A COMPARATIVE STUDY OF MATERNAL EVENTS WITH TIGHT GLYCEMIC CONTROL IN DIABETIC PREGNANCIES

Samar Banerjee*, Uday Sankar Ghosh, Sankar Nath Mitra*****

ABSTRACT

Diabetic pregnancies are associated with increased obstetric and diabetic maternal complications, which can be lowered by normoglycemia. Two hundred forty diabetic pregnancies were selected and segregated into gestational diabetes mellitus (GDM,176) and pre gestational diabetes mellitus (PGDM,64). Each group was divided into 3 sub groups according to the terminal levels of glycemic indices. Tight control group (TC) had fasting plasma glucose (FPG) < 70 mg. /dl, 2 hr. postprandial plasma glucose (PPPG) < 100 mg. /dl. HBA_{1C} < 6.5%; acceptable control group (AC) had FPG 70-95 mg/dl. , PPPG 100-120, HBA_{1C} 6.5-7.5% and uncontrolled group (UC) had FPG > 95mg. /dl, PPPG > 120mg/dl and HBA_{1C} > 7.5%. Intra-group and international data comparisons of complications were done for the parameters of lower segment caesarean section (LSCS), pregnancy induced hypertension (PIH), preterm labor (PTL), wound sepsis (WS), and postpartum hemorrhage (PPH).

LSCS had a very high incidence for all sub groups. Tight control increased LSCS and lowered the incidences of PTL and WS in GDM but other parameters were unaltered. In PGDM, LSCS increased significantly with tight control but the rest was unaffected. Total complications excluding LSCS were not significantly different between the UC sub groups of GDM and PGDM. Compared to the international data GDM outcome was worse while PGDM results were similar.

In conclusion, tight control was beneficial for preventing some, but not all maternal complications. The role in PGDM was not very clear, probably, preconception status and associated vasculopathy were important confounding factors.

KEY WORDS: Pregnancy; Diabetes; Tight glycemic control; Maternal outcomes.

INTRODUCTION

Diabetes mellitus is a common disorder complicating pregnancy and can lead to maternal complications (1-6) .There was a time when diabetes was inconsistent with conception, and those few who conceived had high maternal mortality (30%) (4). Though the concept of pregestational diabetes mellitus (PGDM) was there, the concept of gestational diabetes mellitus (GDM) crystallized around late 50s (5). PGDM has more impact than GDM on outcome and this is not dependent on the type of diabetes mellitus (DM) but primarily on the extent of vasculopathy (6). Maintenance of blood glucose level within normal range diminishes the incidences of maternal complications (7). In the Indian context, data about the effective level of glycaemic control is limited (8, 9, 11). Common maternal complications include caesarean section, pregnancy induced hypertension, preterm labor, preterm delivery, wound sepsis, postpartum hemorrhage, pyelonephritis, hydramnios, diabetic ketoacidosis (DKA), hypoglycemia, ecclampsia and maternal mortality (7, 6, 10). There are also certain associated risk factors other than hyperglycemia which can confound the outcomes (age > 30, BMI > 30 etc) (3). Our aim was to determine the incidence of maternal complications in Indian diabetic mothers with tight glycemic control or otherwise and comparison with relevant international data.

MATERIALS AND METHODS

This prospective study was undertaken at N.R.S. Medical College and Hospital, Kolkata. Consecutive cases of pregnancy diabetes were selected and matched from the antenatal clinic of Gynecology and Obstetric Department between April 2001 and March 2004. Cases were advised to attend the antenatal OPD four weekly up to 28 weeks of pregnancy, and then every two weeks up to 36 weeks and weekly thereafter. They were admitted if required.

*Professor, **Associate Professor, ***Assistant Professor, NRS Medical College, Kolkata, India

Simultaneous glycemic monitoring and therapy adjustment was done from the diabetes clinic. Plasma glucose (venous blood) was estimated by enzymatic method. The cases were segregated into two groups (1) Gestational Diabetes Mellitus (GDM) (2) Pre-Gestational Diabetes Mellitus (PGDM) (12). The maternal outcome parameters included were lower segment caesarean section (LSCS), pregnancy induced hypertension (PIH), pre term labor (PTL) wound sepsis (WS) and post partum hemorrhage (PPH) (13).

GDM cases were selected on the basis of Carpenter and Coustan's modification of O'Sullivan-Mahan's criteria (13). PGDM were those subjects having definite history of pre-pregnancy hyperglycemia documented by previous blood sugar reports and showing fasting plasma glucose level (FPG) = 126 mg/dl (any trimester) (14). Patients with clinical peripheral vasculopathy, neuropathy, retinopathy, 3+ proteinuria or rapidly deteriorating renal function and cardiac failure were excluded.

Post selection , both GDM and PGDM were put on diet and light exercise for 2 weeks, then FPG and 2 hr. postprandial plasma glucose (PPPG) were repeated (15, 16). Cases having FPG >95 mg/dl and/ or PPPG >120 mg/dl were given insulin therapy. Those not requiring insulin were also followed up weekly (15-17). HbA_{1C} was done monthly and finally at the end of third trimester. Vaginal delivery was encouraged for all (18). LSCS was done in patients of uncontrolled pre-eclampsia, ante partum hemorrhage, pre labor rupture of membrane, non-progression of labor, fetal distress and in patients who completed 40 weeks of pregnancy without onset of labor (18). Tight glycemic control (TC) was the goal for all the cases, however, at the end of the study all cases could not fulfill the target and so both GDM and PGDM groups were divided into three sub-groups (19-21, 28). For cases with variable parameters HBA_{1C} level was decisive for sub group segregation.

The criteria for the sub-group division were: *Tight glycemic control* (TC): Patients with FPG level ‹70 mg/dl, 2 hr PPPG level ‹100 mg/dl, and HbA_{1C} ‹6.5%; *Acceptable glycemic control* (AC): Patients with FPG level between 70-95 mg/dl, 2 hr PPPG level between 100-120 mg/dl and HbA_{1C} between 6.5-7.5%. *Uncontrolled glycemic group* (UC): Patients with FPG level >95 mg/dl, 2 hr. PPPG level >120 mg/dl and HbA_{1C} >7.5%. These groups emerged due to variation in the initial reporting and lapses in the follow up by the case herself. Control group was not allowed by the ethical committee. The subgroups acted as their own controls.

The statistical analysis of complications and risk factors between various groups were done by standard error of difference between two means and standard error of difference between two proportions for a large sample. A p value of less than 0.05 was taken to be significant.

OBSERVATIONS

A total of 289 cases were screened consecutively, of which 27 cases were lost in follow-up, 12 were excluded because they had vasculopathy, retinopathy, nephropathy or neuropathy and 10 excluded for the purpose of age and risk factor matching. Ultimately, 240 cases were selected, of which 176 were in the GDM group and 64 in PGDM group. The mean age in the GDM group was 29.48±4.23 years and in PGDM 28.18±5.5 years ($p > 0.05$) and the BMI (at presentation) was 30.29±6.32 vs. 27.63±3.62 ($p < 0.05$). Of the GDM cases, 44 (25%) were detected before 24 weeks, 32 (18.2%) between 24 and 28 weeks, 72 (40.9%) between 29 and 34 weeks and 28 (15.9%) beyond 34 weeks. Of the 64 PGDM cases, 48 (75%) had diabetes for less than 5 years, 8 patients presented before 24 weeks (23.4%), 11 (17.2%) between 24 and 29 weeks, 7 (10.9%) between 29 and 34 weeks and 38 (59.4%) after 34 weeks.

Table 1: Distribution of Maternal Complications

	Complications % (=n)						Cases with complications excluding LSCS%(n=)	
	LSCS	PIH	PTL	WS	PPH			
GDM	TC	95.45	33.3	4.16	0	4.16	33.3	TC+AC
n=176	n=96							34.3
	AC	72.92	27.27	18.18	9.09	0	36.3	
	n=44							
	UC	88.9	33.3	11.1	0	0	44.4	
	n=36							
PGDM	TC	100	0	0	0	0	0	TC+AC
n=64	n=4							16.7
	AC	60	20	0	0	0	20	
	n=20							
	UC	50	30	10	0	0	40	
	n=40							

LSCS – Lower segment caesarean section, PIH-pregnancy induced hypertension, PTL – Pre-term labor, WS-Wound sepsis, PPH – Post partum hemorrhage. n= number of cases, TC-Tight control, AC-Acceptable control, UC-Uncontrolled

The GDM and PGDM groups were matched by the following risk factors: age =30 years, BMI = 30, past history of (h/o) macrosomia, perinatal death, family h/o DM, hypothyroidism, unbooked status. For multiparity and past h/o GDM there was significant inter-group difference (11.4% vs. 0%; 6.8% vs. 12.5%). Intra group risk factor variability was not done. In the GDM group, age =30 years had the highest incidence (45.5%), while in the PGDM group, family h/o DM had the highest incidence. Of the GDM patients, 96 achieved tight control (TC), 44 had acceptable control (AC) and 36 were uncontrolled (UC). In the PGDM group, 4 had tight Control (TC), 20 had acceptable control (AC), and 40 were uncontrolled (UC). In 16 patients (9.09%) of the TC subgroups of GDM and 10 patients (15.67%) of AC, sub groups of PGDM reported documented hypoglycemia. There was no report of diabetic ketoacidosis or appearance of retinopathy or nephropathy. The incidence of significant maternal hypoglycemic attacks was not very high**.** Only two patients of the PGDM sub group had a PPPG more than 300 mg/dl. Most of the uncontrolled patients had a PPPG level < 220 mg/dl and the FPG < 140 mg/dl**.** Table - 1 depicts the distribution of the maternal complications. Table-2 shows the analyses of the results and Table-3 outlines the comparison and statistical significance of our data with similar international data.

Table 2: Complications Observed in Study Group.

	Gestational Diabetes Mellitus	Pre-gestational Diabetes Mellitus
Lower Segment Caesarean Section (LSCS)	TC > AC. (p< 0.01), AC vs. UC (NS), TC vs. UC (NS)	TC>UC (p<0.05), TC vs. AC and AC vs. UC (NS)
Pregnancy induced hypertension (PIH)	TC vs. AC vs. UC (NS)	TC vs. AC vs. UC (NS)
Pre-term labor (PTL)	TC vs. UC (NS), AC vs. UC (NS) AC > TC (p< 0.01)	TC vs. AC vs. UC (NS)
Wound sepsis (WS)	TC vs. UC (NS), AC vs. UC (NS), AC > TC (P < 0.01)	Incidence was nil in all the sub groups.
Post Partum hemorrhage (PPH)	TC vs. AC vs. UC (NS)	Incidence was nil in all the sub groups.
Complications	TC vs. AC vs. UC (NS)	TC vs. AC vs. UC (NS)

TC: Tight Control *UC: Uncontrolled*
AC: Acceptable Control *NS: Not Significant*

DISCUSSION

Controversy exists about the ideal degree of the glycemic control for maximum benefits (21). The 4th International Workshop conference on GDM has proposed FPG=95 mg/dl 1 hr. PPPG=140 mg/dl and 2 hrs. PPPG =120 mg/dl as the glycemic targets (13). The DCCT Research group had also set a FPG level of 70-100 mg/dl and 1 hr. PPPG level =140 mg/dl as the target values, for their intensive therapy for the PGDM patients (28). The first sub-group with the lowest glycemic indices was regarded as tight control (TC) subgroup. The 2nd subgroup of patients conformed to the glycemic goals of the well-known trials – accepted control group (AC) (16, 20, 21). In our study, 24 out of 36 cases of UC subgroup of GDM group and 28 out of 40 cases of PGDM group attended the antenatal clinic at or after 38 weeks of pregnancy, so effective control could not be implemented.

Table 3: Comparisons with International Data

	GDM	SIGNIFICANCE	PGDM	SIGNIFICANCE
LSCS	[18] Hod et al vs. AC [22]Moses et al vs. TC	AC >Hod P<0.01 TC>Moses P<0.01	DCCT vs. TC AC UC	NS NS NS
PIH	Coustan[7] et al vs. TC. AC, UC. AC,	[7]Coustan < TC, UC – p< 0.01.	[25]Demarini et al vs. TC AC UC	NS NS NS
PRETERM LABOUR	[23]Goldman et al vs. TC AC UC	 NS S(P < 0.05) NS	[28]DCCT vs. TC AC UC	NS NS NS
WOUND SEPSIS	[29]Jacobson et al. vs. TC AC UC	Jacobson > TC (p< 0.05) NS Jacobson > UC (p< 0.05)	No comparable data	
POSTPARTUM HAEMORRHAGE	No comparable data		No comparable data	

S = significant, NS=not significant

Incidences of caesarean section were 95.45%, 72.92% and 88.9% in the TC, AC, and UC subgroups of GDM respectively. In the PGDM group it was 100%, 60% and 50% respectively. In the GDM group the incidence of caesarean section in the TC sub group was significantly higher than that the AC sub group while TC was significantly more compared to the UC in case of PGDM patients. The incidences of caesarean sections in all the subgroups of GDM in the present study were higher as compared to those of previous workers [Hod et al (18), Moses et al (22)]. However, the outcome for PGDM patients did not differ with those of the intensive regimen group of DCCT. The high incidence in the GDM sub groups could not

be related specifically to any of the other obstetric complications or a large baby size. This might be related to lack of modern intrapartum and post partum monitoring facilities as well as apprehension of loosing a valuable pregnancy on part of the Obstetrician (23, 24).

The incidence of PIH in all the sub groups was not found to be significantly different. Compared to the International data, the GDM sub groups showed a significantly higher incidence [Coustan et al (7) $p< 0.01$], however, for the PGDM patients, there was no difference with Demarini et al (25). Probably, dietary salt intake and increased sensitivity played an important role for the GDM. Insulin for a short duration is also known for retaining sodium. For the PGDM cases, already present but clinically undetected vasculopathy might have been responsible (24.26, 27).

Incidence of preterm labor in the TC sub group of GDM was significantly less than the AC sub group (4.16% vs. 18.18%), though there was no difference with UC sub group. For the PGDM patients, there was no significant difference between the sub groups. AC sub group of GDM showed significantly higher incidence compared to those reported by Goldman et al. (23). GDM data of this study did not differ with DCCT (29). No correlation was done with preterm delivery. The range of plasma glucose in the AC subgroup was probably more conducive to certain infections in the genital tract and or pain sensation was better perceived at this range (7, 14, 23). Fetal size might also have been responsible, lack of difference between TC and UC is an indicator.

Wound sepsis was 9.09% in the AC sub group of GDM. This was not found in other sub groups. This is also comparable with International data [Jacobson et al (29), 12.4%]. This also suggests that this range of glucose is probably more conducive to infections. However, the absence of this finding in the PGDM group is rather intriguing. Probably, local vascular conditions (vasculopathy) present in all the subgroups but not apparent on usual clinical detection, was responsible for such a finding (1, 7).

The incidence of PPH was 4.16% in the TC subgroup of GDM. No other sub group had this complication. No comparable data in this respect is available in the literature. Probably, tighter control of sugar leads to some form of neovascularisation in the uterus. However, this finding does not have any statistical significance.

Total complications (except LSCS) of all the sub groups were comparable except the tight control group of PGDM which showed a lower trend (0%) though it was not significant.

Caesarean section shows the highest incidence in all sub groups, with the TC subgroups showing a significantly higher incidence. Pregnancy induced hypertension in GDM patients is a significant problem at all levels of glycemic control. The tight control in GDM patients lowers incidences of PTL and WS but does not favorably alter other parameters. For the PGDM patients the status of intra partum glycemia may not be necessarily associated with outcome alterations in a country like ours. Probably uteroplacental vasculopathy (most of our cases being type 2 DM with a higher chance of late detection),which could not be correlated with apparent clinical vasculopathy, played an important role or the preconception status is more pivotal. However, the PGDM data of our group was surprisingly comparable to those of the International groups [DCCT (28) and Demirini et al (25)], who had a higher incidence of type 1 DM for their PGDM patients.

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