Original Paper

Large for Gestational Age Babies Born To Diabetic and Non-Diabetic Mothers

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Abstract

Introduction: Foetal growth and development is a complex process that involves the interrelationship among the mother, placenta and fetus. Both high and low birth weight infants are associated with the highest prevalence of diabetes. Women with diabetes are at greater risks, because of their pregnancy related complications.

Objective: To compare the characteristics of groups of LGA (large for gestational age) babies born to pre-diabetic mothers (DM) and gestational diabetic mothers (GDM) with control infants born to apparently healthy non-diabetic mothers (NDM).

Materials and Methods: This was a prospective cohort study of 251 newborn-mother pairs (n: DM=86; GDM=86 and NDM=79) recruited from the Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Dhaka. Detailed anthropometric measurements of infants were taken at birth in the hospital. LGA babies had birth weights greater than the 90th percentile for their gestational age for sex and SGA (small for gestational age) babies usually had birth weights below the 10th percentile for babies of the same gestational age for sex.

Results: Only 10(11.6%) babies were found LGA in the GDM group as opposed to 3 each for DM and NDM group. There was a significant group difference in the incidences of SGA babies. Around 16% to 18% were there in the DM and GDM groups, as opposed to much higher rate (30.4%) in the NDM group.

Conclusion: Newborns from both DM and GDM groups showed greater values compared to that of the NDM group in all anthropometric measures except length and head circumference suggesting intrauterine growth acceleration in them.

Key-words: Diabetic mother, LGA, SGA babies.

Introduction

Any deviation from the normal growth, be it intrauterine growth retardation or excessive fetal growth from any cause, increases the risk of intrauterine or subsequent health of the fetuses. Both epidemiological studies and animal model experiments show that under-nutrition as well as over- nutrition during pregnancy and or lactation induces stable alterations to the physiological and structural phenotype of the offspring resulting in abnormal health conditions[1-3]. A number of studies have confirmed the association between birth weight and impaired glucose tolerance and non-insulin dependent diabetes in later lives[1, 4-7].

The term 'large-for-gestational-age' (LGA) has mainly been used for newborns with (estimated) weight > 90th percentile or above 2 SDs for gestational age[8]. Macrosomia is a term mostly used for newborns with a birth weight above a certain limit. However, there is no general agreement what this limit should be. Birth weights above 4000, 4200 and 4500 g are being used as definitions of macrosomia[9,10]. The birth of LGA infants (birth weight≥90th centile) is the most frequent of the complications seen in pregnancies of women with type 1 diabetes[11-17] and this is associated with increased morbidity of both mother and child[5,18,19]. Large for age and macrosomic babies are also common for type 2 diabetes and also for GDM[20,21]. Historically, large fetuses were obstetrical concerns mainly for diabetic pregnancies, but during the recent decades, however, an overall increase, about 15-25% of large babies in different populations around the world arouse caution in general[22-26]. Therefore, the obstetrical and neonatal complications associated with delivery of big babies have become a frequent challenge[27]. Long-term health risks like obesity, metabolic syndrome, hypertension and cancer are found frequently associated with these babies[28-36].

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Materials and Methods

This was a prospective cohort study. Pregnant mothers attending for their delivery at the BIRDEM Hospital, Dhaka were enrolled in the study. A total of 251 newborn-mother pairs, pre-gestational diabetic (n: DM=86), gestational diabetic (GDM=86) and non-diabetic (NDM=79) were recruited from the same hospital according to the set criterion of definition for the individual group as defined by the hospital authority during the period from 2003 to 2005. The hospital record books helped in the identification of the subjects at the time of enrolment. Detailed anthropometric measurements of infants were taken at birth in the hospital.

Inclusion criteria

a. Mothers with viable singleton babies
b. Mother's age: 21 to 35 years
c. Monthly income of the family in Taka: Tk10, 000 to 30,000
d. Mother's education: Grade VIII or above
e. For DM group, all cases of pre-gestational diabetic pregnancy irrespective of duration and minor complication.
f. For GDM group, all cases of gestational diabetic pregnancy irrespective of duration and complication.

Exclusion criteria

a. Birth orders more than five.
b. Mothers not willing to stay in the study for the whole period.

The groups were matched on the following characteristics:
a. Sex
b. Mothers education
c. Mothers occupation

Data Analysis

Data were entered into a SPSS spreadsheet and analyzed using SPSS windows version 17. The distributions were examined for normality and when required were normalized by appropriate transformations. Differences between the groups were examined using 't-tests' and 'general linear model univariate analyses' for continuous variables.

Results

In the analyses (Analyses of co-variance) concerning all newborn's anthropometric measurements, gestational age was controlled as most of the babies were selectively delivered by caesarean sections at different time although the mode of delivery was not different between the groups. Furthermore, sex was controlled as a universal-confounder.

Table-I: Anthropometric measurements of newborns (mean and SE) by groups

Characteristics	DM (n=86)		GDM (n=86)		NDM (n=79)		Group statistics		
	Mean	SE	Mean	SE	Mean	SE	df	F	P-value
Weight (g)	3080	0.05	3240	0.05	2990	0.05	2, 244	5.67	0.004
Length (cm)[1]	48.33	0.26	48.91	0.28	48.96	0.26	2, 216	1.73	0.179
Circumferences									
Head (cm)[2]	33.43	0.14	33.82	0.14	33.76	0.14	2, 243	2.29	0.103
MAC (cm)[1]	10.29	0.10	10.63	0.11	9.88	0.10	2, 216	13.01	<0.001
CalfC (cm)[1]	10.92	0.11	11.17	0.11	10.49	0.11	2, 216	10.23	<0.001
ThighC (cm)[1]	16.14	0.20	16.84	0.22	15.46	0.20	2, 216	10.80	<0.001
ChestC (cm)[1]	32.46	0.19	32.73	0.20	31.99	0.19	2, 216	3.71	0.026
AdomenC(cm)[1]	31.04	0.25	31.56	0.26	30.57	0.25	2, 216	3.80	0.024
Ponderal Index[3]	2.77	0.04	2.81	0.05	2.58	0.04	2, 218	9.41	<0.001
BMI[1]	13.33	0.19	13.68	0.20	12.56	0.18	2, 222	9.40	<0.001

1) n: DM:76; GDM:68; NDM:79; 2) n: GDM:85. BMI: wt(kg)/height(m)^2; 3) Ponderal Index: [wt(g)/ht(cm)^3] x100

Table-I describes newborn's anthropometric measurements (mean±SE) by different groups. There were significant group differences in newborn's weight, MAC, calf, thigh, chest and abdominal circumferences except birth length and head circumference. Both BMI and Ponderal index at birth were significantly different amongst the groups.

Table-II: Between group comparisons of newborns on different birth anthropometric measurements

	DM — NDM		GDM — NDM	
	Mean difference	95% CI for difference	Mean difference	95% CI for difference
Weight (g)	0.167	-0.34, 0.009	0.215*	0.035, 0.394
Length (cm)	-0.63	-1.54, 0.27	-0.06	-0.98, 0.87
HeadC (cm)	-0.33	-0.81, 0.16	0.06	-0.42, 0.54
MAC (cm)	0.42**	0.07, 0.77	0.76***	0.40, 1.11
CalfC (cm)	0.43**	0.07, 0.79	0.68 ***	0.31, 1.06
ThighC (cm)	0.68	-0.02, 1.38	1.38***	0.66, 2.09
ChestC (cm)	0.48	-0.18, 1.13	0.74*	0.07, 1.41
AbdominalC (cm)	0.47	-0.38, 1.31	0.99*	0.12, 1.86
Ponderal Index	0.19*	0.05, 0.34	0.23*	0.08, 0.40
BMI	0.77*	0.14, 1.40	1.12*	0.48 1.76

*P<0.05; **P<0.01; ***P<0.001; BMI: wt(kg)/height(m)^2; Ponderal Index: [wt(g)/ht(cm)^3]x100

In multiple comparisons (Table-II), newborns from the DM group were found to have greater values in 6 measurements except length and head circumference. However, significant values were shown only for MAC (10.3±0.1 vs. 9.9±0.1; p<0.001) and calf circumference (10.9±0.1 vs. 10.5±0.1; p<0.001). On the other hand, newborns from the GDM group showed significantly higher values compared to the NDM group in almost all anthropometric measurements [weight: 3.2±0.05 vs. 3.0±0.05; p=0.004; MAC: 10.6±0.1 vs. 9.9±0.1; p<0.001; calf circumference: 11.2±0.1 vs. 10.5±0.1; p<0.001; thigh circumference: 16.8±0.2 vs. 15.5±0.5; p<0.001; chest circumference: 32.7±0.2 vs. 32.0±0.2; p=0.026 and abdominal circumference: 31.6±0.3 vs. 30.6±0.3; p=0.024] except length and head circumference. Both BMI and Ponderal index at birth were significantly higher for DM (BMI: 13.3±0.2 vs.12.6±0.2; p=0.003 and PI: 2.77±0.04 vs. 2.58±0.04; p=0.001) and GDM (BMI: 13.7±0.2 vs.12.6±0.2; p<0.001 and PI: 2.81±0.05 vs. 2.58±0.04; p<0.001) groups compared to the NDM group.

Table-III: Incidence of SGA, AGA and LGA babies by different groups

	DM (n=86)	GDM (n=86)	NDM (n=79)	P-value for DM	P-value for GDM
Small for Gestational Age (SGA)	16(18.6%)	14(16.3%)	24(30.4%)	0.078	0.032
Appropriate for Gestational Age (AGA)	67(77.9%)	62(72.1%)	52(65.8%)	0.084	0.384
Large for Gestational Age (LGA)	3(3.5%)	10(11.6%)	3(3.8%)	0.916	0.062

Table-III describes distribution of LGA, SGA and AGA babies by different groups. For identification of SGA, AGA and LGA babies, US Nationality Reference Table was used[37]. In this study, decimal gestational age was calculated for identification of SGA, AGA and LGA babies using those tables. LGA babies had birth weights greater than the 90th percentile for their gestational age for sex and SGA babies usually had birth weights below the 10th percentile for babies of the same gestational age for sex. Only 10(11.6%) babies were found LGA in the GDM group as opposed to 3 each for DM and NDM group. There was a significance group difference in the incidences of SGA babies. Around 16% to 18% were there in the DM and GDM groups, as opposed to much higher rate (30.4%) in the NDM group.

Table-IV: Number of ICU babies by groups

ICU babies	DM (n=86)	GDM (n=86)	NDM (n=79)	P-value DM	P-value GDM
Total	15	23	3	0.005	<0.001
% of ICU babies in groups	36.6	56.1	7.3	x	x
Respiratory distress	15	21	1	x	x
Surgery (volvulus) with resp. distress	1	0	0	x	x
Cleft plate	0	1	1	x	x
Blood transfusion	0	0	1	x	x
Ear defect with resp. distress	1	1	0	x	x

Table-IV describes number of ICU babies by groups. Fifteen (36.6%) babies from DM and 23 (56.1%) from GDM group were admitted to the ICU of the hospital as opposed to 3(7.3%) from the NDM group. Numbers of ICU babies at birth were significantly higher for DM and GDM groups compared to the NDM group.

Table-V: Newborn's APGAR score (mean and SE) by groups

	DM (n=86)	GDM (n=73)	NDM (n=67)	P-value DM	P-value GDM
Apgar score in 1 minute	7.50 ±0.21	7.66 ±0.23	8.09 ±0.08	0.010	0.074
Apgar score in 5 minute	9.09 ±0.25	9.19 ±0.27	9.76 ±0.06	0.011	0.040

Table-V describes newborn's APGAR score by groups. Mean 'APGAR' scores at 1 minute and 5 minute were significantly lower for DM and GDM groups compared to NDM group.

Discussion

Mean gestational age of the newborns was found lower in the DM and GDM groups compared to the NDM group. Around 90% mothers had undergone caesarean section(C/S) and there were no significant differences between the groups. No information was available for the indication for C/S, but it is expected that it was done earlier for DM and GDM groups as a precautionary measure. Mean 'APGAR' scores at 1 minute and 5 minute were significantly lower for DM and GDM groups compared to NDM group. Six percent babies from DM and 9.2% from GDM group were admitted to the ICU of the hospital as opposed to 1.2% from the NDM group. The finding suggests vulnerability of the newborns is more in the diabetic groups and this stems from their intrauterine lives, which might be a reason for earlier C/S for them. So, gestational age was controlled in all analyses.

After controlling gestational age and sex, newborns from the DM group were found to have greater values compared to that of the NDM group in all anthropometric measures except length and head circumference. The significant ones were calf circumference, MAC, ponderal index and BMI. Similarly, newborns of GDM group compared to the NDM group were found to have significantly greater values in all anthropometric measures except length and head circumference. Sparing of head and length signify that this accelerated growth is mainly due to effects in later half of intrauterine lives and involve mainly fat accumulation in spacious tissues. This is usually seen in disproportionate IUGR (intrauterine growth restriction) babies where growth restriction occurring in later half of pregnancies spare head and length and there is lower proportion of visceral and fat tissues[38,39]. In that strict sense, these babies can be termed as 'disproportionate IUGA (intrauterine growth accelerated)' babies. These babies might differ from other LGA babies from non-diabetic mothers.

Increased sizes of the babies often terming as LGA (Large for gestational age: above 90th percentile for gestational age) 40, or macrocosmic infants (more than 4000g)[40-44] are common in diabetic mothers. It is obvious that accumulation of metabolites mainly fat is important, but a detailed examination of all easier anthropometric indicators usually is not reported earlier. Most of the studies explored the prevalence of LGA or macrosomia[45-48]. The effect of metabolic abnormalities in mothers with diabetes that lead to different consequences including somatic changes has been elaborately discussed by Buchana and Kitzmille in a review[49]. Poorly controlled diabetes during the first trimester of pregnancy, and in particular during the first six weeks of intrauterine development, has been associated with a spectrum of developmental abnormalities ranging from growth retardation to discrete congenital anomalies of the nervous, cardiovascular, renal, and skeletal systems to spontaneous abortion. Although sample selection for this study categorically excluded any congenital abnormalities, but subsequent to enrolment few infants were diagnosed with minor congenital defects: 1 cleft palate each in the GDM and NDM group, congenital malformation of ear, 1 each in the DM and GDM group and 1 malformation of the intestine that required surgery in the DM group. It is to be emphasized that the diabetic mothers in this study were supposed to be adequately controlled in the hospital situation. If growth retardation is considered, 16 babies (18.6%) in the DM group, 14(16.3%) in the GDM group were found SGA (small for gestational age) as opposed to 24(30.4%) babies in the NDM group. It is difficult to elicit the exact causes of IUGR, but underlying mechanism of this restricted growth may be different between diabetic groups and the NDM group. The epidemiological correlates of birth weight and subsequent development of diabetes is emphasized in the Pima Indian population, where the curve was found U shaped[50], indicating both LGA and SGA babies are at risk. In this population, around 17% of babies from diabetic mothers and 30% from normal mothers are a concern for future risk from diabetes because of SGA.

In their review[49], the authors also stated that in contrast to the impaired development that result from poorly controlled maternal diabetes during early pregnancy, poor-control during the latter two thirds of gestation are usually associated with accelerated foetal growth and a risk of large-for-gestational-age (LGA) babies. Jorgen Pedersen for the first time hypothesised that hyperglycemia-hyperinsulinemia[51] was the cause of accelerated fetal growth. Maternal hyperglycemia results in increased delivery of glucose to the fetus, which in turn experiences earlier maturation of pancreatic insulin secretion. The excess calories and hyperinsulinemia result in over-growth of the fetus and in particular, of fetal insulin-sensitive tissues (e.g. subcutaneous fat, liver, striated and cardiac muscle). Over-activity of pancreatic ß-cell leads to hypoglycemia in the neonatal period as well. Clinical observations linking maternal hyperglycemia to fetal overgrowth and hyperinsulinemia support Pedersen's hypothesis[52,53]. In this well controlled hospital situation, a total of 3 babies (3.5%) were found LGA in the DM group, 10 (11.6%) in the GDM group as opposed to 3 (3.8%) babies in the NDM group. Similarly, when birth weight cut-off value was considered, 3, 8 and 1 babies showed birth weight 4000g and above in DM, GDM and NDM groups respectively. Apart from obvious LGA or macrosomia, do the infants from well-controlled diabetic mothers in hospital situation vary in anthropometric measures from that of the normal babies of non- diabetic mothers? As a whole the newborns of DM and GDM group in this population showed higher values in all anthropometric indicators except length and head circumference. Shireen in her PhD[54] dissertation also showed higher values for newborns of DM compared to that of NDM mothers on all anthropometric measures except length. In the present study, GDM group showed further growth acceleration than the DM group in comparison to the NDM group.

Circulating plasma leptin levels in mothers correlate with plasma insulin concentration as well as with maternal adipose tissue mass and often considered a marker of insulin resistance and obesity[55]. Recent data showed that diabetic mothers had increased plasma leptin concentrations during and after pregnancy[56-58] and cord leptin concentrations correlated with the foetus's weight at birth as well as with other fetal anthropometric indices[59]. This study, unfortunately, did not have serum leptin levels of mothers during or after pregnancy or in the cord blood and failed to explore these associations.

Conclusion

The association of diabetes with high birth weight is largely explained by the presence of maternal diabetes during pregnancy. Despite the excess of diabetes associated with low birth weight this accounted for only 6% of diabetes in this population. An alternative hypothesis is proposed that the association of diabetes and low birth weight may reflect selective survival of small infants genetically predisposed to diabetes and other insulin resistance syndromes. This finding is quite impressive; however, further replicate and well-controlled studies are needed to confirm this.

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