PAPERS AND SHORT REPORTS

Does random blood glucose sampling outdate testing for glycosuria in the detection of diabetes during pregnancy?

T LIND, J ANDERSON

Abstract

A random blood glucose concentration was determined in 2403 pregnant women attending an antenatal clinic at between 28 and 32 weeks' gestation. The calculated 99% cut off values were 6·1 mmol/l (110 mg/100 ml) within two hours after a meal and 5·6 mmol/l (101 mg/100 ml) more than two hours after a meal. Patients with a blood glucose concentration in excess of these values were referred for a 75 g oral glucose tolerance test. Of 59 referred, four were found to have previously unsuspected but unequivocal diabetes mellitus and another four to have impaired glucose tolerance on the basis of the World Health Organisation's criteria.

Screening all antenatal patients by randomly measuring blood glucose concentrations is not only cheap and efficient but also does not interfere with the routine of busy antenatal clinics.

Introduction

For many years the urine of women attending antenatal clinics has been tested for the presence of glucose in the belief that this is an efficient way of detecting diabetes mellitus. It is now recognised that about half of all healthy pregnant women excrete increased amounts of glucose, and the amount of such losses varies not only between individuals but within individuals from occasion to occasion.[1] That the increased excretion is physiological rather than indicative of any disorder of carbohydrate metabolism is shown by mothers with persistent and heavy glycosuria during normal pregnancy reverting to a normal non-glycosuric state within six days after delivery, sometimes within 48 hours.[2]

Medical Research Council Human Reproduction Group, Princess Mary Maternity Hospital, Newcastle upon Tyne NE2 3BD

T LIND, MB, MRCOG, consultant obstetrician

Department of Medicine, Royal Victoria Infirmary, Newcastle upon Tyne

J ANDERSON, MB, FRCP, senior lecturer and consultant physician

Correspondence to: Mr T Lind.

The diagnosis of diabetes mellitus is based on blood glucose concentrations exceeding certain values at specific times after an oral glucose load. The particular concentrations used have varied somewhat depending on the organisation quoted, but the criteria defined by the World Health Organisation[3] are similar to those of the European Association for the Study of Diabetes[4] and the National Diabetes Data Group[5] and are achieving widespread acceptance. These criteria define a fasting venous plasma glucose concentration of 8·0 mmol/l (144 mg/100 ml) or higher as diagnostic of diabetes. A fasting concentration of less than 6 mmol/l (108 mg/100 ml) excludes the diagnosis. When a tolerance test with 75 g glucose by mouth is performed a venous plasma glucose concentration of 11·0 mmol/l (198 mg/100 ml) or more, two hours after the glucose load, is indicative of diabetes mellitus; concentrations between 8·0 and 10·9 mmol/l (144 and 196 mg/100 ml) after two hours indicate impaired glucose tolerance.

As performing an oral glucose tolerance test on every pregnant woman would be impractical and expensive a study was undertaken to assess the range of glucose concentrations in blood samples randomly obtained during the course of normal visits to the antenatal clinic.[6] In 100 healthy patients the mean venous blood glucose concentration within two hours after a meal was 4·8 mmol/l (86 mg/100 ml) with a standard deviation of 0·7 mmol/l (12·6 mg/100 ml) yielding a 99% cut off value of 6·4 mmol/l (115 mg/100 ml). The equivalent cut off value determined from 86 women who had eaten more than two hours previously was 5·8 mmol/l (105 mg/100 ml). Here we report our findings when these criteria were prospectively applied to 2485 women attending an antenatal clinic at between 28 and 32 weeks' gestation during one year.

Patients and methods

A venous blood sample is obtained, for determination of glucose concentration, from every patient attending the antenatal clinic of this hospital at the initial booking visit and again between 28 and 32 weeks' gestation. Because the duration of gestation at booking varies between patients and because some go on to abort spontaneously only those attending at between 28 and 32 weeks' gestation will be discussed. Excluding those already known to have diabetes mellitus, samples were obtained from 2485 such patients, but in 53 instances the blood glucose report could not be traced. We excluded 28 women who had twin pregnancies and one who had a

triplet pregnancy for the sake of uniformity despite their blood glucose concentrations being within the range to be discussed. This left 2403 patients for subsequent analysis, in 2285 of whom the time of the last meal had been accurately recorded. In the remaining 118 this interval was recorded only as "more than" or "less than" two hours previously.

Results

The 2285 patients for whom an accurate time had been recorded were divided into nine groups according to the time of sampling, in half hours, since their last meal; the mean blood glucose concentration was determined for each group together with the standard deviation and the calculated 99% cut off value (table I). They were then divided into only two groups according to whether their last meal was within two hours before sampling. This allowed all 2403 patients to be used. Mean (SD) concentrations and 99% cut off values were calculated again (table II). The cut off values were slightly different from those applied, being 6·1 (110) rather than 6·4 mmol/l (115 mg/100 ml) within two hours after a meal and 5·6 (101) rather than 5·8 mmol/l (105 mg/100 ml) more than two hours after a meal.

Fifty nine patients (2·6%) were referred for various reasons for glucose tolerance testing with 75 g glucose by mouth (figure). Thirty eight were referred on the basis of their random blood glucose concentration, though in only 32 (1·4%) had this actually exceeded the 99% cut off value. Of the 38, two were found to have unequivocal diabetes mellitus (and are further discussed below). Four others had post load concentrations indicative of impaired glucose tolerance during the pregnancy, according to the criteria of the World Health Organisation, but reverted to normal after delivery. The remaining 32 patients were normal, though seven would have been regarded as having some degree of carbohydrate intolerance on the basis of the British Diabetic Association's recommendations—that is, a capillary blood glucose concentration greater than 7·0 mmol/l (126 mg/100 ml) two hours after a 50 g oral glucose load.[7] These patients were asked to attend our clinic but had uncomplicated pregnancies resulting in the birth of live healthy babies; all reverted to a completely normal response after delivery. At the time of their oral glucose tolerance test all had fasting blood glucose concentrations below 6·0 mmol/l (108 mg/100 ml).

Seven patients were referred for oral glucose tolerance testing on the basis of glycosuria. Our practice had been to refer pregnant women who displayed glycosuria in freshly passed urine on two or more occasions; the definition of glycosuria was a positive response to a commercial reagent strip (Multistix). All were normal by the standards of the World Health Organisation, though two could be regarded as having impaired glucose tolerance by the criteria of the British Diabetic Association; they were both normal after delivery. Six patients were referred on the basis of having previously had a large baby, and all gave a normal response to oral glucose tolerance testing. Two were investigated because they had been called diabetic in a previous pregnancy; one gave a normal response to oral glucose tolerance testing and the other qualified as having impaired glucose tolerance according to the post load criteria of the World Health Organisation but was completely normal after delivery. The remaining six patients were referred for a variety of reasons but were all found to be normal (figure).

Altogether four patients were diagnosed as having diabetes mellitus, two on the basis of their responses to oral glucose tolerance testing at two hours as described above and two on their random blood glucose concentrations alone (16·4 and 21·9 mmol/l (296 and 395 mg/100 ml) respectively). None had any of the "stigmata" of diabetes such as a family history of the disease or a bad obstetric history and none had been symptomatic in the sense that they had sought advice from either their general practitioner or the antenatal clinic; only one had had glycosuria detected at a previous visit to the clinic. Three patients required insulin treatment during pregnancy, one of whom remained insulin dependent afterwards; she subsequently had a second successful pregnancy. Another was changed from insulin to gliclazide after delivery but subsequently became insulin dependent, and the third achieved dietary control after delivery and did not require further treatment despite her response to oral glucose tolerance testing being unequivocally diabetic. The fourth patient found to have diabetes responded well to dietary management during pregnancy and continued to do so afterwards, but repeated oral glucose tolerance testing showed persistently impaired glucose tolerance by the standards of the World Health Organisation. All had normal, vaginal deliveries of live healthy babies.

TABLE I—*Blood glucose concentrations in accurately timed samples from 2285 antenatal patients*

Time (mean) after meal (min)	No of patients	Blood glucose (mmol/l)	
		Mean (SD)	99% cut off
1-30 (21)	173	4·62 (0·71)	6·3
31-60 (47)	144	4·52 (0·82)	6·4
61-90 (82)	213	4·39 (0·80)	6·3
91-120 (110)	428	4·34 (0·69)	5·9
121-150 (139)	449	4·25 (0·67)	5·8
151-180 (169)	340	4·15 (0·62)	5·6
181-210 (196)	247	4·05 (0·59)	5·4
211-240 (227)	122	4·01 (0·56)	5·3
⩾241 (377)	169	3·91 (0·56)	4·5

Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml.

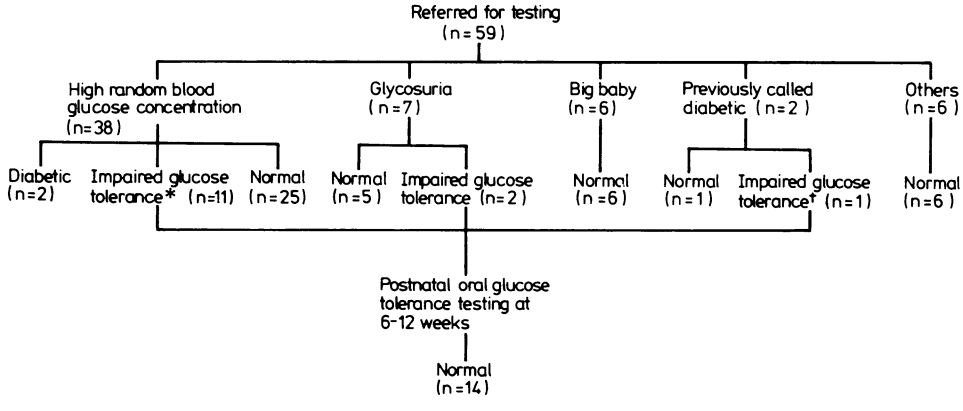
TABLE II—*Blood glucose concentrations in all 2403 patients screened at 28-32 weeks' gestation according to whether blood was taken within two hours after a meal*

Time after meal (min)	No of patients	Blood glucose (mmol/l)	
		Mean (SD)	99% cut off
1-120	992	4·43 (0·73)	6·1
⩾121	1411	4·11 (0·63)	5·6

Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml.

Discussion

Several practical points emerge from this study. In both the initial group[6] and the present much larger group the data suggest that about 99% of a normal healthy pregnant population are unlikely to have a random venous blood glucose concentration much above 6·3 mmol/l (114 mg/100 ml) even shortly



Reasons for requesting oral glucose tolerance testing and outcome in 59 patients.

*Four according to criteria of the World Health Organisation plus seven according to criteria of the British Diabetic Association.

†According to criteria of the World Health Organisation.

after a meal. Thus diabetic patients defined as those with random venous concentrations of at least 11 mmol/l (198 mg/100 ml) will be five standard deviations or more above the highest postprandial mean blood glucose concentration. Although we cannot say that we did not miss some diabetic patients in our series, these data suggest that this was unlikely; the incidence too (four in 2403 or one in 600 of a female population of reproductive years) was about the expected figure.

The stages of pregnancy at which samples for random determination of glucose concentration were obtained were those when blood was required for other routine antenatal tests; thus the cost of the needle and syringe was shared with several other tests. If the commonly used Multistix for testing urine, which give much unnecessary data and cost about 8 pence each, were replaced by a simple reagent strip to detect proteinuria only (at about 4 pence) the savings would help to compensate for the automated measurement of the blood glucose concentration. Clinic routine is not disrupted, the patients are not delayed or inconvenienced, and any increased laboratory cost can be balanced by saving on unnecessary urine tests. On the basis of random blood glucose screening two patients were diagnosed as having diabetes mellitus and 32 were correctly referred for an oral glucose tolerance test—that is, excluding the six patients in whom the blood glucose concentrations did not exceed the cut off values. Of these, a further two were found to have diabetes and 11 impaired glucose tolerance. Of 21 women referred for an oral glucose tolerance test for other reasons, three had impaired glucose tolerance. From another viewpoint, none of the diabetic patients was missed by the random checking of blood glucose concentration but only one of the four might have been referred for an oral glucose tolerance test on the basis of her glycosuria.

Is it necessary, however, to look for diabetes mellitus at all? The incidence of diabetes appears to be increasing rather than decreasing,[8 9] and, though mortality and morbidity rates for females appear to be better than for males, they are still high[10] and show wide regional variations. The sooner pregnant diabetic women can be detected and returned to a normoglycaemic state the better their prognosis should be. The obstetrician must also be concerned for the fetus. In many hospitals now the perinatal mortality for diabetic mothers is not much greater than for the population at large,[11] which almost certainly reflects the increasing care taken in controlling the metabolic state of the mother. If a look for diabetes mellitus is accepted as a necessary part of good antenatal care random measurement of blood glucose concentration offers an easy, efficient, and relatively inexpensive method for doing this.

We thank Professor K G M M Alberti, Dr P A Smith, and our colleagues in the department of clinical biochemistry of the Royal Victoria Infirmary, Newcastle upon Tyne, for their help and co-operation with this study.

References

1 Lind T, Hytten FE. The excretion of glucose during normal pregnancy. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1972;**79**: 961-5.
2 Davison JM, Lovedale C. The excretion of glucose during normal pregnancy and after delivery. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1974;**81**:30-4.
3 WHO. Expert Committee on Diabetes Mellitus. Report. *WHO Tech Rep Ser* 1980;No 646.
4 Keen H, Jarrett RJ, Alberti KGMM. Diabetes mellitus: a new look at diagnostic criteria. *Diabetologia* 1979;**16**:283-6.
5 National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 1979;**28**:1039-57.
6 Lind T, McDougall AN. Antenatal screening for diabetes mellitus by random blood glucose sampling. *Br J Obstet Gynaecol* 1981;**88**:346-51.
7 FitzGerald MG, Keen H. Diagnostic classification of diabetes. *Lancet* 1964;i: 1325-6.
8 Melton LJ 3rd, Pasquale J, Palumbo PJ, Chu CP. Incidence of diabetes mellitus by clinical type. *Diabetes Care* 1983;**6**:75-86.
9 Calnan M, Peckham CS. Incidence of insulin-dependent diabetes in the first sixteen years of life. *Lancet* 1977;i:589-90.
10 Patterson CC, Thorogood M, Smith PG, Heasman MA, Clarke JA, Mann JI. Epidemiology of type 1 (insulin-dependent) diabetes in Scotland 1968-1976: evidence of an increasing incidence. *Diabetologia* 1983;**24**:238-43.
11 Molsted-Pederson L. Preterm labour and perinatal mortality in diabetic pregnancy—obstetric considerations. In: Sutherland HW, Stowers JM, eds. *Carbohydrate metabolism in pregnancy and the newborn*. Berlin: Springer-Verlag, 1978:392-406.

(*Accepted 26 September 1984*)

HLA-DR typing in coeliac disease: evidence for genetic heterogeneity

A ELLIS, C J TAYLOR, M DILLON-REMMY, J C WOODROW, R B McCONNELL

Abstract

Sixty nine propositi from a family study of coeliac disease were typed for HLA-DR antigens. Sixty three (91%) were found to carry the antigen DR3, which was a significantly greater proportion ($p = 9{\cdot}6 \times 10^{-24}$) than among the 168 controls (26%). Concurrently 42 children with the disease were DR typed. Not only was the frequency of DR3 significantly increased in these patients (86% versus 26% in controls; $p = 3{\cdot}1 \times 10^{-12}$) but so also was the frequency of DR7 (patients 60%, controls 29%; $p = 5{\cdot}8 \times 10^{-4}$). When those propositi whose coeliac disease presented before the age of 20 were combined with the childhood coeliac group and a comparison made between these patients and the remainder of the propositi, all of whom presented when they were older than 20, the childhood onset group had a significant excess of DR7 ($p = 2{\cdot}2 \times 10^{-3}$) and a significant deficiency of DR2 ($p = 3{\cdot}5 \times 10^{-3}$).

These findings indicate that childhood coeliac disease and adult coeliac disease are genetically heterogeneous.

Gastroenterology Unit, Broadgreen Hospital, Liverpool L14 3LB
A ELLIS, MD, MRCP, consultant physician and gastroenterologist
R B McCONNELL, MD, FRCP, consultant physician and gastroenterologist

Department of Child Health and Tropical Child Health, Alder Hey Children's Hospital, Liverpool L12 2AP
C J TAYLOR, MRCP, lecturer
M DILLON-REMMY, MB, DTCH, research assistant

Department of Medicine, University of Liverpool, Liverpool L69 3BX
J C WOODROW, MD, FRCP, professor of medicine

Correspondence to: Dr A Ellis.

Introduction

An association between coeliac disease and the histocompatibility antigen HLA-DR3 has been reported in all the populations