GLUCOSE TOLERANCE IN NEWBORN INFANTS OF HEALTHY MOTHERS: ITS RELATIONSHIP TO THE MOTHERS' INSULIN RESPONSE TO GLUCOSE INFUSION

By

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ABSTRACT

It has earlier been postulated that a low insulin response to a glucose infusion is characteristic for the prediabetic individual (Cerasi & Luft 1967c). There is also evidence that some infants of individuals with low insulin response might have a carbohydrate metabolism that is in some respects similar to that of newborn infants to diabetic mothers (Edström et al. 1974).

In the present study 15 infants to low insulin responders (ILR) and 22 infants to high insulin responders (IHR) were subjected to an intravenous glucose load (IVGTT) at 2–24 h age. A significant difference in glucose tolerance was found between the groups, the mean k-value for the ILR being 1.39 ± 0.41 and that for the IHR 1.05 ± 0.09 (P < 0.05).

No mothers were found to have a gestational diabetes (with the possible exception of one low insulin responders) but during late pregnancy the mean k-value at IVGTT in the low responders decreased from non-pregnant values (the mean difference being 0.41 ± 0.20, P < 0.025) while the high responders did not show a corresponding decrease (mean difference 0.12 ± 0.25, P > 0.05).

No other differences between the groups of infants that could influence the k-value could be found apart from the mothers being low or high
insulin responders. Our findings show that a low insulin response in the mothers might affect the glucose tolerance of the foetus even in the absence of continuous maternal hyperglycaemia in late pregnancy.

Diabetes during pregnancy is known to affect the carbohydrate metabolism of the newborn infant, giving a higher disappearance rate for glucose than is seen in the infants of healthy mothers (v. Euler et al. 1964; Mölsted Pedersen 1972a,b; Persson et al. 1973). This is true also for gestational diabetes although to a lesser degree (Isles et al. 1968; Persson et al. 1973). In a previous study (Edström et al. 1974) the insulin response to a glucose infusion (GIT) was followed during pregnancy in a group of women. None of the women in the group with a low insulin response – among which the prediabetic individuals can be expected to be found – developed a gestational diabetes. In spite of that, a number of their infants (ILR) showed a pronounced insulin response at an intravenous glucose tolerance test (IVGTT) or a high k-value (Edström & Thalme, to be published) but the groups were small and the differences from the infants of high insulin responders (IHR) not significant.

The present study was undertaken on a larger group of infants in order to see whether the disappearance rates of glucose in the infant is in any way related to the mother’s insulin response also when diabetes is not present during the pregnancy.

**MATERIAL AND METHODS**

Thirty-seven infants were subjected to an IVGTT at 2–24 h after birth and their 35 mothers underwent a GIT at varying intervals (7 weeks to 5 years) after delivery. Twenty-two of these infants were studied in connection to a prospective study of their mothers’ insulin response during pregnancy (Edström et al. 1974). Of the remaining 15 infants 2 were studied because of high birth weight only, 5 because of suspected gestational diabetes in their mothers (one or several k-values below 1.0 during the pregnancy in question), and the remaining 8 as normal controls.

The women and their infants were divided into subgroups according to the mother’s insulin response at GIT, performed according to the technique described by Cerasi & Luft (1967a). Women with an immediate insulin response to glucose (expressed as the computed parameter $k_{it}$, see below) less than 2.00 are here called “low responders”, and those with a $k_{it}$ equal to or more than 2.00 are called “high responders”. Their infants are referred to as ILR and IHR respectively. Twenty-one women were characterized as high and 14 as low responders, and they delivered 22 and 15 infants, respectively. No multiple births were encountered.

The glucose infusion test (GIT) was performed in fasting non-pregnant women using a glucose dose of 500 mg per kg body weight as a priming injection followed by infusion of 20 mg per kg and minute during 60 min. The technique has been described elsewhere (Edström et al. 1974). In 21 subjects 2 GIT were performed with
an interval of a few months, and in these instances the mean value has been used for calculations.

Four parameters, computed from the insulin-glucose curves, have been used to characterize the insulin response in relation to the glucose stimulus:

\( k_{11} \) is a constant determining the amount of insulin released initially in proportion to the increase in blood glucose,

\( k_{12} \) is a constant determining the amount of insulin produced and released post-initially during the GIT in relation to the glucose level,

\( b \) is the slope of the post-initial plasma insulin increase due to glucose infusion,

\( k_y \) is a constant determining the effect of plasma insulin upon glucose uptake.

The intravenous glucose tolerance test (IVGTT) was performed in all women within a few days before or after the GIT, using 25 g of glucose in 50% solution. Also here the mean value was used for 20 women undergoing 2 tests post-partum. An IVGTT was also performed during the last trimester in all but 3 women.

In the infants the IVGTT was performed 2–24 h after birth. Twenty-six of them received glucose in a dose of 1.5 g per kg body weight (25–50% solution), which was injected either via a scalp vein or in the umbilical artery. Eleven of the infants, investigated previously by one of the authors, received 1.0 g glucose per kg body weight (30%/solution) in an antecubital vein (Persson, to be published). The proportion of IHR and ILR was similar for both doses used. Furthermore, no significant differences were found within the groups of IHR and ILR between the \( k \)-values obtained with the 2 different doses (Table 2). Consequently, it was considered possible to pool the material for further calculations.

In both mothers and infants capillary blood samples were taken before the glucose injection, and thereafter at 10 min interval for one hour. The \( k \)-value was calculated, using absolute glucose values, according to the formula:

\[
k = \frac{0.693 \times 100}{t^{\frac{1}{2}}}
\]

Blood glucose was determined using a commercial glucose oxidase preparation (Kabi Reagens, Stockholm). For plasma insulin measurements a double antibody radioimmunoassay was used (Hales & Randle 1963).

Statistical methods. – Comparisons between mean values were made using Student’s \( t \)-test, and for the infants Mann-Whitney’s ranking test. For tables and methods used, see Snedecor & Cochran (1967).

**RESULTS**

**Mothers**

The high responders were slightly older than the low responders and had a somewhat higher parity, the mean age for the groups (\( \bar{x} \pm \text{SEM} \)) being 28.8 ± 0.7 and 26.9 ± 0.7 years, respectively. The mean body weight of the high responders was 62.5 ± 0.2 kg as compared to 55.1 ± 1.7 kg for the low responders \( (P < 0.025) \); body height showed no difference \( (166.3 \pm 1.4 \text{ and } 166.1 \pm 1.6 \text{ cm}, \text{respectively}) \). Three high responders had a body weight above 120 per cent of the normal mean for their body height \( (125, 126 \text{ and } 136 \%); \text{Documenta Geigy 1966}) \); no other subjects were overweight.
Mean values for blood glucose (solid line) and plasma insulin (broken line) in 21 high insulin responders and 14 low insulin responders during GIT in the non-pregnant state. Vertical bars denote standard error of the mean (SEM).

The mean glucose and insulin levels during GIT are shown in Fig. 1. With similar glucose levels during the test in the 2 groups the plasma insulin levels are significantly lower in the low responders \( (P < 0.005) \) during the whole hour of infusion but not later. The fasting values of glucose and insulin at GIT did not differ significantly between the groups (Table 1).

The computed parameters for the insulin response are given in Table 1. The parameter used for dividing the mothers into high and low responders, \( k_{11} \), of course was significantly higher in the former group. The \( k_{12} \) did not differ, while \( b \) was higher and \( k_a \) lower in the high responders.

Twenty-one women underwent 2 GIT after delivery with a varying interval \( (6.3 \pm 1.0 \text{ months, range 1–60 months}) \). The mean difference in \( k_{11} \) was \( 0.04 \pm 0.08 \ (P > 0.05) \). There was no detectable change in immediate insulin response to GIT with time.

The mothers' k-values at IVGTT after pregnancy were all above 1.0. The lowest value found was 1.17 in 2 of the high responders. The mean values after pregnancy did not differ significantly between the groups (Table 1). During pregnancy, in the last trimester, the mean k-value for the 20 high responders
Table 1.
Mean values for the different parameters of the insulin response to GIT (see text), the k-value at IVGTT and fasting values of blood glucose and plasma insulin, in 21 women with a high insulin response to glucose and 14 women with a low response, when tested in the non-pregnant state.

<table>
<thead>
<tr>
<th>Group</th>
<th>( k_{11} )</th>
<th>( k_{12} )</th>
<th>( b )</th>
<th>( k_g )</th>
<th>k-value</th>
<th>Fasting values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Glucose mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>per 100 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insulin ( \mu U ) per ml</td>
</tr>
<tr>
<td><strong>High insulin responders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \bar{x} )</td>
<td>2.32</td>
<td>2.70</td>
<td>2.18</td>
<td>1.67</td>
<td>2.05</td>
<td>77.3</td>
</tr>
<tr>
<td><strong>SEM</strong></td>
<td>0.03</td>
<td>0.06</td>
<td>0.05</td>
<td>0.04</td>
<td>0.15</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Low insulin responders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \bar{x} )</td>
<td>2.23</td>
<td>2.70</td>
<td>2.18</td>
<td>1.80</td>
<td>1.96</td>
<td>81.8</td>
</tr>
<tr>
<td><strong>SEM</strong></td>
<td>0.03</td>
<td>0.08</td>
<td>0.07</td>
<td>0.03</td>
<td>0.12</td>
<td>2.5</td>
</tr>
</tbody>
</table>

**Significance of difference (df = 33)**

| \( t \) | 12.258 | 0.000 | 4.067 | 2.031 | 0.417 | 1.725 | 1.127 |
| \( P \) | < 0.001 | NS    | < 0.001 | ≈ 0.05 | NS    | NS | NS |

tested was 1.89 ± 0.17 and for the 14 low responders 1.57 ± 0.14, the difference being non-significant \( (P > 0.05) \). In the low responder group the k-value during pregnancy was considerably lower than that observed after pregnancy \( (\bar{x}_D = 0.41 ± 0.20, P < 0.025) \). In the high responders no significant decrease during pregnancy was observed \( (\bar{x}_D = 0.12 ± 0.25, P > 0.05) \). Three high responders and 2 low responders from the group of women studied retrospectively showed a k-value below 1.0 at one occasion during the last trimester of pregnancy (the actual values being 0.92, 0.98, 0.89 and 0.92, 0.89 respectively). In 4 of these k-value at a new IVGTT, during pregnancy was above 1.0, and the mean value for each of them was also above 1.0. In the remaining low responder, with a k-value of 0.89, the IVGTT was not repeated during pregnancy.

**Infants**

The gestational age was the same in both groups, 40.6 ± 0.2 weeks for IHR and 40.7 ± 0.4 for ILR. The birth weight was the same in both groups, 3.725 ± 135 g for IHR as compared to 3.618 ± 117 g for ILR. Six IHR and 1 ILR had a birthweight above the 90th percentile for their gestational age...
Table 2.
Mean k-values at IVGTT in the infants, with different doses of glucose used and in the two groups of IHR and ILR.

<table>
<thead>
<tr>
<th>Group</th>
<th>Glucose dose given at the IVGTT</th>
<th>Total per group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.5 g/kg</td>
<td>1.0 g/kg</td>
</tr>
<tr>
<td>IHR</td>
<td>0.99</td>
<td>1.08</td>
</tr>
<tr>
<td></td>
<td>0.22</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>ILR</td>
<td>1.38</td>
<td>1.40</td>
</tr>
<tr>
<td></td>
<td>0.34</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>11</td>
</tr>
</tbody>
</table>

(Engström & Sterky 1966), and 3 IHR below the 10th percentile. No correlation was found between the infant’s weight and its k-value ($r = 0.14$, $n = 37$, $P > 0.05$). None of the infants had a neonatal symptomatic hypoglycaemia.

When the higher glucose dose, 1.5 g per kg body weight, was used for the IVGTT no significant difference in k-value from the dose of 1.0 g was noted in either IHR or ILR (Table 2). The mean k-value for the whole group of

![Fig. 2.](image)

Distribution of k-value at IVGTT of 22 IHR and 15 ILR. Hatched columns denote IHR and dotted columns ILR. M = median value for the group.
IHR was 1.05 ± 0.09, which was significantly lower than that of 1.39 ± 0.14 for ILR \( P < 0.05 \). The distribution of the individual k-values within each group of infants is seen in Fig. 2. There was a marked shift to the right in the ILR group, and the distribution within this group was similar to that within a group of infants of diabetic mothers (IDM). No increase in k-value with time was found during the first 24 h after birth \( (r = 0.11; n = 37; y = 1.10 + 0.01 x) \).

**DISCUSSION**

By definition, the low insulin responders had a lower initial response to glucose infusion and also a slower secondary rise in plasma insulin. Fasting blood glucose and k-values in the non-pregnant low responders were well within normal limits, but the glucose level tended to be somewhat higher and the k-value somewhat lower than in the high responders. The decrease in k-value *during* late pregnancy was definitely more pronounced in the low than in the high responders. In the previous study of pregnant high and low responders none of the women showed a k-value below 1.0 \( (Edström et al. 1974) \). In the present study a k-value below 1.0 was recorded in 5 subjects. Actually, this had originally been the reason for performing an IVGTT in the infants of these 5 mothers. I 4 of these mothers gestational diabetes could be excluded since a repeated test showed normal values and since the fasting blood sugar was normal. In the remaining subject the IVGTT was not repeated during pregnancy. However, she was seen again during a later pregnancy, and then the k-value in the last trimester was 1.77.

The mean body weight of the high responders was higher than that of the low responders, the difference being 7.4 kg \( (P < 0.025) \). However, the mean weight for both groups of women fell well within normal limits for the body weight. On the other hand, 3 high responders had a body weight somewhat above 120\% of the normal mean for their body height. It is unlikely that these small differences would considerably have affected the results of the GIT. Possibly, the 3 slightly obese women might have demonstrated a somewhat more pronounced insulin response than those with a normal body weight (below 120\%). However, as shown by *Luft et al.* (1968), it is unlikely that these women actually belonged to the group of low responders, since low insulin response most probably remains low when the subject in question becomes obese.

The distribution of k-values at IVGTT in the 2 groups of infants here studied shows a shift towards higher k-values in the ILR as compared to the IHR. The mean k-value for the ILR was found to be significantly higher than that for the IHR. Also, in spite of the fact that gestational diabetes could
not be shown in the mothers, the mean k-value for the ILR is similar to that previously found in infants of mothers with gestational diabetes or very strictly regulated insulin-requiring diabetes (Isles et al. 1968; Mølsted Pedersen 1972a,b; Persson et al. 1973; Thalme & Edström, to be published).

In some of the subjects the GIT was performed a long time after the birth of the infant, and the insulin response could possibly have changed with time. On the other hand, the immediate insulin response to GIT (kij) has earlier been shown to remain stable when tested after an interval of about one year (Cerasi & Luft 1967b). This finding is confirmed by the present study, and the insulin response seems to remain unchanged at least during a considerable time in the age group here concerned.

The k-value at IVGTT in newborn infants is influenced also by factors not related to the mother's carbohydrate tolerance during pregnancy. Thus a high k-value during the first day of life is seen, except in IDM, also in symptomatic neonatal hypoglycaemia (Gentz et al. 1969; le Dune 1972), and in overweight babies (Gentz et al. 1967). On the other hand, a lower mean value is seen in premature infants (Cornbladt et al. 1963). Factors such as these cannot explain the above-mentioned differences in k-values between the 2 groups, since no symptomatic neonatal hypoglycaemia and no difference in birth weight or gestational length were recorded.

In the present study the IVGTT in 11 of the infants was performed with a lower dose of glucose, 1.0 g, as compared with 1.5 g per kg body weight in the rest. Opinions are diverging as to whether a difference in the glucose dose used at IVGTT influences the disappearance rate of glucose. In adults no attention is usually paid to the glucose dose used in relation to the body weight, and in paired experiments no important differences in k-values have been encountered using different doses within the range 0.5–1.5 g/kg body weight (Moorehouse et al. 1963; Wahlberg 1966). In newborn infants similar systematic studies cannot be performed regarding the effect on k-value of different glucose doses, as the k-value has been shown to increase when the IVGTT is repeated the same day (Bowie et al. 1963), and as the normally low k-value in the newborn increases rapidly after the first 24 h of starvation (Mølsted Pedersen 1972b; Persson et al. 1973). In this material, however, there was no significant difference in mean k-value with the 2 glucose doses here used (1.0 and 1.5 g). This is also in agreement with earlier reports concerning k-values using the dose levels 0.5 and 1.0 g (Mølsted Pedersen 1972a; Bowie et al. 1963; Isles et al. 1968; Persson et al. 1973).

Thus the only factor remaining that seems to be definitely related to the infants' ability to rapidly remove the injected glucose from the blood, is their mothers' insulin response to GIT. The low insulin responders to a large extent delivered infants with a high glucose tolerance while the high responders did not. It seems logical to attribute this to a prediabetic state in a large proportion
of the low insulin responders investigated, in spite of the fact that most of them had a completely normal carbohydrate tolerance during late pregnancy. Hagen (1961) found that women with potential diabetes (classified on clinical criteria only) tended to have higher blood glucose levels during pregnancy than normal women. Furthermore, Asplund (1972) has shown that even a minute increase in blood glucose for a few days in pregnant rat increased the insulin response to glucose stimulus in their litter.

In a previous paper (Edström et al. 1974) we have shown that the low responders' blood glucose levels during GIT in late pregnancy are slightly higher than that of the high responders, and this is probably true also for their post-prandial blood glucose levels. This might be enough to stimulate the foetal pancreas and to develop a higher capacity for the newborn infant to handle a glucose load.

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