PAPERS AND ORIGINALS

Carbohydrate Metabolism in Pregnancy

Part I—Diurnal Plasma Glucose Profile in Normal and Diabetic Women

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Summary

Diurnal plasma glucose profiles and oral glucose tolerance during pregnancy were studied in normal women, chemical diabetics, and insulin-requiring diabetics. In normal women the mean diurnal plasma glucose rose by only 0·22 mmol/l (4 mg/100 ml) during pregnancy. Mild chemical diabetes resulted in an increase in both the mean diurnal glucose concentration and the fluctuation of plasma glucose levels during the day.

Fluctuation in glucose concentration in insulin-dependent diabetics was about three times that found in non-diabetic women of similar gestation, with relative hyperglycaemia during the day and hypoglycaemia at night.

In non-diabetic women and those with chemical diabetes the mean diurnal glucose correlated closely with the total area under the three-hour oral glucose tolerance curve and significantly, but less closely, with the two-hour glucose tolerance test value.

Introduction

Diabetes in pregnancy is one of the few metabolic disorders which change the environment in which the fetus develops; the incidence of fetal complications such as malformations, macrosomia, hyperinsulinism, and stillbirth is increased, which may be the result of a relatively minor disturbance of glucose homoeostasis. Yet to diagnose diabetes in pregnancy we tend to rely on an artificial glucose challenge in the form of a glucose tolerance test (G.T.T.), the results of which have never been shown to correlate closely with the outcome of the pregnancy nor with the glucose environment to which the developing fetus is exposed.

Our aim was to investigate the diurnal concentration and variability of plasma glucose in normal and diabetic women. The results were also compared with some of the accepted indices of glucose tolerance derived from the standard 50-g oral G.T.T.

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Patients and Methods (Table I)

Of the 50 patients studied 13 were insulin-dependent diabetic women who had all been on insulin treatment before pregnancy for six to 26 years, 31 had one or more features of potential diabetes,[1] and six were control patients.

Each patient was admitted to a metabolic ward and the study started at 10 a.m. Blood samples were collected via an indwelling catheter in an antecubital vein every hour during the day, when the patient was encouraged to be active, and every two hours during the night until 9 a.m. the next morning. A total daily carbohydrate intake of 180 g was provided, of which 40 g was consumed at home as part of the patient's breakfast. A standard three-hour 50-g oral G.T.T. with half-hourly blood samples was then performed between 9 a.m. and noon.

Patients were assigned to either a "normal" or a "chemical diabetic" group depending on the result of the G.T.T. performed in the last trimester of pregnancy, the response to this test being assessed in terms of area under the three-hour glucose curve.[2] In non-pregnant patients a glucose area of 44·4 units (800 traditional units) correlates closely with other widely used criteria of abnormal glucose tolerance[3] and is taken to indicate chemical diabetes; in view, however, of the small decline in fasting plasma glucose which occurs during pregnancy[4-6] we reduced the upper limit of normal for the third trimester to 41·6 units (70 traditional units).

Twenty-four of the patients studied were classified as "normal" and 13 as "chemical diabetics." The chemical diabetes was mild in all cases, only three patients with fasting plasma glucose levels of 5·61, 5·72, and 6·33 mmol/l (101, 103, and 114 mg/100 ml) having significantly raised levels. No difference was found between the results of the six controls and those of the 18 "potential diabetics" with a normal G.T.T. and the two groups were therefore combined for analysis (cross-sectional study). Nine women, including the six controls, were studied both in the mid-trimester between 12 and 22 weeks and again in late pregnancy between 32 and 35 weeks (longitudinal study). The remaining patients were all studied in the last trimester of pregnancy.

The insulin-dependent diabetic women were studied between 32 and 36 weeks, after at least two weeks in hospital, when optimal diabetic control had been achieved with careful dietary carbohydrate management and twice-daily injections of soluble and isophane insulin. Table I shows that the normal, chemical diabetic, and insulin-requiring diabetic groups were well-matched for age, weight, height, and gestation.

Plasma glucose was measured using a glucose oxidase-peroxidase method[7] and plasma insulin by radioimmunoassay.[8]

To assess the relation between the diurnal glucose profile and G.T.T. results several indices were derived from the glucose tolerance curve. These included the total area under the curve, the incremental area (calculated by subtracting the area under the fasting value from the total area), the "H" index,[9] and the two-hour plasma glucose value.[1]

The diurnal glucose data were analysed twice. Firstly, the mean of all values obtained from 10 a.m. to 8 a.m. the next morning was calculated and called the "mean diurnal plasma glucose." Secondly, the mean of the values from 10 a.m. to 8 p.m. was calculated and called the "mean daytime plasma glucose." The mean diurnal plasma glucose reflected the integrated plasma glucose concentration to which the fetus was exposed, while the mean daytine plasma glucose, being limited to the food intake period, was expected to reflect more closely maternal carbohydrate tolerance.

To investigate the suggestion that high maternal glucose concentrations and large fluctuations in the maternal plasma glucose level may have an adverse effect on the carbohydrate metabolism of the fetus,[10] the maximum plasma glucose recorded during the study and the diurnal range of plasma glucose values were also recorded.

Student's t test, linear regression analysis, and Spearman's correlation coefficients were used for statistical analysis of the data.

Results

Changes during Pregnancy in Normal Women.—Mean plasma glucose remained below 5·6 mmol/l (100 mg/100 ml) except during the hour after a meal in the nine women studied in both early and late pregnancy (fig. 1). Preprandial plasma glucose levels were, however, generally lower in late pregnancy and postprandial levels higher. These differences were significant at midday, two hours after lunch, and one and two hours after the evening meal. The diurnal plasma glucose range was greater in late than in early pregnancy (table II). Neither mean diurnal nor mean daytime plasma glucose increased significantly as pregnancy progressed, the rise in each case being about 0·22 mmol/l (4 mg/100 ml). There was also no significant change in the total or incremental area under the G.T.T. curve, the G.T.T. two-hour plasma glucose, or the H index (table III). Plasma insulin was increased throughout the day in late pregnancy, this being most apparent after meals (fig. 1). To relate insulin concentration to the prevailing glucose stimulus insulin:glucose ratios were calculated.

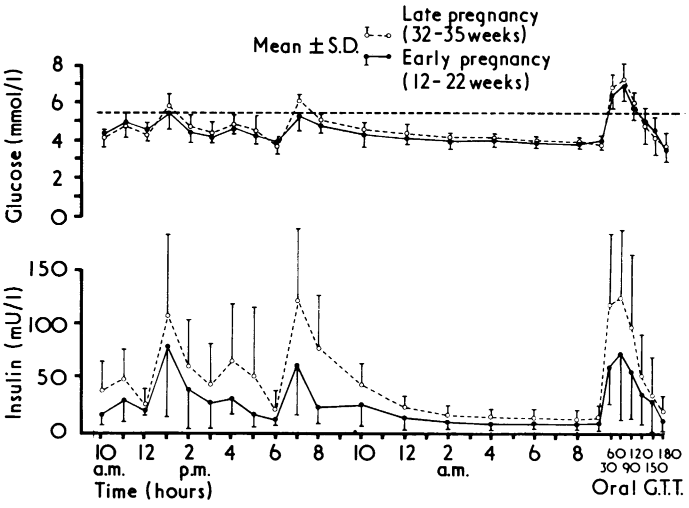

FIG. 1—Plasma glucose and insulin concentrations during diurnal profile and oral G.T.T. in nine normal women studied in early and late pregnancy.
Conversion: SI to Traditional Units—1 mmol/l ≈ 18 mg/100 ml.

In late pregnancy the mean value for this ratio was almost doubled during both the diurnal study (P = 0·003) and the G.T.T. (P = 0·001).

Comparison between Normal and Chemical Diabetic Patients.—Results from the 24 normal patients were compared with those from the 13 chemical diabetics. The mean diurnal plasma glucose of the chemical diabetic group was much higher than that of the normal patients (table II, fig. 2). The mean daytime plasma glucose exceeded the mean diurnal plasma glucose concentration by 0·18 mmol/l (3·3 mg/100 ml) for the normal women and by 0·32 mmol/l (5·5 mg/100 ml) for the chemical diabetics, indicating a similar day and night pattern for the two groups. Glucose levels fluctuated more, however, in the chemical diabetics. The mean value for the H index was significantly lower in the normal group (table III). Insulin concentrations were much lower and responses to glucose significantly impaired in the chemical diabetics (fig. 2). The daytime and G.T.T. insulin: glucose area ratios were also significantly lower in these women.

Diurnal Profiles of Insulin Dependent Diabetics.—Mean glucose values in the insulin-requiring diabetics were higher than normal, with increased variability (fig. 3, table II). Diurnal fluctuations were also much greater. The mean daytime glucose value exceeded the mean diurnal value by 0·57 mmol/l (10·6 mg/100 ml)—a greater difference than for either the normal or the chemical diabetic groups —because of high plasma glucose concentrations after breakfast in the diabetics and a strong tendency to hypoglycaemia during the night. Thus, whereas the mean (±S.D.) of the lowest glucose concentrations during the study in the normal group was 3·7±0·5 mmol/l (67·1±

TABLE I—*Details of 50 Patients Studied (the Nine Normal Women in Longitudinal Study are included in Cross-sectional Study). Results are Means ± S.D.*

	No. of Women	Age (Years)	Weight at Delivery (kg)	Height (cm)	Gestation at Study (Weeks)	No. of Parous Patients	Parity (Range)
Normal subjects (longitudinal study)	9	27·1 ± 3·8	71·88 ± 12·20	161·6 ± 3·4	19·2 ± 3·2 33·3 ± 1·1	1	0-1
Normal subjects (cross-sectional study)	24	26·4 ± 6·1	72·41 ± 15·70	159·8 ± 5·8	33·8 ± 2·2	9	0-3
Chemical diabetics	13	27·5 ± 6·1	73·60 ± 9·77	161·5 ± 5·7	33·2 ± 2·9	6	0-4
Insulin-dependent diabetics	13	25·5 ± 4·0	70·28 ± 7·38	161·4 ± 7·4	34·0 ± 2·7	6	0-2

TABLE II—*Diurnal Indices of Carbohydrate Tolerance in All Study Groups. Glucose is expressed as mmol/l. Results are Means ± S.D.*

	Normal Subjects (Longitudinal study; n = 9)		Normal Subjects (Cross-sectional Study; n = 24)	Chemical Diabetics (n = 13)	Insulin-dependent Diabetics (n = 13)
	Early Pregnancy	Late Pregnancy			
Mean diurnal plasma glucose	4·53 ± 0·29	4·73 ± 0·29	4·69 ± 0·37	5·59 ± 1·03	5·88 ± 1·19
Mean daytime plasma glucose	4·68 ± 0·27	4·91 ± 0·41	4·89 ± 0·43	5·91 ± 1·13	6·47 ± 1·75
Maximum diurnal plasma glucose	5·93 ± 0·58	6·35 ± 0·44	6·29 ± 0·93	8·04 ± 1·49	9·93 ± 2·18
Diurnal plasma glucose range	2·05 ± 0·43	2·56 ± 0·38	2·57 ± 1·02	3·81 ± 1·23	6·95 ± 2·04
Diurnal insulin:glucose ratio	5·2 ± 3·1	9·2 ± 4·7	9·6 ± 4·7	5·8 ± 2·0	
Daytime insulin:glucose ratio	7·9 ± 4·7	13·5 ± 7·6	12·6 ± 7·0	8·3 ± 3·2	

Conversion: SI to Traditional Units—Glucose: 1 mmol/l = 18 mg/100 ml.

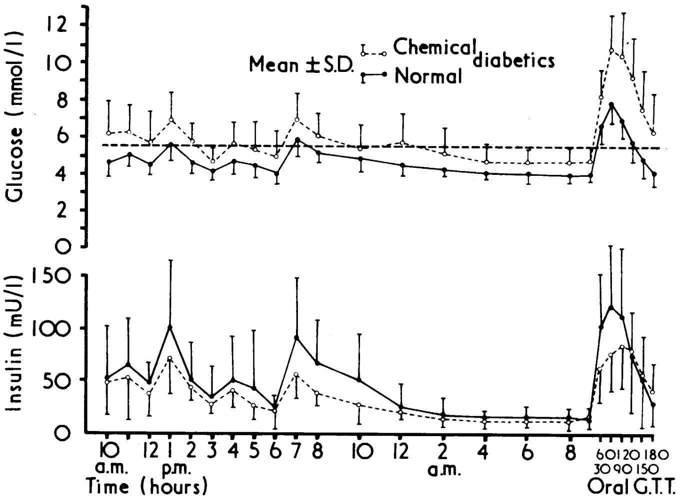

FIG. 2—Plasma glucose and insulin concentrations during diurnal profile and oral G.T.T. in 24 normal and 13 chemical diabetic women studied during last trimester of pregnancy.

TABLE III—*Oral Glucose Tolerance Indices in all Study Groups. Results are Means±S.D.*

	Normal Subjects (Longitudinal Study; n=9) Early	Normal Subjects (Longitudinal Study; n=9) Late	Normal Subjects (Cross-sectional Study; n=24)	Chemical Diabetics (n=13)
Total area	34·0±3·4	34·5±3·1	36·3±3·2	51·9±9·6
Incremental area	9·0±3·7	10·0±2·9	12·3±4·1	23·3±6·7
2-Hour plasma glucose (mmol/l)	5·3±0·73	5·1±0·95	5·8±1·1	92·3±2·3
H index	6·9±1·9	6·8±2·1	10·4±5·3	14·8±6·6
G.T.T. insulin:glucose area ratio	7·9±5·4	13·1±6·5	13·5±6·1	8·1±4·0

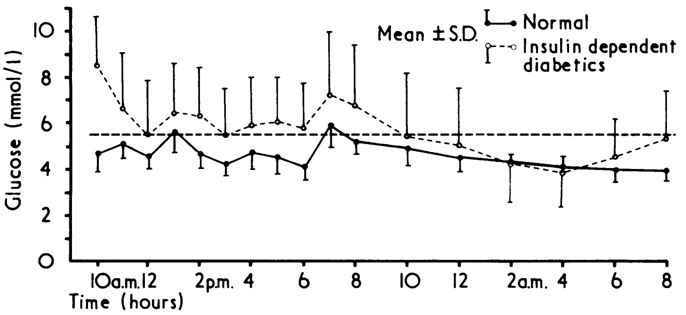

FIG. 3—Diurnal glucose concentrations in 13 insulin-dependent diabetics and nine women with normal glucose tolerance studied between 32 and 35 weeks of pregnancy.

8·9 mg/100 ml) it was 2·9±0·7 mmol/l (53·8±11·7 mg/100 ml) in the insulin-treated diabetics (P=0·001). In contrast, the minimum plasma glucose in the chemical diabetic group was much higher (4·2±0·9 mmol/l (76·3±15·5 mg/100 ml); P=0·001).

Comparison between Diurnal Glucose Profile and G.T.T.—Despite the fact that all but three chemical diabetics had normal fasting plasma glucose values highly significant correlations were found between glucose functions derived from the diurnal profiles and the oral G.T.Ts. The best correlation was between the total area under the G.T.T. curve and the mean diurnal plasma glucose level (fig. IV). As predicted, incremental glucose tolerance area correlated better with mean daytime than with mean diurnal plasma glucose. This was not, however, true for the total area, to which the fasting plasma glucose makes a significant contribution. The H index displayed the weakest correlation of the four glucose tolerance indices.

The peak plasma insulin after a meal in normal women in late pregnancy was similar to that after an oral glucose load, despite the relatively lower plasma glucose concentrations after food. In the 13

TABLE IV—*Coefficient of Linear Correlation (r) between Oral G.T.T. and Diurnal/Daytime Indices in 24 Normal and 13 Chemical Diabetic Patients*

	Mean Diurnal Plasma Glucose	Mean Daytime Plasma Glucose	Maximum Diurnal Plasma Glucose	Diurnal Plasma Glucose Range
Total area	0·827*	0·808*	0·781*	0·568‡
Incremental area	0·687*	0·726*	0·754*	0·667*
2-Hour plasma glucose	0·760*	0·766*	0·737*	0·581*
H index	0·403*	0·438*	0·358†	0·308§

*P<0·0001. †P<0·02. ‡P<0·001. §P<0·05.

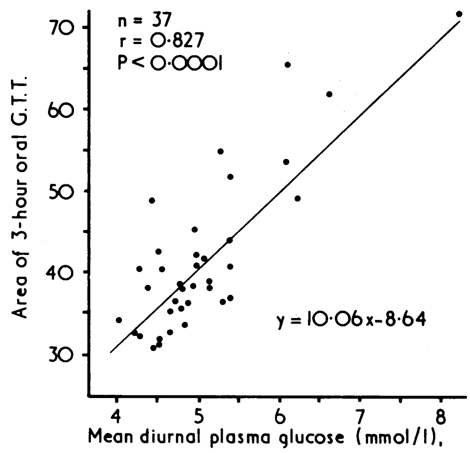

FIG. 4—Correlation between mean diurnal plasma glucose and total area under three-hour oral G.T.T. curve.

chemical diabetic patients, however, the insulin-glucose ratio 60 minutes after lunch was significantly greater than that at the same interval after a glucose load.

Discussion

The results obtained from normal women show the effect of pregnancy on the diurnal concentration and variability of glucose and insulin. The most remarkable feature of the diurnal profile in normal pregnancy was the constancy of the plasma glucose concentration, which rarely exceeded 5·6 mmol/l (100 mg/100 ml), except during the hour after a meal, and was well maintained at night. The fetus is thus provided with a constant glucose environment that is ideal for development and which makes no demands on its control mechanisms until it is separated from the mother. With advancing pregnancy the diurnal glucose concentration showed only a slight increase, but this was associated with a greatly increased insulin response to food. Unlike others[6 11] we found no significant alteration in glucose tolerance in late pregnancy. There was, however, some loss of homoeostasis as shown by the lower preprandial and higher postprandial glucose levels. Perhaps the tendency to greater fluctuation of glucose concentration prepares the fetus for extrauterine life by increasing the sensitivity of the fetal β-cell to glucose. The results in late pregnancy are consistent with the concept of a balance between accelerated fasting[12 13] and decreased insulin sensitivity.[14]

Mean insulin concentration was lower throughout the day in the chemical diabetic women, with a higher mean diurnal glucose concentration and greater fluctuation after meals. It is of interest, however, that the insulin:glucose ratio of chemical diabetics after a meal was greater than that after oral glucose. It suggests that in these patients a protein-carbohydrate mixture may compensate, at least partly, for the relative insensitivity of the pancreatic β-cell to glucose. It thus underlines one limitation of the oral G.T.T. as a test of overall metabolic performance.

By current standards the women who needed insulin had well controlled diabetes. Their mean diurnal glucose of 5·88 mmol/l (106 mg/100 ml) reflected the usefulness of the four routine preprandial blood samples taken to monitor blood sugar in the ward before the study. Closer inspection of their diurnal profiles, however, showed definite deviations from the normal. During the day their mean glucose concentration was 6·47 mmol/l (116·6 mg/100 ml; normal 4·69 mmol/l (84·6 mg/100 ml)), while at night hypoglycaemia developed with a mean for the lowest glucose concentration of 2·9 mmol/l (53·8 mg/100 ml; normal 3·7 mmol/l (67·1 mg/100 ml)). This difference between day and night values was associated with an increased diurnal variability which was nearly three times that of normal women at the same period of gestation.

Though control was satisfactory so far as the mother's health was concerned such an unstable glucose environment may have adverse effects on the developing fetus. Many workers have suggested that poor diabetic control in early pregnancy may be responsible for abnormal fetal development; neurological defects have been seen in the offspring of diabetic mothers.[15 16] More specifically, the frequent nocturnal hypoglycaemia observed among insulin-treated diabetics may, in severe cases, be a factor responsible for abnormal embryogenesis or perhaps for unexpected death of the hyperinsulinaemic fetus[17] during the last trimester of pregnancy.[18] Thus, every attempt should be made to normalize the maternal plasma glucose so far as possible throughout the 24 hours.

The total area under the three-hour oral glucose tolerance curve was the function which correlated best with the mean diurnal plasma glucose concentration in normal and chemically diabetic women on a standard diet. The fasting plasma glucose concentration contributes directly to the calculation of both the mean diurnal plasma glucose concentration and the total area under the oral glucose tolerance curve, both of which increase as the fasting plasma glucose increases. Thus a strong correlation between the total oral glucose tolerance area and the mean diurnal glucose is inevitable in a group of people with a wide range of fasting glucose values; only three of our patients, however, had a plasma glucose greater than 5·6 mmol/l (100 mg/100 ml): 5·61, 5·72, and 6·33 mmol/l (101, 103, and 114 mg/100 ml).

There was also a highly significant correlation between the G.T.T. two-hour plasma glucose level and the diurnal glucose levels, which supports the widespread use of the G.T.T. two-hour value for identifying patients with impaired carbohydrate tolerance.[1] The two-hour plasma glucose level, however, showed much greater variability in the "normal" range than the area under the curve, which limits its usefulness.[2]

The H index has the advantage over other indices of carbohydrate tolerance that it is independent of both the source of the blood sample and also the method of glucose measurement and hence facilitates comparison of the results of different laboratories. It also uses all the information derived from the glucose tolerance test and takes into account the time at which the peak glucose concentration occurs. Lind *et al.*[6] have shown a progressive rise in the H index with advancing pregnancy in women with glucose tolerance judged to be normal by conventional criteria. We saw no significant difference, however, between the H index at 18 and at 34 weeks of pregnancy in the normal group. Our findings do, however, confirm that raised values occur in chemical diabetic patients. Though this index of glucose tolerance may be valuable for showing changes in the shape of the curve during pregnancy it seems to be of limited use for assessing the glucose concentration prevailing in pregnant women with normal or borderline carbohydrate tolerance.

Our findings on maternal carbohydrate tolerance are related to the glucose metabolism of the newborn in Part II.

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Part II—Relation between Maternal Glucose Tolerance and Glucose Metabolism in the Newborn

Summary

The objective of clinical management of the pregnant diabetic woman is to prevent the serious adverse effects of an abnormal glucose environment on the fetus. Neonatal glucose assimilation and insulin release over the first two hours of life were correlated with various indices of maternal carbohydrate metabolism in the third trimester. Of the 31 mothers studied 21 were defined as normal and 10 as having chemical diabetes.

Neonatal glucose assimilation during the first two hours of life correlated strongly with functions of both maternal glucose tolerance and mean diurnal glucose level, the strongest correlation being with the area under the three-hour oral glucose tolerance curve ($P < 0·001$). Two-hour neonatal plasma glucose values of under 1·7 mmol/l (30 mg/100 ml) were found only in the newborn of women whose glucose tolerance area measured over 41·6 area units (750 traditional units); thus, even in the borderline diabetic range glucose tolerance testing during the last trimester of pregnancy may be valuable in predicting likelihood of neonatal hypoglycaemia. The findings also shed light on the possible sensitizing role of mild maternal hyperglycaemia on fetal insulin production and secretion.

Introduction

Chemical diabetes in late pregnancy carries an increased risk of unexpected fetal and neonatal death.[1 2] Part of the problem in patients with chemical diabetes is to know beforehand how