Neonatal pancreatic function in infants born to mothers with gestational and overt diabetes

T. J. DE VILLIERS, C. M. MACFARLANE, N. TSAKALAKOS, J. J. F. TALJAARD

Summary

Neonatal pancreatic function was assessed in infants born to non-diabetic mothers and to mothers with well-controlled gestational diabetes (GD) and overt diabetes (OD) using cord blood C-peptide estimations and the calculation of cord C-peptide/glucose ratios. Exaggerated pancreatic function was present in infants born to mothers with GD. In these infants the increased cord C-peptide values and cord C-peptide/glucose ratios correlated with their increased birth weight ratios. These results could not be explained on the basis of maternal hyperglycaemia and a possible intrinsic difference in pancreatic response between infants born to mothers with GD and those born to mothers with OD is suggested.  

Pedersen et al.\textsuperscript{1} have proposed that maternal hyperglycaemia due to poorly controlled diabetes during pregnancy can lead to fetal hyperglycaemia and hyperinsulinaemia, contributing to an increase in cord blood C-peptide/glucose ratio and that this ratio correlated with the birth weight ratio (BWR) of these neonates. They suggested that this increased ratio indicates an appropriately high fetal pancreatic beta-cell response to prevailing blood glucose values. An earlier study by Sosenko et al.\textsuperscript{2} also demonstrated a significant increase in cord C-peptide values in diabetic pregnancy. This was associated with the presence of macrosomia and subsequent neonatal hypoglycaemia, but an association of these results with maternal diabetic control was not investigated. Even with excellent prenatal care, 20% of infants born to mothers with gestational diabetes (GD) and 25% of those born to mothers with overt diabetes (OD) have birth weights in excess of 4000 g,\textsuperscript{3} compared with an incidence of 9\% for the general hospital population.\textsuperscript{4} In addition, attempts to correlate maternal glycosylated haemoglobin values with birth weight have produced conflicting results about the influence of maternal diabetic control on neonatal macrosomia.\textsuperscript{5,6}

The aim of this study was to determine the neonatal pancreatic response in infants born to non-diabetic mothers and to mothers with well-controlled diabetes using cord blood C-peptide estimations and the cord blood C-peptide/glucose ratio as criteria. Emphasis has been placed on differences between infants born to mothers with GD and those born to mothers with OD.

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Patients and methods

Twenty pregnant diabetic women and 12 pregnant non-diabetic women were studied prospectively. Patients with vascular disease were carefully excluded. The non-diabetic subjects had

had a normal result on glucose tolerance testing during pregnancy as judged by the criteria of O’Sullivan and Mahan.12 Twelve patients had GD, the criteria for the diagnosis of which were an abnormal result on glucose tolerance testing12 early in pregnancy and a fasting plasma glucose level of less than 5.8 mmol/l. Treatment of GD consisted of a standard diabetic diet with a ratio of carbohydrates/fat/protein of 45%/35%/20%. Kilojoules were adjusted for body weight. After an initial period of hospitalization during which daily plasma glucose profiles confirmed adequate control of the diabetes by diet, the patients were seen once a week for 1 day in hospital. The aim of dietary therapy was to keep the 2-hour postprandial plasma glucose level below 8.3 mmol/l. By this criterion all patients were considered to be well controlled.

Eight patients had OD, this being diagnosed when fasting plasma glucose levels exceeded 5.8 mmol/l. Treatment consisted of appropriate administration of insulin to maintain a fasting plasma glucose value below 5.8 mmol/l and a 2-hour postprandial value below 8.3 mmol/l. Treatment was conducted on an inpatient basis for most of the duration of their pregnancies.

All patients received an intravenous infusion of 5% dextrose in water during labour at a rate of less than 10 g/h. It has been shown that this has no effect on cord blood insulin levels.8 Intrapartum euglycaemia (i.e. between 3.8 and 6 mmol/l) was controlled by frequent estimations of the maternal glucose level. Examination of the maternal age distribution showed that both OD patients (33.0 ± 5.2 years) and GD patients (30.6 ± 7.2 years) were significantly older than the non-diabetic subjects (26.1 ± 5.7 years).

Infants born to the mothers already described were studied. No infants were born before 36 weeks’ gestation and the groups were adjusted for body weight.

Only 2 infants examined were macrosomic (BWR > 1.2) and both of these were delivered to mothers with GD.

were delivered by elective caesarean section. Gestational age was determined postnatally using the Dubowitz assessment2 and the BWR was calculated by dividing the actual birth weight by the 50th percentile for gestational age using percentile charts appropriate for the local population.10 Maternal venous blood and mixed umbilical cord blood samples were collected at delivery11 before the babies had taken their first breath. Serum for the determination of C-peptide levels was separated and stored at −20°C until assayed by a radio-immunossay procedure (Byk-Mallinkrodt Kit; Dietzenbach, Germany). Because of the presence of anti-insulin antibody pro-insulin complexes in the blood of insulin-treated mothers and their infants, specimens from these patients were pretreated with polyethylene glycol before estimation of C-peptide.12 Appropriate standards were treated in a similar manner. Plasma glucose in maternal and cord blood was measured on a Beckman glucose analyser (Astra 8 Routine Analyser).

Maternal venous blood was also collected into tubes containing ethylenediamine tetra-acetic acid and stored at 4°C until the total glycosylated haemoglobin (HbA1c) levels were measured. This was done within 4 days of specimen collection using a commercial microcolumn chromatographic procedure (DCA Diagnostic Chemical Association, USA). Our normal range for HbA1c is 5.5–8.5%. Statistical analysis of the results was carried out with parametric statistics (Student’s t test and linear regression).

Results

Neonatal cord blood C-peptide levels were significantly higher in the infants born to the mothers with GD, although there was no significant difference in cord glucose levels between the three groups (Table I). The cord blood C-peptide/glucose ratio was significantly higher in the infants born to the mothers with GD (Table I), and the C-peptide levels and C-peptide/glucose ratios correlated with the increased BWRs (Figs 1 and 2) in this group of neonates. These correlations were absent in the other two groups studied.

<table>
<thead>
<tr>
<th>TABLE I. NEONATAL VALUES (MEAN ± SE)</th>
<th>Non-diabetic</th>
<th>OD</th>
<th>GD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (kg)</td>
<td>3.487 ± 1.26</td>
<td>3.323 ± 1.62</td>
<td>3.741 ± 1.20</td>
</tr>
<tr>
<td>Gestational age (wks)</td>
<td>39.25 ± 0.32</td>
<td>38.62 ± 0.53</td>
<td>38.92 ± 0.31</td>
</tr>
<tr>
<td>BWR</td>
<td>1.04 ± 0.03</td>
<td>1.06 ± 0.04</td>
<td>1.16 ± 0.04**</td>
</tr>
<tr>
<td>Cord C-peptide (pmol/l)</td>
<td>412 ± 59</td>
<td>465 ± 58</td>
<td>679 ± 92*</td>
</tr>
<tr>
<td>Cord glucose (mmol/l)</td>
<td>6.5 ± 0.67</td>
<td>6.8 ± 0.84</td>
<td>5.9 ± 0.69</td>
</tr>
<tr>
<td>C-peptide/glucose ratio (pmol/mmol)</td>
<td>75 ± 9.2</td>
<td>62.7 ± 7.7</td>
<td>106 ± 17.1**</td>
</tr>
</tbody>
</table>

Only 2 infants examined were macrosomic (BWR > 1.2) and both of these were delivered to mothers with GD.

*P < 0.02.
**P < 0.05.

<table>
<thead>
<tr>
<th>TABLE II. MATERNAL VALUES (MEAN ± SE)</th>
<th>Non-diabetic</th>
<th>OD</th>
<th>GD</th>
</tr>
</thead>
<tbody>
<tr>
<td>% HbA1c</td>
<td>6.8 ± 0.2</td>
<td>7.0 ± 0.46</td>
<td>7.0 ± 0.17</td>
</tr>
<tr>
<td>C-peptide (pmol/l)</td>
<td>556 ± 96</td>
<td>281 ± 89***</td>
<td>1159 ± 202**</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.2 ± 0.36</td>
<td>6.4 ± 0.88</td>
<td>5.8 ± 0.39</td>
</tr>
<tr>
<td>C-peptide/glucose ratio (pmol/mmol)</td>
<td>105 ± 12.7</td>
<td>65 ± 5.6</td>
<td>205 ± 30*</td>
</tr>
</tbody>
</table>

*P < 0.01.
**P < 0.02.
***P < 0.05.
The HbA₁c values were similar and within the normal range in the three groups of patients studied (Table I). There was no correlation between the HbA₁c value and BWR in any of the groups. Maternal glucose values were similar and within the normal range in all cases although, as expected, the C-peptide values were lower in the patients with OD, and this gave a lower C-peptide/glucose ratio in this group (Table I). C-peptide values were increased in the GD mothers and the C-peptide/glucose ratio was also significantly increased in this group (Table I). Maternal C-peptide levels in the non-diabetic subjects and in the patients with GD did not correlate with HbA₁c or neonatal C-peptide values or BWR but did correlate with maternal glucose values in the presence of GD (Fig. 3). Cord C-peptide values in the presence of GD also correlated with cord blood glucose values (Fig. 4).

Discussion

The insulin status of the fetus remains a central issue in the management of diabetic pregnancy. In the long term it has been associated with fetal macrosomia, while in the short term it serves as an indicator of impending neonatal hypoglycaemia. As such, the insulin status of the infant born to the diabetic mother has been thought to serve as a sensitive indicator of successful management of the diabetic pregnancy. The pregnant diabetic population includes a wide spectrum of abnormal glucose metabolism, and confusion exists over the correct classification of such patients, especially when diabetes mellitus is first diagnosed in pregnancy. In this study we divided the patients studied into two groups. Patients with elevated fasting glucose levels (>5.8 mmol/l) (OD) were treated with insulin, whereas those with normal fasting glucose values (<5.8 mmol/l) but an abnormal glucose tolerance test result (GD) were treated by diet alone. This latter group meets the criteria of GD defined by Coustan. Our study, although performed on a small number of patients, yields significant information regarding a difference in pancreatic function between infants born to mothers with OD and those whose mothers had GD which to our knowledge has not previously been reported. Although maternal plasma glucose levels were considered well controlled in both groups by the same criteria (fasting and postprandial glucose levels and percentage HbA₁c), a significantly higher cord C-peptide/glucose ratio was present in infants born to mothers with GD (Table I). This ratio correlated with the BWR of these infants (Fig. 2) and the BWR was significantly increased (Table I). This difference between the two diabetic groups is further emphasized when our results are compared with those obtained by Burke et al. The cord C-peptide/glucose ratios obtained by Burke et al. in infants born to non-diabetics and those born to mothers with well-
controlled OD (approximately 30 and 28 pmol/mmol respectively) compare with our own results, but the value obtained for our patients with well-controlled GD (Table I) agrees with values obtained by Burke et al. in infants born to mothers with poorly controlled OD (approximately 105 pmol/mmol). These authors commented that poor control of OD in their patients led not only to an increased but also to an exaggerated response of the fetal beta cells to their environmental glucose level. Although this seems to imply poor control of GD in our patients we were nevertheless satisfied with control according to our criteria. Ogata et al. have reported increased cord C-peptide/glucose ratios in both patients with OD (159 pmol/mmol) and those with GD (145 pmol/mmol). Since our study and the work of Burke et al. showed that the presence of optimal maternal glucose control of OD resulted in cord C-peptide/glucose ratios of 62.7 (Table I) and 28 pmol/mmol respectively, it is suggested that maternal glucose control in the presence of OD was suboptimal in the study of Ogata et al. No comment can be made on the control of their GD patients, although the authors themselves state that the control of their diabetic patients was not "fully normalized."

It has been shown that the determination of total maternal glycosylated haemoglobin values is not a completely reliable index of fetal outcome in diabetic pregnancy. Our results agree with this as they show no correlation between HbA1 values and BWR or neonatal C-peptide values. We have to rely on repeated measurements of fasting and 2-hour postprandial glucose values as indices of diabetic control. Maternal C-peptide values in our normal and GD groups were not related to HbA1, BWR or neonatal C-peptide values, but they did correlate with prevailing blood glucose levels in mothers and neonates in both groups (Figs 3 and 4) (unpublished results). Maternal C-peptide values are therefore not a useful measure of diabetic control, but rather a measure of pancreatic response to prevailing blood glucose levels.

Our results lead us to propose a possible intrinsic difference in pancreatic response between infants born to mothers with GD and those born to mothers with OD. Further support for the concept of GD as a distinct condition with exaggerated pancreatic function is supported by the high C-peptide values and C-peptide/glucose ratio evident in the maternal plasma in our GD group (Table II). A genetic factor in GD could lead to fetal pancreatic beta-cell hyperplasia, and we suggest this as the basis for the difference in neonatal pancreatic function in our OD and GD groups. Genetic differences between various types of non-pregnant diabetics have previously been described, based on studies of concordance or histocompatibility antigens, but results with islet cell antibodies are somewhat unclear and the position with regard to GD has not yet been finalized. Our proposal is compatible with our results, although somewhat different from the "tissue culture" formulation of pregnancy proposed by Freinkel and Metzger. Certainly the genetic component (if present) is only a contributing factor to the problem of the fetus of the diabetic mother. Nevertheless, if maternal glycaemic control in GD operates in part via an intrinsic hyperplastic fetal pancreas, then prevention of fetal complications (e.g. macrosomia and neonatal hypoglycaemia) demands more careful glycaemic control of the mother. This may be possible by combined treatment with diet or insulin or through the combined use of different insulin preparations to achieve better stabilization of the mother with GD. This is of some importance as the number of pregnant women affected by OD has been reported to be about 10 times higher than that of pregnant women with OD.

REFERENCES