The Insulin Response to Glucose Infusion in Normal Human Pregnancy

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Summary. To study insulin response and insulin sensitivity a glucose infusion test was devised. Twenty normal non-pregnant and twenty normal pregnant women had an intravenous glucose tolerance test followed by a glucose infusion test. In a normal pregnant group at 38–40 weeks gestation ($n = 20$) the plasma insulin response was found to be 3.7 times greater than that observed in a normal non-pregnant group ($n = 20$), while in the normal pregnant group the insulin sensitivity index was only 18 per cent of that observed in the non-pregnant group. Intravenous glucose tolerance in the non-pregnant women was observed to correlate with the insulin sensitivity index ($r = 0.61$, $p < 0.05$) but in the pregnant women it correlated with the insulin response ($r = 0.66$, $p < 0.01$). These findings support the hypothesis that in the non-pregnant state intravenous glucose tolerance may be primarily related to insulin sensitivity while during pregnancy it may be related to the degree of compensatory hyperinsulinism.

Key words: Human pregnancy, glucose infusion test, insulin response, insulin sensitivity, intravenous glucose tolerance test, human placental lactogen, progesterone, oestradiol 17- β .

homeostasis [1]. Peripheral insulin responses have been studied in pregnancy using 25 g single or double dose glucose injection techniques [2, 3, 4]. Since these methods do not relate the glucose dose to the distribution compartment the insulinogenic stimulus may not be constant between subjects. Comparative analysis of such individual insulin responses is thereby limited.

Using a high dose glucose infusion method Cerasi and Luft have shown that a meaningful index for comparison may be obtained by relating the insulin response to the glycaemic stimulus. Their extensive studies [5, 6] demonstrate clearly that the glucose infusion test (GIT) can provide an assessment of pancreatic beta cell function which may reveal degrees of metabolic abnormality beyond the limits of the standard glucose tolerance tests.

The present study was undertaken to define more clearly the physiological insulinogenic adaptation of human pregnancy in relation to glucose homeostasis. A glucose infusion test and an intravenous glucose tolerance test (IVGTT) were used.

Materials and Methods

Patient Selection

Twenty normal non-pregnant nulliparae, and twenty normal pregnant women (15 primigravidae and 5 multiparae) at 38 to 40 weeks gestation, were selected for study. None had a history of abnormal glucose tolerance or any features of potential diabetes [7]. None had any other diseases or were taking any drugs. None of the non-pregnant nulliparae had ever taken the contraceptive pill. All the pregnant women were sure of the date of their last menstruation, and had normal pregnancies before and after the tests. The mean ages of the non-pregnant women and the pregnant women were 22.9 ± 1.6 years and 24.5 ± 4.2 years respectively. All subjects were below the 85th centile standard of body weight [8]. In the pregnant group this was estimated from the calculated

The physiological aspects of maternal energy metabolism in human pregnancy are not clearly understood, but it is believed that metabolic realignments occur in order to provide the fetus with an advantageous nutritional environment for growth and development. Maternal hyperinsulinism is thought to be a secondary compensatory mechanism related to the maintenance of maternal glucose

pre-pregnant weight [9]. The percentages of ideal body weight for the non-pregnant group and the pregnant group were 101 ± 6 and 98 ± 6 respectively. The infant birth weights in the pregnant group were all below the 95th centile [10].

The study was approved by the Hospital Ethical Committee, and each patient gave her informed consent.

Procedures

Intravenous Glucose Tolerance Test. After an overnight fast from 2200 hours, and a 30-minute rest, each woman had a 25 g IVGTT at 1000 hours. The fasting venous samples were withdrawn at 5 min intervals from an antecubital vein. Twenty-five g glucose (50 g/100 ml) was injected into the opposite antecubital vein over 3 min. Thereafter venous samples were taken at 4, 10, 20, 25, 30, 35, 40, 45, 50 and 60 min from completion of the injection. All samples were centrifuged immediately and plasma glucose was estimated by a glucose oxidase method in a Beckman glucose analyser. The test result was expressed as the Increment Index which is calculated using the formula $\frac{69.3}{t_{1/2}}$ [11]. $t_{1/2}$ is derived using the incremental plasma glucose decay curve, that is, using the fasting plasma glucose level as the base-line.

Glucose Infusion Test. Two to seven days later each woman had a GIT after an overnight fast from 2200 h. Prior to the test the bladder was emptied. The right and left antecubital veins were cannulated and the subject placed in a recumbent position with at least 45° left lateral tilt to the pelvis after a 30 min rest. A loading dose of 400 mg of glucose/kg body weight was injected as a 50 g/100 ml solution over 3 min, and an adjustable infusion of 20 g/100 ml glucose was started in the same arm.

Two $\times$ 1.5 ml fasting venous samples were withdrawn from the opposite arm at 5 min intervals. On completion of the loading dose similar samples were withdrawn at 0, 1, 2, 3, 4, 5, 7, and 10 min, and every 5 min thereafter until 90 min. All samples were decanted into heparinised containers. Plasma glucose was estimated within 2 min of withdrawal in the fasting, 4 and 10 min samples and in every sample thereafter until 90 min by the glucose oxidase method in a Beckman Glucose Analyser. This provided the means of maintaining the plasma glucose level at around 260 to 270 mg/100 ml over the 90 min test period by adjusting the glucose infusion.

On completion of the test the bladder was emptied, the urine volume measured, and urinary glucose estimated by the glucose oxidase method. The volume of infused glucose was recorded. The plasma was separated from all samples and stored at -18°C for plasma insulin analysis [12].

In the pregnant group a 5 ml fasting venous sample was also withdrawn, the plasma separated and stored at -18°C for later estimation of plasma progesterone, human placental lactogen, and oestradiol 17- β .

Analysis of Results

Summated Insulin Response

Having observed the plasma insulin response over 90 min and by applying circulating insulin half-life values, the summated amount of insulin delivered to the circulation at any point up to 90 min may be estimated. The non-pregnancy and pregnancy circulating insulin half-life values reported by Burt and David-

son [13] were used for this calculation, i. e. for up to 20 min half-life values of 4.0 min and 4.3 min and for 20 min and over of 8.5 and 8.7 min for the non-pregnant and pregnant women respectively.

The calculation of the summated insulin response was based on the following formula of Thorell and co-workers [14].

Formula 1: Summated Insulin Response $t = I_t + k \cdot \text{Area}_t$

Formula 2: $k = \frac{\log 2}{t_{1/2}}$

where I = Insulin concentration ($\mu\text{U/ml}$), t = time (min), k = elimination rate constant (fraction of plasma pool/min), and $t_{1/2}$ = circulating insulin half-life (min).

The summated insulin response at t was dependent on the summated area at t and the constant k which changed at 20 min. The following insulin response correction factor was added to values calculated from 20 min when the longer circulating insulin half-life values were applied to the early insulin response phase up to 10 min.

Insulin Response Correction Factor = $I_{10} + k \cdot \text{Area } 10$.

Insulin Delivery Rate

The rate of insulin delivery to the circulation is based on the formula:

$$f = kI + \frac{dI}{dt} \quad [14]$$

where f = Insulin Delivery Rate ($\mu\text{U/ml/min}$).

Insulin Sensitivity Index

The concept is based on the principle that an assessment of the biological sensitivity to endogenous insulin may be provided by relating the amount of glucose infused to maintain the plasma glucose level constant to the summated plasma insulin response over the same period. The following formula was applied:

$$\text{ISI} = \frac{\text{Total glucose infused (mg)} - \text{urinary glucose (mg)/kg body weight}}{\text{Summated 90-min plasma insulin response } (\mu\text{U/ml})}$$

The ISI was estimated for each individual.

Results are presented as mean $\pm$ SD values. Student's t test of significance was applied throughout. For lognormal distributions this test was applied using the logarithms of the values.

Fig. 1. Plasma glucose levels maintained at infusion in normal non-pregnant and normal pregnant women. Mean (solid line) $\pm$ SD (shaded area). The plasma glucose was elevated by an IV loading dose of 400 mg glucose/kg body weight over 3 min and maintained by a variable infusion of 20 g/100 ml glucose

Results

Fasting Plasma Glucose and Insulin

The mean fasting plasma glucose was significantly lower in the pregnant women at 74 ± 5 mg/100 ml compared with 83 ± 8 mg/100 ml for the non-pregnant women ($p < 0.01$). The mean fasting plasma insulin was significantly higher in the pregnant group at 14 ± 5 μ U/ml compared with 9 ± 4 μ U/ml for the non-pregnant group ($p < 0.01$).

Intravenous Glucose Tolerance

In all subjects the increment index of the IVGTT was normal, i. e. above 2.97. The normal nulliparous group had a mean increment index of 5.57 ± 1.82 compared with the lower mean of 4.40 ± 1.51 for the normal pregnant group. The difference was significant ($p < 0.05$).

Glucose Infusion Test

The mean plasma glucose levels maintained at infusion are shown in Figure 1. This confirms that the levels in each group were maintained at around

Fig. 2. Biphasic plasma insulin responses in normal non-pregnant and normal pregnant women. Mean (solid line) $\pm$ SEM (shaded area). In each group the plasma glucose was constant at around 260–270 mg/100 ml over 90 min. The immediate first phase responses are followed by the later second phase response

260–270 mg/100 ml. The overall mean of the individual mean plasma glucose levels was 264 ± 15 mg/100 ml for the non-pregnant group and 268 ± 8 mg/100 ml for the pregnant group.

Plasma Insulin Response

When the incremental plasma insulin values were plotted against time, biphasic plasma insulin response patterns were observed in all subjects. Figure 2 represents the mean incremental plasma insulin response over 90 min in each group. The mean first and second phase insulin responses were greater in the pregnant group.

From these mean incremental insulin responses the mean summated 90-min insulin responses were calculated for each group. In the pregnant group 2041 μ U insulin/ml plasma had been delivered compared with 554 μ U insulin/ml plasma for the non-pregnant group. This indicated an insulin response 3.7 times greater in the pregnant group.

Plasma Insulin Delivery Rate

The peripheral plasma insulin delivery rates were calculated for each group. In the pregnant group there

Table 1. First and second phase plasma insulin responses and summated 90 minute plasma insulin responses in normal non-pregnant and normal pregnant women. The first phase response was calculated to 4 and 3 min for the non-pregnant and pregnant women respectively. Thereafter the second phase response continued to 90 min. The summated 90 min insulin response included the first and second phases

Group	First phase insulin response ($\mu\text{U/ml}$)		Second phase insulin response ($\mu\text{U/ml}$)		Summated 90 minute insulin response ($\mu\text{U/ml}$)	
	Mean	Range	Mean	Range	Mean	Range
Normal non-pregnant (n = 20)	105	25–289	449	89–1017	554	114–1244
Normal pregnant (n = 20)	280 ^a	130–640	1760 ^a	635–3090	2041 ^a	765–3667

^a $p < 0.001$ compared with normal non-pregnant values

was an initial very rapid rate of insulin delivery which rose to a peak of $63 \mu\text{U/ml/min}$. This was followed by a latent phase of 2 min. The onset of the second phase commenced at 3 min and from 5 min the rate tended to be constant over the 90 min with a mean delivery rate of $23 \mu\text{U/ml/min}$.

In the non-pregnant group the first phase delivery rate rose rapidly to a peak of $21 \mu\text{U/ml/min}$. There was no latent period before the second phase became evident at 4 min. Throughout the second phase delivery rate tended to be constant with a mean of $6 \mu\text{U/ml/min}$.

Individual Summated Plasma Insulin Responses

Using the second phase onset times indicated by the insulin delivery rate data the summated first phase and summated second phase insulin responses were calculated for each group. The means and ranges are shown in Table 1 along with the summated 90 min insulin response data. Compared with the non-pregnant group the means in each case were significantly greater in the pregnant group.

Insulin Sensitivity Index

The mean insulin sensitivity index in the pregnant group was 0.53 ± 0.21 . The mean insulin sensitivity index in the non-pregnant group was 3.10 ± 1.67 . The difference was highly significant ($p < 0.001$). The low value in pregnancy of 18% of the non-pregnant value indicates a reduction in biological sensitivity to endogenous insulin in late normal pregnancy.

Correlation Data Analysis

Significant positive correlations were found between the first and second insulin response phases for both the normal non-pregnant group ($r = 0.82$ $p < 0.01$) and for the normal pregnant group ($r = 0.53$ $p < 0.05$).

In the non-pregnant group when three "low" insulin responders [5] were excluded a significant

positive correlation was observed between insulin sensitivity index and increment index ($r = 0.61$ $p < 0.05$). There was no significant correlation between insulin response and increment index.

In the pregnant group there was a significant positive correlation between the summated first phase insulin response and increment index ($r = 0.65$ $p < 0.01$). No other insulin response or insulin sensitivity correlations with increment index were significant.

In the normal pregnant group the mean fasting plasma progesterone was $446 \pm 159 \text{ nmol/l}$, the mean fasting plasma human placental lactogen was $77 \pm 24 \mu\text{g/l}$, and the mean fasting plasma oestradiol $17\text{-}\beta$ was $29.4 \pm 6.3 \mu\text{g/l}$. A significant positive correlation was observed between fasting plasma progesterone and increment index of the IVGTT ($r = 0.63$ $p < 0.05$). No other correlations were significant.

Discussion

This study confirms previous observations of diminished intravenous glucose tolerance in late pregnancy [7, 15, 16]. The corresponding decrease in fasting plasma glucose and elevation in fasting plasma insulin levels are also well known [2, 3, 16].

In all subjects the insulin response to the loading dose followed by a maintenance infusion was clearly biphasic. In a glucose dose response study Cerasi and co-workers [17] found sigmoidally distributed dose response relationships similar for the early and late insulin response phases and suggested that basically the same mechanism controls each phase. The observed correlation between first and second phase insulin responses supports their conclusions.

Insulin half-life is not significantly affected by pregnancy [18]. The values adopted for this study [13] are not only similar for the non-pregnant and pregnant states but are also close to others which have been independently assessed for the early phase [19, 20] and for the later phase [21] of the insulin

decay curve. Furthermore these values were relevant for this study since they had been similarly derived in non-pregnant and pregnant women over prolonged study periods (60 min).

The mean insulin response in late pregnancy was 3.7 times greater than that observed in non-pregnant women. Since the GIT is essentially a stress test of β -cell function this increase may not quantitatively relate exactly to the physiological state and may represent the degree of enhanced β -cell reactivity to glycaemic stimulation only. This increase is similar to the estimates of Spellacy and co-workers [22] and Burt and co-workers [4], but the mechanism is not clear. The specific gestational insulinogenic factors are unlikely to have a direct β -cell effect since the fasting plasma insulin level in the pregnant group was only 50% greater than the mean in the non-pregnant group. The mode of action of these factors may therefore be related to the potentiation of the glucose induced insulin response as suggested by Cerasi and Luft [23] as a mechanism for other insulinogenic agents.

Theoretically the insulin sensitivity index provides an index of biological sensitivity to endogenous insulin. As insulin passes into the systemic circulation it is partially metabolised by the liver, but the relative activity in terms of glucose disposal in the non-pregnant and pregnant states is not known [24, 25]. Unaccountable hepatic metabolic activity may therefore be a source of error inherent in the insulin sensitivity index. In the pregnant women no account could be taken of the infused glucose transfer to the fetal compartment. Since this error would tend to raise the insulin sensitivity index the values obtained may tend to underestimate the degree of insulin resistance in late pregnancy.

The results in this study are consistent with the hypothesis that the raised insulin response during pregnancy may be a compensatory mechanism related to primary gestational insulin resistance. Glucose tolerance in the "fed" state is thereby maintained. In this study the insulin sensitivity index in the normal pregnant group was only 18% of that in the normal nulliparous group while the pregnancy hyperinsulinism factor of 370% mathematically fails to compensate adequately. This observed deficit in insulinogenic compensation may account for the diminished IV glucose tolerance of late pregnancy.

Correlation analysis of the data suggests that in the non-pregnant state insulin sensitivity may be the primary factor influencing glucose tolerance while during pregnancy the insulin response to the injected glucose may be the dominant influence. For the purposes of these analyses it was reasonable to exclude from the data the "low" insulin responders since the

low insulin response may be an indicator of potential pathology [5] and may be associated with a compensatory increase in hepatic insulin sensitivity [26]. These results support the conclusions of Reaven and Olefsky [27] who found only a "modest correlation" between insulin response and K value of the IVGTT in non-pregnant subjects, and on reviewing other work [28, 29, 30, 31, 32] they concluded that there was "no unique high degree of correlation" between the insulin response and glucose tolerance. The present study is consistent with the hypothesis that during pregnancy when diminished biological sensitivity to endogenous insulin would tend to depress maternal glucose homeostasis the degree of glucose tolerance which is maintained is dependent on the efficiency of the compensatory insulinogenic mechanism.

In an attempt to assess the role of the placental hormones as mediators of the pregnancy metabolic realignments, correlation was sought between fasting plasma progesterone, human placental lactogen and oestradiol 17- β and increment index, the insulin response and insulin sensitivity index data. The significant positive correlation observed between fasting plasma progesterone and increment index suggests that this hormone may have a role. However, this conclusion is limited by the failure to observe an associated correlation with insulin response. The failure to observe any other associations is not at variance with the belief that each of these hormones may influence pregnancy glucose homeostasis [33, 34, 35, 36, 37], but this failure does suggest that the gestational realignments are subject to multifactorial regulation.

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