

Evidence of hyperinsulinaemia and hypoxaemia in the cord blood of neonates born to mothers with gestational diabetes

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Summary

Increased cord blood C-peptide levels in neonates born to mothers with gestational diabetes (GD) were directly correlated with the increased relative birth weight ratio (BWR) of these neonates. In addition, the percentage oxygen saturation of the cord blood was inversely correlated with cord blood C-peptide levels and with the relative BWR. These correlations were absent in neonates delivered to normal mothers. The results indicate the presence of both hyperinsulinaemia and mild hypoxaemia in neonates of mothers with GD. In poorly controlled diabetic pregnancy this hypoxaemia may constitute an important fetal risk factor.

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Macrosomia in infants born to diabetic mothers is most commonly attributed to poor blood glucose control in the mother¹⁻³ and the development of hyperinsulinaemia in the fetus.^{4,5} In addition, it has been shown that poor control of diabetes in adults gives rise to increased levels of glycosylated haemoglobin.⁶⁻⁸ It has been suggested that this increase in abnormal haemoglobin may affect maternal^{9,10} and placental¹¹ oxygen transport, and that this may constitute an additional fetal risk factor during diabetic pregnancy. In pregnant insulin-dependent diabetic patients, Widness *et al.*¹² found no correlation between HbA_{1c} and maternal P₅₀ (partial pressure of oxygen at which haemoglobin is 50% saturated with oxygen) values, although in a separate study they did suggest that the increased umbilical plasma erythropoietin found in the neonates of their diabetic patients might be mediated by fetal hypoxia.¹³ The presence of fetal hypoxia in human diabetic pregnancy was suggested as early as 1954 by Berglund and Zetterström.¹⁴ This suggestion was made on the basis of increased erythropoiesis and decreased oxygen saturation in the umbilical cord blood of 3 infants born to diabetic mothers. However, the presence of vascular disease was not excluded in these patients. More recently, Philipps *et al.*¹⁵ have shown that infusion of tolbutamide into pregnant ewes through a fetal venous catheter increased fetal insulin release and fetal glucose consumption, and produced mild hypoxaemia as measured by an increased umbilical venous-arterial oxygen content difference. This is in

agreement with the earlier work of Carson *et al.*¹⁶ and Quissell *et al.*¹⁷ in fetal lambs. They showed that sustained fetal hyperinsulinism (plasma insulin level $316 \pm 60 \mu\text{U/ml}$ for ± 48 hours) was associated with a fall in arterial oxygen content^{16,17} and with increased fetal oxygen consumption¹⁷ in these animals.

We wished to investigate this possibility further, to determine whether fetal hypoxaemia was present in diabetic pregnancy and to ascertain whether it was related to the fetal hyperinsulinism often found in infants born to diabetic mothers.

Patients and methods

There were 13 pregnant patients with gestational diabetes (GD) and their neonates in the study. Diabetes was diagnosed early in pregnancy on the basis of an abnormal glucose tolerance test result¹⁸ and a fasting blood glucose level $< 5,8 \text{ mmol/l}$. Patients with vascular complications were carefully excluded and the mothers of the infants studied were considered to have well-controlled diabetes according to established criteria, i.e. fasting blood glucose value $< 5,8 \text{ mmol/l}$, 2-hour postprandial glucose level $< 8,3 \text{ mmol/l}$, and normal levels of total glycosylated haemoglobin (HbA_{1(a+b+c)}). They were treated with a standard diabetic diet.¹⁹

No placental dysfunction or pre-eclampsia was present, and in 12 cases there was a normal, uncomplicated vaginal delivery at term, while in 1 case the infant was delivered by elective caesarean section at 39½ weeks. This baby was subsequently shown to be macrosomic. No oxygen or nitrous oxide was administered during labour and intrapartum euglycaemia was monitored by frequent estimation of blood glucose levels.

Twelve normal mothers and their neonates (all delivered by normal, uncomplicated vaginal delivery) were examined as controls. All patients (diabetics and controls) received an intravenous infusion of 5% dextrose in water during labour at an infusion rate of $< 10 \text{ g/h}$. It has been shown that this has no effect on cord blood insulin levels.²⁰ Apgar scores for all infants were within the normal range and informed consent for the study was obtained from each patient studied. The study was carried out in accordance with the requirements of the Ethical Committee of this hospital.

Maternal venous blood was collected on the day of delivery and umbilical cord blood was collected at delivery,²¹ before the babies had taken their first breath. No epidural or other anaesthetic was administered to mothers who had a normal vaginal delivery. There was no evidence of cord compression during delivery and in each patient studied the second stage of labour was not unduly prolonged.

Relative birth weight ratios (BWRs) were determined after Dubowitz examination²² using birth weight charts appropriate for the local population.²³

C-peptide levels in umbilical cord blood specimens taken at delivery²¹ were determined after polyethylene glycol precipitation²⁴ using a commercial radio-immunoassay kit from Byk-Mallinckrodt (Germany).

The percentage of oxygen saturation of cord blood was measured on an Instrumentation Laboratory (IL) co-oximeter

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Model 282 (Massachusetts) and the partial pressure of oxygen (Po₂) on an IL blood gas analyser Model 613. Both parameters were measured in samples obtained anaerobically from umbilical cord blood at delivery.

Plasma glucose levels were determined by a conventional glucose oxidase method (Beckman Astra-8 Routine Analyser) and total HbA₁ was measured on EDTA plasma using a commercial kit (Diagnostic Corporation of America, Arlington, Texas) utilizing an ion-exchange microcolumn chromatographic procedure.

Comparison of means was carried out using the Mann-Whitney U test and visual presentations were calculated using linear regression analyses; significance was calculated by the Spearman-Rank correlation test (two-tailed analyses).

Results

There was no significant difference in gestational age between the two groups of neonates (Table I). Relative BWR and cord blood C-peptide values were significantly higher in neonates born to the mothers with GD (Table I). The percentage oxygen saturation and Po₂ were lower (although this was not significant) in neonates born to the mothers with GD (Table I). There was no difference in cord blood pH in the two groups, and if a birth weight above the 90th percentile for gestational age is taken to indicate fetal macrosomia,³ then 2 of the babies examined were macrosomic, and both of these

Patient class	BWR	C peptide (ng/ml)	Po ₂ (kPa)	Oxygen saturation (%)
GD	1,49	3,2	3,1	43,3
GD	1,48	2,6	3,0	40,3

babies were born to mothers with GD. Their BWRs and cord blood C-peptide, percentage oxygen saturation and Po₂ values are shown in Table II. One of these babies was delivered by elective caesarean section and the other was delivered normally at 36 weeks.

The increase in C-peptide levels present in the neonates of the GD patients was directly correlated with BWR (Fig. 1) and inversely with oxygen saturation values (Fig. 2). The oxygen saturation values in these neonates showed an inverse correlation with BWR (Fig. 3). These correlations were not present in neonates delivered to normal mothers.

Discussion

The results presented are consistent with the proposal that hyperinsulinism in the fetuses of the GD patients in this study

	Non-diabetic (N = 12)	GD (N = 13)
Gestational age (wks)	39,25 ± 1,16 (12)	38,92 ± 1,18 (13)
Maternal HbA ₁ (%)	6,8 ± 0,7 (12)	7,0 ± 0,6 (13)
Cord glucose (mmol/l)	6,5 ± 2,4 (12)	5,9 ± 2,5 (13)
Cord pH	7,29 ± 0,08 (9)	7,28 ± 0,10 (10)
BWR	1,04 ± 0,10 (12)	1,16 ± 0,16* (12)
Cord C peptide (ng/ml)	1,31 ± 0,53 (12)	2,16 ± 1,06* (13)
Cord oxygen saturation (%)	65,58 ± 11,91 (9)	55,43 ± 1,53 (10)
Cord Po ₂ (kPa)	4,33 ± 0,76 (9)	3,94 ± 1,01 (10)

Figures in brackets refer to the number of patients examined. One patient did undergo a Dubowitz examination, and machine breakdown reduced the number of blood gas determinations.
*P < 0,05.

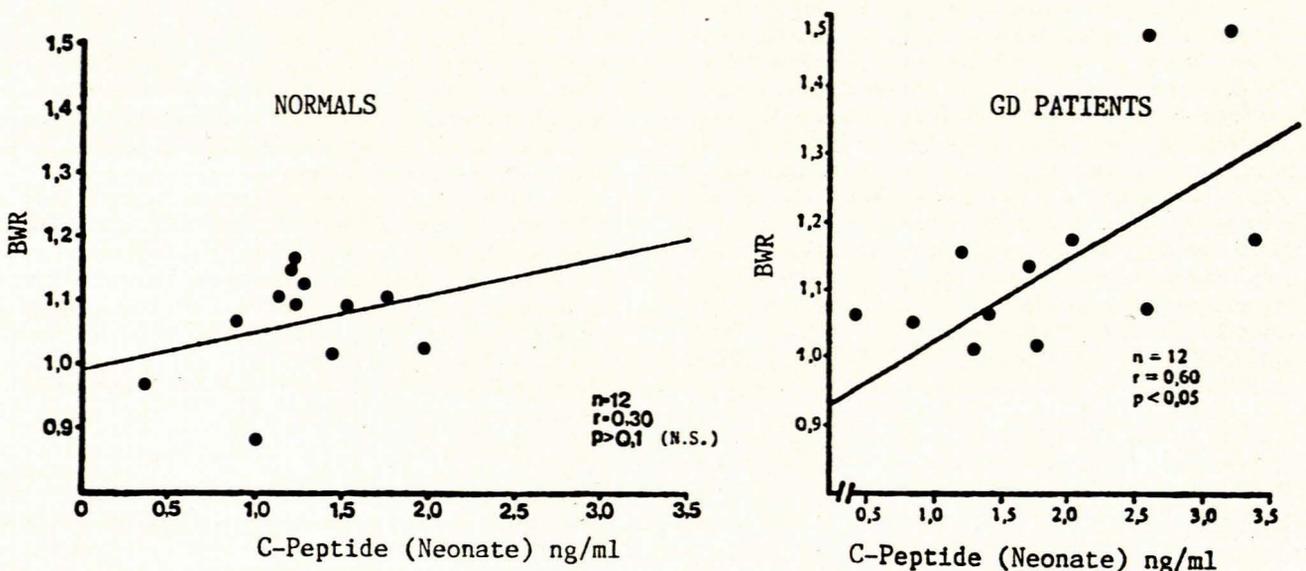


Fig. 1. BWR v. cord blood C-peptide values.

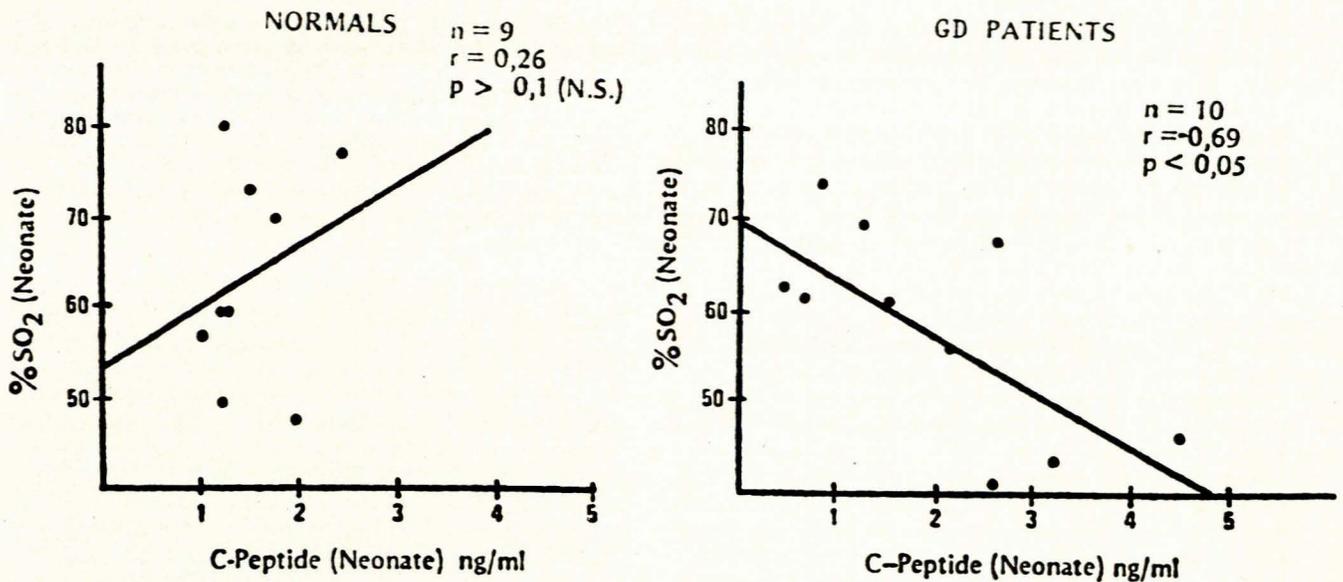


Fig. 2. Percentage oxygen saturation in cord blood v. cord blood C-peptide values.

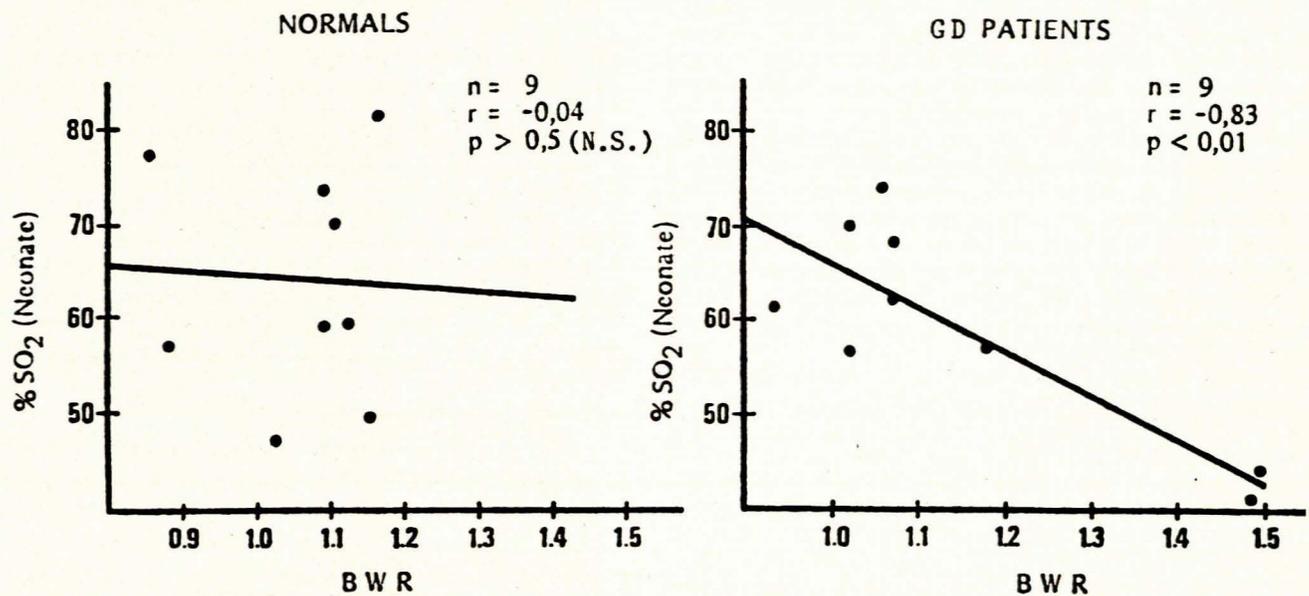


Fig. 3. Percentage oxygen saturation in cord blood v. BWR.

may lead to the development of relative fetal hypoxaemia. In this respect they agree with the work of Carson *et al.*,¹⁶ Quissell *et al.*¹⁷ and Philipps *et al.*¹⁵ in fetal lambs, and with that of Widness *et al.*¹³ in subjects with GD and rhesus monkeys.

It is difficult to be certain how closely the values in neonatal cord blood reflect fetal values *in utero* during the third trimester. Various techniques have been used to assess fetal function *in utero* (e.g. examination of autopsy material^{25,26} and multiple catheterization¹⁵⁻¹⁷). Serial sampling from amniotic fluid and serial ultrasonography were used in an elegant clinical study by Ogata *et al.*,⁵ although neither of these latter techniques would be useful in monitoring oxygenation of the fetus. Sampling from cord blood at term has been used previously to assess fetal pancreatic function,^{3,4,13} and the results which we obtained using this procedure, while subject to the exigencies of labour and not ideal as a measure of *in utero* fetal experience, gave results which were consistent with those obtained by other workers using other sampling procedures and (in some

cases) experimental animals. We feel that the mild fetal hypoxaemia detected cannot be attributed to complications during delivery or to placental abnormalities, since these patients were excluded from this study. The conditions of labour and gestational age at term (Table I) were similar in the two groups studied, and we do not believe that these factors influenced our results.

Euglycaemia was maintained during labour and there was no difference in cord blood glucose levels in the two groups of infants (Table I). In addition, the patients with GD studied were considered to be well controlled, and HbA₁ values were within the normal range (Table I). Increased amounts of minor maternal haemoglobin components therefore did not contribute to the neonatal hypoxaemia which we found in these infants. In spite of the good control of diabetes in the mothers with GD, cord blood levels of C peptide (Table I) were raised, and their neonates also showed a significant increase in BWR (Table I) in comparison with neonates delivered to normal mothers. The mild neonatal hypoxaemia

which we found may be a consequence of this increase in fetal weight, and we feel that the process was in progress before birth, i.e. present *in utero*. The increase in BWR and C-peptide in the neonates of the mothers with GD and the correlation of BWR with cord blood C-peptide values (Fig. 1) suggest that fetal hyperinsulinism results in heavier babies being born to the mothers with GD. This agrees with previously published results.¹⁻⁵ In addition, the BWR (Fig. 3) and the C-peptide values (Fig. 2) in the neonates of the mothers with GD were inversely correlated with percentage oxygen saturation. These correlations were absent in neonates delivered to normal mothers. This suggests that the mild hypoxaemia found in the neonates born to mothers with GD may be secondary to an insulin-induced increase in fetal weight.

Although the percentage oxygen saturation and P_{O_2} were not significantly lower in the infants of the mothers with GD (Table I), only 2 of these babies were macrosomic. The correlations in Figs 1, 2 and 3 suggest that with poor control of diabetes (all our patients were considered well controlled), larger babies and significantly lower percentage oxygen saturation and P_{O_2} values would develop. In the 2 macrosomic babies examined, in spite of apparently good diabetic control, C-peptide values were higher and this fetal hyperinsulinaemia was associated with lower percentage oxygen saturation and P_{O_2} values than were present in the other infants examined (Table II). One of these babies was delivered by caesarean section while the other had a normal vaginal delivery.

Widness *et al.*¹³ could find no difference in umbilical P_{O_2} values between neonates of normal mothers and those with GD (caesarean section), and they could find no correlation between umbilical arterial P_{O_2} and cord blood erythropoietin in the neonates born to the mothers with GD. They did, however, correlate ΔP_{O_2} ($P_{uVO_2} - P_{uaO_2}$) values with erythropoietin levels in these latter neonates. The neonates born to the mothers with GD in their study had significantly higher birth weights and umbilical plasma insulin and erythropoietin levels than infants born to normal mothers. These results agree with our findings.

The percentage oxygen saturation is proportional to the oxygen content of the blood, and although neither the oxygen content of the cord blood nor the fetal oxygen consumption was measured, we feel that the percentage oxygen saturation is a useful index of hypoxaemia. It has been used previously^{11,14} together with measurements of fetal erythropoiesis¹⁴ for this purpose. In addition, cord blood fetal haemoglobin and 2,3-diphosphoglyceric acid levels were significantly increased (unpublished observations) in the neonates born to the mothers with GD. This, together with the lower percentage oxygen saturation and P_{O_2} values found (Table I), is consistent with the presence of hypoxic stress in these neonates.

We believe that our results are consistent with an insulin effect on fetal oxygenation, albeit secondary to an increase in fetal weight, in the fetuses of mothers with GD in the absence of vascular disease. They indicate the presence of mild fetal hypoxaemia *in utero* during the third trimester of pregnancy in women with GD. This agrees with the work of Berglund and Zetterström,¹⁴ and like them we suggest that interruption of difficult diabetic pregnancies after 35-36 weeks of gestation but before term seems advisable.

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