out in Britain before the universal use of varicella vaccine can be seriously considered. This does not preclude more extensive selective use of the vaccine in those at special risk, such as immunosuppressed patients.

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Reference values for 75 g oral glucose tolerance test in pregnancy

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Abstract

A 75 g oral glucose tolerance test was performed in 212 pregnant women with no predisposing factors suggesting glucose intolerance to establish the normal pattern of glucose metabolism in pregnancy. Reference values for the test were established for the middle of pregnancy (14-20 weeks, n=43) and late pregnancy (28-37 weeks, n=168). One woman was excluded because she had diabetes that required treatment with insulin. There were statistically significant differences between the two groups for samples taken both one and two hours after the glucose load. Reference ranges for the interpretation of the glucose tolerance test in pregnancy should therefore take account of the period of gestation.

Arbitrary upper limits of normal (represented by the 97.5 centile) two hours after a 75 g oral glucose load are proposed at 7.5 and 9.6 mmol/l for the second and third trimesters, respectively.

Introduction

The oral glucose tolerance test is a well established method of identifying patients with abnormal carbohydrate metabolism. Though the influence of pregnancy on glucose tolerance has often been investigated, there are discrepancies among the reports: the glucose tolerance test has been reported to be unchanged¹ or impaired.^{2,3} A possible explanation of these opposing views may be variations in the carrying out of the test and in the interpretation of the data.

Methodological changes have taken place in the measurement of plasma glucose concentrations during the last 20 years. Earlier studies used the alkaline ferricyanide method, but this has been superseded by more specific enzyme assays that give results about

10% lower, are more sensitive, and specify the normal range with better precision.

Criteria for an abnormal oral glucose tolerance test result during pregnancy have been proposed with different glucose loads. O'Sullivan and Mahan reported reference values for 752 unselected pregnant women given a load of 100 g.⁴ Although many pregnant women vomit after such a large load, these criteria are still widely accepted in North America (table I). No allowance was made for alteration in glucose tolerance with advancing gestation. Other investigators showed subtle and progressive changes in the response curve to oral glucose with the advancement of the pregnancy.^{3,5} Abell and Beischer proposed reference values using a 50 g glucose load; these were obtained from 2000 unselected pregnant women between 32 and 34 weeks' gestation.⁶ Their results at the 95th centile were significantly lower than those of O'Sullivan (table II).²

TABLE I—Proposed upper limits of normal plasma glucose concentrations after 100 g oral glucose tolerance test⁴

	Time (hours)			
	0 (Fasting)	1	2	3
Glucose (mg/100 ml)	90	165	145	125
Glucose (mmol/l)	5.00	9.17	8.06	6.94

TABLE II—Proposed upper limit of normal plasma glucose concentrations after 50 g oral glucose tolerance test performed between 32 and 34 weeks' gestation⁶

	Time (hours)			
	0 (Fasting)	1	2	3
Glucose (mg/100 ml)	93	165	128	103
Glucose (mmol/l)	5.17	9.17	7.11	5.89

As a consequence of these opposing views a standardised glucose load of 75 g was recommended by an international working party in 1979,⁷ and this has been accepted by the expert committee on diabetes of the World Health Organisation.⁸ There have, nevertheless, been no studies to determine the reference values for the 75 g oral glucose tolerance test in pregnancy, and the present study was designed to remedy this.

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Subjects and methods

The subjects were recruited from the antenatal clinics at the Princess Anne Hospital, Southampton. All gave informed consent to participate in the study. The following were excluded: known diabetics; those with a family history of diabetes in first degree relatives; those who had had a previous baby weighing more than 4000 g, a previous stillborn infant, or an infant with congenital malformation; those who had had a previous neonatal death, or three or more abortions; those weighing more than 85.0 kg at the time of registering at the clinic or who were over 35 years old; and those with a multiple pregnancy.

The mean age of the subjects when they first registered at the clinic was 26.0 years (range 19-34), and in the third trimester 26.3 years (range 15-35). The mean parity for subjects when first registered was 0.85 (range 0-4), and in the third trimester 0.95 (range 0-5).

The subjects attended at 0900 after an overnight fast. After 15 minutes' rest they were each given a 75 g load of anhydrous glucose dissolved in water and flavoured with pure lemon juice to drink within five minutes. Three women, at 17, 30, and 36 weeks' gestation, were excluded from the study at this stage because of vomiting. In the remaining 212, 2 ml samples of venous blood were withdrawn just before and one and two hours after the ingestion of glucose and collected into fluoride oxalate tubes. They were immediately centrifuged and the plasma separated and frozen at -20°C until analysis.

Plasma glucose concentrations were measured by a kinetic glucose dehydrogenase assay (E Merck, Darmstadt) on an Instrumentation Laboratory (IL) Multistat III centrifugal analyser. The interassay coefficient of variation at 7.9 mmol/l was 1.8% (n=23).

The subjects were divided into three groups depending on length of gestation. Group 1 (n=43) were at 14-20 weeks, group 2 (n=125) at 28-32 weeks, and group 3 (n=44) at 36-37 weeks. Birth weight, fetal abnormalities, sex of the infant, and neonatal outcome were recorded for all participants.

The plasma glucose concentrations one and two hours after the oral glucose load had been taken were not normally distributed and were therefore logarithmically transformed and expressed as geometric means and 2.5 and 97.5 centile limits (two standard deviations above and below the mean). The significance of differences were then analysed by Student's *t* test.

Results

Of 215 pregnant women, 212 completed the study, three having been excluded because of vomiting (1.4%). All the infants were born alive and there were no neonatal deaths. No congenital malformations were detected within the first 48 hours of life. The birth weights of all infants were compared with the Southampton chart for normal birth weights (T Wheeler, personal communication). There were three babies whose birth weight was less than 2.5 centile and two babies whose birth weight was greater than the 97.5 centile, but the removal of their data did not affect the ranges of the plasma glucose concentrations. There was one patient in group 2 whose results showed that she was diabetic (fasting concentration 5.9 mmol/l, at one hour 12.8 mmol/l, and at two hours 13.0 mmol/l); she required treatment with insulin during her pregnancy. Her results were excluded from the study. This patient gave birth to the largest baby (4420 g).

TABLE III—Geometric mean and 2.5 and 97.5 centile plasma glucose concentrations (mmol/l) before and after 75 g glucose load

	Group 1 (n=43)			Groups 2 and 3 combined (n=168)		
	Time (hours)			Time (hours)		
	0	1	2	0	1	2
Mean	4.19	5.02	4.91	4.07	6.71	6.11
2.5 Centile	3.59	2.87	3.20	3.40	4.11	3.89
97.5 Centile	4.88	8.78	7.53	4.85	10.98	9.59

The fasting plasma glucose concentrations did not differ significantly among the three groups. There were no significant differences between all results (fasting, at one hour, and at two hours) in groups 2 and 3 and they were therefore combined to give the reference values for the oral glucose tolerance test in late pregnancy (table III). There were significant differences in the plasma glucose concentrations between group 1 and the combined groups 2 and 3 both one hour ($p<0.001$) and two hours ($p<0.001$) after the glucose load (table III).

Figure 1 shows the distribution of plasma glucose concentrations before

and one hour after the 75 g load for groups 2 and 3 combined. A comparison of the results after fasting and the glucose concentrations at two hours is shown in figure 2. Figure 3 shows the difference in distribution of the concentrations at two hours between the second and third trimesters. For comparison the World Health Organisation's recommended plasma glucose concentrations after fasting are <6 mmol/l (normal), $6.1-7.8$ mmol/l (impaired glucose tolerance), and >7.8 mmol/l (diabetes mellitus). The

FIG 1—Distribution of fasting plasma glucose concentrations (hatched area) and those one hour after 75 g glucose load in third trimester (groups 2 and 3 combined).

FIG 2—Distribution of fasting plasma glucose concentrations (hatched area) and those two hours after 75 g glucose load in third trimester (groups 2 and 3 combined).

FIG 3—Distribution of plasma glucose concentrations in second (hatched area) and third trimester two hours after 75 g glucose load. Upper limits of normal were set at 7.5 and 9.6 mmol/l for second and third trimesters, respectively.

limits recommended two hours after a 75 g oral glucose tolerance test are <7.7 mmol/l (normal), 7.8-11.0 (impaired glucose tolerance), and >11.0 (diabetes mellitus).

Parity did not correlate with plasma glucose concentrations in any group.

Discussion

There is an association between impaired glucose tolerance and hyperglycaemia in pregnancy, on the one hand, and the incidence of intrauterine death and the number and severity of fetal malformations, on the other. Important clinical decisions are therefore made on the basis of the results of oral glucose tolerance tests during pregnancy, and it is essential that the reference values for the test are standardised and take into account the physiological changes in carbohydrate metabolism that occur during pregnancy. This study confirms that the geometric mean plasma glucose concentrations and the 2.5 and 97.5 centiles one and two hours after an oral glucose load differ significantly between mid and late pregnancy.

The effect of the size of the oral loading dose of glucose has not been adequately studied in pregnancy. In normal non-pregnant subjects it seems to have only a minor effect, but De Noble and van't Laar have shown that in subjects with slight intolerance to glucose the results of the tolerance test after a 50 g oral dose of glucose were significantly lower than those after a 100 g oral dose.⁹ Because there are practical difficulties in tolerating and retaining the large 100 g glucose load (especially by pregnant women) the World Health Organisation's expert committee on diabetes mellitus¹⁰ recommended 75 g as the loading dose for the oral glucose tolerance test and laid down standards for non-pregnant subjects. Only three (1.4%) of our patients experienced vomiting after a 75 g dose of glucose.

The present study, which intentionally concentrated on the beginning of the third trimester, when data are likely to be of most value to clinicians, showed that, though the fasting plasma glucose ranges fell within the World Health Organisation's normal range for

non-pregnant subjects, the concentrations one and two hours after the loading dose showed a reduction in glucose tolerance in the third trimester. It should be noted that the upper limit of normal at two hours in the second trimester is close to the World Health Organisation's recommendation of 7.7 mmol/l for non-pregnant subjects.

We therefore propose that for a "Southampton population" the upper limits of normal for plasma glucose concentrations two hours after a 75 g oral glucose tolerance test for the second and third trimesters are 7.5 and 9.6 mmol/l, respectively.

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Median age at death as an indicator of premature mortality

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Abstract

The median age at death from certain diseases was calculated for each year for 1969-85 and compared with that at death from all causes. The results indicated the impact of these diseases in terms of premature mortality and changes over time. Cancer was a more important cause of premature mortality among women than among men. For cancer of the cervix the median age at death increased appreciably whereas for cancer of the lung in women it slightly decreased. The median age at death is easy to calculate, does not require standardisation, and has a useful role.

Introduction

Most of the various methods used to describe the mortality from specific diseases are based on relating the incident cases to the population at risk, thereby creating a rate. When comparing rates based on populations that differ in their age distribution standardisation is necessary. As the risk of most diseases increases with age a rate is not very effective for showing the impact of diseases in terms of premature mortality. Premature mortality may be expressed as the potential years of life lost, and various methods have been developed to obtain comparable measures of premature mortality¹ (B Rennermalm, Scandinavian Population Studies No 8, in preparation). Here we present a method for indicating premature mortality based on the median age at death.

Subjects and methods

The median age at death in months from all causes was obtained by listing all deaths in the Swedish Cause of Death Registry for each year from 1969 up to and including 1985 by the age in months at the time of death. The middle case was identified. If there was an even number of deaths the median was considered to be the mean of the age of the two middle cases. The same

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