

Metabolic changes in pregnancy relevant to diabetes mellitus

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Summary

The alterations in carbohydrate metabolism during pregnancy are discussed and possible mechanisms for these changes are put forward. It is stressed that the raised levels of plasma glucose, the enhanced response to insulin and the decreased tissue sensitivity to insulin are all features of normal pregnancy. It may be difficult to distinguish this from very early forms of diabetes mellitus during pregnancy, the detection of which is briefly considered.

Introduction

While doctors agree that there is a range of 'normal' physiological values many seem to believe that there are relatively narrow limits to this range and any conspicuous deviation from it can only be caused by disease. Yet even among healthy people there must be allowances for age, sex and 'fitness'; it is improbable that the physiological responses of a 20-year-old male athlete are indistinguishable from those of a 60-year-old housewife. This comparison would no doubt be judged unfair by most doctors because the differences in physiological status would be self-evident. But pregnancy induces major physiological adaptations in the mother which are less obvious but may, in some instances, be so marked as to mimic disease. The changes occurring in carbohydrate metabolism are a particularly good example because allowances are rarely made for any pregnancy effect when 'diabetes' is suspected. It is the purpose of the author to discuss in this paper the influence of normal, uncomplicated pregnancy upon carbohydrate metabolism and help to define the circumstances in which true diabetes mellitus might be suspected.

Pregnancy influence upon carbohydrate metabolism

All the data to be described have been obtained using a standard 50 g oral glucose tolerance test (OGTT) unless some other procedure is specified. The reasons for the preference of this test over the intravenous glucose tolerance test have been discussed elsewhere (Lind, 1975).

Fasting plasma values

Glucose. It is generally accepted that the fasting

plasma glucose value is lower during pregnancy (Bleicher, O'Sullivan and Freinkel, 1964; Tyson and Merimee, 1970) but the exact timing of this change has been generally attributed to the first trimester. Lind, Billewicz and Brown (1973) in a longitudinal study of 19 healthy women performed a standard 50 g OGTT at 10, 20, 30 and 38 weeks' gestation and again at 10-12 weeks after delivery, the same patients therefore acting as their own non-pregnant control group. The fasting concentration was significantly lower than the non-pregnant value by 10 weeks of pregnancy but there was no significant decrease thereafter (Table 1).

TABLE 1. The fasting and 2-hr plasma glucose and insulin concentrations throughout pregnancy and 10-12 weeks *post partum* in 19 healthy women following a 50 g OGTT together with the time at which the peak plasma glucose and insulin values occurred

Value		Gestation (weeks)				
		PN	10	20	30	38
Fasting	glucose	4.6	4.2	4.0	4.2	3.9
	insulin	5.5	4.5	4.5	7.0	7.5
2-hr	glucose	4.3	4.9	3.9	4.4	4.5
	insulin	12.3	18.1	15.9	22.4	27.0
Peak time (min)	glucose	34.1	34.7	36.5	47.7	55.0
	insulin	44.1	40.8	45.8	53.7	57.4

glucose (mmol/l); insulin (μ u./ml); PN - 10-12 weeks postnatal; OGTT, oral glucose tolerance test.

Insulin. This does not change in the same way as glucose. The same group of women had a small but statistically significant rise in fasting insulin concentration - but by the end of pregnancy. The timing was thus different and seems to preclude any cause-and-effect relation between fasting glucose and insulin levels (Table 1). Similar findings were reported by Kühl and Holst (1976).

Glucagon. In a study of 8 normal healthy women having a standard OGTT between 16 and 24 weeks' gestation, again between 35 and 38 weeks' gestation and finally 6-8 weeks *post partum*, Kühl and Holst (1976) found the fasting plasma glucagon to be

significantly elevated during late pregnancy relative to the postpartum value (153.7 ± 17.2 pg/ml compared to 118.1 ± 10.1 pg/ml).

Despite the raised fasting glucagon levels in late pregnancy, the plasma glucose values do not increase; this is probably because the increase in plasma insulin concentration is proportionately greater at this time. The same authors found the fasting ratio of insulin to glucagon to be 1.8 ± 0.4 during late pregnancy but 1.1 ± 0.2 *post partum* when compared on a molar basis.

Response to an oral glucose load

Glucose response. As pregnancy progresses, the time to reach the maximum glucose concentration increases; in the subjects studied by Lind *et al* (1973) the mean time to the peak plasma glucose level was 55 min at 38 weeks' gestation compared to the non-pregnant value of 34 min. Despite this delay the fasting level is still regained by 2 hr in most women (Table 1).

Insulin response. The effect of pregnancy upon the insulin response is even more striking. The peak value increases progressively and the time to reach the maximum concentration is delayed. By 2 hr the level is still well above the fasting concentration (Table 1).

Glucagon response. During late pregnancy the decrement in plasma glucagon values following a glucose load is greater than *post partum*; the nadir is also reached later. *Post partum* the lowest glucagon concentration is achieved at about 60 min but is delayed to 120 min during late pregnancy (Kuhl and Holst, 1976).

Possible explanations for these pregnancy effects

There are several theoretical possibilities which can be considered:

Inadequate maternal insulin production

While the maternal insulin response is increased during pregnancy it could reflect her maximum production rate and still be insufficient to maintain 'normal' glucose homeostasis. During a study of renal reabsorption of glucose performed in the MRC Reproduction and Growth Unit, Newcastle upon Tyne, 10 women were infused with dextrose solution at 16, 26 and 36 weeks' gestation and again 10–12 weeks *post partum*. The idea was to achieve a stable plasma glucose concentration of about 11.3 mmol/l at each stage of pregnancy and to maintain this for at least 80 min; the mean values achieved at each stage of pregnancy are given in Table 2. The change in insulin response as pregnancy progressed was quite dramatic; using the average values at 80 min infusion time, the insulin concentration increased from a non-pregnant value of 66 μ u./ml to 199 μ u./

TABLE 2. Plasma glucose (mmol/l) and insulin (μ u./ml) concentrations during glucose infusions at various stages of pregnancy

Gestation (weeks)		Infusion time (min)			
		0	40	60	80
10–12 PN	glucose	5.0	12.9	12.5	12.9
	insulin	5.7	35.1	48.9	66.4
16	glucose	4.3	10.1	10.0	10.0
	insulin	6.6	79.5	87.5	89.5
26	glucose	4.4	10.9	10.9	10.9
	insulin	12.7	93.0	94.2	115.6
36	glucose	4.6	11.0	11.8	11.8
	insulin	16	130.2	163.2	198.6

PN – Postnatal.

ml at 36 weeks' gestation. It seems probable that pregnant women can increase their insulin production whenever needed; the apparently limited response during pregnancy is therefore likely to be a specific physiological adjustment rather than an inability on the part of the mother to produce more insulin.

Increased proinsulin production

In the insulin immunoassay used in this unit (Lind *et al.*, 1972) the antibody (Burroughs Wellcome RD 10) reacts with proinsulin almost as well as with insulin (proinsulin/insulin cross-reaction 0.86/1.0) As proinsulin is only about one fifth as biologically active as insulin any increase from this source would be shown by immunoassay but not reflected in glucose control. However, in the present patients, separation of proinsulin from insulin by column chromatography and subsequent assay of the fractions has failed to show any increase in circulating proinsulin concentrations during pregnancy. Similar findings have been reported by others (Phelps *et al.*, 1975; Kühl, 1977).

Insulin metabolism

The raised amount of circulating insulin could be due to a decreased clearance rate from the circulation rather than an increase in production. To study this possibility women were chosen at 34–38 weeks gestation as being in good general health, free of any family history or other stigmata of diabetes and having an uncomplicated pregnancy. After an overnight fast of at least 12 hr, each was given an intravenous bolus of insulin on the basis of 0.02 u./kg body weight. The test was repeated at 10 weeks *post partum* and again after a further interval of 4 weeks. During the last occasion an infusion of growth hormone release inhibitory hormone (GHRH or

somatostatin) was given to inhibit any endogenous insulin production. The calculated half-life of insulin on each occasion was about 3.5 min showing that pregnancy has no effect on the kinetics of insulin (Lind *et al.*, 1977). This is in keeping with the report of Bellmann and Hartmann (1975) using human data and natural rather than radioiodinated insulin.

Glucose tolerance factor

It has been suggested that chromium, incorporated into a specific organic complex in the body, named glucose tolerance factor (GTF), is a necessary intermediary between the insulin molecule and its cell membrane receptors (Mertz, 1967). If this is so, a deficiency of GTF could explain those forms of carbohydrate disturbance in which high plasma glucose concentrations are associated with normal or increased plasma insulin values such as maturity onset diabetes and pregnancy (Glinsmann, Feldman and Mertz, 1966; Hambidge, 1971). In a Western society, depletion of chromium stores because of dietary deficiency is unlikely, but a relative deficiency state might result from a reduced ability to absorb chromium, an inability to convert sufficient inorganic chromium into the active organic form, GTF, or from an increased urinary excretion of chromium or GTF. The first 2 possibilities might account for some of the milder forms of diabetes mellitus while the third possibility could account for the changes in carbohydrate response during pregnancy. The physiological increase in glomerular filtration rate might lead to an increased urinary loss of chromium, or GTF, which in some pregnant women, may cause 'carbohydrate intolerance'.

To test this hypothesis 20 healthy, non-diabetic, pregnant women aged 21–23 years were recruited; after random allocation 10 were asked to take brewer's yeast (a natural compound rich in GTF (Mertz, 1967)) and 10 acted as control subjects. All of these patients were subsequently delivered of healthy infants after uncomplicated pregnancies.

Each patient fasted overnight for at least 12 hr and then had a standard 50 g OGTT; this first test was undertaken at about 30 weeks' gestation. The 10 patients being tested were then asked to take 10 g/day of brewer's yeast (*Saccharomyces uvarum* [= *carlsbergensis*]) in fruit juice; this contains about 11 µg of GTF (Toepfer *et al.*, 1973). The control subjects drank the same volume of fruit juice daily. After 2 weeks the OGTT was repeated.

A more elaborate test programme was undertaken in 11 maturity onset diabetic patients controlled by diet alone, and in 17 non-pregnant women. These women were tested at regular intervals during the menstrual cycle because of the known variation in the OGTT response curve during the follicular and luteal phases.

Paired *t*-tests were used to show the variability between tests within patients; there was considerable test variation in the pregnant, non-pregnant and diabetic subjects but no 'improvement' whatsoever in carbohydrate tolerance in any of the subjects studied, whether or not they took yeast.

It would seem unlikely that deficiency of chromium or GTF is a major cause of carbohydrate intolerance during pregnancy in a Western society.

Insulin resistance

Tissue resistance to insulin effect can be implied from 3 main findings: the increased insulin response to a glucose stimulus, the reduced peripheral uptake of glucose and finally the change in glucagon response.

Insulin response to glucose. The increase in circulating insulin levels has been discussed previously and summarized in Tables 1 and 2. By term, the fasting level has increased, more circulating insulin is found 2 hr after a glucose load, and glucose infusions promote an enhanced insulin response.

Reduced peripheral uptake of glucose. In the reported study of insulin half-life (Lind *et al.*, 1977) it was found that an intravenous dose of insulin of 0.02 u./kg body-weight given to fasted pregnant women at about 36 weeks' gestation reduced the fasting plasma glucose by about one mmol/l. A similar dose given to the same women 10–12 weeks after delivery reduced the fasting level by about 1.8 mmol/l.

Glucagon response. Four women in the above study had their glucagon determined by a specific immunoassay which cross-reacted to less than 0.1% with human gut glucagon (Kühl and Holst, 1976). Blood samples were obtained at one-min intervals for 3 min before the insulin injection; the concentrations of plasma glucose, insulin and glucagon were determined and the means of the 3 measurements in each patient taken as the normal 'fasting levels'. After injection of the insulin one min was allowed for mixing then further blood samples were obtained at one-min intervals for 30 min; full details of the methods have been published elsewhere (Lind *et al.*, 1977). The mean peak insulin value for the 4 patients in late pregnancy was 210 µu./ml and the fasting insulin level was regained in each patient by about 19 min; essentially similar findings were recorded when the test was repeated 10–12 weeks after delivery. During late pregnancy (35–39 weeks) the insulin-induced hypoglycaemia appeared to stimulate a small glucagon response; while this response was somewhat erratic, the values tended to remain above the fasting concentration. In the non-pregnant state the glucagon values were depressed below the fasting value for about 22 min, i.e. when the injected insulin had largely disappeared. This suggests that

the pancreatic islet cells are less sensitive to the effects of circulating insulin during pregnancy.

Preliminary conclusions

These data were all derived from perfectly healthy women having uncomplicated pregnancies, and the same women acted as their own non-pregnant control group. Thus 'carbohydrate intolerance' manifested as higher plasma glucose values, an enhanced insulin response, and a decreased tissue sensitivity to insulin are features of normal pregnancy. Why these changes occur is difficult to define; the altered hormonal milieu of pregnancy is usually held to be responsible and this is probably so. Certainly the changes rapidly revert to normal after delivery (Lind and Harris, 1976). However it would be an oversimplification to hold any one hormone, such as human placental lactogen, responsible; the whole complex of altered maternal adaptations, including changes in protein and fat metabolism, probably combine to influence changes in carbohydrate homeostasis. The clinical problem is to define the upper limit of the normal range of pregnancy responses from the early forms of diabetes mellitus.

The diagnosis of disordered carbohydrate metabolism

The practice of detecting diabetes mellitus from the presence of glycosuria is based upon the fact that a significant increase in blood glucose will produce a filtered load of glucose in the proximal renal tubule which the kidney is incapable of absorbing. This is not true of pregnancy; about 50% of all healthy, pregnant women have glycosuria at some stage while their blood glucose levels remain well within normal limits (Davison and Hytten, 1975). This is not, therefore, a sufficiently selective screening procedure for antenatal clinics; if the obstetrician wishes to detect women with abnormally elevated blood glucose concentrations, then it is blood glucose which ought to be determined.

Glycosylated haemoglobin

Space does not permit of a detailed account of the development of the glycosylated haemoglobins, currently denoted as Hb A_{1(a+b+c)}, as possible monitors of diabetic status and the reader is referred to Rahbar (1968); Trivelli, Ranney and Lai (1971); Bunn *et al.* (1976); Fitzgibbons, Koler and Jones (1976) and Koenig *et al.* (1976) among others. In essence it appears that the glycosylated haemoglobins form some 6–8% of the total haemoglobin in a normal healthy population but about 12–14% in reasonably well controlled insulin-dependent diabetics. As these haemoglobins are slow to form and relatively irreversible once formed they may offer a method of checking long-term blood glucose control in treated diabetics. The longer the blood glucose

concentration remains elevated the greater will be the proportion of Hb A_{1(a+b+c)}. Thus diabetics attending a clinic will have their immediate status determined by blood or urinary glucose profiles, but a knowledge of the proportion of glycosylated haemoglobin may allow the clinician to assess what degree of control the patient has achieved over the previous 4–8 weeks.

The possible roles for these haemoglobins can be considered by the obstetrician: (i) such determinations may offer a further method of controlling pregnant diabetic patients and (ii) they may offer a screening method for unsuspected diabetes during pregnancy.

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