Original Article

Postpartum development of type 1 diabetes in Asian Indian women with gestational diabetes

Ranjit Unnikrishnan, Coimbatore Subramanian Shanthi Rani, Ranjit Mohan Anjana, Subash Chandrabose Uthra, Jaydeep Vidya, Ganesan Uma Sankari, Ulagamathesan Venkatesan, Saravanan Jeba Rani, Viswanathan Mohan

Madras Diabetes Research Foundation and Dr. Mohan's Diabetes Specialities Centre, Chennai, Tamil Nadu, India

A B S T R A C T

Aim: To study the postpartum conversion of gestational diabetes mellitus (GDM) to different types of diabetes among Asian Indian women. **Materials and Methods:** Using data from electronic medical records, 418 women with GDM seen at a tertiary diabetes care center for diabetes in Chennai in South India between 1991 and 2014 were evaluated for development of diabetes postpartum. **Results:** Of the 418 GDM women followed up postpartum, 388 progressed to diabetes. Of these 359 (92.5%) developed type 2 diabetes (T2DM) and 29 women (7.5%) developed type 1 diabetes (T1DM). The median time to development of T1DM was 2 years (interquartile range 2 [IQR]) while for T2DM it was 5 years (IQR 6). Women who developed T1DM had significantly lower mean body mass index (BMI) (20.4 ± 2.8 vs. 27.5 ± 4.4 kg/m^2, $P = 0.001$), and higher fasting plasma glucose (222 ± 105 vs. 165 ± 62 mg/dl $P = 0.008$) and glycated hemoglobin levels (10.2 ± 2.7 vs. $8.5 \pm 2.1\%$ $P < 0.001$) compared to those who developed T2DM. Glutamic acid decarboxylase (GAD) autoantibodies were present in 24/29 (82.7%) of women who developed T1DM. **Conclusion:** A small but significant proportion of women with GDM progress to T1DM postpartum. Measurement of GAD antibodies in leaner women with more severe diabetes could help to identify women who are likely to develop T1DM and thus prevent their presentation with acute hyperglycemic emergencies after delivery.

Key words: Asian Indians, gestational diabetes mellitus, glutamic acid decarboxylase, postpartum, South Asians, type 1 diabetes, type 2 diabetes

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance of any severity with onset or first recognition during pregnancy.[1,2] GDM is postulated to result from the inability of the pregnant woman's pancreatic beta-cell to increase its output of insulin in the face of increasing insulin resistance during pregnancy. GDM complicates 2–17% of pregnancies, depending on the ethnic background of the population studied as well as the diagnostic test and glycemic cut-off values used.[3]

In most cases of GDM, diabetes resolves postpartum; however, these women remain at increased risk of development of diabetes in the future. While the majority of these women go on to develop type 2 diabetes (T2DM) later[4,5] it is increasingly being recognized that a small but significant proportion of women with GDM can also

Corresponding Author: Dr. Viswanathan Mohan,
Madras Diabetes Research Foundation and Dr. Mohan's Diabetes Specialities Centre, No. 6, Conran Smith Road, Gopalapuram, Chennai - 600 086. Tamil Nadu, India.
E-mail: drmohans@diabetes.ind.in

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develop type 1 diabetes (T1DM). However, data concerning the progression of GDM to T1DM is scarce and is confined to studies from Europe,[6] where the population prevalence of T1DM is comparatively higher. It is not known whether conversion of GDM to T1DM occurs in other populations, where the background incidence of T1DM is low and where the disease may consequently be overlooked, with disastrous results.

The present study reports on the development of T1DM and T2DM in women previously diagnosed with GDM and compares the clinical and biochemical characteristics of these two groups.

MATERIALS AND METHODS

In this retrospective clinic-based study, clinical data of 418 women with GDM seen between the year 1991 and 2014 at a tertiary care diabetes center at Chennai in South India were evaluated for development of diabetes postpartum from electronic medical records. Being a referral diabetes center which attracts patients from different parts of the country, postpartum follow-up of these women is a challenge as they normally do not come for the follow-up to our center after the delivery. In this paper, we report on the postpartum follow-up data on those women for whom information on clinical profile, mean time to development of T1DM and other clinical details were available.

Anthropometric and biochemical assessment

Anthropometric details (height, weight, waist circumference, and hip circumference) and blood pressure were measured using standardized techniques[7] and body mass index (BMI) calculated using the formula BMI = weight (in kg)/(height in m) ^{2}.

Biochemical analyses were done in our laboratory which is certified by the National Accreditation Board for testing and calibration Laboratories and the College of American Pathologists on a Hitachi-912 Autoanalyser (Hitachi, Germany) using kits supplied by Roche Diagnostics (Basel, Switzerland), for estimation of Plasma glucose (Glucose oxidase-peroxidase method), Serum cholesterol (cholesterol oxidase–peroxidase–amidopyrine method), Serum triglyceride (glycerol phosphate oxidase–peroxidase–amidopyrine Method) and high-density lipoprotein (HDL) cholesterol (direct method). Glycated hemoglobin (HbA1C) was estimated by high-pressure liquid chromatography using the Variant machine (Bio-Rad, Hercules, California, USA).

Fasting and stimulated (postbreakfast) C-peptide levels were estimated by the electrochemiluminescence method on an Elecsys2010 machine (Hitachi). To obtain the stimulated C-peptide value, a blood sample was drawn 90 min after a standard South Indian breakfast, as published earlier.[8,9]

Glutamic acid decarboxylase (GAD) antibodies were measured on a Bio-Rad plate reader (model 680) using an enzyme-linked immunosorbent assay kit (EUROIMMUN, Lubeck, Germany). The normal limit for GAD antibody assay in our laboratory is <10 IU/mL.

Definitions

Family history of diabetes was considered as positive if either or both the parents had diabetes.

GDM was diagnosed based on the modified Carpenter and Coustan criteria.[10]

T1DM was diagnosed based on history of diabetic ketoacidosis or presence of ketonuria, fasting and stimulated C-peptide values <0.6 pmol/mL, absence of pancreatic calculi on abdominal X-ray, and continuous requirement of insulin for control of hyperglycemia.[11]

T2DM was diagnosed based on the absence of ketosis, good b-cell reserve as shown by stimulated C-peptide assay (>0.6 pmol/mL), absence of pancreatic calculi on abdominal X-ray, and response to oral hypoglycemic agents.

Statistical analyses

Statistical Package for Social Sciences (SPSS) version 15 (SPSS Inc. Chicago) was used to analyze the data. Chi-square and independent *t*-tests were used to assess the differences in categorical and continuous variables between two groups (GDM to type-1 and GDM to type-2). *P* <0.05 was considered statistically significant.

RESULTS

Clinical characteristics

Of the 418 GDM women who were followed postpartum, 388 progressed to diabetes which included 359 women (92.5%) with T2DM and 29 (7.5%) with T1DM [Figure 1]. Table 1 compares the clinical and biochemical parameters of these two groups of women. The median time to development of T1DM was 2 years (interquartile range [IQR] 2) while that to T2DM was 5 years (IQR 6). Women who developed T1DM were significantly younger than those who progressed to T2DM at the time of gestation (25.9 ± 4.3 years vs. 29.8 ± 4.7 *P* ≤ 0.001) as well as at the time of postpartum follow-up visit (mean age: 39.4 ± 8.5 years vs. 43.6 ± 7.8 years, *P* = 0.017). At the time of follow-up, women with T1DM had diabetes
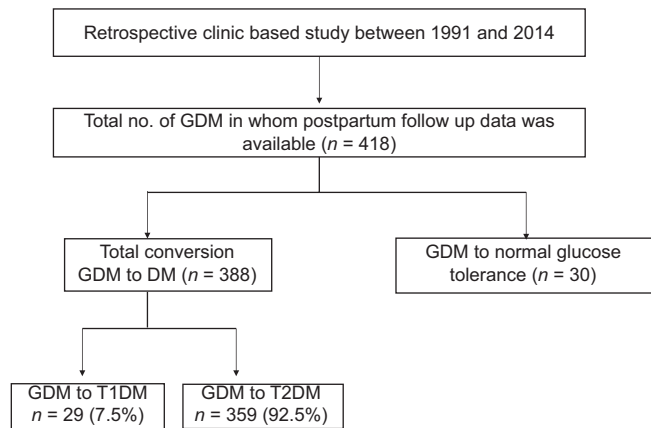
Figure 1: Flow chart of the study population

| Retrospective clinic based study between 1991 and 2014 |
| Total no. of GDM in whom postpartum follow up data was available (*n* = 418) |
| Total conversion GDM to DM (*n* = 388) | GDM to normal glucose tolerance (*n* = 30) |
| GDM to T1DM *n* = 29 (7.5%) | GDM to T2DM *n* = 359 (92.5%) |

Table 1: Clinical characteristics of the study population

Variables	*n*	GDM to type 1 diabetes (*n*=29)	*n*	GDM to type 2 diabetes (*n*=359)	*P*
Age (years)	29	39.4±8.5	359	43.6±7.8	0.017
Mean time to develop type 1 diabetes mellitus	29	1.9±1.0	292	5.9±4.8	<0.001
Median (IQR)		2 (2)		5 (6)	
Mean age at the time of GDM	29	25.9±4.3	296	29.8±4.7	<0.001
Duration of diabetes (years)	29	13.3±9.4	359	10.7±7.2	0.156
GAD positive (%)	29	24 (82.7)	26	3 (11.5)	<0.001
Cesarean delivery *n* (%)	24	13 (54.2)	296	188 (63.5)	0.363
Birth weight of the child (kg)	22	3.5±0.6	288	3.1±0.8	0.004
Family history positive *n* (%)	29	14 (48.3)	359	327 (91.1)	<0.001
Treatment during pregnancy *n* (%)					
Insulin	29	29 (100)	311	254 (81.7)	0.096
On diet				57 (18.3)	
Body mass index (kg/m²)	28	20.4±2.8	358	27.5±4.4	0.001
Systolic blood pressure (mm/Hg)	28	116±11	356	123±16	0.08
Diastolic blood pressure (mm/Hg)	28	74±7	357	79±9	<0.001
Fasting blood glucose (mg/dl)	29	222±105	356	165±62	0.008
Glycated hemoglobin (%)	29	10.2±2.7	338	8.5±2.1	<0.001
C- peptide fasting (pmol/mL)	28	0.29±0.09	169	0.95±0.39	<0.001
C-peptide stimulated (pmol/mL)	28	0.39±0.21	164	2.5±5.1	<0.001
Cholesterol (mg/dl)	25	170±31	329	178±37.9	0.206
Triglyceride (mg/dl)	25	91±39	328	158±109	0.001
HDL cholesterol (mg/dl)	25	54±9.5	328	41.8±9.1	0.001
LDL cholesterol (mg/dl)	25	94.3±31.4	322	107±32.2	0.083

GDM: Gestational diabetes mellitus, IQR: Inter quartile range, GAD: Glutamic acid decarboxylase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

longer than those with T2DM, although the difference was not statistically significant (mean duration of diabetes: 13.3 ± 9.4 vs. 10.7 ± 7.2 years; *P* = 0.156). Women with T1DM had significantly lower BMI than those with T2DM (20.4 ± 2.8 vs. 27.5 ± 4.4 kg/m²; *P* = 0.001). Both systolic and diastolic blood pressures were higher in women with T2DM when compared to those with T1DM.

Fasting plasma glucose (FPG) (*P* = 0.008) and HbA1c (*P* < 0.001) were higher in women who developed T1DM compared to those with T2DM. Serum triglyceride levels were higher (*P* = 0.001) among women with T2DM while HDL cholesterol levels were lower (*P* = 0.001). A positive family history of diabetes was more frequent in T2DM than T1DM (91.1% vs. 48.3%; *P* < 0.001). All the women (100%) who developed type 1 diabetes had been treated with insulin during pregnancy, as compared to 81.7% of those who developed T2DM. C-peptide levels were considerably lower in those who developed T1DM (*P* < 0.001)

Of the 29 women who developed T1DM, 13 (54.2%) gave a history of cesarean delivery as compared to 188 of the 359 who developed T2DM (63.5%). The mean birth weight of children of women who developed TIDM was 3.5 ± 0.6 kg, as compared to 3.1 ± 0.8 kg in the T2DM group. Postpartum GAD antibody titers were positive in 24 out of 29 (82.7%) women who developed T1DM.

DISCUSSION

The development of T2DM following GDM has been well-characterized.[12-15] However, the progression of GDM to T1DM has not received much attention, particularly in non-European populations. Our study reports, for the first time, the development of T1DM in women with a prior history of GDM in an Asian Indian population. Our results show that a small but significant proportion of Asian Indian women with GDM progress to T1DM.

Our results suggest that the progression of GDM to T1DM occurs faster than the progression to T2DM (mean time to development of diabetes postpartum = 1.9 ± 1.0 vs. 5.9 ± 4.8 years). Studies in European populations have shown that 50% of women with GDM, who progress to T1DM do so within 1 year, and 83%, within 4 years.[16] This reflects the rapidity of the autoimmune destruction of beta-cells and underscores the need for regular screening for diabetes in women with a history of GDM so as to enable an early diagnosis and prevent presentation in acute hyperglycemic crises.

Eighty-three percent of women who progressed to T1DM had a positive titer of GAD autoantibodies. While we do not have data on the autoantibody status of these women during pregnancy, as the diagnosis of T1DM was made after the delivery, pancreatic autoantibody positivity during pregnancy has been shown to be predictive of future T1DM in studies conducted elsewhere. Two large studies in Danish[17,18] and German[19] populations point to GAD antibodies as the best predictor of T1DM in GDM. Only one study has estimated the prevalence of antibody to zinc transporter 8 (ZnT8) in women with GDM, and this study concluded that ZnT8 would contribute about 2% to autoantibody positivity among women with GDM, who are negative for other autoantibodies.[20] The German study mentioned above, with a follow-up period

of up to 7 years, revealed that the risk of developing T1DM in antibody-positive women was 29% versus 2% in antibody-negative individuals.[19] While routine measurement of autoantibodies in women with GDM might help identify those who are likely to progress to T1DM postpartum, the advantages of this approach need to be assessed in the context of its cost-effectiveness particularly in resource-constrained settings as the incidence of T1DM is low.

Our women who developed T1DM were found to have lower postpartum BMI compared to those who developed T2DM. Women with autoimmune GDM have been earlier shown to have lower BMI, lower waist circumference, less weight gain during pregnancy, and lower fasting insulin levels compared to women with nonautoimmune gestational diabetes.[21,22] These parameters might help to identify a subset of women with GDM who are likely to progress to T1DM postpartum; however, these findings need to be evaluated by larger prospective studies.

Our results show that all the women who subsequently developed T1DM had been treated with insulin during pregnancy, as compared to 83% of women who subsequently developed T2DM. This could suggest the presence of higher degrees of hyperglycemia during pregnancy in the former group, necessitating the initiation of insulin.[23] Fuchtenbusch *et al.*[19] have shown a higher prevalence of autoantibodies in women with gestational diabetes treated with insulin than in those treated with diet. An earlier study showed that 73% of islet cell antibody-positive women with GDM were under insulin treatment.[24]

In our study, family history of diabetes was more frequent in women who developed T2DM than in those who developed T1DM. A family history of T2DM has been shown to be a risk factor for GDM.[24] Our results suggest that women who develop GDM in the absence of a family history of diabetes might be the ones who would likely develop T1DM.

Our study has several limitations. As our center is a tertiary referral clinic for diabetes, it is likely that there could have been a referral bias, with those women who have developed diabetes more likely to return for a follow-up visit. Second, we were not able to obtain clinical, biochemical, and immunologic parameters in many of the women during the pregnancy as they had not been under our care for GDM and had only been subsequently referred to us following the postpartum development of diabetes. However, the strength of the study is the fairly large numbers of GDM women studied and the follow-up data including conversion to diabetes. Furthermore, this is the first report of the development of T1DM after GDM in a South Asian population.

CONCLUSION

A small but significant proportion of Asian Indian women with GDM progress to T1DM postpartum. Measurement of pancreatic autoantibodies like GAD in those who are leaner, have no family history of diabetes and have more severe hyperglycemia could help in early detection of those who are likely to develop T1DM and thus prevent presentation with acute hyperglycemic emergencies.

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Conflicts of interest
There are no conflicts of interest.

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