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EVALUATING THE EFFECTS OF GESTATIONAL DIABETES MELLITUS ON FETAL BIRTH WEIGHT

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Abstract

This study was aimed at evaluating the association between gestational diabetes mellitus (GDM) and fetal birth weight considering duration of pregnancy, maternal age and body mass index (BMI). This was a retrospective cross-sectional study followed by cohort type of study. Initially, pregnant women in their 24 to 28th week of gestation were selected for determining their fasting blood glucose (FBG) level and blood glucose level 2 hrs after 75 g oral glucose intake. The cut-off value for the diagnosis of GDM was > 5.3 mmol/l for FBG level and > 8.6 mmol/l for taking 75 g oral glucose intake after 2 hrs. Both GDM and control group subjects were followed up to neonatal period to find out neonatal outcomes. Among the total 215 subjects, 84 pregnant women were selected with GDM and rest 131 were control. It is found that GDM alone had a significant ($p = 0.05$) positive effect on both the duration of pregnancy and fetal birth weight, but not on maternal BMI. Both the effects of duration of pregnancy and GDM are considered together on fetal birth weight, only GDM had significant impact on fetal birth weight compared to the control group. Similarly, when the effect of maternal BMI and GDM is considered together on fetal birth weight, only GDM group was found to have significant effect on fetal birth weight. Parallel results were observed for the effect of both maternal age and GDM on fetal birth weight. In binary logistic regression analysis, when the differences are considered in maternal age, duration of pregnancy and maternal BMI along with GDM, both maternal age ≥ 35 years (OR: 9.43, $p = 0.001$) and GDM (OR: 10.60, $p = 0.003$) was found to have significant positive effect on fetal birth weight. It was found that the GDM showed significant influence on fetal birth weight considering the effects of maternal age, duration of pregnancy and maternal BMI.

Introduction

GDM is quite common affecting around 3 - 10% of pregnancies worldwide(1). In Bangladesh, prevalence of GDM is also quite high with frequencies around 7 - 14% (2-4). Any degree of glucose intolerance detected during pregnancy is termed GDM. However, the hormone produced during pregnancy might have increased the resistance to insulin resulting in developing GDM(5). GDM may lead to congenital malformations and predispose both mother and babies to an increased risk of complications (5). The major

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effects of GDM on mothers include abortion, pre-eclampsia, maternal distress, perinatal injuries, repeated urinary tract infection (UTI), labor injury, operative interference, failure of lactation, etc[5,6]. On the other hand, the major effects of GDM on fetus include congenital malformation, fetal macrosomia, birth injury and neonatal morbidities like neonatal jaundice, respiratory distress syndrome, polycythemia, hypoglycaemia, hypocalcemia, etc.[4,7-9]. Also, GDM accounts for long term health risks for both the mother and babies in later life[4]. Among the many health risks, higher birth weight of the infant is the most common adverse infant outcome of GDM mother [10-11].

Fetal growth is mainly determined by complex interaction between *in utero* environment and genetic factors. GDM can change the *in utero* environment that might affect the fetus growth. This might be happening because the high glucose level in the bloodstream of mother crosses the placenta which triggers the infant's pancreas to make extra insulin[10]. This hyperinsulinemia leads to increase in total adipose tissue and organ size, which subsequently lead to gain foetus weight. This can cause the infants to grow too large (macrosomia). Macrosomia is defined when the birth weight of infant is greater than 4000 g[10]. Babies born to GDM mother have 15 - 45% chance of developing macrosomia which is three-folds higher compared to the non-diabetic control mother. Macrosomic fetus often develops a unique pattern of growth, including larger shoulder, thicker upper extremity skinfold, decreased head to shoulder ratio, higher body fat, etc.[12]. Since, fetal shoulder and abdominal girth size are reasonably large compared to head size, the chance of shoulder dystocia has increased[10]. Other complications of fetal macrosomia include hypoglycaemia at birth, clavicle fractures, neonatal jaundice, congenital defects, etc.[10,13]. Not only that, infants of GDM mother have higher chance of suffering from obesity and diabetes in later life [14].

Thus, it is quite obvious from other studies that there has been an independent association between GDM and fetal macrosomia [4,10-11]. However, maternal age ≥ 35 years, overdue pregnancy period and high maternal BMI are the other important maternal health characteristics that also affect fetal macrosomia as well[15-17]. These fetal macrosomia affecting factors might influence on each other as well. But no study has been done so far evaluating the effects of GDM on fetal birth weight considering maternal age, duration of pregnancy and maternal BMI. This study for the first time attempted to evaluate the association between GDM and fetal birth weight considering maternal age, maternal BMI and duration of pregnancy among the Bangladeshi urban pregnant women. In this study, first authors investigated the combined effect of GDM and maternal age; GDM and maternal BMI and GDM and duration of pregnancy on fetal birth weight. Next, they used logistic regression model to evaluate what extent GDM affects fetal birth weight considering maternal age, duration of pregnancy and maternal BMI.

Materials and Methods

The study was conducted among 215 Bangladeshi pregnant women aged between 16 and 41 years who agreed in writing to participate in the study. Before conducting the study, participants were notified about the purpose of study and the respondents had given rights to withdraw themselves from the study at any time. Participants' anonymity and confidentiality were also ensured all through the study. The study was conducted considering all the ethical issues and was approved by the Ethical Review Committee of the Faculty of Biological Sciences, University of Dhaka (Ref. no. 81/Biol. Scs.).

The study included participants who were admitted in Dhaka Medical College hospital, Bangladesh and gave birth to the same hospital. Participants with previous history of diabetes or using drugs that significantly affect glucose metabolism were excluded from the study. Maternal health indicators including blood pressure, weight and height of pregnant women were measured at the time of visit, and their other demographic characteristics like age, history of other diseases were collected using self-reported questionnaire.

Sample size was calculated using the formula: $n = z^2p (1 - p)/d^2$; where z = Standard normal deviation at 95% confidence level, p = prevalence of pregnant women in Bangladesh, d = margin of error and n = sample size.

Considering prevalence of pregnant women in Bangladesh (p) = 50% or 0.5 (since the actual number is unknown), z = 1.96, margin of error (d) = 6% = 0.06; then at 95% confidence interval, sample size (n) becomes 266. However, authors added 20% non-response as it is a public hospital and patients are from all socio-economic classes, so getting consent from everyone is a challenge. Considering all factors, the sample size becomes 318. In all there were a total of 215 respondents.

Maternal BMI was categorized into underweight (BMI < 18.5), normal weight (18.5 - 25) and overweight (> 25) according to WHO classification[18]. Duration of pregnancy was categorized into pre-term (< 37 weeks), term (37 - 42 weeks) and post-term (> 42 weeks) according to the previous study [4].The birth weight was categorized into LBW (< 2500 grams), normal weight (2500 - 4000 g) and macrosomia (> 4000 grams) according to previous study[19]. Maternal age was classified into age < 35 years and age ≥ 35 years, since maternal age over 35 years was considered as a risk factor of fetal macrosomia[17].

Screening of GDM was performed to pregnant women in their 24 to 28th week of gestation by measuring their fasting blood glucose (FBG) level and blood glucose level 2 hrs after ingestion of 75 g oral glucose intake using autoanalyzer (Huma Star 3000, Human Diagnostics Worldwide, Germany). Blood glucose level was determined using colorimetric method according to the manufacturer's protocol. Each time 5 ml of blood was taken in a vacutainer tube and kept upright position for 20 - 30 min. Later, centrifuge was performed at 6000 rpm for 5 min to collect serum.

The cutoff value for the diagnosis of GDM was > 5.3 mmol/l for FBG level and > 8.6 mmol/l for taking 75 g oral glucose drink after 2 hrs[4]. Through this test, a total 84 pregnant women were selected with GDM. For every GDM woman, 1.5 non-GDM pregnant women was taken as control, giving as a total of 131 control subjects.

Both the GDM and control group of 215 pregnant women were followed up to the neonatal period to evaluate neonatal outcomes including fetal birth weight. The weight of the new-born babies was measured using baby weighing machine at the hospital and neonate's health information was collected from the medical report from the hospital after maintaining standard procedures.

Data analysis was done using SPSS program version 24 software (SPSS Inc., Chicago, USA). Quantitative variables were presented as mean ± Sd, and categorical variables were shown in percentage. Since, the data followed normal distributions, for analysing categorical variables, Pearson's χ^2 (Chi square) test was performed to investigate the difference between each group and for continuous variables, t test was performed. The level of significance of each result was set at $p < 0.05$. All statistical tests were two-sided. Binary logistic regression analysis was also performed to determine the adjusted associations between GDM and neonatal birth weight.

Results and Discussion

Out of 215 selected participants aged between 16 and 41 years, 84 women were found having GDM and the rest of the 131 participants without GDM were taken as control. Maternal and fetal health characteristics or the control and GDM group were shown in Table 1.

In Table 1, pregnant women complicated with GDM were found significantly older (30.25 ± 4.71 years) than the control participants (25.43 ± 4.86 years). Maternal morbidities such as hypertension (38.1 vs 22.1% in control) was significantly ($p = 0.01$) more frequent in the GDM group than the control group whereas other morbidities including gestational edema (48.9 vs 27.4% in GDM, $p = 0.002$) and anaemia (62.6 vs. 29.8% in GDM, $p = 0.00$) were significantly more prevalent in the control group. However, both groups had almost similar frequency of urinary tract infection (UTI) (29.8 vs 30.5% in control).

On the other hand, GDM complicated mother had increased incidence of macrosomia (16.7 vs 1.5% in control) and normal weight babies (65.5 vs 43.5% in control) whereas the control group had a higher incidence of low birth weight (LBW) (55 vs 17.9% in GDM), perinatal jaundice (52.7 vs 36.9% in GDM, $p = 0.26$) and pre-term delivery (52.7vs 41.7% in GDM).There was no maternal mortality in both groups and only one perinatal mortality was found in case of the control group. The mean birth weight of the GDM group was 3288.09 ± 85.63 g which was significantly ($p = 0.00$) higher than the mean birth weight of the control group (2507.25 ± 59.84 g). The duration of pregnancy

for the GDM group was found 37.62 ± 2.69 weeks that was significantly (p = 0.04) higher than that of control group (36.40 ± 3.19) weeks. The mean BMI for GDM group was found 26.51 ± 4.40 kg/m^2, whereas for the control group, the mean BMI was 26.34 ± 6.10 kg/m^2. The differences between these two groups were not statistically significant (p = 0.823) (Table 1).

Table 1. Maternal and fetal health characteristics among the GDM and control group.

Variable	Control (n = 131)	GDM (n = 84)	p
Age (years)	25.43 ± 4.86	30.25 ± 4.71	0.001
Gestational hypertension			
Yes	29 (22.1%)	32 (38.1%)	0.01
No	102 (77.9%)	52 (61.9%)	
Gestational UTI			
Yes	40 (30.5%)	26 (29.8%)	0.53
No	91 (69.5%)	58 (70.2%)	
Gestational edema			
Yes	64 (48.9%)	23 (27.4%)	0.002
No	67 (51.1%)	61 (72.6%)	
Gestational anaemia			
Yes	82 (62.6%)	25 (29.8%)	0.00
No	49 (37.4%)	59 (70.2%)	
Duration of pregnancy (weeks)	36.40±3.19	37.62±2.69	0.04
Maternal BMI (kg/m^2)	26.34 ± 6.10	26.51 ± 4.40	0.823
Birth weight (g)	2507.25 ± 59.84	3288.09 ± 85.63	0.00
LBW	72 (55%)	15 (17.9%)	
Normal weight	57 (43.5%)	55 (65.5%)	
Macrosomia	02 (1.5%)	14 (16.6%)	
Perinatal mortality			
Yes	01 (0.76%)	0 (0%)	0.89
No	130 (99.24%)	84 (100%)	

Since overdue pregnancy period is considered as one of the risk factors for fetal macrosomia [10], we investigated the effect of duration of pregnancy on fetal birth weight in GDM complicated pregnancies.

It was found that in case of both pre-term and term delivery, GDM independently increased fetal birth weight in the GDM group than the control group (Table 2). The mean birth weight of control group in case of pre-term delivery was found 2028.26 ± 51.53 g which was significantly (p = 0.01) lower than the GDM group (2845.71 ± 136.80 g). On the other hand, the mean birth weight of control group in case of term delivery was 3040.32 ± 63.13 g, whereas for the GDM group this was 3572.34 ± 85.57 g which was significantly (p = 0.001) higher as well. Finally, in terms of post-term delivery, the mean birth weight of the GDM group was found 4350.00 ± 250 g; however, no single post-term delivery case was found in present study in case of the control group.

It was speculated in previous study [16] that maternal BMI augments the effect on fetal birth weight in pregnancies complicated by GDM. In accordance with that, BMI of the participants were categorized into three different categories to observe whether or not increase or decrease of maternal BMI from the normal range could affect on fetal birth weight together with GDM.

Table 2. Effect of duration of pregnancy, maternal BMI and maternal age on fetal birth weight in GDM and control group.

Variables	Fetal birth weight (g) (Mean ± Sd.		
	Control (n = 131)	GDM (n = 84)	p
Pregnancy duration			
Pre-term (< 37 weeks)	2028.26 ± 51.53 (n = 69)	2845.71 ± 136.80 (n = 35)	0.01
Term (37 - 42 weeks)	3040 ± 63.13 (n = 62)	3572.34 ± 85.57 (n = 47)	0.001
Post-term (42 weeks)	(n = 0)	4350 ± 250 (n = 02)	
Maternal BMI			
Underweight (< 18.5)	2390 ± 382.88 (n = 5)	(n=0)	
Normal weight (18.5 - 25)	2472.66 ± 80.71 (n = 64)	3100 ± 140.69 (n = 37)	0.001
Overweight (> 25)	2552.41 ± 91.28 (n = 62)	3436.17 ± 101.85 (n = 47)	0.0001
Maternal age			
Age ≥ 35 years	2144.44 ± 350.83 (n = 9)	3618.75 ± 211.98 (n = 16)	0.00
Age < 35 years	2534.02 ± 58.69 (n = 122)	3210.29 ± 91.55 (n = 68)	0.001

Here, it was found that in both normal and overweight cases, the fetal birth weight of GDM group was significantly ($p = 0.001$ and $p = 0.0001$, respectively) higher than the control group mother (Table 2). The mean fetal birth weight of the GDM group in case of normal weight was found 3100 ± 140.69 g which was significantly higher ($p = 0.001$) than that of the control group (2472.66 ± 80.71 g). Similarly, in case of overweight category, the mean birth weight of GDM was 3436.17 ± 101.85 g that was significantly higher ($p = 0.0001$) than the control group (2552.41 ± 91.2 g). In case of underweight group, the mean birth weight for the control group women was found 2390 ± 382.88 g; however, no single case of underweight mother was observed in the GDM group.

The effect of maternal age on fetal birth weight in GDM complicated pregnancies was evaluated since maternal age ≥ 35 years is considered as one of the risk factors of neonate's higher birth weight[17]. For this purpose, we divided maternal age into two categories: maternal age ≥ 35 years and maternal age < 35 years.

Here, it was observed that in case of maternal age ≥ 35 years**,** the fetal birth weight of GDM group was found 3618.75 ± 211.98 g and that for control group was found 2144.44 ± 350.83 g. The differences between these two groups was found statistically significant ($p = 0.00$). Similarly, in case of maternal age < 35 years, the fetal birth weight was found 3210.29 ± 91.55 g and that for the control group was found 2534.02 ± 58.69 g. The differences between them are also statistically significant ($p = 0.0001$).

Binary logistic regression analysis was performed to evaluate the association of fetal macrosomia with GDM after adjustments for duration of pregnancy, maternal age, and maternal BMI. Here, the presence or absence of fetal macrosomia was taken as dependent variable and maternal GDM, maternal age, duration of pregnancy and maternal BMI were taken as independent variables. Furthermore, independent variables were categorized considering the subjects (control group), BMI (normal weight), duration of pregnancy (term delivery) and maternal age (age < 35 years) as reference group.

It was found that after adjustments for maternal age, pregnancy duration and maternal BMI, GDM increased the likelihood of delivering babies with fetal macrosomia 10.60 chances more than those who had not GDM. Besides, maternal age ≥35 years (OR = 9.43) also significantly (p = 0.001) affected fetal macrosmia after adjustments for maternal GDM, duration of pregnancy and maternal BMI.

Table 3. Adjusted odds ratio (95% CI) of fetal macrosomia.

Variables	Category of characteristics	OR (95% CI)	p
Subjects	Control	Reference	
	GDM	10.60 (2.24 - 50.11)	0.003
Maternal age (year)	Age < 35	Reference	
	Age ≥ 35	9.43 (2.64 - 33.69)	0.001
Duration of pregnancy	Term (37 - 42)	Reference	
(weeks)	Pre-term (< 37)	0.29 (0.07 - 1.16)	0.09
Maternal BMI	Normal weight	Reference	
	Overweight	1.72 (0.51 - 5.90)	0.38

Fetal macrosomia is one of the major outcomes of GDM complicated pregnancy [4,10-11]. In accordance with other studies, present study also showed that GDM significantly increased the risk of delivering babies with fetal macrosomia. Other maternal health characteristics that cause fetal macrosomia include high maternal BMI, longer duration of pregnancy, maternal age ≥ 35 years, etc. [4,10,16,20, 21]. However, to date there are no reports on investigation of association between fetal birth weight and GDM considering maternal BMI, duration of pregnancy and maternal age in Bangladesh. This study so far is the first attempt to determine the association between GDM and fetal birth weight among the Bangladeshi urban women considering all these confounding risk factors. In the present study, authors found that considering maternal age, duration of pregnancy and maternal BMI, fetal birth weight was significantly affected by GDM.

Present result correlates with some previous reports that showed significant positive association between duration of pregnancy and GDM[16,22]. In this study, it is found that the duration of pregnancy in the GDM group was 37.62 ± 2.69 weeks that was significantly (p = 0.04) higher than the control group (36.40 ± 3.19) weeks. Furthermore, earlier report showed that duration of pregnancy, not the GDM was positively associated with fetal birth weight[16]. However, in contrast, here it is found that GDM increased fetal

birth weight irrespective of duration of pregnancy, since in both pre-term (< 37 weeks) and term (37 - 42 weeks) delivery cases, GDM significantly increased fetal birth weight than the control group. However, our study did not find any case of post-term delivery case which was the reason behind failure to show relationship between post-term (> 42 weeks) delivery and fetal birth weight among the GDM and control subjects. The increased number of caesarean deliveries in Bangladesh most probably prevents the occurrence of post-term delivery in many of the cases [23].

Previous studies showed that GDM increased maternal BMI [16,24] and augmented the effect of fetal macrosomia in presence of GDM[16,20]. However, in contrast to earlier reports, the present study didn't find any significant differences in maternal BMI between GDM and control group. Rather, we found that in both normal weight and overweight categories, GDM independently increased neonatal birth weight compared to control group. Since, weight gain during pregnancy is a normal phenomenon, here our study of control group mother might also experience increasing trends in BMI. However, one of the limitations of this study was not to include pre-pregnancy BMI profile of both groups which will give much clearer picture in this sense.

It is further demonstrated that advanced maternal age (age ≥ 35 years) reduced fetal birth weight (mean: 2144.44 ± 350.83) in the control group, but not in the GDM group (3618.75 ± 211.98). This correlates with earlier studies that mentioned advanced maternal age (age ≥ 35 years) increased the risks of LBW in control subjects[25,26]. Similarly, maternal age < 35 years also caused significant differences therefore argues that incidence of high fetal birth weight was determined mostly by GDM, not particularly by maternal age. However, when we consider differences in maternal BMI, GDM and duration of pregnancy, maternal age ≥ 35 years found to affect fetal macrosmia (OR = 9.43) significantly ($p = 0.01$). This finding correlates with previous studies which showed that advanced maternal age increased the risk of fetal macrosomia[17]. Present binary logistic regression analysis also showed several-folds (OR = 10.60) increase in chance of developing fetal macrosomia due to GDM when we considered differences in maternal age, maternal BMI and duration of pregnancy.

There are some limitations associated with the present study. Amongst those, the most important was relatively a small number of study subjects. Only 215 participants were included in this study, where 84 were diagnosed as GDM and rest 131 were control. Furthermore, after categorizing BMI and pregnancy period of our study participants, we had observed fewer cases of underweight and post-term delivery which prevented us to get an accurate picture of their effect on fetal birth weight in GDM complicated pregnancies. Besides, data including age and history of other diseases were obtained through self-reported questionnaire without checking their authenticity. As a measure of diabetes, we measured both FBG and blood glucose 2 hrs after ingestion of 75 g oral glucose solution. However, we did not measure HbA1c level of our participants, which

might give much a clear picture of long-term complications of diabetes [27]. Finally, the data were collected from subjects who were admitted in Dhaka Medical College Hospital, Bangladesh and gave birth to same hospital which might not represent whole scenario of Bangladesh. However, in spite of some limitations, it is concluded that GDM affect neonatal birth weight regardless of maternal age, duration of pregnancy and maternal BMI.

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