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Incidence and Risk Factors of Hypoglycaemia in Large-For-Gestational Age Newborns of Non-Diabetic Mothers in a Tertiary Care Hospital

Authors
Sandeep C Prakash[1], Namganglung Golmei[2], B. Sarita[3], Ch. Shyamsunder[4], Ch. Mangi[5]
[1]Junior Resident, [2]Assistant Professor, [3]Senior Resiident, [4]Associate Professor, [5]Professor,
Department of Pediatrics, Regional Institute of Medical Sciences, Imphal, India

Abstract
Background: *Large for gestational age (LGA) is defined as a weight that lies above the 90th percentile for that gestational age. Large babies are at risk of increased adverse maternal and neonatal outcomes. Neonatal complications include difficult deliveries, shoulder dystocia, plexus injuries, congenital anomalies etc. and various metabolic derangements – hypoglycemia, hyperbilirubinemia, hypocalcemia and polycythemia. The risk of hypoglycemia in LGA babies is independent of whether the mother has diabetes or not.*
Aims and Objects: *To determine the incidence and study the various risk factors of hypoglycaemia in LGA infants of non-diabetic mothers. Methodology: In this hospital based cross sectional descriptive study, LGA newborns delivered to non-diabetic mothers in Regional Institute of Medical Sciences (RIMS), Imphal and brought to the Department of Pediatrics, RIMS, Imphal were included in the study for blood glucose monitoring.*
Results: *A total of 106 LGA babies were studied during the period from 1st October 2012 to 30th September 2014. 16 (15.1%) babies were hypoglycaemic (<40mg/dl) during the first 24 hours of life. Of these, the incidence of hypoglycaemia at 2, 2-6 and 6-24 hours of life were found to be 8.5%, 3.8% and 2.8% respectively of the total hypoglycaemic cases. Hypoglycaemia was not observed in LGA babies born to mothers who were less than 20 years of age but significantly increased as mothers' age progressed - 31.3% in 20-34 to 68.8% in more than 35 years age group (p=0.000). Babies born by LSCS operation had statistically significant hypoglycemia (p=0.041) as compared to assisted ventouse or normal deliveries. Increasing incidence of hypoglycemia occurred as the neonatal weight increased – from 8% in <4500 gm to 31% in 4500-5000 gm group (p=0.005). Babies with Apgar score <6 at 5 min was also at risk of hypoglycemia (p=0.001). No statistically significant co-relations were observed between hypoglycemia and period of gestation, parity and babies' sex.*
Keywords: *LGA, newborns, LSCS, hypoglycaemia.*

Introduction

Large for gestational age (LGA) is defined as a weight that lies above the 90th percentile for that gestational age.[1] Macrosomia, also termed as big baby syndrome, is sometimes used synonymously with LGA, or, is otherwise defined as a baby that weighs 4000 grams or greater regardless of gestational age.[2] Excessive fetal growth can occur because of genetic factors or increased supply of nutrients. Other determining factors include -

maternal diabetes, maternal impaired glucose, prolonged gestation, maternal obesity, multiparity and male sex.[3,4] LGA babies are at risk of many complications such as difficult delivery, neonatal injuries and metabolic complications like hyperbilirubinemia, hypoglycemia, hypocalcemia, polycythemia etc.[5,6]

During intrauterine life, transplacental transport supplies various nutrients including glucose, which is the most important fetal energy substrate to the growing fetus. With the abrupt cessation of maternal supply of glucose immediately after birth, transient hypoglycaemia is common in LGA infants because of the physiologic immaturity of pathways of glucose homeostasis and glucose values reach a nadir at 2-3 hours of life.[7,8] This may be compounded by a delay in initiation of breastfeeding. Even though a newborn infant can indigenously produce glucose at a rate corresponding to 4-6 mg/kg/min, it is not sufficient for the newborn's energy needs.[8]

Hypoglycemia is a frequent neonatal problem frequently encountered in risk groups such as immature and low birth weight infants, infants of mothers with diabetes and infants born large for gestational age.[7] It is usually defined as a serum glucose less than 35 mg/dl at less than 3 hours of age, less than 40 mg/dl at 3 to 24 hours of age, and less than 45 mg/dl at more than 24 hours of age.[9] World Health Organization (WHO) defines hypoglycaemia as blood glucose level of less than 45 mg/dL. Operational threshold has been defined as blood glucose level of less than 40 mg/dL (plasma glucose level less than 45 mg/dL).[10] If undiagnosed and untreated, hypoglycaemia may cause subtle or overt brain damage in the newborn infant.[7,11]

Though many studies are available for LGA infants of diabetic mothers, there is only limited information on metabolism in newborn LGA infants born to non-diabetic mothers. The risk of neonatal hypoglycemia and risks of metabolic diseases later in life makes it essential to study postnatal metabolic adaptation in these infants.[12] Moreover, there is no consensus regarding the necessity to test large-for-gestational-age neonates of non-diabetic mothers routinely.

The present study was therefore undertaken to determine the extent of neonatal hypoglycaemia in the first 24 hours of life in large-for-gestational-age newborn infants of non-diabetic mothers delivered in Regional Institute of Medical Sciences (RIMS) Hospital, Imphal, Manipur, India and presenting to the Pediatric ward and to identify possible maternal and neonatal predictors of the condition.

Materials and Methods

Designed as a hospital based cross sectional study, LGA babies delivered to non-diabetic mothers in RIMS Hospital and brought to the Department of Paediatrics for blood glucose monitoring were considered. The study variables included maternal age, religion, parity, period of gestation, mode of delivery, birth weight, sex of the newborn, history of birth asphyxia (Apgar score at 5 min) and any other metabolic complication other then hypoglycemia were recorded. All live new borns weighing more than 90th percentile for the gestational age or >4000 grams at birth, delivered to mothers with no history of diabetes and gestational age > 37 weeks were included in the study. LGA babies - delivered to mothers with history of diabetes mellitus, gestational diabetes mellitus, pregnancy induced hypertension and pre-eclampsia, delivered outside RIMS Hospital, <37 weeks gestational age, having severe cardio-respiratory compromise, with gross congenital anomalies and whose parents declined consent were excluded from the study. LGA infants fulfilling the inclusion criteria were evaluated for hypoglycaemia by capillary blood obtained by heel-stick with a glucometer (One Touch Select, Johnson & Johnson). The first post natal glucose testing was performed at 60 minutes after the first feeding and the subsequent measurements of neonatal glucose was performed before every feeding at 2, 4, 6, 12 and 24 hours of life. In the present study, a blood sugar level <40 mg/dl is taken as hypoglycaemia. Appropriate interven-

tions were planned for hypoglycemic cases [9] and those neonates with clinical problems were observed in the neonatal intensive care unit (NICU) until they were clinically stable. Due approval from the Institutional Ethical Committee was obtained before the initiation of the study.

Findings were recorded in a pre-designed performa, and the incidence of hypoglycaemia in newborns LGA of non-diabetic mother and observations or variations according to maternal age, religion, parity, period of gestation, mode of delivery, sex of the newborn, birth weight, history of birth asphyxia (Apgar score at 5 minutes) and any metabolic complications were determined and the results analyzed using SPSS version 21.0 and chi-square test was used where applicable for testing the significance of difference. P value of <0.05 was taken as significant for the obtained results.

Results

During the study period there were a total of 22948 deliveries, out of which 1606 LGA babies were born giving an incidence of 70.0/1000 live births. 106(6.6%) LGA babies brought to Pediatrics department for blood sugar monitoring fulfilled the inclusion criteria, were studied and 16 of them had hypoglycemia during the first 24 hours of life constituting 15.1% of the total study population. The incidence of hypoglycemia was found to be maximum (n=9;8.5%) within the first 2 hours of life and subsequently decreased thereafter (Table -1). Between 2 to 6 hours of life moderate decrease of hypoglycemia 3.8% (n=4) was observed during this period. The number of infants who remained at risk decreased further after 6 hours of life and hypoglycemia was diagnosed in 2.8% of infants (n=3) between 6 and 24 hours of life.

The number of LGA males were 67(63.2%) in comparison to 39(36.8%) LGA females with male to female ratio of 1.7 :1 (Table -2). Out of the total 16 hypoglycemic neonates - male babies were 11 and females 5 in number (p = 0.617).

Age of the non-diabetic mothers delivering LGA babies ranged from 19 to 43 years with a mean of 30.5 years. Hypoglycemia was not recorded in LGA babies born to mothers who were <20 years of age but its incidence significantly increased from 31.3% in the maternal age group 20-34 years to 68.8% in mothers aged >35 years (p=0.000) (Table – 3). Hypoglycemia was observed in 5 (31.2%) of primipara mothers, 9(56.3%) in mothers who were multipara and 2(12.5%) in grand multipara with insignificant co-relation (p=0.280). Neonates born at <40 weeks period of gestation (POG) experienced hypoglycemia most (n=11;68.7%) followed by 25.0% (n=4) for 40-42 weeks gestational period. And it further decreased to 6.3 % (n=1) when the POG was > 40 weeks (p= 0.405).

Of the total 106 studied cases, 64(60.4%) LGA babies were delivered by lower segment cesarian section (LSCS) operation out of which 14 (87.5%) developed hypoglycemia, which was followed by 2(12.5%) in ventouse assisted deliveries (p=0.041). There was no documented hypoglycemia the babies borne by normal vaginal delivery (NVD) (Table -3).

The birth weight of the 106 macrosomic babies in the study ranged from 4100 to 5300 grams with a mean of 4367 grams. Of the 106 macrosomic neonates, 75(70.8%) weighed between 4000 – 4499 grams, 29 (27.3%) between 4500-4999 grams and 2 (1.9%) were 5000 grams and above (Table – 2). Amongst the LGA babies, the incidence of hypoglycemia was maximum in the weight group 4500-5000 grams (n=9;56.2%); hypoglycemia rate also significantly increased from 8% of the neonates less than 4500 grams to 31% in 4500-5000 grams group which further rose to 50% in neonates 5000 grams and above (p=0.005).

7(6.6%) of the total 106 LGA babies in the study had perinatal birth asphyxia (Apgar score <6 at 5 min). 4(57.1%) had statistically significant hypoglycemia (p=0.001) and the remaining 3 (42.9%) were euglycemic (Table-2).

Hypocalcemia (<7mg/dl) was observed in 3 of the 16 cases (*p*=0.004)(Table -2). It was also found that there were 7 cases of traumatic birth injury (cephalhematoma - 4, craniao-facial lacerations - 2 and brachial plexus injury - 1) in the macrosomic babies who had presented for blood sugar monitoring.

There were a total of 21 hospital admissions of the macrosomic babies who were admitted for management of birth trauma, respiratory distress, perinatal depression and feeding problems. There were no mortalities.

Table - 1. Distribution of hypoglycaemic LGA babies during the first 24 hours of life.

Hours of life	No. of neonates with hypoglycemia	Percentage
< 2	9	8.5
2-6	4	3.8
6-24	3	2.8
Total Hypoglycemics	16	15.1
Total no. LGA cases	106	100.0

Table – 2. Co-relation between neonatal variables and hypoglycaemia

Neonatal variables		Hypoglycaemia		Total no. (%)	*P - value*
		Yes no. (%)	No no. (%)		
Sex	Female	5 (31.2)	34 (37.8)	39 (36.8)	p=0.617
	Male	11 (68.8)	56 (62.2)	67 (63.2)	
Birth weight (gm)	< 4500	6 (37.5)	69 (76.7)	75 (70.8)	p = 0.005
	4500-5000	9 (56.2)	20 (22.2)	29 (27.3)	
	> 5000	1 (6.3)	1 (1.1)	2 (1.9)	
Apgar score at 5 min.	< 6	4 (25)	3 (3.3)	7 (6.6)	p =0 .001
	> 6	12 (75.0)	87 (96.7)	99 (93.4)	
Serum Calcium	>7mg/dl	13 (12.9)	88 (87.1)	101 (100.0)	p=0 .004
	<7mg/dl	3 (60.0)	2 (40.0)	5 (100.0)	

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gm – gram; mg – milligram; min.- minute; dl - decilitre

Table :- 3 . Co-relation between maternal variables and neonatal hypoglycaemia

Maternal variables		Hypoglycaemia		Total no. (%)	*p-value*
		Yes no. (%)	No no. (%)		
Age (years)	< 20	0 (0.0)	1 (1.1)	1 (0.9)	p= 0.000
	20-34	5 (31.2)	73 (81.1)	78 (73.6)	
	> 35	11 (68.8)	16 (17.8)	27 (25.5)	
Parity	Primi	5 (31.2)	30 (33.4)	35 (33.0)	p=0.280
	2-4	9 (56.3)	57 (63.3)	66 (62.3)	
	> 5	2 (12.5)	3 (3.3)	5 (4.7)	
Period of gestation (weeks)	< 40	11 (68.7)	46 (51.1)	57 (53.8)	p=0.405
	40 - 42	4 (25.0)	38 (42.2)	42 (39.6)	
	> 42	1 (6.3)	6 (6.7)	7 (6.6)	
Mode of delivery	LSCS	14 (87.5)	50 (55.6)	64 (60.4)	p = 0.041
	VAD	2 (12.5)	26 (28.9)	28 (26.4)	
	NVD	0 (0.0)	14 (15.6)	14 (13.2)	

LSCS –lower segment cesarian section; VAD – ventouse assisted delivery; NVD – normal vaginal delivery

Discussion

In the present study, 1606 babies weighing more than 4000 grams were born out of a total of 22948 deliveries giving an incidence of 70.0/1000 live births. 106 (6.6%) of the 1606 LGA babies fulfilled the inclusion criteria and 16 (15.1%) of them had hypoglycaemia during the first 24 hours of life. It was further observed that the incidence of hypoglycemia at 2 hour of life was found to be maximum at 8.5% which further decreased to 3.8% at 2-6 hours and 2.8% respectively at 2-6 hours and 6-24 hours of life respectively (Table – 1). Schaefer-Graf *et al,*[13] also reported a similar finding of 16% hypoglycemic rate and decreasing incidence of hypoglycemia during the first few hours of life - from 9.2% within the 1st hour of life, to 3.5% between 2 - 5 hours (cumulative) of life, and 2.4% between 6 and 24 hours of life in macrosomic infants of non-diabetic mothers during the first 24 hours of life.

Neonatal hypoglycemia was not observed in those LGA babies born to these mothers <20 years of age but increased significantly (*p*=.000) from 31.2% to 68.8% in the age group 20-34 years to > 35 years of age (Table - 3). But in a study by Essel *et al,*[14] hypoglycaemic LGA babies born to women <20 years of age was 5.7% of the newborns, and as maternal age increased, so was the frequency of hypoglycemia from 25.6% to 62.3%. Bekdas M *et al*[15] also reported hypoglycemic rate of 3.9% of LGA babies born to women under 20 years and 3% to women over 40 years. Gestational age over 35 years has also been reported to be an important risk factor for macrosomic infant deliveries by non-diabetic mothers by other authors.[16,17] Our present study also substantiates this view.

It is estimated that the caesarean delivery rate in macrosomic infants varies between 37% and 54%.[16] In the present study, 60.4% (n=64) of the LGA babies were delivered by lower segment caesarean section; 26.4% were ventouse assisted and the remainder 13.2% were normal vaginal deliveries (Table -3). 14(21.9%) of the LGA babies delivered by LSCS developed hypoglyc-emia which was followed by 2(7.1%) in VAD. There was no recorded incidence of hypoglycemia in NVD babies. Bekdas M *et al*[15] found that 15% of the babies who had undergone LSCS and 4% of the babies delivered vaginally had hypoglycemia especially during the first 2 hours of life. Nassar *et al*[5] also observed that hypoglycaemia was more prevalent among macrosomic babies born through caesarean section (*p*=0.003). The higher rate of hypoglycemia in the LGA babies delivered by LSCS could be explained by the fact that most of the babies could not be initiated on direct breast feeding immediately after birth due to the surgery or the effects of anaesthesia on the mother.

Out of the studied 106 macrosomic infants, 75 (70.8%) were between 4000–4499 grams, 29 (27.3%) between 4500-4999 grams and 2 (1.9%) were 5000 grams and greater. Similar findings were also reported by others.[15,17] It was also observed that the maximum incidence of hypoglycaemia was found in the weight group 4500-5000 grams (n=9;31%) (Table-2). The incidence of hypoglycaemia significantly increased from 8% of the neonates in the group <4500 grams to 31% in the group 4500-5000 grams which further rose to 50% in neonates >5000 grams and above (*p*=.005). Schaefer-Graf *et al*[18] too, reported that out of the total hypoglycaemic LGA babies, 55.9% of them had an increase in incidence of hypoglycemia with increase in birth weight. Hypoglycaemia was also positively associated with birth weight, ranging from 0.8% in infants with a birth weight of 4000–4499 gm to 25% in infants with a birth weight of ≥5000 gm when compared to appropriate for gestational age (AGA) babies (*p*=0.008).[18] The increase in incidence of hypoglycemia with increase in weight is due to the fact that the larger the baby, more will be his metabolic and caloric requirement. Therefore, these babies should be immediately fed by direct breast feeding or formula feed if mother is unable to initiate breast feeding for any reason. With one study reporting that C-peptide level is high in the cord blood of the infants with non-diabetic mothers, it may be

imperative to measure blood glucose regularly like in the infants with diabetic mothers.[19]

Akin *et al.*[17] in their study found that perinatal asphyxia in macrosomic infants varied between 0.9% and 4.6%. In the present study, a slightly higher value of 6.6% (n=7) of the LGA babies having an Apgar score of ≤6 at 5 minutes of life was observed (Table – 2). Of the 7 neonates having perinatal birth asphyxia, 4(25%) were found to have hypoglycaemia, which was statistically significant (p=0.001). Birth asphyxia has been stated to be one of the causes of hyperinsulinemic hypoglycaemia and may be associated with an increase risk of brain injury since it not only decreases serum glucose level but also prevents the brain from utilizing secondary fuel sources by suppressing fatty acid release and ketone body synthesis.[1] Schaefer-Graf *et al*[13] in their study found that hypoglycaemia was associated with only 1.5% of perinatal birth asphyxia at 5 minutes. The higher number in our study could be because of the small sample size of 106 in comparision to 887 in the study conducted by Schaefer-Graf *et al.* [13]

Hypocalcemia was observed in 5 LGA babies in the present study out of which 3 had hypoglycemia (p=.004). Hypocalcemia as such may not cause hypoglycemia but whenever hypoglycemia is documented in LGA baby of non-diabetic mother, the presence of concomitant hypocalcemia should be considered especially when hypocalcaemic symptoms are not relieved by treatment with intravenous dextrose fluid.

Conclusion

Hypoglycemia in neonates is a commonly preventable problem and large for gestational age neonates are also potentially at risk even if they are asymptomatic. In order to reduce early infant mortality and neuro-developmental sequelae in later life early screening and intervention aimed at the detection and treatment of large for gestational age infants who are at risk is emphasized.

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Dr. Ch. Mangi will act as the guarantor for this paper.

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