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Incidence and risk factors of hypocalcemia in late preterm newborns with intrauterine growth restriction: a hospital-based cross-sectional study.

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Abstract

Background: Hypocalcemia is a common metabolic disturbance in the neonatal period, and preterm neonates and those with intrauterine growth restriction (IUGR) are recognised as high-risk groups. Data specific to late preterm IUGR newborns are limited. This study estimated the incidence of hypocalcemia and identified associated maternal and perinatal risk factors in this subgroup.***Methods:*** A hospital-based cross-sectional study was conducted at a tertiary care teaching hospital in Sullia, Karnataka, over 18 months (June 2023–December 2024). Ninety late preterm (34 weeks to 36 weeks 6 days of gestation) IUGR newborns were enrolled by purposive sampling. Perinatal, maternal and biochemical variables were recorded, and paired venous samples for serum total and ionized calcium were drawn between 24 and 48 hours of life. Hypocalcemia was defined as serum total calcium <7 mg/dL (<1.75 mmol/L) or ionized calcium <4 mg/dL (<1 mmol/L). Data were analysed using SPSS v16 with the t test and chi-square test; p<0.05 was significant.***Results:*** The overall incidence of hypocalcemia was 3.33% (3/90): early-onset in 2 (2.22%) and late-onset in 1 (1.11%); 87 (96.66%) were normocalcemic. Early-onset hypocalcemia was significantly associated with lower birth weight (p=0.020), maternal hypothyroidism (p=0.0002) and oligohydramnios (p=0.0055). Late-onset hypocalcemia was significantly associated with lower serum magnesium (p<0.0001), lower serum 25-hydroxyvitamin D (p=0.0002) and formula feeding (p=0.033). Serum phosphorus, creatinine and alkaline phosphatase did not differ significantly between groups.***Conclusion:*** Hypocalcemia was infrequent (3.33%) among late preterm IUGR newborns but was linked to identifiable maternal and neonatal risk factors. Lower birth weight, maternal hypothyroidism and oligohydramnios predisposed to early-onset disease, while hypomagnesemia and formula feeding predisposed to late-onset disease. Targeted calcium monitoring and appropriate feeding strategies are warranted in at-risk neonates

Keywords: Hypocalcemia, Late preterm, Intrauterine growth restriction, Serum calcium, Neonate, Risk factors.

INTRODUCTION

Hypocalcemia is one of the most common metabolic disturbances of the neonatal period, and its frequency is higher among neonates born preterm or with intrauterine growth restriction (IUGR).[1,2] Calcium is essential for neuromuscular function, cellular signalling and bone metabolism, and neonatal hypocalcemia may manifest as jitteriness, irritability, poor feeding, apnea or seizures.[1,3] Because most affected neonates are asymptomatic, the condition can remain undetected unless at-risk infants are screened.

The higher susceptibility of preterm infants is attributed to abrupt cessation of transplacental calcium supply at birth, an exaggerated postnatal fall in serum calcium, relatively delayed and blunted parathyroid hormone (PTH) response, and elevated calcitonin levels.[1,2] Serum calcium normally reaches its nadir within 48 hours and returns to mid-normal values by about 72 hours of life. Neonatal hypocalcemia is classified by timing of onset: early-onset within the first 72 hours, and late-onset thereafter, typically towards the end of the first week.[4,6].

Ionized calcium is the biologically active fraction and is preferred for diagnosis, since total calcium may be misleading in ill, premature or hypoalbuminemic neonates.[5] IUGR infants are considered particularly vulnerable because of reduced intrauterine calcium accretion and limited skeletal stores, and this risk is compounded when they are also born late preterm.[3] Late preterm infants (34 to 36 weeks 6 days) are frequently managed as though they were term, yet they retain a degree of physiological immaturity that may predispose to metabolic morbidity.

Despite the recognised vulnerability of both groups, data specific to the overlap population of late preterm IUGR newborns are limited. The present study was therefore undertaken to estimate the incidence of hypocalcemia in late preterm IUGR newborns and to identify the maternal and perinatal factors contributing to it.

MATERIALS AND METHODS

Study design, setting and population

This hospital-based cross-sectional study was conducted in the Department of Pediatrics of a tertiary care teaching hospital in Sullia, Dakshina Kannada, Karnataka, over an 18-month period (June 2023 to December 2024). Late preterm newborns, defined as those born between 34 weeks and 36 weeks 6 days of gestation, who had IUGR were eligible. IUGR was defined as a birth weight below the 10th percentile for gestational age. Gestational age was assessed using the modified Ballard score, and symmetrical versus asymmetrical IUGR was categorised using the ponderal index. Written informed consent was obtained from parents, and the study was approved by the institutional ethics committee.

Sample size

Taking an expected hypocalcemia prevalence of 15% among late preterm newborns from an earlier report by Nawaz et al,[8] and applying the formula $N = 4pq/L^2$ with an allowable error (L) of 7.5%, the required sample size was 90. Ninety eligible neonates were enrolled by purposive sampling.

Data collection and definitions

Perinatal and maternal variables recorded included gestational age, birth weight, mode of delivery, Apgar scores, time to first feed, mode of feeding (including formula feeding), maternal hypothyroidism, oligohydramnios, diabetes mellitus, pregnancy-induced hypertension and antenatal magnesium administration. A venous sample was drawn between 24 and 48 hours of life; a plain vial was used for serum total calcium and a lithium-heparin vial for ionized calcium, together with blood glucose, magnesium, phosphorus, creatinine, alkaline phosphatase and 25-hydroxyvitamin D. Hypocalcemia was defined as serum total calcium <7 mg/dL (<1.75 mmol/L) or ionized calcium <4 mg/dL (<1 mmol/L). Hypocalcemia occurring within 72 hours was classified as early-onset and that occurring after 72 hours as late-onset.[6,7].

Statistical analysis

Data were entered in Microsoft Excel and analysed using SPSS version 16. Qualitative data were expressed as frequencies and percentages, and quantitative data as mean ± standard deviation. The independent-samples t test was used for continuous variables and the chi-square test for categorical variables. A p value <0.05 was considered statistically significant.

RESULTS

Ninety late preterm IUGR neonates were studied. Fifty-four (60%) were born between 35 and 36 weeks, 28 (31.1%) between 36 and 37 weeks, and 8 (8.9%) between 34 and 35 weeks. Mean birth weight rose with gestational age, from 1678.8 g at 34–35 weeks to 1905.3 g at 35–36 weeks and 2150.5 g at 36–37 weeks. The mean Apgar score was 7.51 ± 0.65 at 1 minute and 8.66 ± 0.47 at 5 minutes. Most neonates received their first feed within 60–75 minutes of birth, and only 5 (5.6%) received any formula feed. The commonest maternal conditions were oligohydramnios (5.6%), hypothyroidism (3.3%) and diabetes mellitus (3.3%) (Table 1).

Mean biochemical values for the cohort were: blood glucose 67.96 ± 5.15 mg/dL, serum calcium 4.57 ± 0.26 mg/dL, magnesium 1.92 ± 0.17 mg/dL, phosphorus 8.46 ± 0.72 mg/dL, creatinine 0.54 ± 0.11 mg/dL, alkaline phosphatase 155.13 ± 11.92 U/L and 25-hydroxyvitamin D 17.8 ± 2.17 ng/mL.

The overall incidence of hypocalcemia was 3.33% (3 of 90). Early-onset hypocalcemia occurred in 2 neonates (2.22%) and late-onset in 1 (1.11%); the remaining 87 (96.66%) were normocalcemic (Table 2).

Among perinatal factors, early-onset hypocalcemia was significantly associated with lower birth weight (1682.5 ± 10.6 g versus 1967.8 ± 169.6 g; p=0.020). Gestational age, Apgar scores, formula feeding and time to first feed were not significantly associated. Among maternal factors, maternal hypothyroidism (p=0.0002) and oligohydramnios (p=0.0055) were significantly associated with early-onset hypocalcemia; one-third of hypocalcemic neonates were born to hypothyroid mothers and one-fifth to mothers with oligohydramnios. On comparison of biochemical parameters, only ionized calcium differed significantly between groups (3.55 ± 0.07 versus 4.61 ± 0.17 mg/dL; p<0.0001); phosphorus, magnesium, creatinine and alkaline phosphatase did not differ significantly (Table 3).

Late-onset hypocalcemia was significantly associated with lower serum calcium (p<0.0001), lower serum magnesium (0.7 versus 1.93 ± 0.12 mg/dL; p<0.0001), lower serum 25-hydroxyvitamin D (12 versus 17.86 ± 2.09 ng/mL; p=0.0002) and

formula feeding (p=0.033). Gestational age, birth weight, Apgar scores, blood glucose, phosphorus, creatinine and alkaline phosphatase were not significantly associated (Table 4).

Table 1. Baseline perinatal, feeding and maternal characteristics of the study population (N=90)

Characteristic	n	%
Gestational age 34–35 weeks	8	8.9
Gestational age 35–36 weeks	54	60.0
Gestational age 36–37 weeks	28	31.1
First feed within 60–75 min	28	31.1
Formula feed given	5	5.6
Maternal oligohydramnios	5	5.6
Maternal hypothyroidism	3	3.3
Maternal diabetes mellitus	3	3.3
Pregnancy-induced hypertension	2	2.2
Antenatal magnesium administration	1	1.1

Table 2. Incidence of hypocalcemia in the study population (N=90)

Category	n	%
Early-onset hypocalcemia	2	2.22
Late-onset hypocalcemia	1	1.11
No hypocalcemia	87	96.66
Total hypocalcemia	**3**	**3.33**

Table 3. Association of early-onset hypocalcemia with perinatal, maternal and biochemical factors

Factor	Hypocalcemia	Normocalcemia	p value
Birth weight (g)	1682.5 ±10.6	1967.8 ±169.6	0.020*
Gestational age (days)	251.5 ±6.4	249.2 ±4.2	0.441
Maternal hypothyroidism (n)	1	2	0.0002*
Oligohydramnios (n)	1	4	0.0055*
Ionized calcium (mg/dL)	3.55 ±0.07	4.61 ±0.17	<0.0001*
Phosphorus (mg/dL)	9.05 ±0.07	8.45 ±0.72	0.244
Magnesium (mmol/L)	1.9 ±0.28	1.92 ±0.17	0.871
Alkaline phosphatase (IU/L)	159 ±15.6	155.0 ±11.9	0.645

*Statistically significant (p<0.05).

Table 4. Association of late-onset hypocalcemia with selected risk factors

Factor	Hypocalcemia	Normocalcemia	p value
Serum calcium (mg/dL)	3.4	4.59 ±0.23	<0.0001*
Serum magnesium (mg/dL)	0.7	1.93 ±0.12	<0.0001*
25-hydroxyvitamin D (ng/mL)	12	17.86 ±2.09	0.0002*
Formula feeding (n)	1	4	0.033*
Birth weight (g)	2100	1959.9 ±173.3	0.259
Phosphorus (mg/dL)	9.3	8.45 ±0.72	0.101
Alkaline phosphatase (U/L)	176	154.9 ±11.8	0.054

*Statistically significant (p<0.05).

DISCUSSION

In this cohort of 90 late preterm IUGR newborns, the overall incidence of hypocalcemia was low at 3.33%, yet distinct maternal and perinatal associations emerged for early- and late-onset disease. The findings are consistent with the view that late preterm IUGR neonates form a vulnerable subgroup in whom targeted monitoring is worthwhile.

Incidence in relation to other studies

The observed incidence is close to the 4.01% reported by Alyasiri in a neonatal intensive care unit[9] and the 2.7% reported from Jordan by Ayash et al.[10] Substantially higher figures have been reported from Yemen (18%),[11] Kenya (21.5%)[12] and Iran (33.5%).[13] These differences likely reflect variation in the definition of hypocalcemia, the case mix (symptomatic versus all neonates, degree of prematurity, presence of birth asphyxia) and sampling methods. The present study focused specifically on asymptomatic and symptomatic late preterm IUGR neonates and used an ionized-calcium-based definition, which may account for the comparatively low incidence.

Risk factors for early-onset hypocalcemia

Lower birth weight was significantly associated with early-onset hypocalcemia, in keeping with previous reports identifying low birth weight as a risk factor in preterm and IUGR neonates.[14,15] The likely mechanism is impaired calcium homeostasis due to suboptimal intrauterine development and reduced skeletal calcium stores, which is particularly pronounced in growth-restricted infants.[19].

Maternal hypothyroidism and oligohydramnios were also significantly associated with early-onset hypocalcemia. Maternal thyroid dysfunction may impair fetal parathyroid development and function, reduce transplacental calcium transfer, and coexist with vitamin D deficiency and delayed skeletal mineralisation, all of which can lower neonatal calcium.[16,17,18] Oligohydramnios, itself associated with growth restriction, may reflect reduced placental perfusion and nutrient transfer, indirectly affecting fetal mineral accretion. As Blaga noted, serum calcium is physiologically unstable in the first days of life owing to abrupt loss of placental supply, low PTH, high calcitonin and physiological acidosis, and growth-restricted infants are especially prone to hypocalcemia that is often asymptomatic and easily missed.[19].

Risk factors for late-onset hypocalcemia

Late-onset hypocalcemia was significantly associated with lower serum magnesium, lower 25-hydroxyvitamin D and formula feeding. Hypomagnesemia impairs PTH secretion and induces peripheral resistance to PTH, thereby lowering serum calcium.[22] Formula and cow-milk feeds carry a high phosphate load that can precipitate hyperphosphatemia and consequent hypocalcemia, a well-described cause of late infantile tetany.[20,21] These observations reinforce the value of early breastfeeding or fortified human milk, which provide more bioavailable calcium and magnesium than formula, in this population.

Biochemical parameters

Serum phosphorus, creatinine and alkaline phosphatase did not differ significantly between neonates with and without hypocalcemia, and mean 25-hydroxyvitamin D for the whole cohort (17.8 ng/mL) lay within the expected neonatal range. The small number of affected neonates and the fixed timing of sampling may have limited the ability to detect biochemical differences, and these findings should be interpreted with that caveat.

Early versus late-onset hypocalcemia

Early-onset hypocalcemia (2.22%) was more frequent than late-onset disease (1.11%), consistent with the literature indicating that late neonatal hypocalcemia is comparatively rare.[7] Because the two forms differ in their biochemical and perinatal associations, they may benefit from different preventive strategies—optimisation of maternal and perinatal factors for early-onset disease, and attention to feeding practices and magnesium status for late-onset disease.

Strengths and limitations

Strengths include the focus on a well-defined high-risk subgroup and the use of ionized calcium for diagnosis. Limitations include the single-centre design, the small number of hypocalcemic cases which precludes multivariable analysis and yields wide confidence around subgroup estimates, purposive sampling, and a single sampling time point that may not have captured the full trajectory of calcium change. Larger multicentre studies are needed to refine these estimates.

Clinical implications

Although uncommon, hypocalcemia in late preterm IUGR newborns can cause serious complications if untreated. The findings support careful calcium monitoring in neonates with low birth weight, maternal hypothyroidism or oligohydramnios, early initiation of breastfeeding or fortified human milk in preference to formula, and attention to magnesium status, as part of a comprehensive, multidisciplinary approach to neonatal care.

CONCLUSION

The incidence of hypocalcemia among late preterm IUGR newborns was low (3.33%), but the condition was linked to identifiable risk factors. Lower birth weight, maternal hypothyroidism and oligohydramnios were significantly associated with early-onset hypocalcemia, whereas hypomagnesemia, lower 25-hydroxyvitamin D and formula feeding were associated with late-onset disease. Targeted screening of at-risk neonates, appropriate feeding strategies favouring breast milk, and attention to maternal health and neonatal magnesium status may help prevent hypocalcemia and its complications in this vulnerable group.

Declarations

Ethics approval and consent

The study was approved by the Institutional Ethics Committee, KVG Medical College and Hospital, Sullia (Approval No. KVGMCIEC202309, dated 26 April 2023). Written informed consent was obtained from the parents/guardians of all participating neonates.

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Author contributions: VG conceived the study, collected and analysed the data, and drafted the manuscript. SR supervised the study and critically revised the manuscript. SB and RLJ contributed to data interpretation and manuscript revision. All authors approved the final version.

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