CLINICAL STUDY OF INCIDENCE OF HYPOGLYCAEMIA IN BREAST-FED LATE PRETERM NEONATES

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ABSTRACT

BACKGROUND

Hypoglycaemia is the most common metabolic abnormality in infancy and childhood. When prolonged or recurrent, they can lead to irreversible brain damage. 10-12% of Indian babies are born preterm <37 weeks. Late preterm are approximately 70% of the preterm births. They are born between 340/7 weeks to 386/7 weeks. The objectives of this study were- 1. to study the incidence of hypoglycaemia in late preterm babies who are on breast feeds since birth. 2. to study the need of regular blood glucose monitoring in early diagnosis of hypoglycaemia in late preterm.

MATERIALS AND METHODS

This is a hospital based observational study which included 120 late preterms and breast-fed babies. Babies who are term, asphyxiated, and on formula feeds are excluded.

RESULTS

Incidence of hypoglycaemia is significant in late preterm, more so, asymptomatic hypoglycaemia (84%) is highest in 24 hrs. Babies <2 Kgs had statistically significant hypoglycaemia. There is linear association with age and babies born to primi.

CONCLUSION

In the present study, hypoglycaemia was seen in late preterm babies in first 24 hours of life.

KEYWORDS

Hypoglycaemia, Blood Glucose Monitoring, Breast Feeding, Late Preterm.

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BACKGROUND

Hypoglycaemia is the most common metabolic abnormality in infancy and childhood. When prolonged or recurrent it is a potent cause of irreversible brain damage leading to cognitive impairment, recurrent seizure activity, cerebral palsy, autonomic dysregulation.[1] However, when promptly diagnosed and supplemented these conditions can be prevented or minimized.

About 10-12% of Indian babies are born preterm <37 weeks are compared to 5-7 & incidence in the west.[2] Birth weight and gestational age have traditionally been used as strong indicators of neonatal death. Preterm births are increasing globally because a fetal, placental and uterine causes and material and other causes.[3] The overall incidence of hypoglycaemia in neonates varies from 0.2 to 11.4% (2000). However, in the presence of certain risk factor i.e. small for date, large for dates, infants of diabetic mother, prematurity etc. the probability of hypoglycaemia increases many fold. Later Preterm is defined as birth between 34 0/7 weeks and 36 6/7 weeks of gestation calculated form the first day of Mother's LMP.[4,5]

Late preterms were considered "Near Term" until recently and were treated on par with term infants. But they are physiologically and metabolically immature and have a higher risk of morbidity and mortality.[5,6,7] Late preterms account for approximately 70% of all preterm births and 8% of total births.[8]

Late preterm babies present with number of feeding challenges including fewer and shorter awake periods and excessive sleepiness. They tire easily during feeding, they have a weak suck and poor muscle tone and may exhibit an inability to sustain sucking and fatiguing easily before finishing a feed. Their tone may be adequate at the start of feeding session but rapidly decreases during the feeding indicating decreased endurance. There is a significant incident of hypoglycaemia in preterm and LBW babies in spite of being on breast feeds.[9] Late preterms are at higher risks for a number of problems including poor feeding hypoglycaemia, hypocalcaemia, Jaundice, infections, respiratory distress, failure to thrive and hospital read mission.[5,6]

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At birth glucose levels fall in neonates who are not fed immediately after birth. This is not seen in neonates with LBW, due to the reduced energy reserve at birth, but neonates of appropriate birth weight will mobilize alternative metabolic substrates (free fatty acids and ketone bodies) in response. This is not seen in neonates with LBW, due to the reduced energy reserve at birth (both liver glycogen and fat and less developed glycogenic pathway (Cowett and Schwartz, 1070).[10] Studies have shown that hypoglycaemia occurring in the first few days of life causes neuro developmental impairment (Lucas et al. 1987).[11-12]

There is still no research basis or consensus regarding the definition of neonatal hypoglycaemia or who is at risk and under what circumstances or when screening should be performed. It is the standard recommendation that babies weighing >1.8 Kg and above can be nursed alone by mother and do not need admission to NICU.[13]

So this study tried to evaluated the incidence of hypoglycaemia in late preterm appropriate for gestational age babies who were on breast feeding it also tried to evaluate the effect of counselling mothers to frequently breast feed their babies, first feeding started as early at first hour of life, how far the counselling has been effective in making mothers breast feed their babies. Babies who developed hypoglycaemia were initially treated with feeds and the protocol for management of neonatal hypoglycaemia was followed.

Aims and Objectives

1. To study the incidence of hypoglycaemia in late preterm babies who are on breastfeeds since birth.
2. To study the read of regular blood glucose monitoring in early diagnosis of hypoglycaemia in late preterm neonates.

Review of Literature

In the Jaiswal et al study "Early Neonatal morbidities in late preterm infants", the incidence of hypoglycaemia was 8.8% in late preterms and 1.4% in term neonates. The glucose was monitored at 12 hourly intervals and all the inborn and late preterms were included and followed up for 7 days for early morbidities.

In a study of Kalyani Srinivas et al "Study of mortality and morbidity pattern of late preterm babies" the inborn late preterms and term babies were assessed for early neonatal morbidities. The incidence of hypoglycaemia in late preterms was more (22%) when compared to present study (15.83%) where they included the babies who required admission in NICU.

Concern arose that hypoglycaemia without clinical associated signs (asymptomatic hypoglycaemia) might also lead to neurological sequelae. This led to an attempt to define hypoglycaemia statistically as blood glucose concentration more than two standard deviations below the man for populations of well full term and low birth weight infants (LBW). This and the introduction in the early 1970's or reagent strip glucose assays (e.g. Dextrostix) for cot side screening of new born at risk, led to clinical classifications of neonatal hypoglycaemia estimated the prevalence of hypoglycaemia (Defined as glucose <1.7 Mmol/L) as 4.4 per 1000 total newborn live births and 15.5 per 1000 low birth weight infants arrived at much higher estimates 11.4% of all nursery admissions and 20.3% of those premature or low birth weights who had blood sugar less than 1.7 Mmol/L, if screened before feeding at 6 hours of age.

Anderson et al (1993) observed that 38% of uncomplicated term infants born in Kathmandu. Nepal showed a blood glucose concentration of less than 2.6 Mmol/L during the first 60 Hours of life.

Incidence of hypoglycaemia other than LBW (preterm neonates and small for gestational age (SGA) neonates) occur in:

1. Perinatal asphyxia in which possible underlying mechanisms include high fuel requirement of anaerobic metabolism, the utilization of stores during the asphyxial episode, and a delay in the normal pattern of metabolic adaptation, so that hepatic fuel production is impaired.
2. Neonatal hyper-insulinism which occurs in infants of diabetic mothers, but hypoglycaemia is rarely of concern except in the infants of the poorly controlled diabetic mothers (London et al 1987. Other conditions resulting in hyperinsulinism are, the islet cell dysregulations syndrome (nesidioblastosis). Beckwith Wiedemann syndrome, and insulin secreting adenoma (Anysley and Soltesza 1987).
3. In born error of metabolism and congenital defects. These include glycogen storage diseases, congenital hypopituitarism, defects of amino acids metabolism (e.g. methyl malonic aciduria) defects of gluconeogenesis (e.g. fructose 1-6- diphosphate deficiency) and defects of ·-Oxidation of fatty acids.

Hypoglycaemia in Late Preterms

Presence of morbidities in late preterm infants can affect there feeding pattern and feeding strategies.[5] These infants present a number of feeding challenges including fewer and shorter awake periods and excessive sleepiness. They tire easily during feeding. They have a weak suck and poor muscle tone, and may exhibit an inability to sustain sucking, and fatiguing easily before finishing a feed. Their tone may be adequate at the start of a feeding session but rapidly decreases during the feeding indicating decreased endurance. There is a significant incidence of hypoglycaemia in preterm and low birth weight babies in spite of being on breast feeds.

Clinical Mechanism	Setting	Expected Duration
Decreased Sub State Availability	Intrauterine Growth Restriction	Transient
	Prematurity	Transient
	Glycogen Storage Disease	Prolonged
	Inborn Errors (e.g. Fructose Intolerance)	Prolonged
Increased Utilization	Perinatal Asphyxia	Transient
	Hypothermia	Transient
Hyperinsulinemia	Infant of Diabetic Mother	Transient
	Wiedemann Syndrome	Prolonged
	Erythroblastosis Foetal	Transient
	Exchange Transfusion	Transient
	Islet Cell Dysplasias	Transient
	Maternal-Agonist Tocolytics	Prolonged
	Improperly Placed Umbilical Artery Catheter	Transient
Other Endocrine Disorders	Hypopituitarism	Prolonged
	Hypothyroidism	Prolonged
	Adrenal Insufficiency	Prolonged
Miscellaneous / Multiple Mechanism	Sepsis	Transient
	Congenital Heart Disease	Transient
	CNS Abnormalities	Prolonged

Table 1. Causes of Neonatal Hypoglycaemia

Paediatric Endocrine Society (PES) and American Academy of Paediatrics (AAP) Neonatal Hypoglycaemia Guidelines in the First 48 Hours after birth and beyond.

Timeline	0-4 Hours	4-24 Hours	24-48 Hours	>48 Hours
AAP	AAP: Asymptomatic screened neonates in first 4 hours, maintain blood glucose >40 mg/dl prior to feeding. Between 4-24 hours maintain blood glucose >45 mg. / dl. If symptomatic – treat if blood glucose is <40 mg/ dl.			
PES	PES (First 48 Hours) Maintain blood glucose >50 mg./dl. Infants who are unable to maintain a blood glucose level >50 mgl.dl. In the first 48 hours of life may be at risk for a disorder causing			PES (After 48 Hours): A blood glucose >60 mg/dl. is recommended by the PES after 48 hours of life infants at risk of having a persistent hypoglycaemia syndrome are recommended by the PES to have a first challenge of 6-8 hours with maintenance of blood glucose >70 mg/dl.

Table 2

Signs and Symptoms

Asymptomatic: It is well known that low BGL may not manifest clinically and be totally asymptomatic.

Symptomatic: Clinical Signs of hypoglycaemia are variable and may include stupor, jitteriness, tremors, apathy, episodes of cyanosis, convulsions, intermittent apnoeic spells, or tachypnoea, weak and high-pitched cry, limpness and lethargy, difficulty in feeding and eye rolling. Episodes of sweating sudden pallor, hypothermia and cardiac arrest have also been reported.

Asymptomatic		
25-45 mg/dl.		**<25 mg/dl**.
Trial Oral Feeding		Follow Symptomatic Hypoglycaemia
Monitor Blood Sugar After 30 to 60 mins		
<45 mg/dl.	<45 mg/dl	
Follow Symptomatic Hypoglycaemia	Monitor Blood Glucose 6-8 hrly.	
	Stop after 48 Hours	

Table 3. Algorithm of Management of Neonatal Hypoglycaemia (Asymptomatic)

Symptomatic (Hypoglycaemia)	
Bolus of 2 ml/Kg 10% dextrose	
I/V Glucose infusion @ 6 mg/kg/min. Monitor 30-60 min. Interval till euglycaemic & then 6 hrly.	
Blood Sugar >45 mg/dl.	Blood Sugar <45 mg/dl.
Stable for 24 Hours on I/V Fluid	Increase Glucose infusion rate @2 mg/kg/min upto 12 mg/kg/min.
Weaning at 2 mg. /kg/min every 6 hrs. monitor 6 hrly. increase oral feed	Refer to Specialist Center
Stop I/V Fluid when rate is 4 mg/kg/min	

Table 4. Algorithm for Management of Neonatal Hypoglycaemia (Symptomatic)

Serum Insulin Levels
Serum Cortisol Levels
Growth Hormone Levels
Blood Ammonia
Blood Lactate Levels
Urine Ketones and reducing Substance
Urine and Sugar Aminoacidogram
Free Fatty Acid Levels.
Galactose 1 Phosphate Uridyl Transferase Levels

Table 5. Investigations to Be Done in Resistant Hypoglycaemia

Drugs that are used include the following:

1. Hydrocortisone 5 mg / kg / day IV or PO in two divided doses for 24 to 48 Hrs.
2. Diazoxide can be given orally 10-25 mg / kg / day in three divided doses. Diazoxide acts by keeping the KATP channels of the beta cells of the pancreas open, thereby reducing the secretion of insulin. It is therefore useful in states of unregulated insulin secretion like in insulinomas.
3. Glucagon 100 g / kg. Subcutaneous or intramuscular (max 300 g) - maximum of three doses. Glucagon acts by mobilizing hepatic glycogen stores, enhancing gluconeogenesis and promoting ketogenesis. These effects are not consistently seen in small for gestational age infants. Side effects of glucagon include vomiting, diarrhoea and hypokalaemia and at high does it may stimulate insulin release.
4. Octreotide (synthetic somatostatin in dose of 2-10 ·pg/kg/day subcutaneously two to three times a day. Do not use diazoxide and glucagon in small for gestational age infants.

Useful Formulae

(a) GIR (mg/kg/min) = $\frac{\text{\% of dextrose being infused x rate (mL/hr.)}}{\text{body weight (in kg) x 6}}$

(b) Infusion Rate (Mg/kg/min = $\frac{\text{IV rate (mL/kg/day) x\% of dextrose}}{144}$

(c) Infusion rate (Mg/kg/min) = Fluid rate (mL/kg/day) x 0.007 x% of dextrose infused

MATERIALS AND METHODS

Type of Study
Hospital Based Observational Study.

Duration of Study
August 2016 to July 2017.

Place
Labour Room, Postnatal Wards, Niloufer Hospital.

Proposed No. of Cases to Be Studied
120

No. of Cases Studied
120

Plasma Glucose levels were monitored for the last preterm neonates at 2, 6, 12, 24, 48 and 72 Hours of life along with the symptoms at the onset of hypoglycaemia using glucometer

Following criteria were used for assessing the neonates-

1. Hypoglycaemia was defined as Glucometer Blood Sugar reading of less than 40 mg / dl.
2. Late Preterm is defined as infants born at gestational age between 34 0/7 weeks and 36 6/7 weeks calculated from the first day of mothers last Menstrual Period(4, 5).

The study is done at Niloufer Hospital, a Tertiary level hospital neonatal unit (Labour Room, Premature Unit, Postnatal Ward). A total of 120 Consecutive late preterm babies' appropriate weight for gestational age were monitored for glucose levels for the study. The babies which were not fitting into the inclusion and exclusion criteria are not considered for the study.

Informed consent from the parents were taken before monitoring the blood glucose levels. The Mothers were counselled about the early and frequent breast feeding of the baby. When the Hypoglycaemia was noted, the level of

glucose was assessed and managed according to be standard AIMS NICU Protocol, 2014. The Hypoglycaemia was confirmed with the laboratory diagnosis.

A predesigned proforma prepared by the clinician was used to record information and the babies were assessed for occurrence of hypoglycaemia against the sex of the baby, weight of the baby, age of onset, parity and age of mother, mode of delivery, gestational age and symptomatology.

Procedure

Samples were collected by heel prick (Capillary Blood) the Glucose level was measured using Sugar Check active glucometer by touching the drop of blood collected to the curve at the edge of the strip. Blood will be drawn into the Strip automatically. Do not place the drop of the blood on the top of the strip. The test will appear within 7 seconds.

Neonates with asymptomatic hypoglycaemia with blood glucose levels between 20 and 40 g/dl were breast fed and glucose was monitored. They were advised for frequent feeds, Babies with symptomatic hypoglycaemia were given bolus of 2 ml/kg 10% dextrose and were transferred of Neonatal Intensive Care Unit (NICU) and managed according to the standard protocol.

Sample Size

Inclusion Criteria

1. All late preterm babies born during a period of 1 year in Niloufer Hospital, delivered by normal vaginal and caesarean section.
2. Breast Fed babies were taken up for this Study.

Exclusion Criteria

1. Birth asphyxia
2. Small for Gestational Age (SGA)
3. Large of Gestational Age (LGA).
4. Babies admitted in NICU
5. Multiple gestation babies.
6. Babies who were started on formula feeds
7. Parents who have not given consent
8. Babies discharged before 72 Hours.

Type of Study

Hospital based observational study.

Ethics

This study was approved by Institutional Ethics Committee at OMC.

Sample Size Estimation

This is an observational longitudinal study as the babies are followed up serially at timed intervals. Here are the formulas used in our Sample Size Calculator:

$$n = \frac{Z^2\ p\ g}{1^2}$$

Where: Z=Z value (e.g. 1.96 for 95% confidence level)

P = percentage picking a choice, expressed as decimal (5 used for sample size needed) q=1p.

l=confidence interval, expressed as decimal, 5% of p and not more than 20% of p (e.g. 04=±4)

Correction for Finite Population

$$new\ n = \frac{n}{1 + \frac{n-1}{pop}}$$

Where: pop = population

Consecutive late preterm babies were included in the study to fulfil the inclusion criteria to reach the requisite 120 samples size. Its calculated based on finite population correction for 300 and 95% confidence level at 5% precision.

Statistical Tools

The information collected regarding all the selected cases was noted in a predesigned proforma and entered in a Microsoft excel sheet. The Statistical analysis was done with the help of computer using SPSS 19.0 version software.

Using this software range, frequencies and percentages are calculated for qualitative variables. Chi Square and p values will also be calculated, p values less than 0.05 will denote the significant relationship.

RESULTS

A total of 120 Late Preterm babies were assessed. Of which, 61 were female and 59 were male babies. In our study, overall incidence of hypoglycaemia was 15.83%. Majority of the hypoglycaemia occurred on the first day (84.21%) and 2nd day (15.78%) with no episodes on third day of life (Table 4).Out of 19 hypoglycaemic babies, 8 (42.1%) were

symptomatic and 11 (57.89%) were asymptomatic in our study hypoglycaemia was slightly more in male babies (Table 3). Out of babies born to 82 multiparous mothers, hypoglycaemia occurred in 9 and out of babies born to 38 primiparous mothers 10 developed hypoglycaemia (Table 5). Considering the mode of delivery, out of 53 babies born by normal vaginal route, 8 had hypoglycaemia and in 67 caesarean born babies, 11 had hypoglycaemia (Table 6).

Out of 19 hypoglycaemia babies 8 (42.1%) belong to 34 weeks group 3 (15.8%) in 35 weeks and 8 (42.1%) belong to 36 weeks (Table 7) in the above gestational age group mentioned, the highest incidence of hypoglycaemia was observed in 34 weeks of age. The incidence of hypoglycaemia in babies born to Mother of <25 Years is 15.3% while babies of mothers >25 years is 16.7% (Table 8). Hypoglycaemia occurred more in babies weighing <2 Kg (52.9%) when compared to babies 2-2.5 Kg and >25 Kg babies (47.36%) (Table 9).

	Symptomatic 8 (42.1%)	**Asymptomatic 11 (57.89%)**	**Incidence (19=15. 83%)**	
Male (61)	4 (40%)	6 (60%	10 (52.6%)	p-Value>0.05
Females (59)	4 (44.4%)	5 (55.5%)	9 (47.4%)	

Table 6. Incidence of Hypoglycaemia

Onset of Hypoglycaemia	**No. of Hypoglycaemic Babies**
< 24 Hrs.	16 (64.2%)
24-48 Hrs.	3 (15.8%)
>48 Hrs.	0

Table 7. Age of Onset of Hypoglycaemia

Parity	**Without Hypoglycaemia**	**With Hypoglycaemia**	**p-Value <0.05**
Multipara (82)	73 (89.0%)	9 (11.0%)	
Primipara (38)	28 (73.7%)	10 (26.3%)	

Table 8. Incidence of Hypoglycaemia in Relation to Parity

Mode of Delivery	**Normal Glucose**	**With Hypoglycaemia[19]**	**p-Value >0.05**
Normal Vagina (53)	45 (84.9%)	8 (15.1%)	
Caesarean (67)	56 (83.6%)	11 (16.4%)	

Table 9. Incidence in Relation to Mode of Delivery

Gestational Age	**Cases without Hypoglycaemia**	**Cases with Hypoglycaemia**	**p-Value>0.05**
34 Weeks	19 (70.4%)	8 (29.6%)	
35 Weeks	21 (87.5%)	3 (12.5%)	
36 Weeks	61 (88.4%)	8 (11.6%)	

Table 10. Incidence of Hypoglycaemia in Relation to Gestational Age

Maternal Age Group	**Without Hypoglycaemia**	**Incidence of Hypoglycaemia**	**p-Value>0.05**
<25 Years (18-24 Years)	61 (84.7%)	11 (15.3%)	
>25 Years	40 (83.3%)	8 (16.7%)	

Table 11. Incidence of Hypoglycaemia in Relation to Maternal Age

Birth Weight	**Without Hypoglycaemia**	**Incidence of Hypoglycaemia**	**p-Value<0.05**
<2 Kg (17)	8 (47.1%)	9 (52.9%)	
2-2.5 Kg. (66)	59 (89.4%)	7 (10.6%)	
>2.5 Kg. (37)	34 (91.9%)	3 (8.1%)	

Table 12. Incidence in Relation to Birth Weight

Asymptomatic	11 (57.9%)	
Symptomatic	8 (42.1%)	
	Dull Activity	3
	No Suck (Poor Feeding)	2
	Apnoea	1

	Jitteriness	2
	Cyanosis	1
	Lethargy, Weak Cry	3
	Seizures	0

Table 13. Symptomatology of Hypoglycaemia

DISCUSSION

In our study the incidence of hypoglycaemia in late preterm newborns was 15.83% in a study by Jaiswal et al, incidence was 8.8% in late preterms when compared to 1.4% in term babies. They included late preterms and term babies to assess the early neonatal morbidity patterns. The blood sugars were monitored at 12 hourly intervals in all later preterm, IUGR (Intrauterine growth restriction) IDM (infant of diabetic mother) and LGA (large for gestation, birth weight >2SD) Infants.

In the study by Singh P et al "Screening for hypoglycaemia in exclusively breast-fed high-risk neonates" the high-risk babies risk babies kept in postnatal wards and who did not require admission to NICU were included. All the mothers who were willing to breast feed their babies were included in their study. Blood Glucose was monitored till 48 Hours of life. The incidence was more (27%) when compared to the present study. It could be because of their study included the high-risk babies late preterms, SGA, LGA and IDM Babies.[14]

In a study by Harris and Weston incidence was 51% in high risk neonates,[15] where all the high-risk babies (Small, large, infant of a diabetic, late preterm, and other) admitted to NICU were included. Higher incidence could be due to the presence of multiple risk factors.

The incidence of hypoglycaemia was 22% by Kalyani Srinivas et al[16] which was ore when compared to the present study in their study all the babies with gestational age between 34 0/7 to 36 6/7 weeks admitted in NIC were observed till discharge or death and were followed up till one month of age. Mothers with medical problems like epilepsy, diabetes, hypertensive disorder, heart disease, and Pregnancy associated complications like PIH, oligohydramnios, antepartum haemorrhage, premature rupture of membranes were included. Neonatal data included gestational age at birth, birth weight, mode of delivery, indication of elective birth, resuscitative measure at birth, Apgar Scores, cause of NICU admission, progress during hospitalization, duration of hospital, stay, mortality and its cause. Inclusion of all the high-risk babies could have resulted in higher incidence of hypoglycaemia.[17]

CONCLUSION

In the present study, hypoglycaemia was seen in babies on day 1 (84.2%) and day 2 of life with no occurrence during the later state. In a study by MA Bhat et al, the main objectives were to find the incidence and risk factors associated with development of hypoglycaemia in small-for-gestational-age (SGA) babies. This was a prospective longitudinal study. The sample included SGA babies and study was done over a period of six months. 127 consecutively born small for gestational age babies were investigated prospectively for the development of hypoglycaemia in first 48 Hours of life. The overall incidence of hypoglycaemia was 25.2% in SGA babies and 98% of the episodes occurred within first 24 hours and as inferred by Hawdon et al, almost all of the episodes of hypoglycaemia in SGA babies occurred within 24 hours. It is probably due to inclusion of only SGA babies.

DE Ak Et al., evaluated the role of early breast feeding on hypoglycaemia and also assessed the impact of exclusive breast feeding on glucose values up to 48 hours of age in healthy normal birth weight and low birth weight babies, including both preterm and small for gestational age babies. The incidence of hypoglycaemia was significantly more in neonates when breast feeding was delayed than early breast feeding (64% vs. 17% $p<0.011$). Maximum number of cases of hypoglycaemia were seen within the first 24 hours of age.

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