample size and measured BS level by glucometer were the limitation of the present study. Larger, multi-center studies with extended follow-up to long-term effects are warranted and ought to be conducted.

In conclusion, DCC of at least 45 seconds after birth for infants born to mothers with GDM enhances Hb levels and Hct without increasing complications such as neonatal hypoglycemia, jaundice, or prolonged hospitalization.

What is already known about this topic?

DCC is recommended for all infants who do not require immediate resuscitation. DCC is beneficial to both preterm and term infants by increasing Hb levels, iron storage, and enhanced long term development outcomes in newborns. Additionally, DCC reduces the need for blood transfusions, decreases the risk of NEC, and lowers the incidence of IVH among newborns. However, DCC might lead to neonatal jaundice and therefore, increased phototherapy treatment. There were limited studies and clear guidelines on the effects of DCC in infants born to GDM mothers.

What does this study add?

DCC of at least 45 seconds after birth for infants born to mothers with GDM enhances Hb levels and Hct without increasing complications such as neonatal hypoglycemia, jaundice, or prolonged hospitalization. It should be performed in neonates who do not require immediate resuscitation.

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Authors' contributions

AW, DP, and KS conceptualized and designed the study; AW collected the data, analyzed, and interpreted the results; AW, DP, AC, KB, and KS prepared the initial manuscripts. All authors reviewed the results and approved the final version of the manuscripts.

Availability of data

All data relevant to this study has been presented in the manuscript. More data requirements were controlled by the institution board according to request.

Conflicts of interest

The authors declare that there is no conflict of interest.

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