HETEROGENEITY OF FETAL GROWTH IN TYPE 1 DIABETIC PREGNANCY


SUMMARY - Objective: To investigate the frequency of macrosomia in an homogeneous cohort of type 1 diabetic mothers and to analyze the influence of maternal factors and glycemic control on the incidence of fetal macrosomia.

Material and methods: Fifty-five consecutive type 1 diabetic first-pregnancies were prospectively studied. Macrosomia was defined by a ponderal index above the 90th percentile. Venous cord blood levels of insulin, C peptide and leptin were measured at delivery. The influence of HbA1c levels and other maternal variables on the occurrence of macrosomia and on the ponderal index was assessed using a stepwise regression logistic model.

Results: The mean (± SD) birth weight was 3482 (± 497) g at 37.4 ± 1.0 weeks gestation. Macrosomia occurred in 29 cases (53.7%). Fetal insulin, C peptide and leptin levels were significantly higher in macrosomic than in non macrosomic infants. Maternal age, duration of diabetes, pregravid body mass index, parity, weight gain during pregnancy, presence of a microangiopathy, nephropathy, smoking habits, gestational hypertension or preeclampsia, and HbA1c levels throughout pregnancy did not differ between mothers of macrosomic and non macrosomic infants. In the stepwise analysis none of these covariates was explanatory of the ponderal index.

Conclusions: The frequency of macrosomia remains very high in infants of type 1 diabetic mothers despite a reasonable degree of glycemic control. The variability of the fetal growth response to mild hyperglycemia prompts for the identification of other factors involved in the modulation of fetal growth.

Key-words: fetal macrosomia, pregnancy, type 1 diabetes mellitus.

RÉSUMÉ - Hétérogénéité de la croissance fœtale chez les femmes diabétiques de type 1.

Objectif : Évaluer la fréquence de la macrosomie dans une cohorte homogène de femmes ayant un diabète de type 1 et analyser l’influence des facteurs maternels et du contrôle glycémique sur la survenue d’une macrosomie.

Matériels et méthodes : Suivi prospectif de 55 premières grossesses consécutives. La macrosomie a été définie par un index pondéral supérieur au 90e percentile. Les concentrations ombilicales en insuline, peptide C et leptine ont été mesurées à l’accouchement. L’influence de l’HbA1c et des facteurs maternels sur la survenue d’une macrosomie a été réalisée en utilisant un modèle de régression logistique pas à pas.

Résultats : Le poids de naissance moyen (± 1 DS) était 3482 (± 497) grammes à 37,4 (± 1,0) semaines d’aménorrhée. Vingt-neuf (53,7 %) enfants étaient macrosomes. Les concentrations ombilicales d’insuline, peptide C et leptine étaient significativement plus élevées chez les macrosomes que chez les non macrosomes. Il n’y avait pas de différence entre ces 2 groupes sur l’âge maternel, l’ancienneté du diabète, l’existence d’une microangiopathie, l’index de masse corporelle pré-conceptionnel, la parité. Au cours de la grossesse, la prise de poids, la fréquence de survenue d’une pré-éclampsie et les taux d’HbA1c étaient comparables dans les 2 groupes.

Conclusions : Aucun des paramètres étudiés ne permet d’expliquer la persistance d’une incidence élevée de macrosomie malgré un contrôle glycémique comparable dans les 2 groupes. Ceci suggère que d’autres facteurs sont des déterminants importants du poids de naissance.

Mots-clés : macrosomie, grossesse, diabète de type 1.
Macrosomia is still a major concern in diabetic pregnancy. Despite a general agreement that fetal hyperinsulinism, due to maternal hyperglycemia, is a main determinant of fetal overgrowth in diabetic pregnancy [1], a clear correlation between maternal glycemia and birth weight has not been established. Clinical studies have reported confusing results showing correlations between the occurrence of macrosomia and glycated hemoglobin (HbA1c) measured either in early pregnancy [2-4] in the third trimester [5], or at delivery [6]. Others have reported that macrosomia was more strongly associated with maternal postprandial glucose levels than with the corresponding fasting glucose or HbA1c levels [7, 8].

One reason for such discrepancies may be the lack of unique definition of macrosomia [9] which would allow to compare the incidence of macrosomia between different series. Macrosomia has been defined as a birth weight above 4000 or above 4500 grams, or as large for gestational age, i.e., above the 90th percentile of birth weight for gestational age. However a definition based on birth weight and gestational age is inaccurate since the phenotype of macrosomic infants is variable. Indeed, macrosomic infants of diabetic mothers are characterized by asymmetric overgrowth [10], increased fat mass [11, 12] and hyperinsulinaemia. The ponderal index (weight in grams X 100/length^3 in centimeters) [13] has been shown to delineate asymmetric fetal overgrowth [14] associated with metabolic abnormalities and increased neonatal morbidity in type 1 diabetic pregnancies [10].

However, despite improved glycemic control before and during pregnancy the incidence of fetal macrosomia is still high in type 1 diabetic pregnancy. A complete and coherent hypothesis is still lacking and the role of factors other than the degree of maternal glycemic control has been suggested [8, 15].

The present study was designed to investigate whether maternal factors, including glycemic control, influence the occurrence of fetal macrosomia.

## METHODS

This prospective study involved 55 women with type 1 diabetes consecutively followed for their pregnancy in the Department of Obstetrics and Gynecology, Cochin – Saint Vincent-de-Paul Hospital. In order to avoid statistical bias due to a mother effect only first pregnancies were considered. All protocols were approved by the institutional ethics review board of Cochin Hospital, Rene Descartes University, and all the mothers gave their informed consent.

Neonatal anthropometric measurements at birth included weight on a calibrated scale, length on a measuring board and head circumference with a measuring tape. Gestational age at delivery was determined from the date of the last menstrual period and was confirmed by first-trimester ultrasonography. Birth weight according to gestational age was used to define appropriate for gestational age (AGA) and large for gestational age (LGA) infants according to the French growth standard curves [16]. The ponderal index (weight x 100/length^3) was used to define macrosomia: infants whose ponderal index was above the 90th percentile (2.85 g/cm^3) [13] were classified as macrosomic, and infants whose ponderal index was between the 10th and 90th percentiles were classified as non macrosomic. Neonatal hypoglycemia was systemically prevented by the injection of glucagon (0.3 mg/kg) at birth. Neonatal hypoglycemia was defined as the occurrence of a serum glucose level of less than 40 mg/dl (2.2 mmol/l) despite prevention.

Fetal blood samples were collected from the umbilical cord at delivery. The blood was immediately centrifuged and serum was stored at –20°C until analysis. Blood glucose was measured by using the glucose oxidase method. Serum insulin and C peptide were measured by radioimmunoassay using reagents provided by CIS BIO International (Gif-sur-Yvette, France). Serum leptin was measured by radioimmunoassay (Linco Research, St.Charles, MO).

Maternal clinical data included age, parity, smoking habit, duration of diabetes, and microangiopathy. Maternal anthropometric measurements during pregnancy included pregravid body mass index and weight gain during pregnancy. A corrected maternal weight gain excluding birth weight and placental weight from the maternal weight gain component during pregnancy was also calculated.

All women were informed about the need for preconception optimization of glycemic control. Preconception care included assessment of diabetic complications, review of dietary habits, intensification of capillary blood glucose self-monitoring (before and 2 hours after each of the three main meals) and optimization of insulin therapy. All women were treated with 3 to 4 daily insulin injections or with continuous subcutaneous infusion using an external pump. Capillary blood glucose target values were < 95 mg/dl (5.3 mmol/L) before meals and < 120 mg/dl (6.7 mmol/L) 2-hours postprandial. Diabetic microangiopathy was defined by the presence of retinopathy on fundus examination and/or on fluorescein retinoangiography as background, pre proliferative or proliferative. Diabetic nephropathy was defined on the basis of excess microalbuminuria or proteinuria. Hypertension was defined as a sustained diastolic blood pressure over 90 mm Hg, preeclampsia as the association of hypertension and proteinuria > 300 mg/24 hours. During pregnancy women were seen every other week at the diabetes clinic and joined a member of the team by phone as often as needed. HbA1c was measured in the preconception period, at booking and every four weeks during pregnancy. HbA1c was measured by HPLC (normal 4.9 ± 0.6%). During labor and delivery
intravenous infusions of glucose and insulin were used with hourly blood glucose monitoring (with a target of 80 to 140 mg/dl).

Categorical data were comparing using Chi-square test. Quantitative data were compared using analysis of variance. Results were expressed as mean ± SD. A stepwise logistic regression model was used to test the effect of covariates on macrosomic status and on ponderal index as a continuous variable to be explained. Covariates introduced in the model were maternal age, pre-pregnancy body mass index, parity, corrected weight gain during pregnancy, diabetes duration, presence of a microangiopathy, insulin daily requirement and increment, smoking habit, gestational hypertension or preeclampsia, and HbA1c. Analysis were performed using SAS statistical software.

## RESULTS

Out of 55 infants, one infant with congenital malformations was excluded from analysis in order to avoid confounding influence of fetal parameters. In the 54 remaining infants the mean (± SD) birth weight was 3482 (± 497) g at 37.4 ± 1.0 weeks of gestation. Two infants (3.7%) had a birth weight above 4500 g, eleven (20.4%) had a birth weight above 4000 g, and 28 (51.9%) had a birth weight above the 90th percentile for gestational age. In our study population, the ponderal index ranged from 1.91 to 3.44 g/cm³. Twenty-nine (53.7%) infants had a ponderal index above the 90th percentile and were classified as macrosomic, 25 (46.3%) had a ponderal index below the 90th percentile and were classified as non macrosomic. No infant had a ponderal index below the 10th percentile. The clinical data of the 54 infants are given in Table I. Placental weight, birth weight and head circumference were significantly higher in macrosomic than in non macrosomic infants. Birth length did not differ between the two groups.

Neonatal hypoglycemia occurred in 9 macrosomic infants and in 3 non macrosomic infants (p = 0.08).

Cord blood insulin and C peptide levels were determined in 24 infants and were significantly higher in macrosomic (n = 15) than in non macrosomic (n = 9) infants, respectively 66.1 ± 18.2 µU/ml vs 16.1 ± 2.1 µU/ml (p = 0.0003), and 1.7 ± 0.5 mmol/ml vs 0.5 ± 0.1 mmol/ml (p = 0.0008). Mean leptin concentrations were significantly higher in macrosomic (37.6 ± 7.5 ng/ml) than in non macrosomic infants (11.1 ± 3.3 ng/ml) (p = 0.004).

Maternal clinical data are shown on Table II. There was no significant difference between mothers of macrosomic and non macrosomic infants concerning age, parity, pregravid body mass index. Although weight gain was greater in the mothers who delivered macrosomic infants, the difference was no longer significant when using corrected values excluding birth weight and placental weight from the maternal weight gain component. Diabetic retinopathy was present in 24 women (background: 16, pre proliferative: 3, proliferative: 5), diabetic nephropathy in 4 (incipiens: 3, mild renal insufficiency: 1), chronic hypertension (i.e. preconceptional) in 4. There was no significant difference in the duration of diabetes, the prevalence of microangiopathy, including nephropathy, the frequency of preconceptional care, HbA1c levels at booking and during pregnancy, insulin requirements at booking (0.72 ± 0.18 versus 0.71 ± 0.30 UI/Kg/day) and increase during pregnancy (0.27 ± 0.22 versus 0.30 ± 0.27 UI/Kg/day). Monthly HbA1c were available in 47 pregnancies, and there was no difference in values at each point in mothers of macrosomic versus non macrosomic infants (Table III). No correlation was observed between the ponderal index and the mean HbA1c level during pregnancy (r = 0.11). Finally, the occurrence of gestational hypertension and preeclampsia was similar in both groups (17%). In the multivariate analysis, none of the studied covariates was associated with macrosomia, particularly HbA1C. In the stepwise multivariate regression analysis in which the ponderal index was considered as the continuous variable to be explained and the various above cited covariates as explanatory, none of the covariates entered the model. During labor, mean maternal glycemia were not different between both groups (127 ± 29 vs 122 ± 24 mg/dl).

## DISCUSSION

In this study including 54 infants of type 1 diabetic mothers, the occurrence of macrosomia could not be

### Table I. Clinical data of macrosomic and non macrosomic infants of type 1 diabetic mothers.

<table>
<thead>
<tr>
<th></th>
<th>Macrosomic n = 29</th>
<th>Non macrosomic n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ponderal index (g/cm³)</td>
<td>3.13 ± 0.16 *</td>
<td>2.65 ± 0.21</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>37.5 ± 0.8</td>
<td>37.2 ± 1.3</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3 681 ± 367 *</td>
<td>3 132 ± 411</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>48.9 ± 1.5</td>
<td>49.0 ± 1.9</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>35.0 ± 1.3</td>
<td>34.1 ± 1.2</td>
</tr>
<tr>
<td>Placental weight (gm)</td>
<td>765 ± 134 *</td>
<td>603 ± 141</td>
</tr>
</tbody>
</table>

Macrosomic infants were compared with non macrosomic infants. Values are mean ± SD. (* p < 0.0001; 1 p < 0.001).
explained by maternal factors, including HbA1c levels throughout pregnancy.

Insulin, C peptide and leptin cord blood levels were significantly higher in macrosomic than in non macrosomic infants. Hyperinsulinemia is a well described characteristic of the macrosomic infant of diabetic mother, and we have previously shown that leptin is also a marker of asymmetric macrosomia [14], which is in keeping with the fact that fetal fat mass is a major determinant of fetal circulating leptin [17]. These results indicate that the infants that we have classified as macrosomic actually had pathological fetal overgrowth.

The rate of macrosomic infants in our study may seem extremely high. In fact, in the literature, the prevalence of macrosomia in diabetic pregnancy varies greatly according to the definition used. It ranged from 24 to more than 50% when the 90th percentile for gestational age was used as a threshold [5, 7, 8, 18]. According to this definition, 51.9% infants were macrosomic in our study. Among the infants born to women intensively treated in the DCCT (Diabetes Control and Complications Trial) 10.9% had a birth weight above 4500 g [19], compared to 3.7% in our series. Furthermore the mean (± SD) birth weight of these infants was 3657 (± 765) g at 37.1 ± 1.9 weeks of gestation, very similar to that in our study, suggesting that a high percentage of infants were actually macrosomic. It should be pointed out that in our study mensal measures of HbA1C were similar to those reported in the intensive treatment group of the DCCT [19].

The persistence of a high rate of macrosomia in type 1 diabetic pregnancies is not unexpected since it is admitted that maternal hyperglycemia induces fetal hyperinsulinemia [1] and fetal overgrowth [20]. Indeed, maternal hyperglycemia, even when minimal, is associated with an increase in the incidence of fetal macrosomia in non diabetic pregnancies [21], and in gestational diabetes mellitus [22]. In type 1 diabetic pregnancies, even in women intensively treated with

| TABLE II. Clinical data of the mothers of macrosomic and non macrosomic infants. |
|-------------------------------------------------|-----------------|-----------------|
| Family data                                      | Macrosomic n = 29 | Non macrosomic n = 25 |
| Maternal age (years)                            | 29.3 ± 4.8       | 29.9 ± 6.1       |
| Parity                                          | 0.3 ± 0.5        | 0.4 ± 0.6        |
| Duration of diabetes (years)                    | 15.2 ± 7.4       | 13.4 ± 8.7       |
| Microangiopathy                                 | 14              | 10              |
| Smoking habit                                   | 7               | 5               |
| Preconceptional care                            | 19              | 19              |
| Pregestational BMI (Kg/m²)                      | 22.8 ± 2.6       | 22.2 ± 1.9       |
| Weight gain (Kg)                                | 14.2 ± 3.6*      | 12.4 ± 4.7       |
| Corrected weight gain (Kg)                      | 9.9 ± 3.6        | 8.6 ± 4.6        |
| HbA1c at booking                               | 7.4 ± 1.0        | 7.6 ± 1.1        |
| Mean HbA1c during pregnancy                     | 6.5 ± 0.8        | 6.5 ± 1.0        |
| HbA1c nadir during pregnancy                    | 5.8 ± 0.7        | 5.8 ± 0.7        |
| Gestational hypertension or preeclampsia        | 5               | 4               |
| Cesarean section                                | 26 *            | 12              |

Mothers of macrosomic infants were compared with mothers of non macrosomic infants. The corrected weight gain excludes birth weight and placental weight from the maternal weight gain component during pregnancy. All values are mean ± SD. (* p < 0.05).

| TABLE III. HbA1c at booking and monthly values in 47 type 1 diabetic mothers of 27 macrosomic and 20 non macrosomic infants. |
|-------------------------------------------------|-----------------|-----------------|
| Booking                                         | 2-6w | 7-10w | 11-15w | 16-19w | 20-24w | 25-28w | 29-32w | 33-37w | Mean | Nadir |
| Macrosomic (n=27)                               | 7.5 ± 1.1 | 7.2 ± 1.1 | 7.2 ± 0.8 | 6.7 ± 0.8 | 6.8 ± 1.4 | 6.3 ± 0.8 | 6.2 ± 0.7 | 6.2 ± 0.6 | 6.3 ± 0.8 | 6.7 ± 0.9 | 5.9 ± 0.8 |
| Non macrosomic (n = 20)                         | 7.5 ± 1.1 | 8.3 ± 3.1 | 7.2 ± 1.9 | 6.7 ± 1.3 | 6.3 ± 0.8 | 6.2 ± 0.8 | 6.3 ± 0.8 | 6.2 ± 0.8 | 6.1 ± 0.8 | 6.6 ± 1.0 | 5.9 ± 0.8 |
| p                                               | 0.77         | 0.54         | 0.33         | 0.69         | 0.30         | 0.61         | 0.91         | 0.52         | 0.54         | 0.54         | 0.77         |

HbA1c at booking and monthly values were compared in 47 type 1 diabetic mothers. w: weeks of gestation. All values are mean ± SD. The 8.3 ± 3.1 level at 2-6w is due to one patient who presented with an extremely high HbA1c (16.9%).
insulin, glycemic control is not normal and HbA1c values are above the normal range for pregnancy [4, 19, 23].

A puzzling issue is the reason why the infants of type 1 diabetic mothers are not all macrosomic. We thus assessed the effect of various maternal factors on the occurrence of macrosomia. In the multivariate analysis, none of the studied covariates was associated with macrosomia. Particularly, we did not observe any difference, at any time of the pregnancy, in the HbA1c levels of mothers of macrosomic and non macrosomic infants, and any correlation between the ponderal index and the mean HbA1c level during pregnancy. Moreover, the stepwise analysis showed that no covariable could explain the ponderal index or the birth weight as a continuous variable. This is in keeping with a study of 65 type 1 diabetic mothers showing that HbA1c accounted for only 23% of the variance in birth weight [3]. A potential limitation of our study is that we have not recorded capillary blood glucose values throughout pregnancy and that HbA1c may not reflect transitory hyperglycemic excursions which have been associated with the occurrence of macrosomia [7, 8]. However, given the HbA1c values measured in our study it is very likely that postprandial glucose levels were abnormal, even in women who delivered non macrosomic infants.

These observations strongly suggest that factors other than glycemic control are involved in the regulation of fetal growth. Other fuels may be supplied to the fetus in abnormal proportions in diabetic pregnancy. Within an apparently homogeneous cohort of diabetic mothers. These observations clearly prompt for the identification of additional factors involved in the control of fetal growth.

**REFERENCES**


