Maternal fructosamine and glycosolated haemoglobin in the prediction of gestational glucose intolerance

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Summary: The value of maternal glycosolated haemoglobin (HBA 1c) and fructosamine in the prediction of gestational diabetes is debated. One hundred high risk patients were grouped as normal, impaired glucose tolerance (IGT) and gestational diabetes mellitus, according to the WHO criteria, after 2 hours, 75 g oral glucose tolerance test (OGTT). Maternal HBA1c and fructosamine were measured at different gestational ages and at the start of labour. The aim of the study was to determine the most sensitive predictor of abnormal glucose tolerance.

Maternal fructosamine was higher in gestational diabetics than in the other two groups, but the difference was not of statistical significance. The values for normal and IGT groups overlapped markedly. The fructosamine test sensitivity was 12.2%, specificity was 94.7% and predictability was 75%.

Glycosolated haemoglobin was significantly higher in IGT and gestational diabetes mellitus (GDM) groups than in the normal group after 36 weeks of gestation. At 32 weeks or less the difference was not of statistical significance. As with fructosamine, there was a wide range of value that overlapped markedly, particularly between the normal and IGT patients. The HBA1c test sensitivity was 19.1%, specificity was 95% and predictability was 81.1%.

This suggests that both HBA1c and fructosamine have very low sensitivity as predictors of gestational glucose intolerance.

Key words: Gestational diabetes; Screening test.

INTRODUCTION

Gestational diabetes by altering the fetal metabolic enviroment in the later half of pregnancy can lead to delayed lung maturation, polyhydramnios, macrosomia, intrauterine death and/or neonatal morbidity and mortality.

As many as 55.7% of delivered mothers in our unit do not have antenatal care (unit statistics 1989). The pregnancy outcome in a proportion of them makes the diagnosis of gestational diabetes highly likely. Therefore, a sensitive post-natal test is needed to identify mothers with undiagnosed GDM if any of the above complications have been present.

The glucose tolerance test returns rapidly to normal, postnatally, in true gestational diabetes (Brudnell, 1985). The blood levels of HBA1c and fructosamine are estblished means of assessing long term glycaemic control in established diabetics (Kennedy *et al.* 1981, and Baker *et al.* 1986). Because of the long biological half life of each protein, they reflect the average blood glucose level in the previous weeks or months. The half life

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for fructosamine is 1-3 weeks and for glycosolated haemoglobins 4-8 weeks (Fraser & Smith, 1979). The value of these levels as markers of poor glycemic control in the short lived GDM, remains controversial with conflicting claims by different assessors. The aim of our study has been to assess which marker HBA1c or fructosamine correlates better with gestational glucose intolerance, so as to use it in the immediate post natal period in assessing mothers that possibly had GDM.

MATERIALS AND METHODS

One hundred patients were recruited into this study from the antenatal clinic. Each patient had one or more risk factors for GDM (Table 1). These patients were further evaluated by 75 g 2 h oral glucose tolerance test optimally done at 27-31 weeks. The WHO criteria for the diagnosis of diabetes or non-diabetes were applied (Table 2 - WHO 1980). Those with normal GTT, but were obese, >30 years or developed polyhydramnios or large for date foetuses had the test repeated at 34-36 weeks. Jovanovic 1, and Peterson C. (1985) recommended testing for glucose tolerance at 27-31 weeks as the yield of earlier testing would be low (0.3% of the population). He also advocated the retesting at 33-36 weeks of higher-risk mothers, so as not to miss the additional 1% yet to develop GDM.

Blood for HBA1c and fructosamine assay was taken at the same time as the fasting sample for OGTT. Measurements were repeated at 32-36 weeks and on admission to labour ward.

Table 1. — *Risk factors for gestational diabetes.*

* Family history of diabetes mellitus
* Obesity
* RBS >6 mmol/l
* Glycosuria
* Maternal age >30 years
* Poor obstetric history, includes:
  - Large baby and suspected large for gestational age in current pregnancy
  - Previous unexplained stillbirths
  - Previous baby with congenital anomalies
  - Gestational diabetes in previous pregnancy
  - Polyhydramnios (past or present)

Table 2. — *Diagnosis of diabetes using 75 g, 2 hours, oral GTT (WHO 1980).*

Fasting blood (venous plasma) glucose
* >8 mmol = diabetes
* <6 mmol = not diabetes

2 hour level
* <8 mmol = not diabetes
* >11 mmol = diabetes

(if no symptoms, one additional level >11 mmol is needed)
* 8-10.9 mmol = impaired glucose tolerance (IGT)

Fructosamine assay was by calorimetric method using Boehringer Mannheim automated analyser (BM/Hitachi System 704). The glycosolated haemoglobin assay was done by the automated ion-exchange chromatography system. Blood glucose measurements were by the hexokinase method using Hitachi System 717.

Patients with abnormal glucose tolerance were seen by a diabetologist, diabetic educator and diaetician. They were advised low carbohydrate diet regimens and blood glucose monitoring at home. Dietry regimen acheived adequate control in all patients but two, who required insulin therapy for optimum control, and four poorly controlled patients who delivered prematurely before initiating insulin therapy.

Twelve patients had elevated blood glucose levels postnatally (>6 mmol/l. preprandial and >8 mmol/l. postprandial) therefore, OGTT was repeated 6 weeks postnatally. Five of them had abnormal OGTT so were excluded from the study as they were considered diabetic rather than gestational diabetics.

According to the results of the OGTT, the patients were grouped into normal, IGT, and gestational diabetes mellitus (GDM) cases. Nine patients had no fructosamine results available, and 8 patients had no HBA1c results, but other results were available for analysis. The mean value for HBA1c and fructosamine, for each group at the different stages of pregnancy, were calculated. The upper normal limit for HBA1c and fructosamine was defined as the mean plus 2 SD. This value was tested as a cut off point for the diagnosis or exclusion of abnormal tolerance.

The sensitivity, specificity and predictability of each test were calculated. The trends of HBA1c and fructosamine, during the course of pregnancy, were assessed in each group. Results were analysed using Student's t-test to assess the significance of the differences between the groups of patients studied.

RESULTS

Out of 95 patients, 42 were normal, 27 were gestational diabetics and 26 had IGT.

During normal pregnancy, maternal fructosamine decreased gradually until the 32nd-36th week, then became stable till delivery (Fig. 1), but the decrease was not of statistical significance (214.8, 202, and 204 mmol/l.at <32, 32-36 and >36 weeks respectively). The fructosamine mean value for the normal group was 206.93 umol/l $\pm$ 20.2.

Gestational diabetics had a higher mean value at different gestational ages but the difference was of no statistical significance. There was a marked overlap between the values for normal and IGT patients. The trend of fructosamine in the abnormal groups was similar to that observed in the normal group, and the decrease during the course of pregnancy was also of no statistical significance (Fig. 3). The fructosamine mean value for the abnormal patients was 214.6 umol/l $\pm$ 22.1. The maternal fructosamine test would have predicted 6

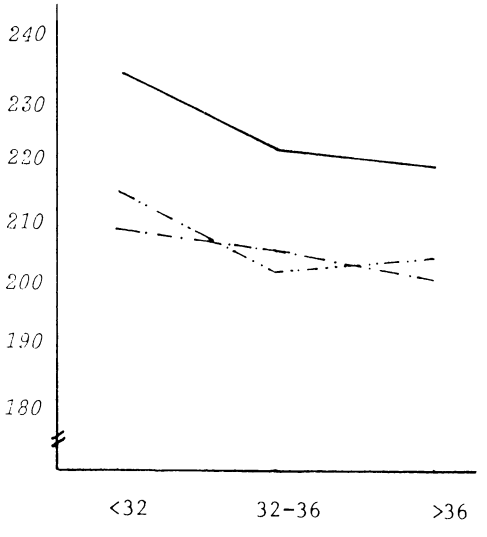

Fig. 1. — Maternal fructosamine (μmol/L) in normal (-··-) IGT (-·-) and gestational diabetics (—).

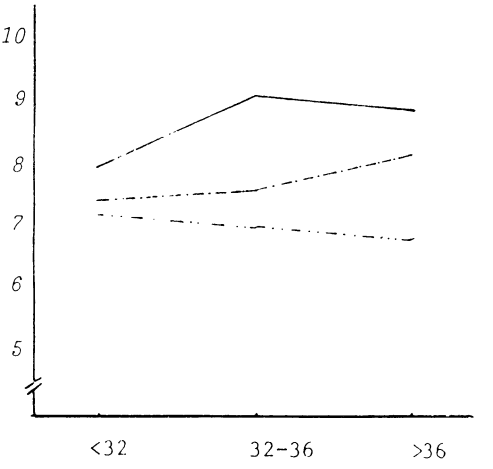

Fig. 2. — Maternal glycosolated Haemoglobin (%) in normal (-··-) IGT (-·-) and gestational diabetics (—).

of 48 abnormal patients, with 42 patients missed and 2 being false positive (12.2% sensitivity, 94.7% specificity and 75% predictability).

Because of the possible effect of dietary control on fructosamine values in the abnormal groups, the sensitivity and specificity of the test were assessed at the time of diagnostic OGTT. They were even lower, being 10.5% and 92.8% respectively.

Glycosolated haemoglobin in normal pregnant women decreased marginally during the course of pregnancy (7.2%, 7.0% and 6.8% at <32, 32-36, and >36 weeks respectively) (see fig. 2). The decrease was of no statistical significance. The mean value for the normal group was 6.9 $\pm$ 1.197.

In the gestational diabetics, HBA1c levels were higher than those of the normal group and the difference was of statistical significance at late stages of pregnancy ($P<0.0001$). But at 32 weeks or less, the difference was not of statistical significance. The levels for the IGT patients were also significantly higher than those for

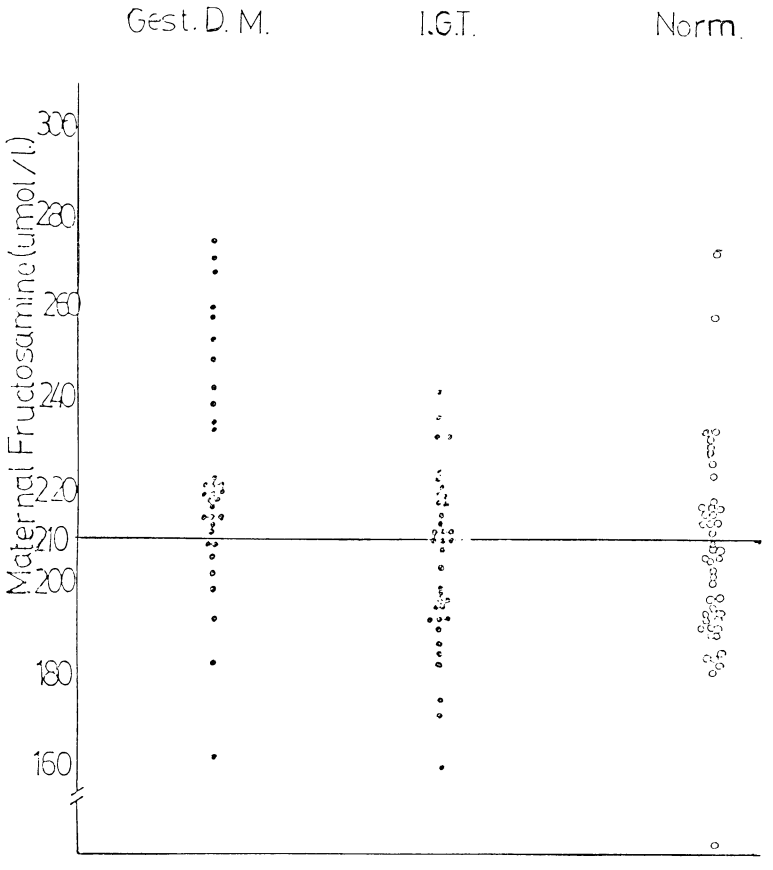

Fig. 3. — Distribution of maternal Fructosamine values in normal (○), IGT and gestational diabetics (●).

the normal group ($P<0.01$). But the difference between the IGT and GDM groups was not of statistical significance. The overlap of values was more marked between the IGT and normal groups (see fig. 4).

In the gestational diabetics, HBA1c levels increased further before declining slightly (7.9%, 9.06%, and 8.8% at <32, 32-36, >36 weeks respectively) (see fig. 2). Though this change did not reach statistical significance, it showed that HBA1c, because of its longer half life, was slower than fructosamine in reflecting the effect of dietary control. The HBA1c mean value for those with abnormal glucose tolerance was 8.16 ± 1.24.

The maternal HBA1c test would predict 9 out of 47 abnormal patients, 38 patients missed and 8 being false positive (19.1% sensitivity, 95% specificity and 75% predictability). It is likely that the dietary regimen had influenced the HBA1c values at later gestation. But on assessing the sensitivity and specificity of HBA1c test performed with the diagnostic OGTT, they were not better, being 16.6% and 94.7% respectively. This confirms that HBA1c as a screening test has very low sensitivity.

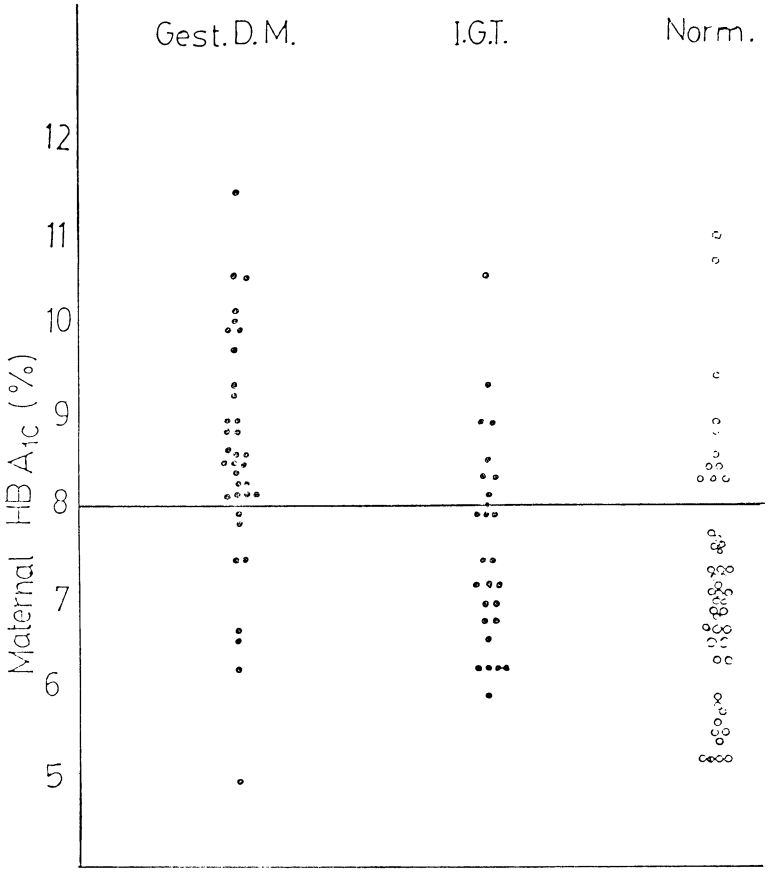

Fig. 4. — Distribution of maternal HbA1c values in normal (○), IGT and gestational diabetics (●).

The values of HBA1c and fructosamine are bound to be higher at late gestation in the untreated abnormal group, because of the longer exposure to high glucose levels. In our treated patients, after 36 weeks, the sensitivity of HBA1c was 36% and of fructosamine was 12.5%. These results, particularly fructosamine, were influenced by the treatment the patients had received. However, it is doubtful if such low sensitivity could have been better in the untreated patients, as we still observed low readings in poorly controlled patients.

DISCUSSION

Abnormal carbohydrate tolerance during pregnancy is associated with fetal and neonatal morbidity and mortality. It tends to recur in subsequent pregnancies and is associated with increased risk of maternal diabetes in later life. It is more prevalent among the Middle East population, than in the West. Nasrat *et al.* (1987) estimated that 20% of their unselected obstetric population in Kuwait had abnormal glucose tolerance, while it is less than 3% in UK (Beard R., 1984) and 3.2% in USA (Jovanovic, 1985).

A large proportion of our patients do not attend for antenatal care; there is a real need for a sensitive postpartum test to assess those patients whose pregnancy outcome suggests gestational diabetes. Controversy exists as to the value of HBA1c and fructosamine as a predictor of gestational diabetes.

Cocilovo (1987) found that HBA1c assays have a low sensitivity, but high specificity. There was a wide range of HBA1c levels in gestational diabetes and therefore overlapping with those of normal pregnant women. HBA1c analysis was also time-consuming, expensive and there was little standardisation between laboratories.

Fructosamine assay is for measuring glycosulated blood proteins. It is a ketoamine, a product of non-enzymatic reaction between a sugar (usually glucose) and a protein (usually albumin). Roberts and Baker (1983) claimed that fructosamine assay detected 85% of gestational diabetes and gave only 5% false positive results. The fructosamine test has the advantages of being fully automated, simple and inexpensive. But Suhonen *et al.* (1989) found that fructosamine values do not correlate with 24 hour glucose profile in the previous 10-35 days as efficiently as HBA1c or glycated protein. He also found the test to be non-specific, with interfering elements accounting for 67% of the fructosamine reading. He concluded that fructosamine test is not an adequate alternative to HBA1c in assessing the long term control of blood glucose. Comtois *et al.* (1989) concluded that it was insensitive as a screening test for gestational diabetes. Corcoy Rosa *et al.* (1990) also identified serum fructosamine as an insensitive parameter for gestational diabetes screening.

Our findings are in agreement with Corcoy Rosa (1990), Suhonen (1989) and Comtois (1989), who found fructosamine to be an insensitive test as a predictor of gestational diabetes. There was a marked overlap of values between the normal and abnormal groups, particularly between the normal and IGT groups. This gave the test poor sensitivity but high specificity. Fructosamine values for gestational diabetes were higher, but they did not differ significantly from normal pregnant women.

Our findings are in disagreement with Roberts and Barker (1983) who found fructosamine test to be efficient in distinguishing 85% of gestational diabetes. Roberts diagnosed gestational diabetes and non-diabetes according to O'Sullivan's criteria, after 3 hours 100 g OGTT. These criteria are less restrictive than the WHO criteria in the diagnosis of gestational diabetes, but do not separate a group with IGT, i.e. IGT and gestational diabetes patients by the WHO criteria, are labelled together as gestational diabetics by O'Sullivan's criteria. Our results are therefore completely different. We found that the test sensitivity at the time of diagnostic OGTT was only 10.5%. Rosa Corcoy (1990) found the test sensitivity to be 8.3%. Salemans T. H. (1987) studied high risk patients for GDM and found fructosamine to have a sensitivity of 17% in detecting GDM. After 36 weeks, the test sensitivity was only 12.5%. However, this result is probably inaccurate because of the influence of the treatment the patient had received.

As for HBA1c, the values for IGT and gestational diabetic groups were significantly higher than those from normal pregnant women at a late stage of pregnancy, but at 32 weeks or less, the difference was not of statistical significance. The test had low sensitivity and high specificity for the diagnosis of abnormal glucose tolerance. This is in agreement with the findings of Cocilovo (1978) and Ross (1984). HBA1c was found to be an insensitive parameter in screening for gestational diabetes even in high risk populations, as its sensitivity at the initial OGTT was only 16.6%.

Beyond 36 weeks gestation, HBA1c had sensitivity of 36% and specificity of 93.75%.

The poor sensitivity of maternal HBA1c and fructosamine is due to the wide range of results that have overlapped markedly, particularly between the normal and IGT patients. Although patients with IGT have a milder degree of glucose intolerance, yet they are at risk for the different diabetes related complications such as stillbirths, pre-eclampsia, macrosomia, birth trauma and neonatal morbidity (Oates and Beischer, 1987). They are also at increased risk for developing diabetes in later life (Oates & Beischer, 1987). IGT patients usually receive dietary advice and close monitoring as gestational diabetics, and may require insulin therapy and are usually induced at term. The ideal test should be able to predict both IGT patients as well as gestational diabetics with adequate sensitivity.

In conclusion, maternal HBA1c and fructosamine do not correlate well with glucose levels in patients with gestational glucose intolerance. They are not sensitive enough to discriminate between the normal and the abnormal groups. As a result, we cannot recommend either test for postnatal testing of mothers who might have had abnormal glucose tolerance during the antecedent pregnancy.

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