ORIGINAL

Association between early-term birth and hypoglycaemia in large-for-gestational-age neonates : A retrospective cohort study

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Abstract : Background : The effect of early-term birth on the development of hypoglycaemia in large-for-gestational-age (LGA) neonates is yet to be clarified. This study aimed to clarify the association between hypoglycaemia and early-term birth in LGA neonates. Methods : This single-centre retrospective cohort study evaluated LGA neonates born at term at Tsurugi Municipal Handa Hospital, Japan. Blood glucose levels were measured immediately and at 1, 2, and 4 hours after birth. The association between early-term birth and hypoglycaemia was evaluated using logistic regression analysis. The prevalence of severe hypoglycaemia and hypoglycaemia according to its timing of development was analysed using Fisher's exact test. Results : In total, 295 neonates were included. Among them, 113 neonates (38.3%) were born at early term and 91 infants (30.8%) had hypoglycaemia. Logistic regression analysis showed a significant association between early-term birth and hypoglycaemia (adjusted odds ratio [95% confidence interval] : 2.691 [1.597 to 4.535]). However, there was no significant between-group difference among those with severe hypoglycaemia. Conclusions : Among LGA neonates, early-term birth is positively associated with neonatal hypoglycaemia. This indicates that among LGA neonates, those born at early term require more careful observation for hypoglycaemia than do those born at later term. J. Med. Invest. 70 : 476-482, August, 2023

Keywords **:** *early-term birth, hypoglycaemia, large for gestational age*

INTRODUCTION

Neonatal hypoglycaemia is one of most common metabolic disorders that require treatment in neonates (1, 2). Although the definition for neonatal hypoglycaemia is not standardised, 5%–15% of neonates have hypoglycaemia at blood glucose level cut-offs of 40–45 mg/dL (3, 4). Importantly, neonatal hypoglycaemia is associated with adverse neurodevelopmental outcomes during early childhood (5, 6). Moreover, it is known to impose a long-term economic burden and adversely affect quality of life (1).

Many neonates with hypoglycaemia are asymptomatic or have non-specific symptoms (7, 8). Therefore, routine measurement of blood glucose has been recommended as a screening strategy for high-risk neonates. Large for gestational age (LGA) is one of the representative targets of screening for neonatal hypoglycaemia, along with preterm birth, small for gestational age, and neonates with gestational diabetes mellitus (GDM) mothers (4, 9). Approximately 8.1%–45% of LGA neonates have low blood glucose level during the infantile period (10-13).

Meanwhile, early-term birth is not considered as a target of screening for neonatal hypoglycaemia but as its risk factor (2, 14). An overlap of risk factors of neonatal hypoglycaemia may lead to a more severe hypoglycemia (11). Moreover, pregnancy periods are shorter in LGA neonates with hypoglycaemia than in those without hypoglycemia (12). This indicates that LGA neonates who are also born at early term have a higher risk of hypoglycaemia than those who are either only LGA or born early term. However, the influence of early-term birth on the development of hypoglycaemia in LGA neonates is yet to be clarified. Understanding the association between early-term birth and the risk of neonatal hypoglycaemia will be helpful for a more efficient resource allocation and patient management, especially in settings with limited medical equipment for blood glucose measurement. Thus, this study aimed to clarify the association between neonatal hypoglycaemia and early-term birth in term LGA neonates.

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METHODS

Study design, setting, and participants

This retrospective cohort study was conducted in Tsurugi Municipal Handa Hospital, a single secondary perinatal centre in Japan that mainly attended to term births and birth from relatively low-risk deliveries. LGA neonates born at term between November 2013 and October 2021 were evaluated. The inclusion criteria were genetic Japanese and singleton birth. The exclusion criteria were requirement of intravenous treatment and transport to tertiary perinatal centre within 4 hours after birth. Breastfeeding was attempted in all neonates 1 hour before blood glucose measurement depending on the postpartum condition of the mother.

This study was approved by the appropriate institutional review board on Tsurugi municipal Handa hospital (IRB number : 125) and complied with the Helsinki Declaration. The need for written informed consent was waived owing to retrospective nature of the study.

Study variables

Data, including sex, parity, maternal GDM, maternal overweight, delivery time, mode of delivery, using uterotonic agents, pH in cord blood (CB), and birth weight, were obtained from the institutional medical records. Hypoglycaemia and severe hypoglycaemia were defined as a blood glucose concentration of <40 mg/dL and <25 mg/dL in whole blood, respectively. LGA was defined as weight ≥90th percentile on the Japanese neonatal anthropometric chart (15). Gestational age was determined based on the result of the ultrasound examination during early pregnancy and birth, with 37–38 gestational weeks defined as early term. The combination of full term (39–40 gestational weeks), late term (41 gestational week), postterm (42 and later gestation weeks) was defined for the comparison to early term as later term, because we anticipated small number of neonates born at late term and postterm. Parity was classified into nulliparous and parous.

Maternal GDM was evaluated based on the result of the 75-g oral glucose tolerance test and was diagnosed as fasting blood glucose level of ≥92 mg/dL, 1-hour value of ≥180 mg dL, and 2-hour value of ≥153 mg/dL (16). Maternal overweight was defined as maternal BMI >30 kg/m^2 at the most recent measurement before delivery (17). Prolonged labour and delivery was defined as a duration of ≥30 hours in nulliparous women and ≥15 hours in parous women. Mode of delivery was classified into caesarean section and normal transvaginal delivery. Use of uterotonic agents was defined as maternal administration of oxytocin or prostaglandin F2α before delivery. Low pH in CB was defined as a levels <7.00 (18). Birth weight was calculated as percentile based on the Japanese neonatal anthropometric chart (15).

Measurement of neonatal blood glucose and cord blood pH

For neonates at high risk of hypoglycaemia, the timing of routine of blood glucose measurement was individualised according to the risk factors (11). For LGA neonates, the blood glucose level is normally the lowest at approximately the first 3 hours after birth, and this trajectory is different from other factors of neonatal hypoglycemia (9, 10). Thus, we focused on the result until 4 hours after birth. Blood glucose levels at the following four time points were measured : immediately after birth and 1, 2, and 4 hours after birth. Whole blood was collected from the heel, and blood glucose was measured using Glutestmint portable glucose meter (Sanwa Chemical Co, Nagoya, Japan) immediately after blood collection.

Samples for pH measurement in CB were collected by an obstetrician by puncturing the artery of the umbilical cord immediately after birth. pH values in these samples were measured using the iSTAT-1 (CG4+ cassettes, Abbott Point of Care, Princeton, NJ, USA).

Bias and study size

To minimise bias, all neonates with complete information were included. Previous studies showed that LGA accounts for approximately 10% of total births, and hypoglycaemia occurs in approximately 30% of LGA neonates (10-13). We planned to conduct logistic regression analysis to evaluate the association between early term hypoglycaemia and eight candidate covariates. The required sample size was 90 neonates with hypoglycaemia, which was 10 times higher than the number of factors (early term, sex, parity, maternal GDM, maternal overweight, delivery time, mode of delivery, using uterotonic agents, low pH in CB) (19).

Statistical analysis

Patient characteristics were compared between neonates born at early term and at later term. Significant variables were identified based on p values in Fisher's exact test. The percentiles of birth weight and pH in CB were compared between groups using the Mann-Whitney U test. Items with significant differences in these analyses were selected as covariates for the logistic regression analysis. Logistic regression analysis was conducted to analyse the association between early-term birth and hypoglycaemia by adjusting for covariates (parity and mode of delivery) selected in the above analysis. In addition, the association of early-term birth with severe hypoglycaemia and the prevalence of hypoglycaemia was analysed according to the timing of hypoglycaemia onset using Fisher's exact test. Neonates who already had hypoglycaemia before the timing were excluded in this analysis. The prevalence of severe hypoglycaemia was also compared using Fisher's exact test. Similarly, Fisher's exact test was used to compare the prevalence of hypoglycaemia between neonates born at 40 weeks of gestation and neonates born at 37–39 weeks of gestation. All statistical analyses were performed using the Statistical Package for Social Sciences version 24.0 (SPSS, IBM Corporation, Armonk, NY, USA). P values <0.05 were considered significant.

RESULTS

Patient characteristics

Among the 302 LGA neonates identified, 6 neonates were given intravenous treatment and 1 neonate was transferred to another hospital within 4 hours after birth for reasons aside from hypoglycaemia. Finally, 295 LGA neonates were evaluated (Figure 1). Overall, 113 neonates (38.3%) were born at early term (18 and 95 neonates were born at 37 and 38 weeks, respectively). Meanwhile, 182 neonates were born at later term (94, 74, and 14 neonates were born at 39, 40, and 41 weeks, respectively). Seven neonates (38.9%), 44 neonates (46.3%), 26 neonates (28.6%) and 14 neonates (15.9%) were born at 37, 38, 39 and 40 and later gestational weeks had hypoglycaemia, respectively. Overall, 91 neonates (30.8%) were diagnosed with hypoglycaemia (13, 62, 12, and 4 neonates developed hypoglycaemia immediately, 1 hour, 2 hours, and 4 hours after birth, respectively) (Table 1). Of

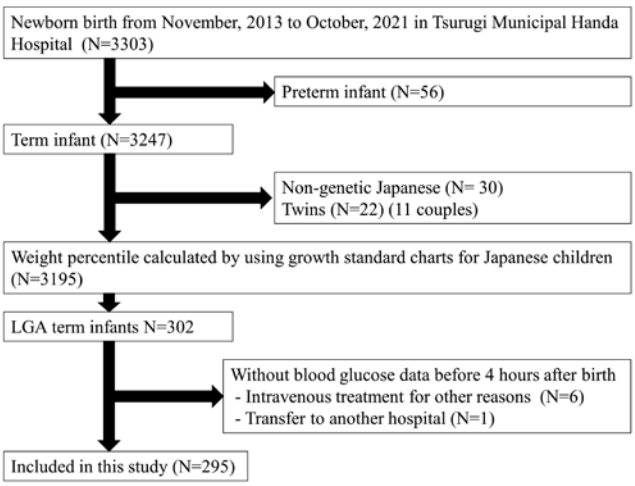

Figure 1. Patient inclusion flowchart.
LGA ; large for gestational age

these, seven neonates had severe hypoglycaemia that occurred 1 hour after birth. All neonates with hypoglycaemia, including those with severe hypoglycaemia, were asymptomatic.

Characteristics of early-term infants

The rate of early-term birth was significantly higher in neonates with hypoglycaemia than in those without hypoglycaemia (56.0% vs 30.4%, P<0.001). The rate of first birth was relatively lower in the hypoglycaemia group than in the no hypoglycaemia group (41.8% vs 55.9%, P=0.032). The prevalence of normal transvaginal delivery was also lower in the hypoglycaemia group (41.8% vs 55.9%, P=0.032). No other factors were significantly different between groups. Birth weight percentile was not significantly different between the hypoglycaemia and no hypoglycaemia groups (median (first quartile–third quartile) : 95.9% (92.4–98.4%) vs 95.6% (92.8–97.6%), P=0.347) (Table 2).

Association between early-term birth and hypoglycaemia in LGA neonates

Early-term birth was associated with hypoglycaemia in LGA neonates. Unadjusted logistic regression analysis showed a significant association between early-term birth and hypoglycaemia (odds ratio (OR) [95% confidence interval (CI)] : 2.920 [1.753 to 4.864], P<0.001). The association remained in the logistic regression analysis adjusted by parity classification and delivery mode (adjusted OR [95% CI] : 2.691 [1.597 to 4.535], P<0.001) (Table 3).

Association between hypoglycaemia onset time and severe hypoglycaemia

Treatment for hypoglycaemia depends on the timing of its development and severity. Therefore, we investigated the

Table 1. Patient characteristics (N = 295)

Characteristics	
Sex (male), N (%)	161 (54.6)
Parity (first delivery), N (%)	152 (51.5)
GDM (yes), N (%)	14 (4.7)
Maternal BMI (overweight*), N (%)	70 (23.7)
Duration of labor (prolonged delivery), N (%)	14 (4.7)
Gestational age (weeks)	
37	18 (6.1)
38	95 (32.2)
39	94 (31.9)
40	74 (25.1)
41	14 (4.7)
Early term (yes), N (%)	113 (38.3)
Mode of delivery (vaginal), N (%)	224 (75.9)
Use of uterotonic agents (yes), N (%)	149 (50.5)
pH in CB (percentile), median (IQR)	7.27 (7.24–7.31)
Low pH in CB† (yes), N (%)	1 (0.4)
Weight percentile (percentile), median (IQR)	95.7 (92.7–98.1)
Hypoglycaemia‡ (yes), N (%)	91 (30.8)
Observational time	
Immediately after birth	13 (4.4)
1 hour after birth	62 (21.0)
2 hours after birth	12 (4.1)
4 hours after birth	4 (1.3)
Gestational age	
37 weeks	7 (38.9)
38 weeks	44 (46.3)
39 weeks	26 (28.6)
40 weeks and later	14 (15.9)
Severe hypoglycaemia§	7 (2.4)

*Maternal overweight : BMI >30 kg/m^2 at immediately before delivery
†Low pH in CB : pH <7.000
‡Hypoglycaemia : blood glucose level <40 mg/dL
§Severe hypoglycaemia : blood glucose <25 mg/dL
Abbreviations : BMI : body mass index ; CB : cord blood ; GDM : gestational diabetes mellitus ; IQR : interquartile range

association of hypoglycaemia onset time with severe hypoglycaemia and early-term birth. The prevalence of hypoglycaemia immediately, 1 hour, and 4 hours after birth were significantly higher in the early term group than in the later term group (8.0% vs 2.2%, P=0.037 ; 31.7% vs 16.3%, P=0.004 ; and 6.1% vs 0.0%, P=0.010, respectively). Meanwhile, there was no significant between-group difference for the prevalence at 2 hours after birth (7.0% vs 4.7%, P=0.530). The prevalence of severe hypoglycaemia was also not significantly between the two groups (1.8% vs 2.7%, P=0.712).

Subgroup analyses

In the first birth subgroup, the prevalence of hypoglycaemia was lower in neonates born at ≥40 weeks than in those born at 37, 38, or 39 weeks (≥40 weeks vs 37 weeks : 8.9% vs 45.5%, P=0.008 ; vs 38 weeks : 8.9% vs 40.5%, P<0.001 ; vs 39 weeks : 8.9% vs 25.6%, P=0.031). In the second or later birth subgroup, the prevalence of hypoglycaemia was lower in neonates born at ≥40 weeks than in those born at 38 weeks (28.1% vs 50. 9%, P=0.045). In subgroup analysis by mode of delivery, in both the caesarean section and normal delivery subgroups, the prevalence of hypoglycaemia was lower among those born ≥40 weeks than among those born at 38 weeks (16.2% vs 44.6%, P=0.001 for the caesarean section subgroup and 14.3% vs 48.7%, P=0.029 for the normal delivery subgroup) (Figure 2).

Table 2. Patient characteristics by presence of hypoglycaemia

Items	Hypoglycaemia		P-values
	Yes (91)	No (204)	
Early-term birth, N (%)	51 (56.0)	62 (30.4)	**<0.001**
Sex (male), N (%)	50 (54.9)	111 (54.4)	>0.999
Parity (first delivery), N (%)	38 (41.8)	114 (55.9)	**0.032**
GDM, N (%)	5 (5.5)	9 (4.4)	0.777
Maternal overweight*, N (%)	24 (26.4)	46 (22.5)	0.554
Prolonged delivery, N (%)	3 (3.3)	11 (5.4)	0.561
Mode of delivery (vaginal), N (%)	61 (67.0)	163 (79.9)	**0.019**
Use of uterotonic agents, N (%)	44 (48.4)	105 (51.5)	0.705
Low pH in CB†, N (%)	0 (0.0)	1 (0.5)	>0.999
pH in CB, median (IQR)	7.283 (7.243–7.318)	7.266 (7.236–7.305)	0.135
Weight percentile (percentile), median (IQR)	95.9 (92.4–98.4)	95.6 (92.8–97.6)	0.347

*Maternal overweight : BMI >30 kg/m^2 at immediately before delivery
†Low pH in CB : pH <7.000
Comparisons in weight percentile and pH in CB between the early term and later term groups are conducted using Mann-Whitney U test. Comparisons in other items are conducted using Fisher's exact test. P values <0.050 are considered statistically significant.
Abbreviations : CB : cord blood ; GDM : gestational diabetes mellitus ; IQR : interquartile range

Table 3. Logistic regression analysis for factors associated with hypoglycaemia

Items	Unadjusted		Adjusted	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Gestational age (Early term)	**2.920 (1.753 to 4.864)**	**<0.001**	**2.691 (1.597 to 4.535)**	**<0.001**

Odds ratios and P values are calculated using logistic regression analysis. Bold numbers indicate statistical significance at P<0.050.
These analyses are adjusted by parity and mode of delivery.
Abbreviations : CI : confidence interval ; OR : odds ratio

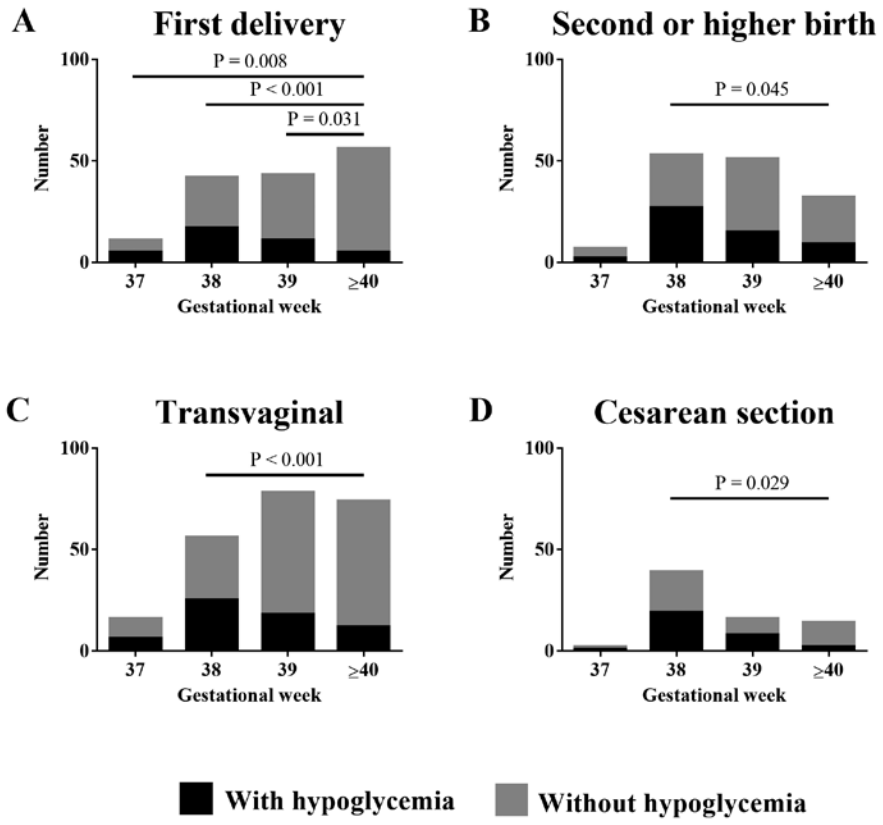

Figure 2. Associations between each gestational age and hypoglycaemia by subgroup of parity classification (first birth and second or higher birth) and mode of delivery (transvaginal and caesarean section). A : First birth subgroup. B : Second or higher birth subgroup. C : Transvaginal delivery subgroup. D : Caesarean section delivery subgroup. The prevalence of hypoglycaemia is compared between neonates born at 40 weeks and neonates born at 37 weeks, 38 weeks, and 39 weeks using Fisher's exact tests. Black bars and grey bars indicate the number of neonates with hypoglycaemia and without hypoglycaemia, respectively. P<.05 is considered significant.

DISCUSSION

This study found that early-term birth was positively associated with neonatal hypoglycaemia in LGA neonates. In addition, hypoglycaemia occurring immediately, 1 hour, and 4 hours after birth was positively associated with early-term birth. Meanwhile, there was no association between early-term birth and severe hypoglycaemia. In subgroup analyses by parity classification (first and second or higher birth) and mode of delivery (transvaginal delivery and caesarean section), the prevalence of hypoglycaemia was relatively higher in neonates born at early term than in neonates born at later term.

Insulin is mainly involved in decreasing blood glucose levels ; accordingly, high insulin levels for stored glycogen is a main cause of hypoglycaemia. LGA neonates have relatively higher levels of insulin in CB than do non-LGA neonates (20, 21). One study showed that insulin levels in CB were higher in neonates born at early term than in those born at later term (22). This high insulin level after birth might explain the high rate of hypoglycaemia in early-term birth and LGA neonates.

Meanwhile, the prevalence of hypoglycaemia at 2 hours after birth was not significantly different between the early term and later term groups. As stated above, early-term birth was associated with hypoglycaemia (i.e. blood glucose levels <40 mg/dL), but not with severe hypoglycaemia (i.e. blood glucose levels <25 mg/dL). After birth, regardless of term, low blood glucose induces secretion of hormones that increase blood glucose (e.g. epinephrine and glucagon) (23-25). Therefore, the decrease in blood glucose levels induced by high insulin levels might also return to normal and maintain blood glucose without severe hypoglycaemia by secretion of these hormones.

In the current study, the prevalence of hypoglycaemia occurring 4 hours after birth was significantly different between the early term and later term groups. Storage of glycogen, which is used to raise blood glucose levels by epinephrine and glucagon, is lower in neonates born at early term than in those born at later term (2, 14). A previous study showed that unlike in adults, in normal neonates, even low blood glucose does not suppress insulin secretion within 2 hours of age (23). Moreover, another study showed a lower breastfeeding rate within 1 hour after birth in infants born at early term than in those born at later term (26). These complex effects might lead to a significant difference in the prevalence of hypoglycaemia at 4 hours after birth between neonates born at early term and those born at later term.

Harris *et al*. reported that among healthy neonates, those born at early term have a lower mean blood glucose level than those born at later term (14). They showed that neonates born at early term had approximately 3 times more hypoglycaemia

episodes (blood glucose level <47 mg/dL) than did those born at later term. Although this study showed similar odds ratios and suggested that this result might be applicable even to neonates with conditions other than LGA, there was a difference in observation term and the definition of blood glucose level between our study and that study. The association between early-term birth and hypoglycaemia in neonatal conditions other than LGA, and the effect of LGA in neonates with early-term birth needs to be clarified in the future.

Early-term birth might have a confounding effect on the association between hypoglycaemia and neurodevelopment. As mentioned above, hypoglycaemia is negatively associated with neurodevelopment (5, 6, 27). Early-term birth is also negatively associated with neurodevelopment in children (28-30). Although we could not show whether hypoglycaemia influences the association between early-term birth and neurodevelopment, future studies should consider early-term birth as a covariate when investigating the association between neurodevelopment and hypoglycaemia.

This study has some limitations. First, this was a single-centre retrospective study, and thus, inherent biases (e.g. in gestational age at birth, indication for caesarean section, and use of uterotonic agents by obstetricians) could not be avoided. However, we attempted to reduce these biases by using multivariate analysis and increasing the number of obstetricians involved in this study through a long study period. Second, our data were limited to data until 4 hours after birth. With respect to the trajectory of blood glucose after birth in LGA, hypoglycaemia was reported to occur at an average of 2.9 hours (9, 10). This might indicate that similar results would be observed in studies with a longer period. Finally, hypoglycaemia was defined as blood glucose levels >40 mg/mL. The most accurate blood glucose level for defining hypoglycaemia is still debated. As mentioned above, the definition of blood glucose may alter the results of the association between early-term birth and hypoglycaemia. Future studies using different blood glucose levels for defining hypoglycaemia are needed.

In conclusion, early-term birth is positively associated with neonatal hypoglycaemia in LGA neonates. Thus, neonates born at early term require more careful observation for hypoglycaemia than those born at later term. Although further studies with a concise definition of blood glucose levels for hypoglycaemia are still needed, the current findings support that early-term birth is an important risk factor for hypoglycaemia.

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CONFLICT OF INTERESTS-DISCLOSURE

All authors have no interest-disclosure.

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