Effect of Tight Glycaemic Control on Fetal Complications in Diabetic Pregnancies

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Abstract

Aims : To find the incidence of fetal complications in Indian diabetic mothers with tight glycaemic control (TC), its comparison with other levels of glycaemic control, i.e., acceptable control (AC), uncontrolled (UC), and relevant international data.

Methods : A total of 240 mothers with diabetes mellitus (DM) and pregnancy were risk-matched and selected from the Antenatal Clinic of NRS Medical College, 176 of whom had gestational diabetes mellitus (GDM) and 64 had pregestational diabetes mellitus (PGDM), and were put on exercise, diet and or insulin therapy. Glycaemic parameters monitored include fasting plasma glucose (FPG), 2 hr. postprandial plasma glucose (PPPG) and HbA_1C. TC had - FPG < 70 mg /dl, PPPG < 100 mg /dl, HBA_1C < 6.5%; AC with FPG 70-95 mg /dl, 2 hr. PPPG 100-120, HBA_1C 6.5-7.5% and UC had FPG > 95 mg/ dl, 2 hr. PPPG > 120mg/dl and HBA_1C > 7.5%. Fetal parameters monitored included large-for-date babies (LGA), small-for-date babies (SFD), birth asphyxia, perinatal death, neonatal hypoglycemia, neonatal hypocalcaemia and congenital anomalies.

Results : (i) LGA - AC had the best results (0% vs. 12.5 and 22.29%); (ii) SFD - TC and AC had worst results (16.7% and 18.18% vs. 0%); (iii) Birth asphyxia - AC fared worse 18.18% vs. 4.16% and 0%; (iv) perinatal death and congenital anomalies showed significant reduction with tight control (4.16% and 0% respectively); (v) Neonatal hypoglycemia is lowered in TC compared with UC while neonatal hypocalcaemia does not show any alteration. For PGDM patients there is little intra-group variability of the parameters. The UC subgroups of GDM fared better than PGDM as far as all complications and congenital anomalies were concerned. Compared with international data, there is a dichotomy of the results of GDM and PGDM.

Conclusion : For GDM patients all parameters may not be uniformly affected by the same degree of glycaemic control. A tight control may not be the only factor to decide on the outcomes for PGDM patients. ©

Introduction

In the early part of the 20th century true diabetes mellitus (DM) was inconsistent with conception, with a very high perinatal mortality (60-70%). With improved glycaemic control and advanced neonatal care perinatal adversities have approached that of non-diabetic mothers.[1-3] The concept of gestational diabetes (GDM) started crystallizing around late 1950s.[6] Vasculopathy emerged as an important influencing factor in the outcome of pregnancies with pre-gestational diabetes mellitus (PGDM).[1] However, the threshold for antihyperglycaemic therapy and the tightness of the glycaemic control are still controversial.[1,4] Maternal hypoglycemia probably does not increase the incidence of congenital anomalies.[14] Careful search of literature provides little data in the Indian perspective.[5]

Aims of the Study

The present study was planned to find out the incidences of fetal complications in Indian diabetic mothers with tight glycaemic control. Comparisons have been made with other levels of glycaemia and relevant international data.

Methods And Materials

This prospective study was undertaken at NRS Medical College and Hospital, Kolkata. Cases with pregnancy and

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diabetes mellitus were selected consecutively from those attending the Antenatal Clinic of Gyne and Obst. Department between April 1999 and March 2003. Detailed clinical history and findings of physical examinations were recorded. Patients were advised to attend the Antenatal OPD every four weeks up to 28 weeks of pregnancy, every two weeks up to 36 weeks and weekly thereafter. They attended the Diabetes Clinic weekly for plasma glucose estimation, diet advice and insulin adjustment accordingly. Plasma glucose of 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).[6,4]

Criteria for selection of cases

(1) GDM cases : On the basis of Carpenter and Coustan's modification of O'Sullivan-Mahan's criteria.[6,1] (2) PGDM cases: Patients having definite history of pregnancy hyperglycaemia documented by previous blood sugar reports and showing fasting plasma glucose level (FPG) ≥ 126 mg/dl (any trimester), were considered as cases of PGDM[1] (3) Cases with clinical vasculopathy, neuropathy, retinopathy and proteinuria more than 2+ were excluded from the study.

Post-selection management

Both GDM and PGDM were put on diet and light exercise for 2 weeks, then FPG and PPPG were repeated.[7] Patients showing FPG > 95 mg/dl and /or 2 hr. post-prandial plasma glucose (PPPG) > 120 mg/dl were subjected to insulin therapy.[1] Cases not requiring insulin were also followed. In all the cases, HbA_1C was done in third trimester. During each antenatal visit, maternal body weight, blood pressure was recorded and the urine was examined for WBC, RBC, albumin, sugar and ketones. Fetal growth was assessed clinically. Ultrasonography was done, once in each trimester to assess fetal growth, fetal congenital anomalies, liquor volume and placental position. Fetal echocardiography was done in selected PGDM cases with poor periconceptional blood sugar control. Vaginal delivery was encouraged in all the cases. Caesarean was done if clinically indicated or the obstetricians thought it was necessary. Post-delivery clinical assessment of the newborn baby was done and chord blood was sent for estimating glucose and calcium levels (within 30 minutes to 4 hours). Fetal complication parameters included were large-for-date (> 90th percentile for gestational age), small-for-date (< 10th percentile for gestational age), birth asphyxia (Apgar score < 6), congenital anomalies, perinatal death (fetal death after 28th week of gestation and up to 1 week after birth), metabolic disorders (hypoglycaemia-defined as less than 35 mg/dl. in term and less than 25 mg/dl. in pre-term babies, hypocalcaemia-defined as less than 7 mg/dl.), if present, were recorded.[8,9]

Both GDM and PGDM groups were divided into the following three sub-groups.[10,11] For patients with variable parameters HbA_1C level decided the group of inclusion. (1) Tight Glycaemic Control (TC) : Patients with FPG level < 70 mg/dl, 2 hr PPPG level < 100 mg/dl, and HbA_1C < 6.5% following treatment. (2) Acceptable glycaemic 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% following treatment. (3) Uncontrolled glycaemic group (UC): Patients with FPG level > 95 mg/dl, 2 hr PPPG level > 120 mg/dl and HbA_1C > 7.5% in spite of treatment were included in this group. These groups were not specifically preplanned, as target was tight control, but were formed during the course of the study due to variation in the initial reporting time and at times lapses in the follow up. No control group was taken as allowing hyperglycaemia to persist deliberately during pregnancy is unethical. The spontaneously evolving subgroups acted as their own controls and the incidences of different fetal complications were finally analysed on a comparative basis amongst these three groups. Comparison with relevant international data has also been done. The statistical significance of complications and risk factors between various groups were done by standard error of difference between two means and standard error of difference between proportions for a large sample. A 'p' value of less than 0.05 was taken to be of significance throughout the study.

Table 1: Distribution of fetal outcome parameters

		Complications % (n)							Cases with complications % (n)	
		LGA	SFD	Birth asphyxia	Perinatal death	Hypo-glycaemia	Hypo-calcaemia	Congenital anomaly		
GDM (n=176)	TC (n=96)	12.5% (12)	16.7% (16)	4.16% (4)	4.16% (4)	12.5% (12)	4.16% (4)	0	37.5% (36)	TC+AC 40% (56)
	AC (n=44)	0	18.18% (8)	18.18% (8)	18.18% (8)	18.18% (8)	9.09% (4)	0	45.45% (20)	
	UC (n=36)	22.2% (8)	0	0	22.2% (8)	22.2% (8)	0	11.1% (4)	55.55% (20)	
PGDM (n=64)	TC (n=4)	0	0	0	0	0	0	0	0	TC+AC 33.3% (8)
	AC (n=20)	0	20% (4)	20% (4)	20% (4)	0	0	0	40% (8)	
	UC (n=40)	20% (8)	30% (12)	0	40% (16)	10% (4)	10% (4)	30% (12)	80% (32)	

* LGA = Large for gestational age, SFD = Small for date

Table 2 : Result analysis

Outcome for GDM patients	Outcome for PGDM patients
1. LGA - TC vs. AC (NS), TC vs. UC (NS), UC > AC (p< 0.01)	1. LGA - TC vs. AC vs. UC - NS
2. SFD - TC > UC (p< 0.01), AC > UC (P < 0.01), TC vs. AC (NS)	2. SFD - TC vs. AC vs. UC - NS
3. Birth asphyxia - TC vs. AC (NS), TC vs. UC (NS), AC > UC (p < 0.05)	3. Birth asphyxia - TC vs. AC vs. UC - NS
4. Perinatal death - TC < UC (p < 0.01), TC < AC (p < 0.05) , AC vs. UC (NS)	4. Perinatal death - TC vs. AC vs., UC - NS
5. Hypoglycemia - TC < UC, (p < 0.01) , TC vs. AC (NS) AC vs. UC (NS)	5. Hypoglycemia - TC vs. AC vs. UC - NS
6. Hypocalcaemia - TC vs. AC vs. UC (NS)	6. Hypocalcaemia - TC vs. AC vs. UC - NS
7. Congenital anomaly - TC < UC, AC < UC (p< 0.05)	7. Congenital anomaly - TC vs. AC vs. UC - NS

NS = Not significant 'p' value.

Observations And Results

A total number of 289 consecutive cases were collected by screening. Twenty-seven cases were lost to follow up, 12 cases were excluded as they were not ultimately fitting the selection criteria and 11 cases were excluded for the purpose of age group and risk factor matching. Ultimately the study was done on 240 patients of which, 176 belonged to the GDM group and 64 to the PGDM group. Mean age of GDM group was 29.48 ± 4.23 years and PGDM group was 28.18 ± 5.5 years (NS). Of the 176 GDM patients 44 were detected before 24 weeks, 32 between 24 and 28 weeks, 72 between 29 and 34 weeks and 28 beyond 34 weeks. Forty-eight of the PGDM patients were detected to have DM for less than 5 years and the rest for more than 5 years. Table 1 enumerates the distribution of fetal adverse outcome parameters amongst the various subgroups. Table 2 depicts the statistical analysis of the results. Comparison with international data is presented in Table 3.

The percentage of complications of the UC subgroups of PGDM was significantly higher than that of the UC subgroups of GDM (55.5% vs. 80% $p < 0.05$). The incidence of congenital anomaly and SFD babies in the UC subgroup of PGDM was significantly higher compared to the UC subgroup of GDM (30% vs. 11.1%; 18.18% vs. 30% respectively). Among the patients with congenital anomalies, patients in the GDM groups two had meningocoele and two had microcephaly. Of the 12 patients of PGDM groups five had microcephaly, two had microcephaly with wide open fontanel, two had hairy pinna and two had left ear deformity with agenesis of right kidney and one had duodenal atresia. All the fetal echocardiograms and Doppler in selected GDM cases with poor control were normal.

Discussion

Diabetes mellitus is a common malady to complicate pregnancy[1,4] Both GDM and PGDM can adversely affect the fetal outcomes.[10] Insulin therapy with tight glycaemic control has shown to reduce these complications significantly[9,10] However, the ideal degree of glycaemic control is still controversial.[16,17,2] The 4th International Workshop Conference of GDM and the DCCT Research Group had their own defined goals.[1,11] In the present study, of the GDM patients 96 (54.5%) belonged to the TC, 44 (25%) to the AC, and 36 (20.5%) to the UC subgroup. Of the 64 PGDM patients four (6.3%) were TC, 20 (31.3%) were AC and 40 (62.5%) belonged to UC subgroup. Twenty-four out of 36 patients of UC sub group of GDM and 28 out of 40 patients of PGDM presented to the antenatal clinic at or after 38 weeks. Effective glycaemic control could not be implemented in these cases, naturally, they acted as controls.

The incidence of LGA babies were 12.5% in the TC subgroups, 22.2% in the UC of GDM and 20% in the UC subgroup of PGDM. UC subgroup of GDM had a significantly higher incidence compared to the AC subgroup, while there was no difference with TC subgroup. Probably persistent hyperglycemia for the UC group and intermittent rebound hyperglycemia for the TC subgroup played an important role.[18] The UC subgroup of GDM showed higher incidence compared to the tight control group of Moses *et al*.[12] The AC subgroup had a lower incidence while with TC subgroup there was no significant difference. For all the subgroups of PGDM there was no difference with DCCT[11] data (intensive therapy arm). The incidences of SFD babies were 16.7% and 18.2% in TC and AC subgroups of GDM patients; 20% and 30% in the AC and UC subgroups of PGDM patients. TC and AC subgroups of GDM had a significantly higher incidence compared to the UC subgroup. This was probably associated with a lower glucose level of the mother.[20] However, no analyses with preterm delivery have been done. The TC and AC subgroups of GDM patients have higher incidences of SDF babies compared to Moses *et al*,[12] however, the PGDM subgroups did not have any difference with the DCCT group.[11,12]

The incidences of neonatal birth asphyxia were 4.16% in TC and 18.2% in AC of GDM patients while it was 20% in AC of PGDM. There was no difference between the TC and AC subgroups of GDM, but the AC subgroup showed a significantly higher incidence compared to the UC subgroup. Higher incidence of SFD babies could be the contributing factor. However, lung maturity function was not assessed. There was no significant difference between the PGDM subgroups. The GDM patients when compared with international data (Persson *et al*)[9] only AC subgroup showed a significantly higher incidence. The UC subgroup of PGDM had a higher incidence when compared to the DCCT group. The incidences of perinatal death were 4.16%, 18.2% and 22.2% in the TC, AC and UC subgroups of GDM respectively while it was 0%, 20% and 40% in TC, AC and UC subgroups of PGDM. The TC subgroup of GDM showed a significantly

Table 3 : Comparison with international data

Outcome parameters	GDM	Significance	PGDM	Significance
LGA	TC vs. Moses *et al*[12]	N.S.	DCCT[11] vs. TC	N.S.
	AC vs. Moses *et al*	AC < Moses p < 0.05	AC	N.S.
	UC vs. Moses *et al* (TC)	UC > Moses (TC) p < 0.05	UC	N.S.
SFD	TC vs. Moses *et al*	TC > Moses p< 0.05	DCCT vs. TC	N.S.
	AC vs. Moses *et al*	AC > Moses p< 0.05	DCCT vs. AC	N.S.
	UC vs. Moses *et al*	N.S.	DCCT vs. UC	UC > DCCT p < 0.01
Birth asphyxia	TC	TC - NS	DCCT vs. TC	N.S.
	AC vs. Persson *et al*[9]	AC > Persson(p<0.01)	DCCT vs. AC	N.S.
	UC	UC - NS	DCCT vs. UC	UC > DCCT p < 0.01
Perinatal death	TC vs., Hod *et al*[13]	TC, AC, and UC >	DCCT vs. TC	N.S.
	AC vs. Hod *et al.*	Hod *et al*	DCCT vs. AC	N.S.
	UC vs. Hod *et al.*	p < 0.01	DCCT vs. UC	UC > DCCT p < 0.01
Neonatal hypoglycaemia	TC	TC> Persson	DCCT vs. TC	DCCT > TC
	AC vs. Persson *et al*[19]	AC> Persson	DCCT vs. AC	> AC
	UC	UC> Persson (p < 0.01)	DCCT vs. UC	> UC (p < 0.01)
Neonatal hypocalcaemia	TC	NS	DCCT vs. TC	N.S.
	AC vs.Weintrobe *et al*[14]	NS	DCCT vs. AC	N.S.
	UC	NS	DCCT vs. UC	N.S.
Congenital anomalies	TC	TC< Schaefer(P<0.01)	DCCT vs. TC	Vs. TC-NS
	AC vs. Schaefer *et al*[15]	NS	DCCT vs. AC	Vs. AC-NS
	UC	NS	DCCT vs. UC	UC > DCCT p < 0.01)

NS : Not significant.

lower incidence compared to the AC and UC subgroup.[16] The PGDM subgroups did not show any significant difference. All the subgroups of GDM showed a higher incidence compared to Hod *et al*.,[13] while only the UC subgroup of PGDM showed a higher incidence compared to the DCCT group. Better neonatal monitoring and intensive care facilities might be responsible for this, but the data for the PGDM patients can not be explained.

Incidence of neonatal hypoglycemia was 12.5%, 18.2% and 22.2% in the TC, AC and UC subgroups of GDM respectively. Of the PGDM only the UC subgroup had a 10% incidence. Of the GDM subgroups TC was significantly less than UC, none of the others were significant.[14] There was no inter-subgroup difference for the PGDM patients. For the GDM patients all the subgroups showed a higher incidence compared to the data of Persson *et al*, [9] while for the PGDM patients the DCCT intensive therapy arm showed a higher incidence compared to all the subgroups. Probably, glycaemic control of Persson *et al* was tighter compared to our study and in case of the DCCT trial our control was better. Neonatal hypocalcaemia was 4.16% and 9.09% of TC and AC of GDM and 10% of UC of PGDM. Other subgroups did not have this complication. This parameter has quite a few confounding variables.[8] Usually, it is found to be lowered with tighter control.[2] For all the subgroups of GDM and PGDM there was no significant difference. There was no significant difference with the international data also (GDM vs. Weintrobe *et al* and PGDM vs. DCCT).[14,15] Incidences of congenital anomalies were 11.1% and 30% in the UC sub groups of GDM and PGDM respectively. None of the other subgroups had this complication. For the GDM patients TC and AC subgroups had a significantly lower incidence of this complication.[4, 14,19] The PGDM patients did not show any inter-subgroup significance of difference. When compared to international data, the TC subgroup of GDM showed a lower incidence compared to Schaefer *et al*[15] while in case of PGDM patients only the UC subgroups showed a higher incidence compared to the DCCT data.

Conclusion

Fetal complications, singly or in combination were found in all the subgroups of GDM patients. PGDM patients showed a higher incidence of SFD babies, congenital anomalies and total complications as a whole.[8] Tighter glycaemic control can favourably alter adverse outcome parameters in case of GDM patients. But its effect on PGDM patients is questionable. Probably factors other than peri-conceptional normoglycaemia play significant role (? vasculopathy, preconception BMI, preconception glycaemic control).[8,17,18] For the GDM patients all the parameters are not uniformly affected by the same level of glycaemia (incidence of LGA was not different in TC and AC subgroup; incidence of birth asphyxia was not different in TC and UC groups; incidence of hypoglycemia was no different in TC and AC group while

for AC group there was a lower incidence of LGA and higher incidence of perinatal death).[16,18] Probably a single tight control blood sugar level can not be prescribed for preventing all the complications.[3,20] When compared with international data, our results show a clear dichotomy between GDM and PGDM patients. PGDM patients of our study with tighter control hardly showed any difference with the DCCT trial group (though most of our patients were Type-2 while those of DCCT were Type-1). The GDM patients results were compared with various international data, for some parameters (AC for LGA, neonatal hypocalcaemia, congenital anomalies) our study results were better while for others (SFD, birth asphyxia in AC, perinatal death and neonatal hypoglycaemia) it was worse.

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