ORIGINAL ARTICLE

Long term prognosis of women with gestational diabetes in a multiethnic population

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Aim: To assess the glucose tolerance of South Asian and Caucasian women with previous gestational diabetes mellitus (GDM).
Method: A retrospective follow-up study of 189 women diagnosed with GDM between 1995 and 2001. Glucose tolerance was reassessed by oral glucose tolerance test at a mean duration since pregnancy of 4.38 years.
Results: South Asian women comprised 65% of the GDM population. Diabetes developed in 36.9% of the population, affecting more South Asian (48.6%) than Caucasian women (25.0%). Women developing diabetes were older at follow-up (mean (SD) 38.8 (5.7) vs 35.9 (5.6) years; $p<0.05$) and had been heavier (body mass index 31.4 (6.3) vs 27.7 (6.7) kg/m^2; $p<0.05$), more hyperglycaemic (Gl_0 6.5 (1.7) vs 5.2 (1.1) mmol/l; $p<0.01$: G_{120} 11.4 (3.3) vs 9.6 (1.8) mmol/l; $p<0.01$: HbA1c 6.4 (1.0) vs 5.6 (0.7); $p<0.01$) and more likely to require insulin during pregnancy (88.1% vs 34.0%; $p<0.01$). Future diabetes was associated with and predicted by HbA1c taken at GDM diagnosis in both South Asian (odds ratio 4.09, 95% confidence interval 1.35 to 12.40; $p<0.05$) and Caucasian women (OR 9.15, 95% CI 1.91 to 43.87; $p<0.01$) as well as by previously reported risk factors of increasing age at follow-up, pregnancy weight, increasing hyperglycaemia and insulin requirement during pregnancy.
Conclusion: GDM represents a significant risk factor for future DM development regardless of ethnicity. Glycated haemoglobin values at GDM diagnosis have value in predicting future diabetes mellitus.

Gestational diabetes mellitus (GDM) is defined as abnormal carbohydrate tolerance that is diagnosed or first recognised in pregnancy[1] and affects approximately 5% of pregnancies.[2] However, the prevalence depends on the population studied and the diagnostic criteria used[3] with an increased frequency of GDM when less stringent diagnostic criteria are used and in ethnic groups who traditionally have a higher rate of type 2 diabetes.[4–6] Differences in the prevalence of GDM reflect the background susceptibility of individual ethnic groups[2 7] and possibly a different stage within the natural history of diabetes at the time of pregnancy.[8]

Previous GDM confers an increased risk of subsequent diabetes mellitus such that 50% of women will have diabetes mellitus after 10 years.[9 10] Several antenatal and maternal factors have been shown to predict this[11–13] and identification of these during the screening of women with GDM may lead to more effective targeting of strategies for primary prevention of diabetes in local populations.[3 14] Glycated haemoglobin (HbA1c), while convenient to measure, has little sensitivity in making the diagnosis of GDM[15] and has been little studied as a risk marker for predicting future diabetes.

A number of studies have suggested that diabetes following GDM develops more rapidly in non-Caucasian groups.[5 16 17] A recent meta-analysis, however, suggested that differences between the ethnic groups studied could largely be explained by standardising diagnostic criteria, duration of follow-up and patient retention.[18] The Leicestershire population consists of a significant minority of women from the Indian subcontinent who have higher rates of glucose intolerance both in and out of pregnancy.[19] This study examined the development of glucose intolerance and its pregnancy associations in this ethnically mixed population.

METHODS

Patients and study design

While the Leicestershire rural population is predominantly Caucasian, there is a large city population of families who have their origins in India and who have migrated in the last 30–40 years from East Africa—mostly Gujerati Hindus and Punjabi Sikhs.

From the early 1980s women with GDM who delivered their baby at the Leicester General Hospital have had the details of their diagnosis and pregnancy recorded on a database. HbA1c measurements were included from 1994 and these were DCCT (Diabetes Control and Complications Trial) aligned from 1995. In 2003 women with GDM diagnosed between 1995 and 2001 were approached and invited to take part in the present study to assess their current glucose tolerance.

Initial diagnosis and management of gestational diabetes mellitus

GDM screening was offered at the time of booking to women considered to be at high risk (obese with body mass index (BMI) >30 kg/m^2, first degree family history of diabetes mellitus or previous adverse pregnancy outcomes–previous GDM, macrosomia or still birth). This was repeated at 24–28 weeks' gestation if the initial test was negative. For those considered to be at "lower-risk" an oral glucose tolerance test (OGTT) was performed in those who developed persistent glycosuria. The diagnosis of GDM was based upon the 75 mg OGTT and World Health Organization criteria for glucose intolerance, whereby GDM was diagnosed on a 2 h venous glucose ⩾7.8 mmol/l.[20] HbA1c at GDM diagnosis was measured using a Bayer DCA 2000 machine (normal range 4.2–6.5%, mean (±2SD) 4.3% to 5.7%) that was subjected to regular quality control as per the manufacturers instructions.

All women with GDM were followed in a specialist joint diabetes–antenatal clinic. Ethnically appropriate dietary advice

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; HbA1c, glycated haemoglobin; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; ROC, receiver operator characteristic

was given and capillary glucose monitoring, fasting and 2 h after meals, was performed. In the event that two readings exceeded target (5.5 mmol/l fasting or 7.0 mmol/l 2 h post meal), insulin treatment was initiated. Maternal blood glucose meter readings were quality assured by comparison with simultaneously obtained laboratory glucose measurement during a separate single-day attendance.

Follow-up study

A total of 189 Caucasian or South Asian women were identified and invited to participate by written invitation. A single reminder was sent after 6 weeks if no response was obtained. In women who had already developed diabetes, the details of the diagnosis were sought and assessed for compliance with WHO diagnostic criteria.[21]

Those with unknown glucose tolerance were asked to attend and underwent 75 mg OGTT testing after an overnight fast. Blood samples were collected by venepuncture and glucose measured using the glucose-oxidase method. Demographic data were obtained for ethnicity, personal and family origin and family history of diabetes. In those who had more than one pregnancy complicated by GDM, the earliest affected pregnancy was regarded as the index case. Women with GDM diagnosed before 20 weeks were excluded on the presumption of possible pre-existing diabetes.

Diabetes and impaired glucose tolerance (IGT) were defined using 1998 WHO criteria whereby diabetes mellitus was diagnosed if any value of plasma glucose was ⩾11.1 mmol/l, and IGT was diagnosed in those with a 2 h value ⩾7.8 mmol/l but <11.1 mmol/l.[21] Impaired fasting glucose (IFG) was diagnosed in those whose fasting glucose was between 6.1–7.0 mmol/l in the absence of defining 2 h criteria. An additional search of the diabetes registers held at the three Leicester hospitals was undertaken to identify those who were already known to secondary care. A subject was included in data analysis only if outcome could be confirmed.

The local ethics committee approved the trial protocol and all women provided written consent.

Statistical analysis

Statistical analysis was performed using SPSS analysis software (SPSS v11.5, SPSS UK Ltd, Woking, Surrey). Differences in age, weight and height, gravidity and measures of glycaemia (OGTT and HbA1c) were tested using independent sample t tests. Differences in nominal data such as family history and for associations of ethnicity were examined using χ^2. Univariate logistic regression was used to analyse predictive factors for the development of diabetes. Receiver operator characteristic (ROC) curves were constructed for glycated haemoglobin to calculate sensitivity and specificity for subsequent diabetes prediction.

RESULTS

Between 1995 and 2001 a potential cohort of 189 South Asian and Caucasian women with GDM were identified. Eleven women were excluded (8 South Asian, 3 Caucasian) as their GDM was diagnosed before the 20th week of gestation and were considered likely to have pre-gestational diabetes. The remaining 178 women (123 South Asian and 66 Caucasian) were invited to participate in the study. Of those invited, 79 South Asian and 26 Caucasian women either failed to respond or declined to participate in the study. The study cohort therefore comprised a total of 73 women (36 South Asian and 37 Caucasian). The average (SD) elapsed time since the index pregnancy was 52.6 (25.2) months (range 0–104 months).

Non-responders

Analysis of the non-responding group revealed no differences in current age, weight at booking, BMI, or week of pregnancy at GDM diagnosis in either ethnic group compared to those who took part. Pregnancy OGGT and HbA1c values were statistically similar. Caucasian non-responders were younger at GDM diagnosis (mean (SD) 29.6 (5.3) vs 32.4 (5.2) years, $p = 0.036$) and more time had elapsed (64.6 (17.9) vs 54.3 (23.2) months, though this did not quite reach significance, $p = 0.052$). In South Asian non-responders elapsed time was significantly longer (67.3 (20.8) vs 50.7 (27.5) months, $p = 0.01$).

Responders

There was no significant difference between South Asian and Caucasian women in duration of follow-up (50.7 (27.5) vs 54.3 (23.2) months), age at booking (31.1 (5.3) vs 32.4 (5.2) years), current age (36.6 (5.5) vs 37.3 (6.0) years), parity (2.0 (1.3) vs 1.8 (1.1)) or proportion with diabetic first degree relative (40.0% vs 35.7%). South Asian women, as expected, were shorter than Caucasians (1.51 (0.3) vs 1.62 (0.1) m; $p<0.05$) and lighter (68.6 (17.0) vs 76.9 (21.5) kg; NS) with an identical BMI (28.8 (5.9) vs 28.8 (7.7) kg/m^2).

Diagnosis and management of GDM in the index pregnancy

There was a trend toward earlier GDM diagnosis in South Asian women, though this was not significant (week of GDM diagnosis 24.9 (6.9) vs 27.6 (6) weeks; $p = 0.083$). South Asian women had higher levels of fasting glycaemia on pregnancy OGTT (6.0 (1.6) vs 5.3 (1.2) mmol/l; $p = 0.044$), though post challenge glucose and HbA1c values were the same between the groups (Gl_{120} 10.7 (2.9) vs 9.7 (2.0) mmol/l and HbA1c (%) 6.0 (1.0) vs 5.8 (0.8)). South Asian women were significantly more likely to have required insulin treatment (70.3% vs 34.2%; $p = 0.004$) during pregnancy and to have required more units per kg (0.92 (0.89) vs 0.50 (0.33) U/kg; $p = 0.038$).

Follow-up study

After a mean duration since pregnancy of 4.38 years (52.6 (25.2) months) 27 women had developed diabetes. Twenty-three women (15 South Asian, 8 Caucasian) had been diagnosed with diabetes in primary care by the time of the study. Of the 43 women attending for the 75 mg OGTT follow-up study, 4 women (3 South Asian, 1 Caucasian) fulfilled the 1998 WHO criteria for diabetes. In addition one South Asian woman was pregnant again at the time of the study with a recurrence of her GDM, and two Caucasian women had recent normal glucose screening arranged by their general practitioners. Overall South Asian women were significantly more likely to have developed diabetes than Caucasians (48.6% vs 25.0%, $p = 0.013$).

Considering that non-responding women were statistically similar to those studied it may be expected that a similar proportion would have developed diabetes and were undetected by the current study either because of subclinical diabetes or because their management took place solely within primary care. Furthermore, a number of women may have avoided medical contact despite more overt symptoms for cultural or other reasons. However, no record of these women was found within the diabetes registers of the Leicestershire hospitals and it is likely, given the stability of the local South Asian population and the tendency at the time for diabetes care provision to occur predominantly within the hospital setting, that the above prevalence is an overestimate of the Leicester GDM population as a whole.

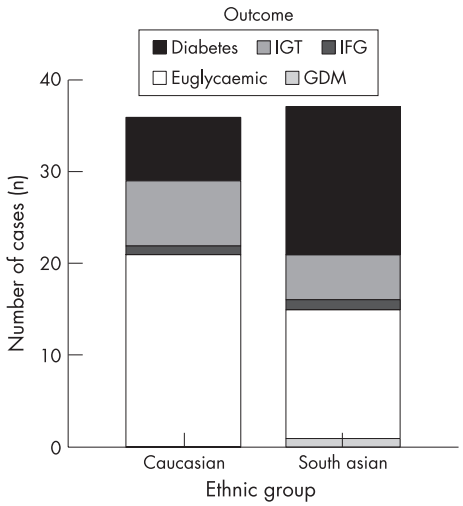

Figure 1 Bar chart showing follow-up glucose tolerance post gestational diabetes mellitus (GDM) by ethnic group. IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Lesser degrees of glucose intolerance were seen at follow up: IGT was present in 14 women (6 Indian, 8 Caucasian) and a further 2 had IFG (fig 1). Abnormal glucose tolerance (IFG, IGT and diabetes mellitus) was therefore present in 58.9% of the followed cohort (67.5% of South Asians, 50.0% of Caucasians).

Associations with the development of diabetes

The development of diabetes was associated with increasing age, both in pregnancy and at follow-up, in Caucasian but not South Asian women (table 1). There was a non-significant trend for women who developed diabetes to be heavier during pregnancy (table1). South Asian women who did develop diabetes were also more likely to have a family history of diabetes.

The development of diabetes was associated with greater pregnancy hyperglycaemia. Diabetic Caucasian women were more hyperglycaemic at all time points on the pregnancy OGTT and had significantly higher HbA1c values than those remaining normoglycaemic. For South Asian women only the HbA1c value was different between the outcome groups, although glucose values on the OGTT both showed a trend to higher values in those destined to develop diabetes. Insulin treatment during pregnancy was similarly associated with future diabetes in Caucasian ($p<0.001$) though not South Asian women ($p = 0.091$) (table 1).

Predicting the development of future diabetes

A number of maternal and antenatal parameters have been identified as having value for predicting subsequent diabetes development[3 17 22] and similar findings were seen in the current study. A significant relationship was found for South Asian ethnicity (odds ratio (OR) 3.93, $p = 0.011$). For both groups increasing age at follow-up and obesity in the pregnancy significantly increased the risk of diabetes within 52 months (table 2). A first degree relative with diabetes significantly increased the risk of post GDM diabetes in South Asian women (OR 9.0, $p<0.001$). Pregnancy hyperglycaemia, in particular HbA1c, was highly predictive for diabetes in both groups (Caucasian OR 9.15, $p<0.01$; South Asian OR 4.95, $p<0.05$). Pregnancy OGTT values were predictive at all both points for Caucasians, and both the fasting glucose and HbA1c predicted diabetes in the South Asian group. Requiring insulin was highly predictive in Caucasian women (OR 23.4, $p<0.01$), but just

Table 1 Comparison of demographic and ante-partum parameters and their relation to glycaemic outcome in women of Caucasian and South Asian origin and previous gestational diabetes

	Whole cohort			Caucasian			South Asian		
	Normal	Diabetes		Normal	Diabetes		Normal	Diabetes	
	n = 48	n = 25	pValue	n = 29	n = 7	pValue	n = 19	n = 18	p Value
Age	35.9 (5.6)	38.8 (5.7)	0.039	36.2 (6.1)	41.7 (3.0)	0.027	35.5 (4.9)	37.7 (6.1)	NS
Age (index)	31.3 (5.1)	32.6 (5.5)	NS	31.4 (5.3)	36.4 (2.2)	0.024	31.1 (5.0)	31.1 (5.7)	NS
Weight (kg)	70.4 (19.5)	76.5 (19.5)	NS	74.4 (20.7)	86.2 (23.2)	NS	64.3 (16.1)	72.7 (17.2)	NS
BMI (kg/m^2)	27.7 (6.7)	31.4 (6.3)	0.048	28.0 (7.4)	36.3 (8.0)	0.078	27.2 (5.7)	30.5 (5.7)	NS
FH (1st deg)	34.1%	75%	NS	37.0%	0.0%*	NS	29.4%	100%	0.049
Gl_0 (mmol/l)	5.2 (1.1)	6.5 (1.7)	0.001	5.0 (0.9)	6.9 (1.4)	0.001	5.5 (1.4)	6.5 (1.8)	0.073
Gl_{120} (mmol/l)	9.6 (1.8)	11.4 (3.3)	0.003	9.2 (1.3)	12.1 (3.1)	0.001	10.2 (2.2)	11.2 (3.4)	NS
HbA1c	5.6 (0.7)	6.4 (1.0)	0.001	5.5 (0.6)	6.5 (0.7)	0.001	5.7 (0.8)	6.4 (1.1)	0.045
Insulin treated	34.0%	88.1%	<0.001	17.8%	100%	<0.001	57.8%	83.3%	0.091

Age, age at time of study; Age (index), age at time of pregnancy; BMI, body mass index; FH (1st deg), family history of diabetes in a first-degree relative; Gl_0 and Gl_{120}: fasting and 2 h glucose values during diagnosis OGTT; HbA1c, glycated haemoglobin; Insulin treated, percentage of women in each cohort treated with insulin during the pregnancy; NS, not significant.
*n = 1.

Table 2 Independent predictors for the development of diabetes following pregnancies affected by gestational diabetes in Caucasian and South Asian women

Univariate logistic regression	Caucasian n = 7		South Asian n = 18	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age	1.31 (1.1 to 1.59)	0.007	1.13 (1.02 to 1.25)	0.02
Age index	1.03 (0.96 to 1.10)	NS	1.03 (0.93 to 1.15)	NS
Booking weight	1.02 (1.01 to 1.05)	<0.01	1.04 (1.03 to 1.08)	0.037
BMI in pregnancy	1.21 (1.05 to 1.29)	<0.01	1.20 (1.11 to 1.36)	<0.01
FH (1st deg)	1.1 (0.98 to 1.27)	NS	9.0 (2.50 to 32.67)	0.001
Insulin treated	23.4 (3.87 to 158.31)	0.001	3.4 (0.62 to 11.19)	NS
Gl_0	5.93 (1.33 to 26.34)	0.019	1.60 (1.09 to 2.45)	0.02
Gl_{120}	2.07 (1.02 to 4.15)	0.042	1.13 (0.89 to 1.41)	NS
HbA1c	9.15 (1.91 to 43.87)	0.006	4.95 (1.35 to 12.40)	0.013

Age, age at time of study; Age (index), age at time of pregnancy; BMI, body mass index; FH (1st deg), family history of diabetes in a first-degree relative; Gl_0 and Gl_{120}: fasting and 2 h glucose values during diagnosis OGTT; HbA1c, glycated haemoglobin; Insulin treated, percentage of women in each cohort treated with insulin during the pregnancy; NS, not significant.

failed to reach significance in South Asians (OR 3.4, p = 0.054) (table 2).

Glycated haemoglobin and risk of future diabetes

This study generated ROC curves to examine the ability of the HbA1c taken at diagnosis to identify those likely to develop diabetes. Areas under the curve were significant in both groups (AUC Caucasian 0.88, p = 0.03; South Asian 0.73, p = 0.024); an HbA1c value in pregnancy below 6.10 would correctly exclude 90.5% of Caucasian women from further testing, and a value of 6.15 would similarly exclude 89.5% of South Asian women.

DISCUSSION

This study represents one of only a few studies following women post GDM that allows the direct comparison of South Asian and Caucasian ethnic groups. It confirms the findings of other studies[7 10 18] showing that gestational diabetes is a significant risk factor for the early development of diabetes, occurring within 5 years of pregnancy, in a young female population. It reinforces the usefulness of increasing age, glycaemia in pregnancy and insulin use as individual risk markers for diabetes. More uniquely it suggests that HbA1c values in pregnancy may be useful for excluding those women not at future risk.

Few studies have examined the value of HbA1c measured in pregnancy, primarily because it has poor sensitivity in the diagnosis of GDM due to the time required to effect changes.[15] In the current study HbA1c taken at GDM diagnosis was associated with and predictive of future diabetes. Furthermore by using HbA1c as a cut off we were able to exclude women at low future risk of diabetes. To our knowledge there are very few comparative studies. A recent French study conducted over 5 years failed to find a difference between outcome groups on the basis of third trimester HbA1c.[23] This may be because HbA1c measured late in pregnancy would necessarily reflect the effects of treatment targeted to attaining near normal levels of glucose. In the present study HbA1c was measured at diagnosis, before treatment, and may therefore better reflect differences in β-cell reserve and those at greatest risk of progression to diabetes.

The natural history of abnormal glucose tolerance following GDM varies widely. Conversion rates to type 2 diabetes have been reported to be as low as 2% or higher than 70%,[18] with several studies suggesting that the development of diabetes occurs more frequently in non-Caucasian groups.[3 5 6 17] The present study found South Asian ethnicity to be associated with an increased risk of developing diabetes and is similar to that seen in a longer term study from Melbourne where 17% of the South Asian population developed diabetes compared to 8.8% of local Caucasians (8.8%).[24] Most recently an 8 year follow-up study in Indian women from Pune reported a cumulative incidence of diabetes of 52%.[25] The current study demonstrates that after an elapsed period of 4–5 years following GDM only a third of South Asian women and half of Caucasians have normal glucose tolerance. Given the importance of early identification of diabetes set out in standard 2 of the National Screening Framework for diabetes, our study strongly supports the need to be proactive in screening women with previous GDM.

The large non-responder rate for this trial was disappointing and was seen particularly in the South Asian group, perhaps reflecting different cultural attitudes to medical studies and to the diagnosis of diabetes. An attempt was made to increase the capture of those who had developed diabetes through examination of local diabetes registers, though diabetic non-responders who were seen wholly within primary care would not have been identified. While it was reassuring that our outcome findings concurred with other larger GDM studies, the low response rate necessarily invites a degree of caution.

Our study confirms that the diagnosis of GDM is a significant predictive factor for the future development of diabetes regardless of ethnicity. Screening and treatment strategies should target South Asian women in particular post delivery. Further examination of the value of HbA1c measurement in the GDM pregnancy should be undertaken as it has the potential to target screening away from those at minimal risk.

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