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Original Article

Neonatal Outcomes of Large-for-Gestational Age Infants with or without Gestational Diabetes Mellitus

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Abstract

Background: Infants are considered Large for Gestational Age (LGA)if their birth weight is greater than the 90th percentile for gestational age. Birth weight is influenced by a number of factors with maternal diabetes being one of the most common risk factor affecting birth weight. They have an increased risk for adverse perinatal outcomes. The aim of the present study was to compare the neonatal outcomes of LGA infants delivered by women with and without gestational diabetes mellitus. **Methods:** This is a prospective study of all live-born LGA infants of 37 weeks of gestation with a birth weight of 4000g admitted at Neonatal ward of Chattagram Maa Shishu-O-General Hospital (CMSOGH) between 1st August 2013 to 31st July 2014. Type of sampling was purposive convenient sampling. A total of 51 neonatal patients were included. Data was collected in case record form. Data collected for the mothers included age, parity, gestational age and mode of delivery. Data for the infants include sex, birth weight, birth length and laboratory test. Outcomes were compared between infants of diabetic mothers (Group A) and infants of non- diabetic mothers (Group B). Then data was analyzed by SPSS 17.0 program and presented by tabular method, diagram and chart. **Results:** Among fifty one study subjects, thirty were Infants of Diabetic Mothers (IDMs) while twenty one were non-IDMs. 19 (63.3%) of the IDMs were male while 11 (36.7%) were female. Among the 21 non-IDMs 10 (47.6%) were male and 11 (52.4%) were female. Male to female ratio was 1.4:1. 5 (16.7%) of the IDMs were delivered vaginally while 25 (83.3%) were delivered by Caesarian Section (CS) where as 8 (38.1%) of the non-IDMs were delivered vaginally while 13 (61.9%) were delivered by CS. Respiratory distress was the most common morbidity affecting 70% of the IDMs and 66.7% of the non-IDMs. TTN accounted for the majority of the respiratory distress cases, occurring in 17 of the IDMs and 12 of the non-IDMs. Regarding analysis of other clinical features, convulsion (63.3%) was present more in IDMs than in non-IDMs (52.4%) cyanosis was found more in IDMs (60%) than non-IDMs (38.1%). Hypoglycemia was found more in IDMs than in non-IDMs. Mean glucose values were 41.06±19.91mg/dl for IDMs and 53.06±28.96mg/dl for the non-IDMs (p=0.001). Hyperbilirubinemia was more frequently observed in IDMs than in non-IDMs. About 17 (56.6%) of the IDMs and 7(33.3%) of the non-IDMs developed jaundice during the period of hospital stay. Polycythemia was not observed in both the groups but PCV was higher in IDMs (53.96±6.36) compared to non-IDMs (50.50±8.76). Hypocalcemia was not peculiar to a specific group. Five of the IDMs had congenital anomaly, of which three of them had cardiac anomaly. One of the non-IDM was suffering from ventricular septal defect. Birth asphyxia was observed more in non-IDMs (71.4%) than in IDMs (53.3%).One of the IDMs and two of the non-IDMs sustained a brachial plexus injury following vaginal delivery.

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On an average, IDMs had a longer duration of hospital stay. Outcome was more fatal in IDMs. About six (20%) of IDMs died compared to two (9.5%) of the non-IDMs. That was found statistically significant (p=<0.05). **Conclusion:** LGA babies with diabetic mother had more adverse outcome in terms of mortality and blood glucose level. More concentration is needed to control blood glucose of mother during pregnancy. Also extra care for the babies is needed to avoid fatal neonatal outcomes.

Key words: Large for gestational age; Hypoglycemia; IDM.

INTRODUCTION

Infants are considered Large for Gestational Age (LGA) if their birth weight is greater than the 90th percentile. Birth weight is influenced by several extrinsic factors, with maternal diabetes being one of the the most common risk factors. Maternal height and Body Mass Index (BMI) as well as weight gain during pregnancy are positively associated with infant size at birth[1]. In a study by Yang et al 45.2% of IDMs were found to be Large for Gestational Age (LGA) compared to only 12.6% of non-IDMs[2]. Macrosomia in IDMs is caused by a combination of hyperinsulinemia and hyperglycemia that results in a striking increase in fat stores and a 12% increase in protein stores during the third trimester of pregnancy[3].

Excessive fetal growth can occur because of genetic factors or increased supply of nutrients. LGA infants can result from being born to obese mothers (Constitutional) and from gestations longer than 42 weeks (Post maturity). Infants of mothers with pre gestational diabetes mellitus or gestational diabetes are exposed to high blood sugar during fetal development, or they may develop high circulating insulin levels and may therefore grow excessively. Women with gestational diabetes with impaired glucose tolerance during late pregnancy may remain undiagnosed and may deliver a macrosomic infant with greater perinatal complications[4].

Infants with Beckwith-Wiedemann syndrome and other genetic disorders that result in early excessive fetal growth, as well as infants with erythroblastosisfetalis, may exhibit as LGA with or without hyperinsulinism enhance growth in infants of diabetic mothers[5].

IDMs are at an increased risk for adverse neonatal outcomes such as hypoglycemia, hyperbilirubinemia, respiratory distress, polycythemia and congenital anomalies among other outcomes[6,7]. LGA complicates these outcomes further as it is associated with increased rates of CS, birth asphyxia and birth injuries such as shoulder dystocia, brachial plexus injury and clavicular fracture[8,9].

Macrosomia is also a risk for developing hypoglycemia in the perinatal period[10]. Hypoglycemia in IDMs is caused by the sudden interruption of glucose delivery from the mother to the neonate without a proportional decrease in insulin. Hypoglycemia is a common neonatal complication that occurs in LGA infants and it has been recognized as a cause of serious long-term neurological morbidity. After the section of the umbilical cord, the deprivation of maternal glucose supply can lead to this condition that generally happens in the first hours of life. It can be asymptomatic or may be accompanied by lethargy, agitation or even convulsion[11,12]. As LGA newborns have an increased risk of hypoglycemia even when they are not the products of diabetic pregnancies, the screening of LGA babies for hypoglycemia is recommended.

Also after the section of umbilical cord, the deprivation of maternal nutrient flow, can lead to hypocalcemia which also generally happens in the first hours of life. It can cause neuromuscular excitability, irritability, apnea and convulsion[11,13,14]. Chronic hyperinsulinemia can lead to an increased erythropoiesis and also to an accelerated hemolysis due to glycation processes, modified hepatic conjugation and modification of the entero-hepatic circulation, that are frequently found in Infants of Diabetic Mothers (IDMs), can lead to hyperbilirubinemia. Hyperbilirubinemia in IDMs is also due to their elevated cell mass. Macrosomic IDMs are prone to bruising during birth and the subcutaneous reabsorption of blood in these patients contributes to the high levels of bilirubin[15].

Chronic fetal hyperinsulinemia results in an elevated metabolic rate, leading to increased oxygen consumption and fetal hypoxemia. One of the effects of fetal hypoxemia is increased synthesis of erythropoietin which can result in polycythemia[10,15]. It is diagnosed by a venous hematocrit >65%. This occurs in about 30% of newborns of diabetic mothers[16].

The excess of insulin in the fetal circulation can delay pulmonary maturation associated with low production of surfactant leading to the respiratory distress syndrome. This condition is about six fold more frequently found in IDMs than in non-IDMs[17]. Delivery by CS is associated with respiratory distress in term infants as a result of the retained lung field (Transient Tachypnea of the Newborn)[18]. Since the incidence of CS is higher in IDMs than in non-IDMs, IDMs will experience respiratory distress more commonly.

In view of high morbidity and mortality associated with LGA IDMs, the aim of this study was to compare neonatal outcomes of LGA infants born to mothers with or without diabetes.

MATERIALS AND METHODS

The study was designed as a descriptive type of study conducted in the Neonatal ward of Chattagram Maa Shishu-O-General Hospital, Chittagong from 1st August 2013 to 31st July 2014.

To compare the neonatal outcomes of LGA infants of diabetic and non-diabetic mothers and to assess and compare the complication of LGA infants of diabetic and non-diabetic mothers.

Neonates admitted in the Neonatal ward of Chattagram Maa Shishu-O-General Hospital (CMSOGH) during study period. A total 51 neonatal patients were included after fulfilling the inclusion-exclusion criteria.

Inclusion criteria

- LGA infants of 37 weeks of gestation born at Chattagram Maa Shishu-O-General Hospital.

Exclusion criteria

- Infants of mothers with preexisting diabetes, pregnancy-induced hypertension and preeclampsia, and other systemic illness during gestation were excluded.
- Premature infants with a gestational age of less than 37 weeks,
- Infants with congenital malformations, infants with known metabolic disorders, and those delivered from multiple pregnancies were also excluded.

Infants whose birth weight was above the 90th percentile were defined as LGA . All LGA infants were routinely evaluated for hypoglycemia by heel-stick at the first and fourth hour. Also these infants are evaluated for polycythemia by venous blood sampling at the fourth hour of life according to our institutional protocol. A further blood glucose measurement was done if an infant was symptomatic. Blood glucose measurements were done by a glucometer (GlucoDr®) routinely. Serum glucose level was checked by a hexokinase method using commercially available kits (Abbott, USA). Primary neonatal outcomes included hypoglycemia, polycythemia and hospital admissions due to hyperbilirubinemia, respiratory distress or other causes during the first week of life. Postnatal weight loss during the first 72 hours of life and need of supplementary feeding are also evaluated. Hypoglycemia was defined as blood glucose <40 mg/dL (2.2 mmol/L)[13]. Peripheral venous hemotocrit value ≥ 65% was defined for polycythemia. The Chi-square test is used to compare nominal variables between the two groups and Student's t test is used to determine numeric variables. Values are expressed as mean ± standard deviation. This study was approved by the institutional ethics committee of Chattagram Maa Shishu-O-General Hospital. To conduct the study written approval from Pediatrics department was taken with due procedure of Institute of Child Health of CMSOGH, including ethical clearance.Informed verbal consent was taken from the local guardian of the patient.

The collected data were analyzed by SPSS method version 17. Means and standard deviation was measured and proportion was expressed in percentage. Anova t-test and other test of significance were done where applicable to compose data. p-value <0.05 was considered significant.

RESULTS

Among 51 LGA infants, male 29(56.9%) predominates female infants 22(43.1%).Among 30 IDM babies, 19 (63.3%) were male and 11 (36.7%) were female. Out of 21 non-IDM babies, female patients were predominant 11(52.4%) than male patient 10(47.6%). Male to female ratio was 1.4:1.

Table 1: Sex distribution.

		Group		Total	p value
		Group A (n=30)	Group B (n=21)	(n=51)	
Sex	Male	19(63.3%)	10(47.6%)	29(56.9%)	0.265
	Female	11(36.7%)	11(52.4%)	22(43.1%)	
Total		30(100%)	21(100%)		

Table 2 : Mode of delivery.

	Group		Total	P Value
	Group A (n=30)	Group B (n=21)		
Mode of NVD	5(16.7%)	8(38.1%)	13(25.5%)	
delivery CS	25(83.3%)	13(61.9%)	38(74.5%)	0.084
Total	30(100%)	21(100%)		

Table 2 shows the mode of deliveryin the study population (n=51). Of the 51 LGA infants, 38 (74.5%) were delivered by Cesarean Section (CS) whereas 13 (25.5%) were delivered by Normal Vaginal Delivery (NVD). Among the 30 IDMs, 25 (83.3%) of were delivered by CS and 5 (16.7%) were delivered vaginally. 13 (61.9%) of 21 non-IDMs were delivered by CS and 8 (38.1%) were by Normal Vaginal Delivery (NVD).

Table 3 : Anthropometric measurement.

	Group A (n=30)	Group B (n=21)	Mean ± SD
Birth weight (In gram)	4551.05 ± 468.4	4332.96 ± 468.41	4442.005 ± 468.41
Birth Length (In cm)	49.82 ± 1.36	50.06 ± 1.51	50.65 ±. 02596
Body mass index (kg/m^2)	18.40 ± 1.78	17.31 ± 1.57	17.855 ± 1.675

Table 3 shows the anthropometric measurement of both the groups. The IDMs have significantly higher birth weight (4551.05 ± 468.4) and BMI (18.40 ± 1.78) than non-IDMs (4332.96 ± 468.41) and (17.31 ± 1.57) respectively.

Table 4 : Clinical features.

Clinical features	Group		Total	p Value
	Group A (n=30)	Group B (n=21)		
Delayed cry	16(53.3%)	15(71.4%)	31(62.35%)	0.193
Respiratory distress	21(70.0%)	14(66.7%)	35(68.6%)	0.801
Convulsion	19(63.3%)	11(52.4%)	30(58.8%)	0.434
Cyanosis	18(60.0%)	8(38.1%)	26(51.0%)	0.124
Lethargy	6(20.6%)	18(60.0)	24(47.1)	0.027
Hyperbilirubinemia	17(56.6%)	7(33.3%)	23(45.09%)	0.691
Congenital anomaly	5(16.7%)	1(4.8%)	6(10.75%)	0.194
Birth Injury	1(3.3%)	2(9.5%)	3(6.4%)	1.000

The table 4 shows the various clinical features of the study subjects. Many of the patients have more than one symptoms. Respiratory distress (70%) Convulsion (63.3%) Cyanosis (60%) Hyperbilirubinemia (56.6%) Congenital anomaly (16.7%) were more prevalent in Group A than in Group B. Percentage of Delayed cry (71.4%) Lethargy (60%) and Birth injury (9.5%) were higher in Group B.

Table 5 : Hematological and biochemical measures.

Group	CBG (mg/dl) Mean ± SD	RBS (mg/dl) Mean ± SD	Hb (g/dl) Mean ± SD	PCV Mean ± SD	S. calcium (mg/dl) Mean ± SD
Group A (n=30)	37.54±8.80	41.06 ±19.91	17.66±2.70	53.96 ±6.36	8.57±.0.53
Group B (n=21)	67.42±55.45	53.06 ±28.96	16.16±2.95	50.50±8.76	8.92±0.92
Total	49.84±38.67	48.09±26.10	17.06±2.88	52.53±7.56	8.71±0.73
p value	0.001	0.001	0.098	0.034	0.032

p value was calculated by unpaired t test.

The above table shows the hematological and biochemical measures of both the groups. The mean ±SD of CBG and RBS of IDM patients were 37.54±8.80mg/dl and 41.06 ±19.91mg/dl respectively which was lower than non-IDMs. This was statistically significant (p=0.001). Mean ±SD of PCV for IDMs were 53.96 ±6.36 and for non-IDMs were 50.50±8.76. But the mean difference between the two groups were not significant. Mean ±SD of Serum calcium level for IDMs were 8.57±.0.53mg/dl and for non-IDMs were 8.92±0.92mg/dl.

Table 6 : Outcome.

	Group			
	Group A (n=30)	Group B (n=21)	Total	p-value
Death	6 (20%)	2 (9.5%)	8 (15.7%)	0.0311
Alive	24 (80%)	19 (90.5%)	43 (84.3%)	

The table above shows the outcome within both the groups. The outcome was fatal in Group A with 6(20%) death than in Group B with 2(9.5%) death. This was statistically significant (p=0.0311).

DISCUSSION

Despite the advances in glycemic control for pregnant diabetic women, infants of diabetic mothers continue to have macrosomia at rates higher than normal[19]. Even in the absence of diabetes during pregnancy, macrosomia on its own is an independent risk factor for adverse neonatal outcomes[20,21].

Hypoglycemia continues to be a challenge in the management of macrosomia. In our study, hypoglycemia was one of the common morbidities occurring more in IDMs than in non-IDMs. This is consistent with the study by Esakoff et al, that showed the incidence of hypoglycemia in LGA infants to be higher in IDMs than in non-IDMs[21]. In our study, mean SD of Capillary Blood Glucose (CBG) and Random Blood Glucose (RBS) were 37.54±8.80mg/dl and 41.06±19.91mg/dl respectively in Group A whereas CBG and RBS in Group B were 67.42±55.45mg/dl and 53.06±28.96mg/dl respectively. A study done by Landon et al found similar findings which was consistent with the findings in the present study[22]. Maternal diabetes had an influence on neonatal blood glucose. In an IDM, hypoglycemia occurs shortly after birth and is as a result of the sudden interruption of glucose delivery from the mother to an already hyperinsulinemic neonate, without a propotional decrease in insulin.

Respiratory distress was the most common morbidity in our study and was mostly attributed to TTN. TTN is the most common cause of neonatal respiratory distress accounting for more than 40% of cases[23]. It is caused by a delay in the reabsorption of fetal lung fiuid and is more common in infants delivered by CS[24]. The incidence of respiratory distress was higher in IDMs (70%) than in non-IDMs (66.7%) although the difference between the two groups was not statistically significant.

Hyperbilirubinemia, another common morbidity in this study, was more common in IDMs than in non-IDMs. Hyperbilirubinemia in IDMs is attributed to the high red blood cell mass.A study by Peevy et al showed that macrosomic IDMs had significantly higher serum bilirubin concentrations than appropriate for gestational age IDMs[25].

Polycythemia is another morbidity in IDMs and affects between 7-20% of IDMs compared to only 3-5% of non-IDMs[26-28]. In this study PCV was found more in Group A although the difference between the two groups were not statistically significant.

Maternal diabetes is a predisposing factor for early neonatal hypocalcemia and occurs in upto 50% of IDMs[29]. In our study, however, the incidence of hypocalcemia was very low and was not peculiar to IDMs.

The present study also demonstrated that the average weight of macrosomic IDMs was higher than that of non-IDMs, resulting in higher rates of delivery by CS. In this study, the Group A have significantly higher birth weight (4551.05±468.4) and Body Mass Index (18.40±1.78) than Group B (4332.96±468.41) and (17.31±1.57) respectively. A similar study done in Turkey also reported the same findings . Delivery by CS was more common in Group A (83.3%) than Group B (61.9%). According to Ozumba et al the overall cesarean section rate was high (36%) among diabetics with previous cesarean section and cephalopelvic disproportion being the commonest indications[30]. There is also increased risk of macrosomia in male infants as compared to female ones. Similarly, in our study, there were significantly more macrosomic male infants.

The incidence of major congenital anomalies is 2-5 times higher in IDMs than in non-IDMs, with cardiac malformations accounting for a majority o these anomalies[31,32]. In our study, 5 (16.7%) of Group A were suffering from congenital anomaly with three of them having congenital heart disease compared to Group B 1 (4.8%) was born with ventricular septal defect.

Regarding outcome of the study patients, the mortality rate was higher in Group A 6 (20%) than in Group B 2 (9.5%). That was found statistically significant ($p<0.05$). Perinatal asphyxia and cardiac anomalies were the common cause of death in the present study. The neonatal mortality rate is over five times than that of infants of non diabetic mothers and is higher at all gestational ages and birth weight for Gestational Age (GA) categories. IDMs also have longer duration of hospital stay.

CONCLUSION

The study shows high incidence of morbidities like respiratory distress, hypoglycemia, hyperbilirubinemia and higher mortality rate in IDMs compared to non-IDMs. Screening of all pregnant women for diabetes, good glycemic control and active management of their children will reduce perinatal morbidity and mortality.

DISCLOSURE

All the authors declared no competing interest.

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