Incidence of Hypoglycemia in High Risk Neonates and Its Relationship with Gestational Age Birth Weight and Ponderal Index

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Abstract:
Background: *Hypoglycemia is one of the most frequently encountered metabolic problems in newborn infants. In general, the incidence varies from 1 to 5%. However, the incidence increases many fold in the presence of risk factors. The absence of overt symptoms at low glucose levels does not rule out central nervous system injury. In order to prevent brain damage, blood glucose should be routinely estimated in the following high risk situations. This present study was planned to study the incidence of hypoglycemia in neonates at high risk and its relationship with birth weight, gestational age and ponderal index; who were admitted in the Neonatal Intensive Care Unit of Regional Institute of Medical and Sciences (RIMS), Imphal.*
Materials and Methods: *This is a hospital based cross sectional study done in the Department of Neonatology, Regional Institute of Medical Sciences, Imphal over a period of 2 years between September 2015 to September 2017. Sample size was calculated to be 1066. The study included very low birth weight infants (<1500 grams), Preterm infants (<35 weeks), Small for gestational age infants (SGA) with birth weight <10th percentile, Infant of diabetic mother (insulin dependent/and gestational diabetes), Large for gestational age (LGA) infants with birth weight >90th percentile, Infants with Rh-hemolytic disease, Infants born to mothers receiving therapy with terbutaline/propranolol/oral hypoglycemic agents.*
Results: *In this present hospital based cross sectional study we found that the total incidence of hypoglycemia in neonates at risk is 16.5% and the incidence of hypoglycemia in babies with gestational age <37 weeks was 21% and with gestational age >37 weeks was 8%. The incidence of hypoglycemia in babies with birth weight <2.5kg was 23 % and with birth weight >2.5 kg was 9%. the incidence of hypoglycemia in babies who are SGA was 21 % and in babies who are AGA was 8%.*
Conclusion: *To conclude the incidence of hypoglycemia was found out to be more in gestational age <37 weeks than gestational age >37 weeks and incidence is more in birth weight <2.5 kg than birth weight > 2.5 kg and incidence is more in SGA babies than LGA babies.*
Keywords: *Hypoglycemia, birth weight, Gestational age, Ponderal Index, SGA babies, VLBW infants.*

I. Background

Hypoglycemia is one of the most frequently encountered metabolic problems in newborn infants. Blood glucose levels in the first hours of life are typically lower than the normal values of older children or adults. Hypoglycemia occurs in about 16% of large for date infants and 15% of small for date babies and is often symptomatic especially in male babies. About one fifth of babies born to mothers with gestational diabetes mellitus may show hypoglycemia.[1]

The incidence of hypoglycemia in preterm babies varies between 5% and 10% and is higher in babies with a birth weight of less than 50th percentile for their gestational age.The operational threshold for hypoglycemia is defined as "that concentration of plasma or whole blood glucose at which clinicians should consider intervention, based on the evidence currently available in literature. This threshold is currently believed to be a blood glucose value of less than 40 mg/dl (plasma less than 45 mg/dl) irrespective of period of gestation, if associated with symptoms of hypoglycemia or if confirmed on repeat analysis in asymptomatic babies is indicative of hypoglycemia. In general, the incidence varies from 1 to 5%.[2] However the incidence increases many fold in thepresence of risk factors. The absence of overt symptoms at low glucose levels does not rule out central nervous system injury.In order to prevent brain damage, blood glucose should be routinely estimated in the following high risk situations i) Small for date babies and smaller of the discordant twins ii) infants of

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diabetic mothers or those with birth weight of above 90th percentile for their period of gestation. iii) Preterm infants < 35 weeks of gestation. iv) Rhesus hemolytic disease of the newborn. v) Babies with prolonged hypoxia, hypothermia, septicemia, cardiac failure, midline syndromic defects and suspected metabolic disorders. vi) Infants on intravenous fluids (I.V) or total parentral nutrition. vii) Babies with symptoms suggestive of hypoglycemia.There is no pathognomic symptoms of hypoglycemia in newborn and there ispoor correlation between the levels of blood glucose and symptomatology. The various factors which result in poor correlation between the blood glucose concentration and symptoms include probable utilization of lactate and glycerol by the brain, reduced peripheral utilization of glucose rather than the total or red blood cell glucose contentand susceptibility of brain to hypoglycemic insult which may be altered by anoxia, hypothermia and intracranial injury.[3]Symptomatic hypoglycemia is associated with poor neurodevelopmental outcome on follow up among survivors.Within the first few hours of life normal asymptomatic baby may have a transient glucose level in the 30s that will either increase spontaneously or after feeding.[4] These babies have excellent prognosis, so a glucose level of <40 mg/dl at any time in any newborn requires a prompt follow up to document normal glucose values. If the value is not increased, an intervention is needed.On the basis of developmental, neuro-anatomic, metabolic and clinical studies, our goal is to maintain the blood glucose level of value above 45 mg/dl in the first day and more than 50 mg/dl thereafter. In RIMS hospital also, we have encountered a number of newborn babies with hypoglycemia.[5] However the exact data – incidence and its relationship with birth weight, gestational age are not well defined. So this present study was planned to study the incidence of hypoglycemia in neonates at high risk and its relationship with birth weight, gestational age and ponderal index; who were admitted in the Pediatric Ward of Regional Institute of Medical and Sciences (RIMS), Imphal.

II. Materials And Methods

This is a hospital based cross sectional study done in the Department of Neonatology, Regional Institute of Medical Sciences, Imphal over a period of 2 years between September 2015 to September 2017.Based on a study conducted by Burns CM et al[14] for mean prevalence of 7.5% for hypoglycemia in high risk neonates, a significance level of 0.05 and a relative error of 20%, sample size was calculated to be 1066. The study included very low birth weight infants (<1500 grams),Preterm infants (<35 weeks), Small for gestational age infants (SGA) with birth weight <10th percentile, Infant of diabetic mother (insulin dependent/and gestational diabetes), Large for gestational age (LGA) infants with birth weight >90th percentile, Infants with Rh-hemolytic disease, Infants born to mothers receiving therapy with terbutaline/propranolol/oral hypoglycemic agents, Neonates with perinatal asphyxia, polycythemia, sepsis, shock, respiratory distress, hypothermia, Infants with morphological growth retardation(birth weight between 10th-90th percentile with features of fetal under-nutrition in the form of skin peeling, loose skin folds and deficient buccal pad of fat), Infants on intravenous fluids and total parenteral nutrition. If the mother's last menstrual period was not known or was uncertain or if the clinical estimate of gestational age did not agree within two weeks of the calculated gestational age or if the birth weight of neonate born outside our hospital was not known or was uncertain or if neonates whose parents were not willing to give consent were not included in the study.After recording detailed neonatal and maternal history along with relevantexamination on the predesigned proforma, neonates were classified by birth weight and gestational age into 9 categories as follows: Preterm SGA, Preterm AGA, Preterm LGA, Term SGA, Term AGA, Term LGA,Post term SGA,Post term AGA, Post-term LGA and birth weight was measured by electronic weighing scale and length by infantometer. Ponderal index was calculated by Wt (in gms) / Length (cm)3, gestational age was calculated by LMP and modified Ballard score. Sampling was done using Glucometer (Accu–Check One touch) which uses bioamperometry as test principle(Glucose Dehydrogenase in the strip converts the glucose in the blood sample to gluconolactone. This reaction creates a harmless electrical current that the glucometer interprets for that blood glucose).Washed hands thoroughly before the procedure, pre-warmed the sole to ensure good perfusion before pricking, used a sterile lancet to prick the child and touched a drop of blood collected to the curve edge of the test strip. No part of yellow colour on the strip was visible after applying the initial drop of blood. Blood was drawn into the strip automatically. Blood drop wasn't placed on the top of the strip. Test result appeared within 30 sec. In all those neonates found to have hypoglycemia , whole blood sample was collected in a fluoride vial by aseptic technique and sent for laboratory examination by the glucose oxidase method and analyzed quickly to avoid erroneously low glucose levels. Screening was done at 2, 6, 12, 24, 48 and 72 hours of age, prior to feeding.Asymptomatic hypoglycemia on a feed trial was tested after one hour of feed. In infants with hypoglycemia on glucose infusion, blood glucose was checked at hourly intervals till euglycemia is achieved and then 6 hourly.Tests was repeated 6 hourly during weaning from infusion therapy. Screening was stopped if at the end of 72 hours, a high risk infant has not had hypoglycemia or an infant on total oral feeds has two consecutive values >50 mg/dl.Ethical approval was obtained from the institutional ethics committee, RIMS Imphal before the commencement of the study. Informed written consent was obtainedfrom the respondents or their parents or caretaker. A code number was assigned and no names were taken to maintain confidentiality. After checking the blood glucose level in

neonates at high risk those who were diagnosed as having hypoglycemia were treated as per guidelines. Data were collected as per proforma which includes maternal history likeGravida, Para, LMP, antenatal history, history of diabetes mellitus, maternal drug intake, obstetric history, medical history, perinatal history, duration of hypoglycemia, treatment history and neonate's particulars like birth weight, gestational age, mode of delivery, place of delivery, clinical symptoms. Screening for hypoglycemia was done at 2, 6, 12,24, 48 and 72 hours of age, prior to feeding. Blood sample was collected using Accucheck glucometer and in all those neonates found to have hypoglycemia, whole blood sample was collected in a fluoride vial by aseptic technique and sent for laboratory examination. Data collected was checked for completeness and consistency and it was compiled and analyzed using SPSS version 20.0. Total no of babies those who had hypoglycemia has been separated and totalincidence were calculated. Then they were categorized depending upon their birthweight as low birth weight (LBW <2.5kg) and normal birth weight (NBW >2.5kg), depending upon their gestational age as term (GA >37 weeks), preterm (GA <37 weeks) and post term (GA>42 weeks), depending upon their ponderal index as small for gestational age (SGA <10th percentile), appropriate for gestational age (AGA between 10th percentileand 90th percentile) and large for gestational age(LGA>90th percentile).Then the incidence of hypoglycemia was calculated among their risk groups and compared. To find out the significance in relationship between the incidence ofhypoglycemia and birthweight, gestational age and ponderal index, Chi-Square test has been used. P value of <0.05 was taken as significant.

III. Results
In this present hospital based cross sectional study we found that the total incidence of hypoglycemia in neonates at risk is 16.5%.

Hypoglycemia	Number of neonates
Present	175
Absent	891
Total	1066

Table 1: Incidence of hypoglycaemia

As depicted in table 1 we found that the total number of patients with hypoglycemia in high risk neonates are 175 and the total number of patients without hypoglycemia are 891.From this the total incidence was calculated was 16.5%.From table 2, we concluded that the incidence of hypoglycemia in babies withgestational age <37 weeks was 21% and incidence of hypoglycemia in babies withgestational age >37 weeks was 8%. The total number and percentage of babies withhypoglycemia among gestational age <37 weeks are 144 and 13.5% respectively andamong gestational age >37 weeks are 31 and 3% respectively. After formulating a two by two table to test the significance we applied Chi-square test and the P value was found out to be 0.035. So from this we concluded that there is a significant relationship exist between the gestational age and incidence of hypoglycemia.

Gestational Age	Hypoglycemia Present		Hypoglycemia Absent		Total	P value
	No.	%	No.	%	N=1066	
< 37 weeks	144	13.5	527	49.5	671	0.035
>37 weeks	31	3	362	34	395	

TABLE 2: Number and percentage of babies with and without hypoglycemia acc. to gestational age

From table 3, it is evident that the incidence of hypoglycemia in babies with birth weight <2.5kg was 23 % and incidence of hypoglycemia in babies with birth weight >2.5 kg was 9%. The total number and percentage of babies with hypoglycemia among birth weight <2.5kg are 128 and 12% respectively and among birth weight >2.5kg are 48 and 4.5 respectively. After formulating a two by two table to test the significance we applied Chi-square test and the P value was found out to be 0.04. So from this weconcluded that there is a significant relationship exist between the birth weight andincidence of hypoglycemia

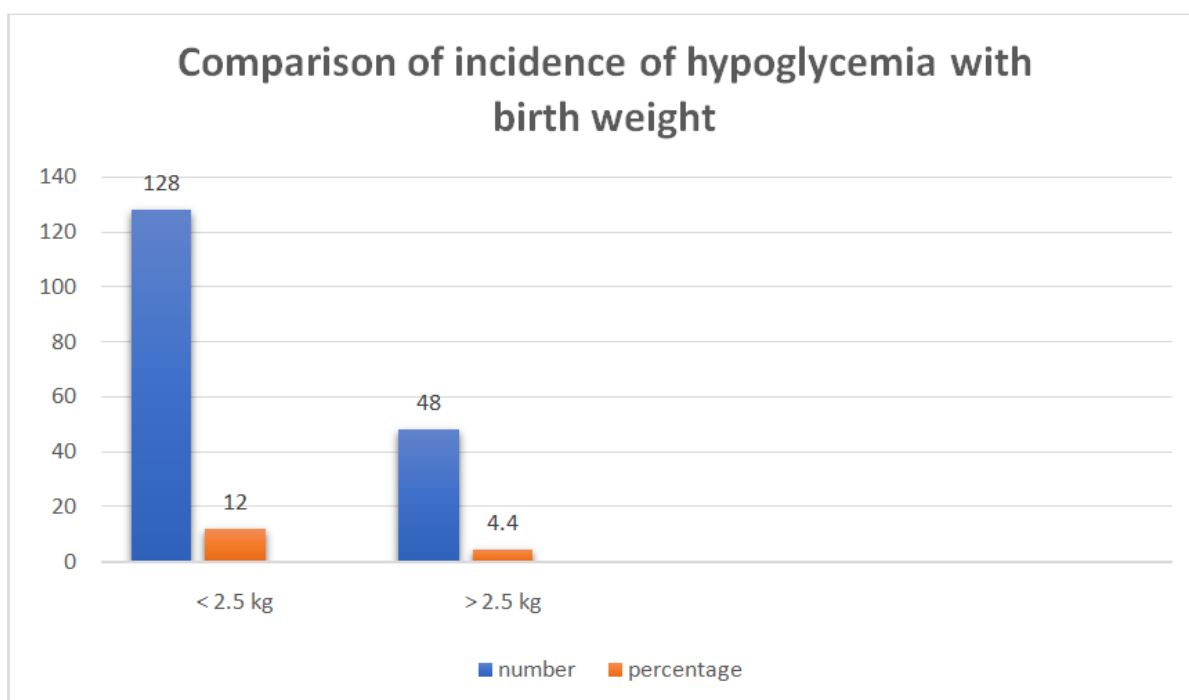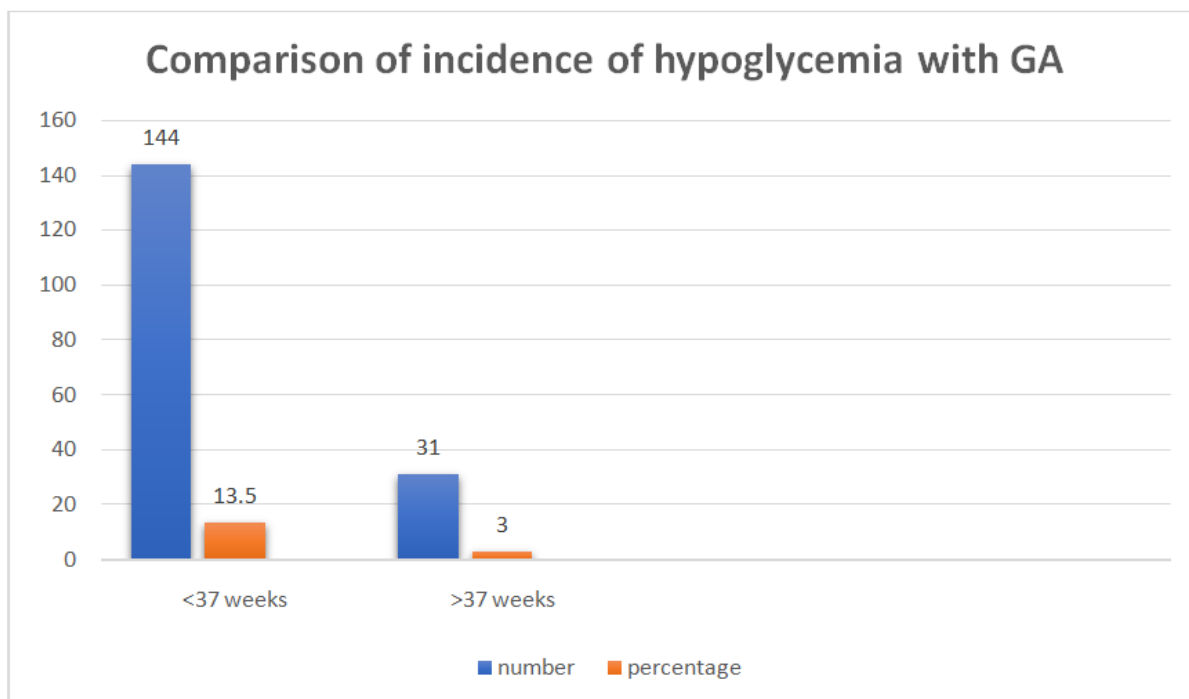| Birth weight	Hypoglycemia Present		Hypoglycemia Absent		Total	P value
	No.	%	No.	%	N= 1066	
<2.5 kg	128	12	410	38.5	538	0.04
>2.5 kg	48	4.5	480	45	528	

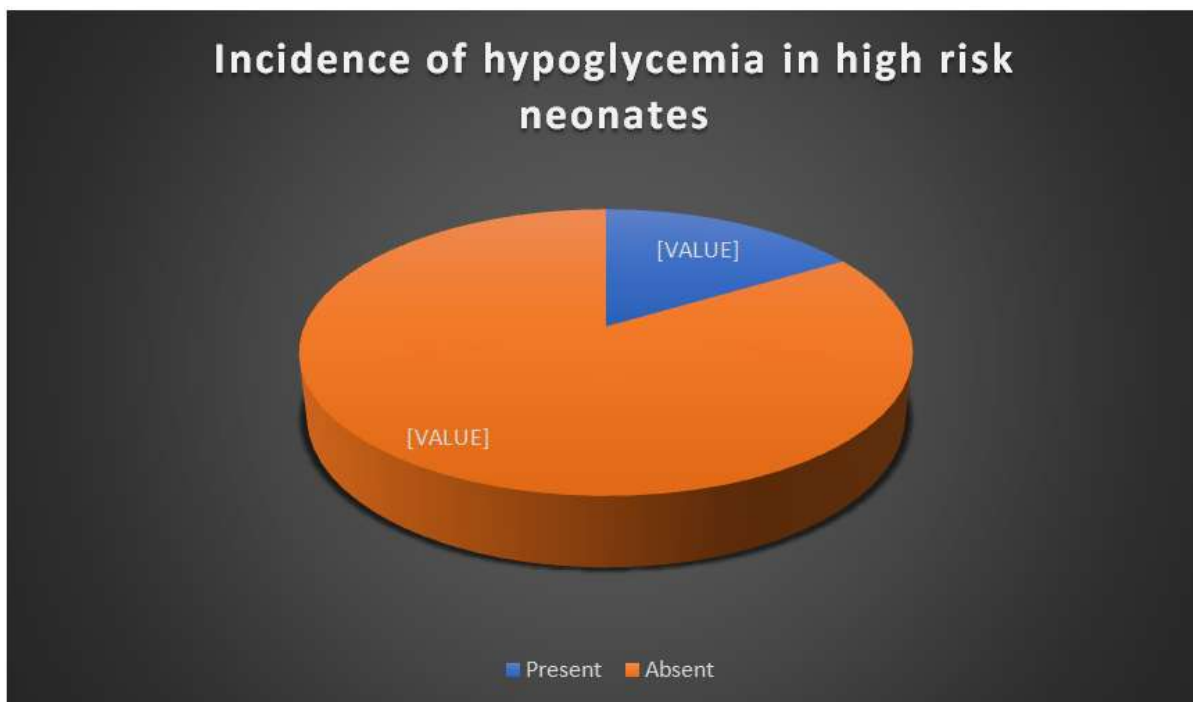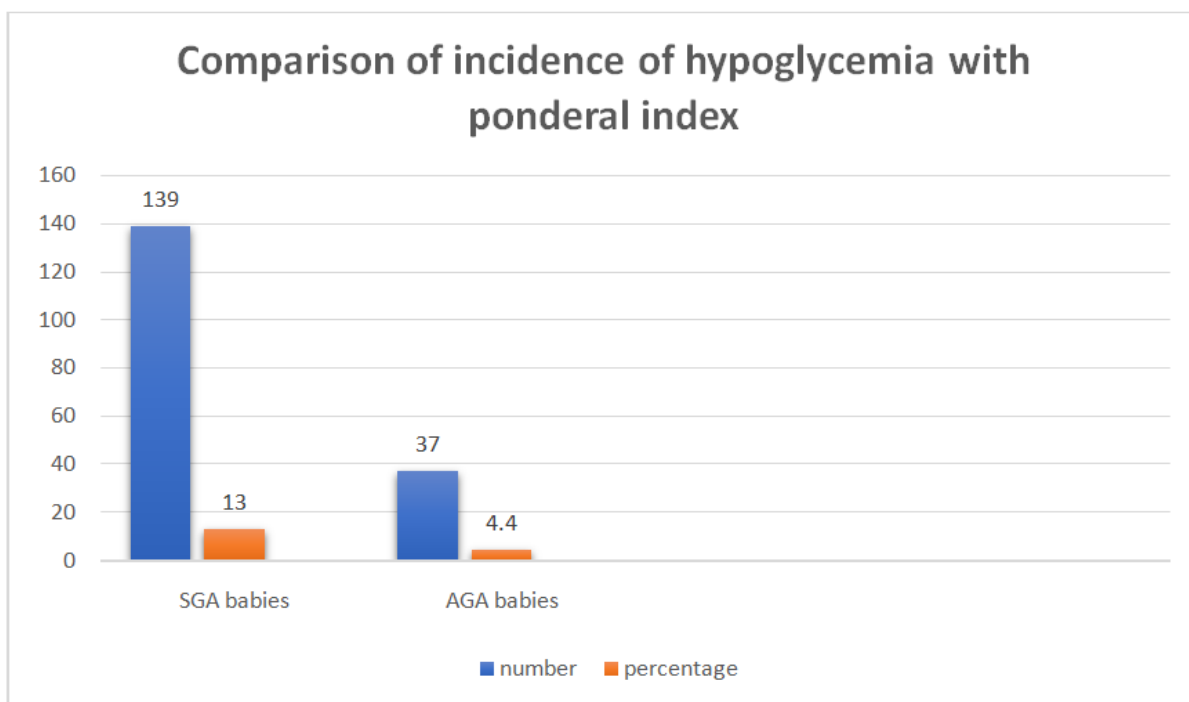**Table 3:** Number of babies with/without hypoglycemia acc. to birth weight

From table 4, we calculated the incidence of hypoglycemia in babies who areSGA was 21 % and incidence of hypoglycemia in babies who are AGA was 8%. Thetotal number and percentage of babies with hypoglycemia among SGA babies 139 are13% respectively and among AGA babies are 37 and 3.5%

respectively. Total number and percentage of babies without hypiglycemia among ponderal index between10-90th percentile are 384 and 36 respectively. Afterformulating a two by two table to test the significance we applied Chi-square test andthe P value was found out to be 0.04. So from this we concluded that there is a significantrelationship exist between the ponderal index and incidence of hypoglycemia.

Ponderal index	Hypoglycemia present		Hypoglycemia absent		Total	P value
	No.	%	No.	%	N=1066	
SGA(<10th percentile)	139	13	506	47.5	645	0.04
AGA(10th – 90th percentile)	37	3.5	384	36	421	

Table 4: Number and percentage of babies with/without hypoglycemia acc. to ponderal index

Comparison of incidence of hypoglycemia with GA

Comparison of incidence of hypoglycemia with birth weight

IV. Discussion

In our present study, the incidence of hypoglycemia at risk neonates were found out to be 16.5%. There were number of studies conducted worldwide regarding incidence of hypoglycemia at high risk neonates.In a hospital based prospective study in a maternity centre in south India in 2005 conducted by CK Sasidharan et al[13], incidence of neonatal hypoglycemia was 41/1000 live births. Eight variables strongly and independently predicted the risk of neonatal hypoglycemia, at least one being present in 89.1% of the hypoglycemic neonates. They included prematurity, low birthweight, maternal diabetes mellitus, delay in initiation of breastfeeding for more than 2h in postnatal period, maternal pre-eclampsia and eclampsia, birth asphyxia, cold stress or hypothermia, and maternal oligo-hydramnios. In our study some of the variables which strongly predicted the incidence of hypoglycemia are gestational age, birth weight, ponderal index with the other factors such as birth

asphyxia, sepsis, hyperbilirubinemia also helps to predict the occurrence of hypoglycemia. Similarly, in our study we found out that the incidence of hypoglycemia in babies with birth weight <2.5kg was 23 % and incidence of hypoglycemia in babies with birth weight >2.5 kg was 9%.In 1970 Kenneth G. Phillips et al[8] from Toronto conducted a study in incidence of hypoglycemia in the low-birth-weight neonates. Of 179 consecutively born single infants whose birth weights were below the twenty-fifth percentile for gestational age,four were hypoglycemic in the first 18 hours of age. Similarly, our study established the significant relationship between the birth weight and incidence of hypoglycemia and in 2015 Indira et al44 studied hypoglycemia amongst neonates admitted in NICU in a tertiary care centre, which is a hospital based prospective study in which 300 new born babies were included and found out percentage of hypoglycemia among the birth weight<2500gm was 9.1% when compared to >2500gms which was 2.2%. There was statistical significant association between hypoglycemia and birth weight of the baby (p = 0.01). In our study we found the incidence of hypoglycemia in babies with gestational age <37 weeks was 21% and incidence of hypoglycemia in babies with gestational age >37 weeks was 8% and the incidence of hypoglycemia in babies who are SGA was 21 % and incidence of hypoglycemia in babies who are AGA was 8% and in 1971 Lula O. Lubchenco et al[11] studied 374 infants from nine birth weight-gestational age groups before the first feeding at 3 to 6 hours after birth. The highest incidence of hypoglycemia, 67% (serum glucose level < 30 mg/100 ml), occurred in the preterm SGA group. It was25% in the term SGA infants and 18% in post-term SGA babies. Out of 1066 babies in our study the incidence of hypoglycemia in babies with gestational age <37 weeks is 21% and with gestational age >37 weeks is 8% and the increased incidence of hypoglycemia in preterm infants can be due to immaturity as there is a direct correlation between blood glucose levels and gestational maturity and birth weight of the baby because the low hepatic glycogen stores and relatively high incidence of hypoxia, hypothermia and respiratory distress syndrome in these babies contributes to hypoglycemia. In 1993 Holtrop PC et al[10] studied the frequency of hypoglycemia in full-term large and small for gestational age newborns and found the frequency of hypoglycemia in LGA infants was 8.1% and in SGA infants, 14.7% respectively. Bhat M et al[12] also studied hypoglycemia in small for gestational age babies to find the incidence and risk factors associated with development of hypoglycemia in small for gestational age (SGA) babies in a prospective longitudinal study and found out the overall incidence ofhypoglycemia was 25.2% in SGA babies and concluded small for gestational age babies are highly prone to develop hypoglycemia. In our present study, the incidence of hypoglycemia in SGA (0-10th percentile) babies is 21% and in AGA(10th – 90th percentile) babies is 8% and the increased incidence in SGA babies can be attributable to the decreased hepatic glycogen stores, discrepancy in the size of the utilizer(brain) and provider (liver glycogen) of glucose, impaired gluconeogenesis and hyperinsulinism in small for gestational babies leading to hypoglycemia.[12]

V. Conclusion

The total incidence of hypoglycemia in neonates at risk was found out to be 16.5%. And similarly the incidence of hypoglycemia in babies with gestational age <37 weeks was 21% and incidence of hypoglycemia in babies with gestational age >37 weeks was 8% and the incidence of hypoglycemia in babies with birth weight <2.5kg was 23 % and incidence of hypoglycemia in babies with birth weight >2.5 kg was 9% and the incidence of hypoglycemia in babies who are SGA was 21 % and incidence of hypoglycemia inbabies who are AGA was 8%. In summary the incidence of hypoglycemia was found out to be more in gestational age <37 weeks than gestational age >37 weeks and incidence is more in birth weight <2.5 kg than birth weight > 2.5 kg and incidence is more in SGA babies than LGA babies.

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