Acta Diabetol (1996) 33: 30–34


ORIGINAL

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# Long-term prognosis of infants of diabetic mothers

## Relationship between metabolic disorders in newborns and adult offspring

Received: 25 February 1995 / Accepted in revised form: 28 October 1995

**Abstract** The aim of our study was to find out whether the metabolic disorders in the newborns of insulin-dependent diabetic mothers (NDM) in the neonatal adaptation period could be associated with their condition in adulthood. We examined 148 children of diabetic mothers (CDM) aged 20.75±0.31 years (mean±SE); 11 were diabetic patients, while in the remaining 137 CDM, the oral glucose tolerance test (OGTT) was performed. CDM were compared with 31 matched control offspring of healthy mothers. Of the characteristic abnormalities occurring in NDM, the following were present in our study: macrosomia, hypoglycaemia, hyperlactacidaemia, hyperbilirubinaemia. In adulthood, the sum of the blood glucose and plasma insulin values during OGTT, body mass index (BMI) and blood pressure were determined. The observed abnormalities and the degree of their relevance in the neonatal period were not related to the sum of blood glucose and plasma insulin levels, BMI and blood pressure in adulthood, but the values of all these parameters in adulthood were significantly higher in CDM than in controls ($P<0.05$–$0.001$).

**Key words** Children of diabetic mothers · Glucose tolerance · Metabolism, newborn

## Introduction

Children of diabetic mothers (CDM) are the subject of frequent studies encompassing the neonatal period [1, 2]. Less frequent are long-term studies concentrating on the conditions of glucose tolerance (GT) and on somatic development in childhood [3, 4]. Studies in these infants at a later stage show an increased frequency of GT abnormalities [5, 6]. None of these studies concern the possible association of the metabolic condition in the neonatal period and the development of CDM up to adulthood.

In our long-term study we have had an opportunity to examine adult CDM who were intensively monitored in the neonatal period. In order to prove or to exclude the possible long-term effect of the short but important newborn adaptation period, we tried to discover whether the disorders in NDM after birth may influence their condition in adulthood.

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## Subjects and methods

The study was based on a series of NDM born in the Institute for the Care of Mother and Child in Prague. All mothers at the time of pregnancy were type 1 diabetic patients (insulin-dependent diabetes mellitus). After delivery, NDM were examined at ten exact time intervals of 5, 15 and 30 min and again in the 1st, 3rd, 6th, 12th, 24th, 48th and 72nd h of life.

### Classification of newborns

1. Fetal macrosomia: evaluated according to the tables valid for our population [7] – birth weight above 95th centile
2. Hypoglycaemia: newborns with capillary blood glucose levels of 1.66 mmol/l and lower
3. Hyperlactacidaemia: lactate values exceeded mean values+2 SD found in normal newborns at the studied intervals after birth [8]
4. Hyperbilirubinaemia: bilirubin level attained values of 250 μmol/l and higher

### Offspring in adulthood

In all, 148 CDM (72 male and 76 female) were examined at the age of 20.75±0.31 years (mean±SE, range 18–26 years) with the exception of the 11 children (3 male and 8 female) in whom diabetes mellitus had already been diagnosed. An oral glucose tolerance test (OGTT) (according to the WHO recommendations) was performed [9]. The venous plasma was examined for glucose and insulin levels. In order to evaluate the exact dynamics of the course of the changes in these levels, blood was withdrawn from the cubital vein at zero, 30, 60, 120 and 180 min, and the sum of all five values of gly-

caemia and insulinaemia was assessed. The body mass index (BMI: body weight in kg/body height in $m^2$) and systolic as well as diastolic blood pressure were measured. All parameters studied were analyzed separately in CDM with normal glucose tolerance (NGT) and impaired glucose tolerance (IGT).

The control group consisted of 31 volunteer offspring of healthy mothers aged 18–26 years without a family history of diabetes. They had no neonatal disorders including macrosomia in their history. The social, economic and other situations were comparable to those of the CDM. The diabetic mothers, their offspring and control individuals were fully informed about the aim of the present study and gave their consent. The protocol was approved by the Institute Ethics Committee.

### Biochemical analyses

In NDM blood glucose and lactate levels were measured by means of Boehringer sets. Bilirubin was measured by the Malloy-Evelyn method. In adulthood glucose in venous plasma was assessed by means of the Beckman analyzer with the use of a specific glucose-oxidase method. At the same time, the levels of immunoreactive plasma insulin were measured by double antibody radioimmunoassay RIA Kit (PL Otwook-Swierk), which had an assay sensitivity of 7.1 pmol/l and an intra-assay coefficient of variation of 5.9% and 4.7% at 49.7 pmol/l and 312.4 pmol/l, respectively. The antibody used in the assay cross-reacts fully with proinsulin and split proinsulin.

### Statistical analyses

The data were assessed by means of the dBASE III programme. The statistical evaluation was performed by *t*-test and chi-square test. All values are reported as mean±SE. Statistical significance was defined as $P<0.05$, $P<0.01$, $P<0.001$.

## Results

Table 1 shows the state of glucose tolerance in CDM according to gender. Figure 1 shows the disorders in NDM in relation to their glucose tolerance in adulthood: there are no significant differences between CDM with normal glucose tolerance who suffered from neonatal macrosomia, hypoglycaemia, hyperlactacidaemia and hyperbilirubinaemia and CDM without these disorders in the neonatal period. We found a higher percentage of diabetes mellitus in adult CDM with neonatal macrosomia, hypoglycaemia, hyperlactacidaemia and hyperbilirubinaemia; however, the differences were not significant.

Table 2 shows the relation of the body weight at birth of CDM to the sum of blood glucose, sum of plasma insu-

**Table 1** Glucose tolerance in the offspring of insulin-dependent diabetic mothers

| | Male | Female | Total (*n*) |
|---|---|---|---|
| Normal glucose tolerance | 61 | 66 | 127 |
| Impaired glucose tolerance | 8 | 2 | 10 |
| Insulin-dependent diabetes mellitus | 2 | 6 | 8 |
| Non-insulin-dependent diabetes mellitus | 1 | 2 | 3 |
| Total | 72 | 76 | 148 |

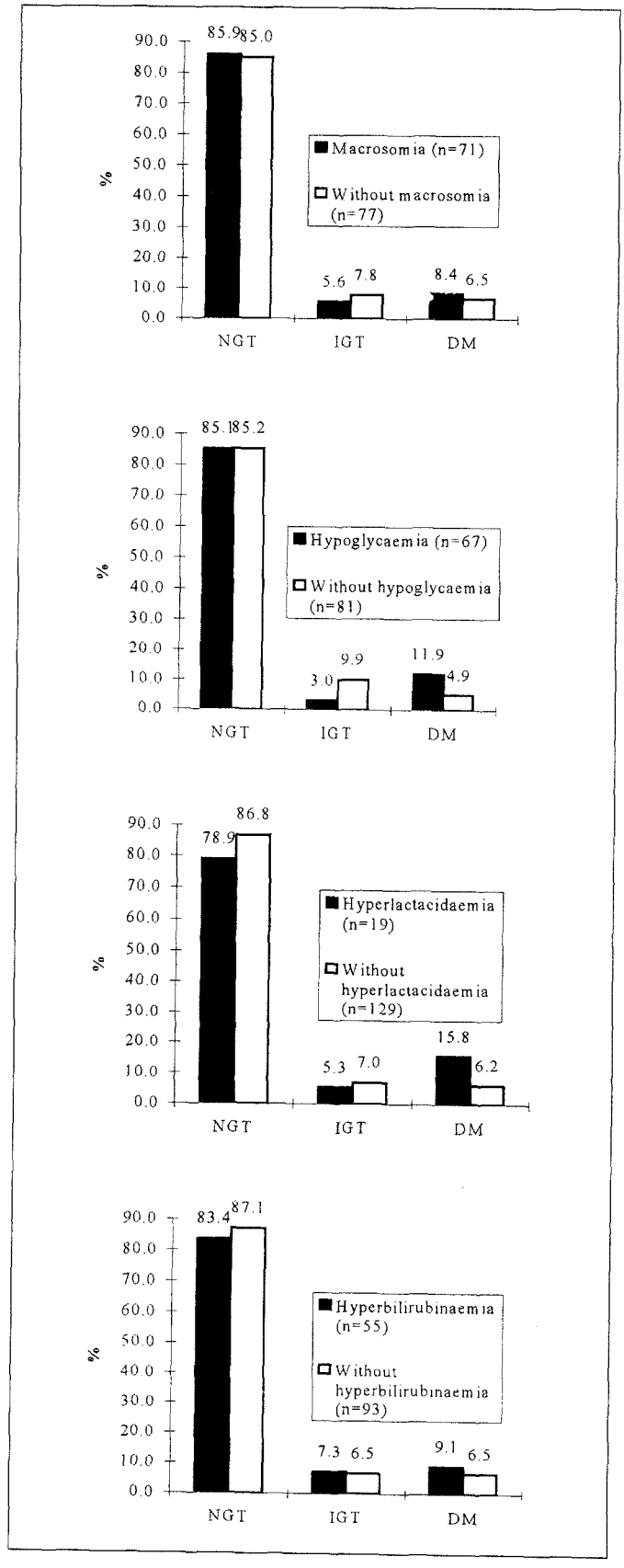


**Fig. 1** Disorders in newborns of diabetic mothers in relationship to their glucose tolerance in adulthood. Normal glucose tolerance (NGT; $n$=127), impaired glucose tolerance (IGT; $n$=10), diabetes mellitus (DM; $n$=11)

**Table 2** Relationship between different birth weights for gestational age in children of insulin-dependent diabetic mothers (CDM) and their condition in adulthood in comparison with control group (mean ± SE); diabetic CDM are not included in the table. All parameters in CDM with impaired glucose tolerance are higher than in the control group and in CDM with normal glucose tolerance. The results of the control group apply also to Tables 3, 4, 5

| | With macrosomia >95th centile | | Without macrosomia | | Control |
|---|---|---|---|---|---|
| Glucose tolerance: | Impaired | Normal | Impaired | Normal | |
| *n* | 4 | 61 | 6 | 66 | 31 |
| Sum of blood glucose (mmol/l) | 38.8 ± 1.6 | 28.7 ± 0.5*** | 41.4 ± 0.4 | 28.1 ± 0.4*** | 25.2 ± 0.4 |
| Sum of plasma insulin (pmol/l) | 2845 ± 567 | 2181 ± 150*** | 3093 ± 319 | 2019 ± 105*** | 1561 ± 109 |
| Body mass index | 26.1 ± 1.5 | 23.9 ± 0.4* | 27.6 ± 10 | 23.1 ± 0.4* | 22.2 ± 0.5 |
| Systolic blood pressure (mmHg) | 127.5 ± 3.2 | 117.4 ± 1.6** | 131.7 ± 6.1 | 115.7 ± 1.4** | 107.0 ± 2.6 |
| Diastolic blood pressure (mmHg) | 82.5 ± 1.4 | 70.8 ± 1.4** | 72.2 ± 4.5 | 69.3 ± 1.5** | 65.7 ± 1.9 |

Differences between CDM with normal glucose tolerance and control group: *$P$<0.05, **$P$<0.01, ***$P$<0.001

**Table 3** Relationship between CDM with and without neonatal hypoglycaemia and their parameters (mean±SE) in adulthood

| | With hypoglycaemia (G<1.66) | | Without hypoglycaemia | |
|---|---|---|---|---|
| Glucose tolerance: | Impaired | Normal | Impaired | Normal |
| *n* | 2 | 54 | 8 | 70 |
| Sum of blood glucose (mmol/l) | 39.7 ± 3.4*** | 27.8 ± 0.5 | 40.5 ± 1.7*** | 28.6 ± 0.4 |
| Sum of plasma insulin (pmol/l) | 3740 ± 210*** | 2053 ± 134 | 2900 ± 301* | 2117 ± 117 |
| Body mass index | 31.8 ± 2.1*** | 23.2 ± 0.4 | 26.5 ± 0.8 | 23.7 ± 0.4 |
| Systolic blood pressure (mmHg) | 120.0 ± 2.2 | 115.4 ± 1.8 | 131.3 ± 4.8** | 117.1 ± 1.4 |
| Diastolic blood pressure (mmHg) | 85.0 ± 1.8*** | 70.0 ± 14 | 74.6 ± 3.6 | 69.9 ± 1.4 |

*$P$<0.05, **$P$<0.01,***$P$<0.001

**Table 4** Relationship between children of diabetic mothers with and without neonatal hyperbilirubinaemia and their parameters (mean ± SE) in adulthood. No statistical differences were found between the CDM with and without hyperbilirubinaemia both in the groups with impaired and with normal glucose tolerance

| | With hyperbilirubinaemia | | Without hyperbilirubinaemia | |
|---|---|---|---|---|
| Glucose tolerance: | Impaired | Normal | Impaired | Normal |
| *n* | 3 | 47 | 7 | 80 |
| Sum of blood glucose (mmol/l) | 40.6 ± 1.3*** | 28.4 ± 0.6 | 40.4 ± 2.0** | 28.3 ± 0.4 |
| Sum of plasma insulin (pmol/l) | 3516 ± 305*** | 2136 ± 173 | 2875 ± 372* | 2069 ± 100 |
| Body mass index | 28.3 ± 2.2 | 23.4 ± 0.4 | 26.8 ± 0.9*** | 23.6 ± 0.3 |
| Systolic blood pressure | 125.0 ± 11.4 | 117.5 ± 1.9 | 132.9 ± 4.5*** | 115.9 ± 1.3 |
| Diastolic blood pressure | 70.0 ± 8.9 | 68.5 ± 0.5 | 77.7 ± 3.1* | 70.6 ± 1.2 |

*$P$<0.05, **$P$<0.01, ***$P$<0.001

lin values, BMI and blood pressure in adulthood, separately in CDM with IGT and NGT. No statistically significant differences were found between CDM with and without fetal macrosomia. The above-mentioned parameters in CDM were compared with the same parameters in the control group of the offspring of healthy mothers. In CDM with NGT, significantly higher values of the sum of glycaemia, sum of insulinaemia, BMI and blood pressure were found compared with the control group. The highest values of all measured parameters were noted in CDM with IGT.

Table 3 shows the relationship between neonatal hypoglycaemia and the condition of CDM in adulthood. Even though the average sum of glycaemia and insulinaemia, BMI and blood pressure are significantly higher in both CDM groups with NGT than in the controls (results of all measured parameters in the control group are presented in Table 2), the significantly higher values of sum of plasma insulin, BMI and diastolic blood pressure ($P$<0.05) were found only in CDM with IGT after neonatal hypoglycaemia compared with CDM without hypoglycaemia.

In the course of monitoring lactate levels at neonates, hyperlactacidaemia was found in 12% of NDM studied. No differences were seen in the parameters studied between the compared NGT groups with and without hyperlactacidaemia.

Studying the influence of neonatal jaundice, we evaluated parameters in adulthood (Table 4). We found no significant differences in the CDM groups compared.

In all CDM groups there were higher values of the sum of glycaemia, sum of insulinaemia, BMI and blood pressure compared with the controls (Table 2) and higher values of these parameters in CDM with IGT than in CDM with NGT ($P<0.05$–$0.001$).

## Discussion

Our detailed examination of CDM in the neonatal period [8, 10] made it possible to evaluate the relationship between individual parameters in newborns and in adults. The intrauterine environment plays an important role in the pathogenesis of disorders in newborns [1, 3, 4]. The complications of pregnant diabetic mothers influence the adaptation of the newborn, but they have no long-term impact on CDM in adulthood, as we recently described [11].

A relatively high occurrence of diabetes mellitus in our CDM can be explained by the fact that two siblings in two of the nine families with diabetes mellitus in offspring were affected. The percentage of IGT in this study corresponded well to those reported in other studies [4, 5].

Fetal insulin production influences fetal growth primarily through increasing fetal fat deposition [12]. Some association was found between overweight newborns and overweight children [1, 5]; in another study no relation was described [13]. We did not find a relation between BMI in adulthood and the degree of neonatal macrosomia, even though the BMI value in the whole CDM series was higher than in controls.

Another characteristic feature of NDM is a sudden drop in glycaemia after birth to hypoglycaemic values. Hypoglycaemia occurs in 2%–50% of NDM, exceptionally more frequently [1, 2]. Our results, given in Table 3, show that there was a relatively high frequency of hypoglycaemia in NDM in the past. Later, with improved care for pregnant diabetic women, the number of hypoglycaemic newborns in our institution decreased [10]. In spite of the fact that hypoglycaemia is frequent and characteristic for NDM and is connected with a number of metabolic disorders in the neonatal period, we did not find statistical differences between the state of CDM with NGT in adulthood with and without neonatal hypoglycaemia; statistical differences ($P<0.05$) in connection with neonatal hypoglycaemia were found only in the CDM group with IGT. Nevertheless, we found significantly higher blood glucose and insulin levels in the entire CDM group than in controls (Table 2): the question remains whether this is a result of a persisting hypertrophy and hyperplasia of the Langerhans islets, which may be connected with insulin resistance in peripheral tissues.

Fetal pancreatic beta-cell hyperplasia is implicated as one of the important pathogenetic factors of both fetal macrosomia and acidaemia. The association between fetal plasma insulin and blood pH has been reported [14]. In previous studies we found more prenatal and postnatal complicating factors and more psychomotoric disorders at the age of 3 years in a group of children with high lactate levels as newborns [10]. In adulthood, these offspring did not reveal any noticeable changes in the parameters studied as compared with CDM without neonatal lactacidaemia.

Hyperbilirubinaemia is observed more frequently in NDM than in normal neonates [1, 2]. Although a number of hypotheses have been put forward, the pathogenesis remains uncertain. Indirect evidence for fetal hypoxia may explain the neonatal polycythaemia and hyperbilirubinaemia with increased erythropoesis; there is also an association with relative hyperinsulinaemia at birth [15].

In conclusion, CDM differ from the children of healthy mothers not only as neonates, but also as adults. Even in CDM with NGT we found higher mean blood glucose and plasma insulin values in the course of OGTT, higher BMI and higher mean blood pressure. The highest values of all measured parameters were seen in CDM groups with IGT. Neonatal morbidity (macrosomia, hypoglycaemia, hyperlactacidaemia and hyperbilirubinaemia) does not correlate with the state of health in early adulthood, but in CDM with neonatal disorders the percentage with diabetes mellitus (Fig. 1) was insignificantly higher. With regard to the fact that similar findings concerning the relation between disorders in newborn and adult CDM have not been published yet, we consider it suitable to acquire additional information in a greater number of institutions. In our view it is important to study in future a new generation of CDM born to diabetic mothers while under intensive treatment for diabetes.

**Acknowledgement** This work was supported by the Internal Grant Agency of the Ministry of Health of Czech Republic N° 0048-3.

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Clinical and Experimental Diabetes and Metabolism
Journal of the European Association for the Study of Diabetes (EASD)

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DBTGAJ 39 (2) 129–250 (1996)
Printed on acid-free paper