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Original Research Article

Fetal growth and its correlation with level of glycemic control in pregnancy with diabetes: an observational study in tertiary care centre of North India

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ABSTRACT

Background: Diabetes in pregnancy is a known risk factor for macrosomia and intensive glycemic control is a well-known strategy to prevent this macrosomia. However, does this tight glycemic control is actually beneficial or is it one of the reasons for small for gestational age babies in these women? Is a clinical enigma. We planned this study to see effects of glycemic control on fetal weight and to answer if tight control is always better.
Methods: This prospective observational study was conducted in the department of obstetrics and gynaecology in a tertiary care centre (King George medical university) over a period of one year (June 2017-June 2018). All pregnant women with GDM and pre-gestational diabetes with singleton pregnancy were registered in the study after proper consent, followed up for glycemic control, fetal weight. Antepartum risk factors and complications of diabetes were also noted in these women.
Results: Total 88 patients included in the study. Five with pre-gestational diabetes, 83 with GDM. Small for gestational age neonates were seen in 54.1% cases, large for gestational age were seen in 2 cases and rest of neonates were appropriate for gestational age. 89.4% had good glycemic control, 7% had over-zealous glycemic control and 3.5% had under-controlled sugars.
Conclusions: The results in the study strongly supported the efficacy of good glycemic control in prevention of LGA/macrosomia. However, optimal glycemic control in third trimester does not guarantee appropriate weight of fetus as incidence of SGA/FGR neonates was fairly high (53.9%) even in good glycemic control group.

Keywords: Diabetes, Fetal growth, Gestational diabetes mellitus, Glycemic control, Pregnancy

INTRODUCTION

Diabetes, whether gestational or pregestational, is a well-known risk factor complicating pregnancies all over the world. Despite significant advancements in diagnosis and management strategies, it still remains a significant medical challenge. Historically, macrosomia is the most observed pattern of growth in pregnancy with diabetes which is explained by the Pederson's hypothesis.[1] However, in our high-risk pregnancy unit dedicated to management of patients with pregestational or gestational diabetes mellitus (GDM), we have observed increasing incidence of small for gestational age (SGA) as compared to large for gestational age (LGA) babies. In long standing diabetes, vasculopathy explains SGA, however, in GDM, vasculopathy of such severe degree is unlikely and alternate explanation needs to be sought for. Various hypotheses have been put forth to explain growth restriction which include overzealous glycemic control, placental insufficiency or poor genetic growth potential of fetus. In 1989, Langer et al first questioned whether intensive glycemic control is always better for fetal outcome and this was again pursued by Parikh et al.[2,3] In 2017 Silva et al proposed that intensive glycemic control

and restriction of weight gain during pregnancy with GDM may increase risk of SGA.[4] Intensive glycemic control in GDM may result in acute and chronic hypoglycemia in mothers leading to fetal hypoglycemia and insulin deficiency which decreases fetal glucose utilization by altering concentration of insulin like growth factor and thereby causing SGA. This study was planned to assess fetal weight pattern in women with diabetes in pregnancy and to evaluate whether overzealous glycemic control results in acute and chronic nutritional deprivation to fetus leading to SGA (proxy)FGR.

METHODS

This prospective observational study done over a period of 1 year (June 2017- June 2018) in department of obstetrics and gynecology of a tertiary care centre in North India (King George medical university) after taking institutional ethical clearance. All pregnant women booked for care received a preliminary assessment using standardized antenatal protocol which included a detailed history, demographic profile and routine antenatal investigations including universal screening for gestational diabetes with 75 gm 2 hours postprandial glucose test (DIPSI) as proposed by ministry of health and family welfare (MOHFW) guidelines 2015 on their 1st visit except in women who previously known diabetics. Women with blood sugar values ≥ 140 mg/dl on DIPSI test diagnosed as GDM. All pregnant women with GDM and all pre-gestational diabetic women with singleton pregnancy were registered after proper informed consent. Medical nutrition therapy (MNT) started in all women with caloric requirement calculated as per Indian council of medical research (ICMR) 1990 expert group guidelines.[5]

Post MNT, fasting and postprandial blood sugar was done after 2 weeks in all women diagnosed in first and second trimester and after one week in women diagnosed in third trimester of pregnancy. Target blood sugar desired in these women were fasting blood sugar <95 mg/dl, postprandial blood sugar <120 mg/dl. Extent of glycemic control was assessed by calculating mean of fasting blood sugar and mean of postprandial blood sugar in each trimester. In the study, as GDM was diagnosed in different trimesters, to bring homogeneity to data mean fasting and postprandial blood sugar value in 3rd trimester was calculated to assess extent of glycemic control in each patient (Table 1).

Table 1: Classification of extent of glycemic control in GDM.

Classification	Mean blood sugar (mg%)	
	Fasting	Postprandial
Good glycemic control	70-95	≤120
Under control	>95	>120
Over control	<70	

Since there are no well-defined guidelines for overzealous glycemic control in pregnancy, we took blood sugar level <70 mg/dl which is considered as hypoglycemia in general population value as reference value for over control. Women who were not controlled on MNT were started on metformin and/or insulin. Most of the women in under controlled group were the ones who first reported to our hospital in third trimester. Vasculopathy or end organ damage was assessed by 24 hours urine protein (for Nephropathy), fundus examination (for retinopathy) and sensory examination (for neuropathy).

In all the women registered in the study efforts were made to ensure a dating scan in first trimester, an anomaly scan in second trimester and one or more growth scan in third trimester. Even though our protocol included 4 weekly monitoring of fetal growth and estimated fetal weight, significant number of women did not visit the outpatient department regularly and therefore, ultrasound report was not available uniformly in third trimester in all women to estimate fetal weight (EFW). Hence, neonatal birth weight, after cutting umbilical cord within 30 minutes of birth using standardized machine in grams, was taken as proxy measure to estimate fetal weight in utero. Birth weight percentile was calculated for each baby by online tool available based on WHO standards.[6] SGA (FGR as proxy) was defined as birth weight <10th percentile for that gestational age and LGA (macrosomia as proxy) was defined as birth weight >90th percentile for that gestational age. Women diagnosed with abnormal fetal growth were managed as per hospital protocols.

Antepartum complications and risk factors, extent of glycemic control, mode of delivery were recorded for all registered women. Perinatal outcomes including mean birth weight, birth weight percentile and need for intensive care in neonatal period were also noted.

Statistical analysis

Data was analyzed using statistical package for social sciences version 21.0. Data has been represented as numbers and percentages. Central tendency has been shown as mean ± standard deviation. For comparison of data, independent samples 't' test and ANOVA have been used for continuous data. Categorical data have been analyzed using chi-square or Fisher exact test. Confidence level of the study was kept at 95%. Hence, a 'p' value less than 0.05 indicated a statistically significant association.

RESULTS

Out of 88 women with diabetes 83 were diagnosed as GDM and the remaining 5 were pre-gestational diabetics. Out of 83 women with GDM, 22 were diagnosed in first trimester, 46 in second and 15 in third trimester respectively. Mean age of women in study was 27.52±4.07 years (20-36 years) and mean BMI at first visit was 22.05±2.47 (18-29.61). Majority (77.3%) belonged to urban area and 79.5% were housewives (Table 2). Occupation was important as it helped in the calculation of level of physical activity (PAL) for calculation of caloric requirements for MNT.

Table 2: Demographic profile of patients in study.

Variables	N	Percent (%)
Age group (Years)		
20-25	29	33.0
26-30	40	45.5
31-35	16	18.2
>35	3	3.4
BMI (kg/m^2)		
Underweight (<18.5)	7	8.0
Normal weight (18.5-24.9)	69	78.4
Overweight (25.0-29.9)	12	13.6
Place of residence		
Rural	20	22.7
Urban	68	77.3
Occupation		
Housewife	70	79.5
Working	18	20.5
Parity		
Primigravida	23	26.1
Multigravida	65	73.9
Mode of delivery		
Vaginal	37	42.0
LSCS	50	56.8

Out of the 88 women in the study, 67 (76.13%) were managed on MNT alone, 19 (21.5%) required MNT with insulin and 2 (2.2%) given metformin with MNT. During follow-up, 9 (10.2%) women developed hypertensive disorder of pregnancy (all of them were preeclamptic), 21 (23.86%) had hypothyroidism and 2 (2.2%) had rheumatic heart disease. None of the women had chronic liver or renal disease or immunological disorders known to affect fetal growth. 3 women were excluded from fetal weight analysis as 2 (2.2%) women had intrauterine death at 32 and 26 weeks of gestation respectively and one woman had to go for medical termination of pregnancy at 18 weeks as fetus had Dandy Walker malformation. Out of 85 women who were analyzed for fetal weight, 76 (89.4%) had good glycemic control, 6 (7%) had over-zealous glycemic control and 3 (3.5%) had under-controlled sugars. Features of vasculopathy were assessed in all women and none had retinopathy or neuropathy. Six (27.2%) women out of 22 (diagnosed in first trimester) had proteinuria, 14 (30.4%) out of 46 (diagnosed in second trimester) and only 2 (13.3%) out of 15 (diagnosed in 3rd trimester) had proteinuria. Among women with pre gestational diabetes, 3 (60%) out of 5 had proteinuria. Out of 9 women with pre-eclampsia, 8 (88.8%) had proteinuria so it was not possible to know whether it because of pre-eclampsia/ complication of diabetes. Proteinuria detected in all these women micro-albuminuria suggesting only mild degree of nephropathy.

The 79 (89.77%) women delivered at term, 5 (5.68%) delivered in late preterm period (34-36^{+6}wk) and 1 had early preterm delivery (28-33+6 week). 46 (54.1%) neonates in the present study were SGA and only 2 (2.3%) neonates were LGA. The remaining 43.5% neonates were appropriate for gestational age (AGA). On further stratification of the AGA neonates based on the birth weight percentile, 29.4% neonates had birth weight between 10th-25th percentile. Hence majority, 83.51%, of neonates had a birth weight towards the lower end of the spectrum (<25th percentile) (Table 3).

Table 3: Distribution of neonates according to their birth weight percentile in pregnant women with diabetes (n=85).

Birth weight (%)	No.	Percentage (%)
<10th	46	54.11
10th-25th	25	29.4
26th-50th	6	7.1
51st-75th	4	4.7
76th-90th	2	2.3
>90th	2	2.3

Table 4: Relation of glycemic control in third trimester with fetal weight, (n=85).

Extent of glycemic control	N	SGA, n=46 (%)	AGA, n=37 (%)	LGA, n=2 (%)	Statistical significance
Good glycemic control (Mean FBS-70-95 mg%) (Mean PPBS-≤120 mg%)	76	41 (53.9)	34 (44.7)	1 (1.3)	χ2=3.61, (df=2); p=0.164
Over-controlled (Mean FBS-<70 mg%)	6	4 (66.7)	2 (33.3)	0 (0)	χ2=0.531, (df=2); p=0.767 (S)
Under-controlled (Mean FBS->95 mg%) (Mean PPBS->120 mg%)	3	1 (33.3)	1 (33.3)	1 (33.3)	χ2=13.2 (df=4); p=0.001

Table 5: Relation of extent of glycemic control in third trimester with mean birth weight, (n=85).

Characteristics	Total, (n=85)	Over controlled, (n=6)	Good glycemic control, (n=76)	Under controlled, (n=3)	Statistical significance
					χ2 and p
Mean birth weight ± SD (gm)	2721±4.52	2526±3.02	2714±4.32	3300±8.54	F=3.178, p=0.047

The 76 out of 85 women had good glycemic control in pregnancy, out of which 41 (53.9%) had SGA neonates, 1 (1.3%) was LGA and remaining 34 (44.7%) were AGA. Six women were in over-controlled group and out of which 4 (66.66%) had SGA and other 2 (33.33%) had AGA neonates. Only 3 women had under-controlled sugars, out of which each had AGA, SGA and LGA (Table 4). Out of 46 SGA neonates in this study, 10 (21.7%) required admission in neonatal care unit. Among the 37 AGA and 2 LGA neonates, the need of admission in NNU was 7 (18.9%) and one (50%) respectively. All these neonates admitted in NNU were discharged before tenth postnatal day.

DISCUSSION

Hyperglycemia whether gestational or pre-gestational is a common malady which complicates pregnancy and Asian ethnicity itself is a high-risk factor for development of gestational diabetes irrespective of pre-pregnancy BMI.[7] Hence, timely diagnosis and appropriate management of diabetes in pregnancy is crucial to avoid maternal and fetal complications. Fetal growth is a complex process affected by various maternal, fetal, and environmental factors. Diabetes in pregnancy is known to cause abnormal fetal growth. Although macrosomia is an accepted pattern of fetal growth in pregnant women with diabetes which is attributed to maternal hyperglycemia, small for gestational age is also frequently reported in this cohort. Small for gestational age (proxy FGR) in long standing diabetes can be explained by vasculopathy, however, in gestational diabetes it remains a clinical enigma. Contrary to literature showing increased rates of macrosomia in diabetes in pregnancy, in our study we found that 54.11% neonates were SGA/FGR.[8] Also 29.4% neonates had birthweight between 10^{th}-25^{th}. This was similar to findings reported by Avalos et al in their study where SGA was more prevalent in GDM mothers.[9]

One of the important goals of management of diabetes in pregnancy is to achieve a good glycemic control to decrease rate of macrosomia. In our study blood sugars were aggressively managed to achieve target fasting and postprandial blood sugars using MNT alone or combining it with metformin and/or insulin as needed. We were able to achieve optimal/good glycemic control in 76(89.4%) women and in this group only one (1.3%) woman had LGA neonate. On analyzing mean birth weight of neonates in this study, under-controlled group had significantly higher mean birth weight (p=0.047) (Table 5). On the other hand, when pregnant women with good and over controlled blood sugars (taken together) were compared with under-controlled group, incidence of LGA was significantly high in under-controlled group (p=0.009) (Table 4). Similarly, results were seen by Banerjee et al in their study where incidence of LGA were higher in uncontrolled group as compared to adequately controlled group[10]

Amongst the 46 women with SGA, only 4(8.6%) mothers had over-zealous blood sugar control. Majority, 41 (89.1%) SGA babies were born to mother with good/optimal glycemic control and thereby indicating that there was no significant effect of extent of glycemic control on fetal weight (Table 4).

Most (66.7%) mothers with over-zealous glycemic control had SGA/FGR neonates but this difference was not statistically significant (p=0.767), perhaps due to fewer number of cases in over-controlled group in the study. Interestingly, in the present study 53.9% mothers had SGA in the study despite good glycemic control suggesting some degree of chronic malnutrition in these women contributing to pathogenesis of SGA. It further raises the question of how tight a glycemic control is too tight? Similar finding was reported by Silva who found overall prevalence of SGA to be 3.5 times higher compared to LGA in 5271 women with GDM.[4]

In pregnancy complicated by diabetes with vascular involvement there is decreased uterine and placental blood flow. This leads to impaired nutrient transfer to the fetus causing fetal growth restriction. Rackham et al in their study provided evidence that hyperglycemia causes vasculopathy affecting utero-placental blood vessels leading to consequent fetal hypoxia and subsequently FGR.[11] In our study out of 46 women with SGA only 14 (30.4%) had microalbuminuria indicating mild degree of nephropathy in them. On the other hand, only 10 (27%) out of 37 AGA and 1 (50%) of 2 LGA neonate had microalbuminuria. On statistical analysis, microalbuminuria which was taken as a proxy measure of nephropathy, was not associated with fetal weight in the study (p=0.76). Majority of women in the study were GDM (94.3%) in which vasculopathy is usually not observed which could be the reason behind this non-association in this study.

Other factors which could affect fetal weight in these women were BMI, fetal gender, hypertensive disorder of pregnancy and heart disease. Maternal obesity is a risk factor for macrosomia. In the present study only two neonates were LGA and neither of the mothers were overweight/obese. On statistical analysis increased maternal weight (BMI> 25 kg/m^2) in this study was not related to altered fetal growth (p=0.206). This difference in the results could be again due to small cohort of women with increased BMI. Moreover, as pre-pregnancy weight was not available for calculating BMI, this could also have skewed the result. Out of the 85 live births 46 (54.1%) were females and remaining 39 (45.8%) were males but there was no relation between gender of the baby and birth weight which was contrary to results published by Macaulay et al in which male gender was a predictor LGA.[12] Hypertensive disorder of pregnancy is considered as a risk factor for SGA due to abnormal placentation. In the present study 9 women (10.2%) had hypertensive disorder of pregnancy out of whom 5 women (more than 50%) had SGA neonates even though association was not statistically significant (p=0.172). SGA is also attributed to fetal hypoxia and is known to occur in women with heart

disease. Rheumatic heart disease was present in only 2 women in this study, although no significant association was seen between fetal weight and heart disease (p=0.420), both these women had SGA neonates suggesting some role of hypoxia in SGA.

Limitations

The setting of the study being a tertiary care centre, fewer women were seen in over-controlled or under-controlled group. This small sample size of cohort with overzealous glycemic control and poor glycemic control could have skewed the results. The cut-offs for overzealous glycemic control taken in the study are arbitrary (same as the cut off for hypoglycemia) as no study/ guideline defines over controlled status for extent of glycemic control in women with gestational and pre-gestational diabetes mellitus.

CONCLUSION

The results in the study strongly supported the efficacy of good glycemic control in prevention of LGA/macrosomia. However, optimal glycemic control in third trimester does not guarantee appropriate growth in fetus as incidence of SGA/FGR neonates was fairly high (53.9%) in these women. The exact cause behind SGA in this cohort of women was elusive. This indicates that other factors like genetic growth potential of fetus, epigenetic factors, placental changes in diabetes and hormonal changes in the mother and fetus may be affecting fetal growth adversely leading to decreased fetal growth/ weight.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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