



Pregnancy Outcomes in Pre-gestational and Gestational Diabetic Women in Comparison to Non-diabetic Women – A Prospective Study in Asian Indian Mothers (CURES-35)

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Abstract

Background and objective : Diabetes can complicate pregnancy but it is not the major complication of pregnancy. Though prevalence of diabetes is alarmingly high among Indians there have been very few studies assessing the effect of diabetes on pregnancy outcomes, particularly comparing pre-gestational diabetes mellitus [PGDM] and gestational diabetes [GDM] with non-diabetic mothers.

Methods : Pregnant women attending the Dr. Mohan's Diabetes Specialities Centre, a tertiary care centre for diabetes in Chennai in southern India were selected for the study. PGDM and GDM were defined using standard criteria. Out of the 245 pregnant women with diabetes registered at the centre, follow up data was available for 225, which included 79 PGDM and 146 GDM subjects. Non-diabetic controls (n=30) were recruited from the ongoing population based study the Chennai Urban Rural Epidemiology Study (CURES). Details of outcome variables including abortions, mode of delivery, congenital anomalies and neonate's birth weight were documented.

Results : Women with PGDM had significantly higher fasting plasma glucose [$p < 0.001$] and fructosamine [$p < 0.001$] levels compared to GDM. Proportion of women who underwent abortions was 0% in non-diabetic controls, 10.1% in PGDM and 2.7% in GDM and the difference between PGDM and GDM was statistically significant [$p = 0.04$]. Prevalence of 'low birth weight' babies in the study groups were, 14.3% in non-diabetic mothers, 12.3% in PGDM and 8.2% in GDM. The prevalence of 'large babies' was higher in GDM [27.6%] and PGDM [19.2%] groups compared to non-diabetic controls [7.1%] but the differences reached statistical significance only in the GDM group [$p = 0.04$]. Prevalence of congenital anomalies was 0% among non-diabetic controls, 3.8% in PGDM and 1.4% in GDM but the differences did not reach statistical significance. A significant increase in frequency of abortions [trend chi square = 5.67, $p = 0.017$] and 'low birth weight' babies [trend chi square = 4.761, $p = 0.029$] was observed with increasing fructosamine levels in the diabetic mothers.

Conclusion : Women with diabetes have worse pregnancy outcomes compared to non-diabetic mothers with and those with pre-gestational diabetes fare worse than those with gestational diabetes. The study emphasizes the fact that strict glycaemic control is extremely important during pregnancy. ©

Diabetes complicates between 1-20% of all pregnancies worldwide, which includes pre-gestational diabetes mellitus (PGDM – also referred to as diabetes complicating pregnancy) and gestational diabetes mellitus (GDM).¹ There are several studies in the west demonstrating that diabetes during pregnancy

is associated with a number of adverse effects on the mother and the neonate.^{2,4} Ethnic differences have been demonstrated not only in the prevalence of PGDM and GDM but also with respect to the outcomes of the pregnancy.^{2,3} Migrant Indians who are well known to have a greater predisposition to diabetes compared to Europeans have also been shown to have a higher prevalence of diabetes during pregnancy.⁴ However there are only a few Indian studies on diabetes in pregnancy.⁵⁻⁸ This is of interest given that India has the largest number of diabetic patients in the world with 31.4 million diabetic subjects in the year 2000.^{8,9} Further,

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it is estimated that nearly 2.5 million women in the reproductive age [20-44 years] are affected by diabetes.¹⁰ This translates to a huge number of PGDM and probably even higher number of GDM. In this context, data on the outcomes of pregnancies in Indian diabetic women (PGDM and GDM) is very important.

Participants and Design

All pregnant women attending the Dr. Mohan's Diabetes Specialities Centre, a tertiary care centre for diabetes in Chennai in southern India during the period of 2000- 2003 were recruited for the study. GDM was defined as any degree of glucose intolerance with its first recognition during pregnancy. Patients with onset of diabetes prior to their last menstrual period were assigned to the PGDM group and this included patients with Type 2 diabetes, Type 1 diabetes and other secondary forms of diabetes like Fibrocalculous Pancreatic Diabetes (FCPD).

Of a consecutive series of 245 pregnant women with diabetes registered at the centre, follow up data was available in 225, which included 79 PGDM and 146 GDM subjects.

Non-responders

There were no significant differences in the baseline clinical and biochemical profile of the 225 'responders' and the 20 'non-responders' [Responders vs non-responders, age: 29 ± 5 years vs 27 ± 7 years, $p=0.23$; fructosamine: 158 ± 63 $\mu\text{mol/l}$ vs 149 ± 43 $\mu\text{mol/l}$, $p=0.53$; HbA1c: $8.2 \pm 1.9\%$ vs $8.1 \pm 1.2\%$, $p=0.82$].

Control population

Non-diabetic pregnant women ($n = 30$) were recruited from our large population based study, the Chennai Urban Rural Epidemiology Study (CURES), an ongoing epidemiological study conducted on a representative population (aged ≥ 20 years) of Chennai. The methodology of the study has been published elsewhere.¹¹ Briefly, in Phase 1 of CURES, 26,001 individuals were recruited based on a systematic random sampling technique. Self reported diabetic subjects on drug treatment of diabetes were classified as 'known diabetic subjects'. Fasting capillary blood glucose was determined in all subjects using a One Touch Basic glucometer (Lifescan, Milpitas, California, USA).

In Phase 2 of CURES, all the known diabetic subjects ($n=1529$) were invited to the centre for detailed studies. In addition, age and sex matched non-diabetic subjects (fasting capillary blood glucose <100 mg/dl) and all subjects with fasting capillary blood glucose ≥ 110 mg/dl based on ADA fasting criteria,¹² underwent oral glucose tolerance tests (OGTT) using 75 gms oral glucose load dissolved in 250ml of water. Those who were confirmed by OGTT to have 2hr post load plasma glucose value ≥ 200 mg/dl based on WHO consulting group criteria¹³ were labelled as 'newly detected diabetic subjects'. Subjects who had fasting plasma glucose <100

mg/dl and 2hr plasma glucose value <140 mg/dl were categorized as normal glucose tolerance (NGT). We identified 30 women with NGT who were in the first or second trimester of pregnancy during phase 1 of CURES and did not develop diabetes thereafter during pregnancy (medical records were scrutinized). Pregnancy outcome variables were studied in these 30 subjects.

Patient evaluation

Details on the medical history, family history of diabetes and obstetric history were collected using a proforma. All the study subjects underwent a complete physical examination and biochemical assessment was done. Sitting blood pressure was recorded to the nearest 2 mm of Hg using a standard mercury sphygmomanometer (Diamond Deluxe BP Apparatus, Pune, India).

A fasting blood sample was taken for biochemical estimation. Biochemical analyses were carried out on Hitachi - 912 Autoanalyser (Hitachi, Germany) using kits supplied by Roche Diagnostics, (Mannheim, Germany). Fasting plasma glucose (GOD - POD method), fructosamine (NBT method), serum cholesterol (CHOD-PAP method), serum triglycerides (GPO-PAP method) and HDL cholesterol (Direct method - polyethylene glycol-pretreated enzymes) were measured. Glycated haemoglobin (HbA1C) was estimated by high-pressure liquid chromatography using the Variant machine (Bio-Rad, Hercules, Calif., USA).

For the non-diabetic controls, from CURES, fructosamine and HbA1c assays were not performed.

Diagnosis of diabetes

Diagnosis of GDM was done using American Diabetes Association (ADA) (NDDG revised criteria of O'Sullivan and Mahan criteria).¹² Diagnosis of diabetes was accepted in the PGDM group if they were on drug treatment for diabetes or had diabetes according to World Health Organization (WHO) 1998 criteria.¹³

Outcome measures : Data regarding neonate's birth weight were obtained from the mother or from hospital discharge summaries. They were classified as 'large babies' if the birth weight was > 3.5 kg and 'low birth weight' if birth weight was < 2.5 kg, only for those who had a full-term delivery.

Details were also collected regarding abortions and mode of delivery. The latter was classified as assisted if it was a caesarean section, vacuum assisted or a forceps assisted delivery. Congenital anomalies, if any, were documented.

Statistical analysis

One-way ANOVA or students "t" test as appropriate was used to compare groups for continuous variables. Chi-square test or Fisher's Exact test as appropriate was used to compare proportions. All analysis was done

using Windows based SPSS statistical package (Version 10.0, Chicago) and p values <0.05 were taken as significant.

RESULTS

Of the 79 PGDM's, 73(92.4%) were recruited in first trimester and the rest were recruited in the second trimester. Among the GDMs 28(19.0%) were recruited in first trimester, 85(58.2%) in second trimester and 33(22.6%) in third trimester.

Characteristics of the study population : Table 1 presents the characteristics of the study groups. Non-diabetic mothers had lower blood pressures compared to diabetic mothers(p<0.01). There was no significant difference in the mean age between the study groups. Fasting plasma glucose [p<0.001] and fructosamine [p<0.001] levels were significantly higher among PGDM compared to GDM. Though the HbA1c values were higher in PGDM, the difference did not reach statistical significance.

Treatment : The PGDM group required intensive therapy and 20 subjects (25.3%) were on multiple insulin regimens, 43(54.4%) on twice daily insulins and the rest were on single dose of insulin injections. Among the GDM group only 47.2% (69/146) were on insulin injections while the rest were treated with diet alone.

Pregnancy outcomes: Table 2 compares the pregnancy outcomes in the study groups. Proportion of women who underwent abortions was 0% in non-diabetic controls, 10.1% in PGDM and 2.7% in GDM and the difference between PGDM and GDM was statistically significant [p = 0.04]. Assisted deliveries were significantly higher among diabetic mothers compared to non-diabetic controls (PGDM : 60.8%, GDM : 59.6%, Non-diabetic subjects : 20.0%, p < 0.001).

There were 2 (6.7%) preterm deliveries in non-diabetic controls, 6(7.6%) in PGDM and 12(8.2%) in GDM and these subjects were excluded from the analysis on birth weight of neonates.

Prevalence of 'low birth weight' babies in the study groups were, 14.3% in non-diabetic mothers, 12.3% in PGDM and 8.2% in GDM and the differences did not reach statistical significance. The prevalence of 'large babies' was significantly higher in GDM compared to non-diabetic controls [27.6% vs 7.1%, p = 0.04]. Though the prevalence of large babies was higher among the PGDM [19.2%] compared to non-diabetic controls, the difference did not reach statistical significance.

Prevalence of congenital anomalies was 0% among non-diabetic controls, 3.8% in PGDM and 1.4% in GDM and the differences did not reach statistical significance.

Table 1 : Clinical characteristics of the study groups

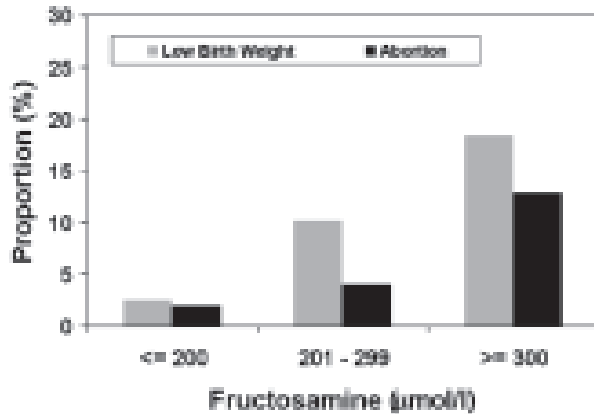
Parameters	Non-diabetic subjects (n = 30)	Pre-gestational diabetes mellitus (n = 79)	Gestational diabetes mellitus (n = 146)
Family history of diabetes n (%)	0	64 (81.0)**	121 (82.3)**
Age (years)	28 ± 4	29 ± 6	29 ± 5
Systolic blood pressure (mm Hg)	109 ± 12	118 ± 10**	119 ± 12**
Diastolic blood pressure (mm Hg)	73 ± 7	78 ± 8*	77 ± 7*
Fasting plasma glucose (mg/dl)			
Baseline	88 ± 11	149 ± 58**	109 ± 35**##
Third trimester	—	116 ± 45	103 ± 45#
Fructosamine (µmol/l)			
Baseline	—	299 ± 100	225 ± 50##
Third trimester	—	218 ± 33	202 ± 30#
HbA1c (%)			
Baseline	—	7.1 ± 1.6	6.8 ± 1.7
Third trimester	—	6.5 ± 1.5	6.2 ± 1.3

*p < 0.01 compared to non-diabetic subjects. **p < 0.001 compared to non-diabetic subjects. #p<0.05 compared to PGDM. ##p<0.001 compared to PGDM. Family history of diabetes was considered positive if either father or mother had diabetes.

Table 2 : Pregnancy outcomes in the study groups

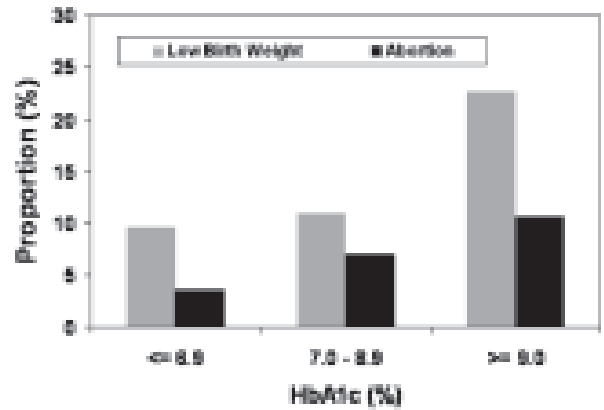
Parameters	Non-diabetic subjects (n = 30)	Pre-gestational diabetes mellitus (n = 79)	Gestational diabetes mellitus (n = 146)
Abortions n (%)	0	8 (10.1)#	4 (2.7)
Assisted n (%)	6 (20.0)	48 (60.8)**	87 (59.6)**
Congenital anomalies n (%)	0%	3 (3.8)	2 (1.4)
Birth weight (n = 28)	(n = 28)	(n = 73)	(n = 134)
Low birth weight n (%)	4 (14.3)	9 (12.3)	11 (8.2)
Large babies n (%)	2 (7.1)	14 (19.2)	37 (27.6)*

*p = 0.04 compared to non-diabetic subjects. **p < 0.001 compared to non-diabetic subjects. #p=0.04 compared to gestational diabetes mellitus.



	Trend chi square	p value
Low birth weight :	4.761	0.029
Abortion :	5.67	0.017

Fig. 1 : Proportion of low birth weight babies and abortions in relation to fructosamine levels.



	Trend chi square	p value
Low birth weight :	2.405	0.121
Abortion :	2.8	0.095

Fig.2 : Proportion of low birth weight babies and abortions in relation to HbA1c levels.

Proportion of abortions and low birth weight was computed according to levels of fructosamine only in the diabetic women. Fig. 1 shows a significant increase in the proportion of abortions (trend chi square = 5.67, p = 0.017) and low birth weight (trend chi square = 9.3, p = 0.003) with increase in fructosamine levels. A similar increase in abortion and low birth weight prevalence rates were also observed with increase in HbA1c but the trend did not reach statistical significance [Fig. 2].

DISCUSSION

Epidemiological studies comparing diabetic and non-diabetic mothers have very clearly demonstrated adverse outcomes in diabetic mothers.^{2,12,14} Further, perinatal mortality and neonatal mortality rates are markedly higher among diabetic, compared to non-diabetic, pregnancies. A study conducted in Norwich showed that perinatal mortality rate in diabetic pregnancies was 48 per 1000 compared to 8.9 per 1000 in non-diabetics and neonatal mortality was also higher in diabetic compared to non-diabetic pregnancies.¹⁵

In our study, among the diabetic mothers, proportion of abortions and assisted deliveries were significantly higher compared to non-diabetic controls and this is in agreement with earlier studies.¹⁶ The frequency of low birth weight babies in non-diabetic controls was 14.3%, which was slightly higher than that observed in the diabetic mothers. However, this is lower than the overall figures reported for India (28%) by the National Family Health Survey [NFHS].¹⁷ This could probably be due to inclusion of study subjects from urban Chennai where people probably belong to higher socio-economic status compared to the whole of India in the NFHS, which includes rural areas and also poorer states like Bihar and Orissa. It may also be due to the small sample size.

The lower prevalence of low birth weight among the diabetic subjects may be a reflection of higher frequency

of macrosomia produced by diabetes. This is further substantiated by the higher prevalence of large babies among the diabetic mothers (Table 2).

Pregnancy outcomes in diabetic women have improved dramatically over years with temporal trends showing a decline in rates of spontaneous abortions in diabetic mothers.¹⁶ However, diabetic mothers still carry a higher risk for fetal morbidity and mortality. A recent prospective study has shown that inspite of planned pregnancies with good glycemic control, diabetic mothers still had higher rates of maternal and perinatal complications.¹⁸ One study from Kolkata also showed that tight diabetes control was not the only factor influencing pregnancy outcomes.⁵

Though there are studies in Asian Indians on the prevalence of PGDM and GDM among pregnant mothers,^{6,16} there have been very few studies comparing the outcomes in these two groups.⁵ In this study, we compared the pregnancy outcomes in mothers with PGDM and GDM. The prevalence of abortions in the GDM group in this study was 2.7% compared to 10.1% in the PGDM group showing that PGDM are at increased risk for abortions. Other studies have also demonstrated higher rates of abnormalities in pregnancy outcomes in PGDM compared to GDM.^{5,18} This is explained by the fact that patients with PGDM generally tend to have more severe diabetes. Moreover, the PGDM group included patients with Type 1 diabetes. It is well known that Type 1 diabetes complicating pregnancy is associated with worse prognosis because of the severity of the condition.¹⁹

The proportion of abortions observed in PGDMs (10.1%) in this study is comparable to that reported in other studies.^{16,20} Among GDMs 2.7% of the mothers had abortions, which is in contrast to an earlier study in India, which showed that there were no abortions among GDMs.⁷ This is probably a reflection of the referral

patterns at different centres. It is well known that blood glucose control as shown by fructosamine or HbA1c levels at the time of conception, is an important determinant of the outcome of the pregnancy. It is likely that the patients were referred to our centre at a later stage by obstetricians and this could adversely influence the outcomes.

The GDM women had a slightly higher frequency of large babies compared to PGDM mothers. This is consistent with earlier studies.¹⁸ The reason could probably be due to insulin resistance as shown by decreased insulin binding and associated metabolic abnormalities, which is more pronounced in GDM than in PGDM.⁶ An earlier study had shown that even women with impaired glucose tolerance had higher rates of large babies compared to normals.¹⁴

Congenital anomalies were more common in the PGDM group than the GDM group although this was not statistically significant. This is comparable to earlier studies.^{5,18}

One of the interesting, but expected observations in this study, is that abortions and occurrence of low birth weight among babies showed a linear relationship with poor glycaemic control as estimated by fructosamine. Poor glycaemic control has been shown to be associated with low birth weight babies, increased incidence of congenital anomalies, spontaneous abortions, perinatal morbidity and mortality and caesarean sections.

Thus the present study indicates the importance of tight glycaemic control during pregnancy. Tight glycaemic control has been shown to reduce both maternal and fetal complications.²¹ This underscores the fact that pre-conceptional screening for diabetes has to be given high priority in high-risk women and tight control of diabetes must be achieved even before conception in those with PGDM.

In conclusion, women with PGDM are at greater risk of unfavorable pregnancy outcomes than GDM. Pregnancy outcomes also depend on glycaemic control and hence tight control of diabetes must be attempted right through the pregnancy, probably starting even before the time of conception through combined pre-pregnancy diabetic clinics, jointly run by diabetologists and obstetricians.

Contributors

VM planned and supervised the study and interpreted the results. MK, a medical student from University of Auckland, New Zealand who did a two month research fellowship at the Dr. Mohan's Diabetes Specialities Centre, Gopalapuram, Chennai recruited pregnant women for the study. The follow up study was done by AKS who also wrote the first draft of the manuscript. RD coordinated the study and assisted in writing the manuscript and performing the statistical analysis.

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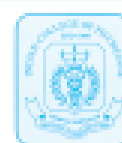
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API Announcement



Election for Posts of API and ICP

Election process by Postal Ballots is on for the following posts of API and ICP for the year 2007-2008:

President Elect	1
Hony. General Secretary	1
Governing Body Members	4
Faculty Council ICP Members	5

Ballot papers for these elections shall be sent to all the members and same need to be sent back to API Office by **31st Aug, 2006**.

In case a member does not receive the ballot paper, he/she can send a written request under his/her signature to API Office at the address given below for issue of duplicate ballot paper so that duplicate ballot paper could be sent to them.

The Association of Physicians of India, Turf Estate # 6 & 7. Off.Dr. E. Moses Road, Opp. Shakti Mills Compound, Near Mahalaxmi Station (West), Mumbai-400 011. Fax: 022-24920263

(Dr. R. K. Singal)
President Elect &
Chief Electoral Officer

(Dr. Falguni S. Parikh)
Member Election Committee