

## Should we treat minor degrees of glucose intolerance in pregnancy?

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**Summary.** - We examined the pregnancy outcome of 112 women classified as minor degrees of glucose intolerance (MDGI) in pregnancy in a screening program based on Carpenter and Coustan's criteria. The MDGI group comprised 49 women with abnormal oral glucose challenge test (OGCT) followed by normal OGTT (group A), and 63 with "borderline" OGTT (1 abnormal value, group B). No treatment was offered to 88 MDGI women, while 26 received dietary advice and metabolic monitoring. A control group was constituted from 112 age- and BMI-matched negative screenees. Similar rates of cesarean sections and macrosomia, but higher rate of large for gestational age (LGA) babies (25.9% vs 14.3%) were found in MDGI, without difference between groups A and B. When comparing treated and untreated MDGI, lower LGA incidence (11.5% vs 30.2%) and no macrosomia were found in the former. In conclusion, untreated MDGI may present excessive fetal growth, which can be normalized by dietary treatment and metabolic monitoring.

**Key words:** minor degrees of glucose tolerance, macrosomia, LGA, screening of gestational diabetes.

**Riassunto** (*Trattare o non trattare le alterazioni minori del metabolismo glucidico in gravidanza?*). - Allo scopo di valutare l'entità clinica di alcune alterazioni minori della tolleranza glucidica in gravidanza (AMTGG), e una eventuale indicazione al trattamento, abbiamo esaminato l'esito della gravidanza in 112 donne classificate come AMTGG in un programma di screening basato sui criteri di Carpenter e Coustan. La casistica comprendeva 49 donne con OGCT elevato e normale OGTT (gruppo A), e 63 con un solo valore OGTT elevato (gruppo B). In 88 donne non è stato impostato alcun trattamento, mentre 26 sono state seguite con dieta e periodici controlli clinici e metabolici. Rispetto a un gruppo di controllo di 112 donne negative allo screening, nel gruppo AMTGG si è registrata una incidenza simile di tagli cesarei e di macrosomi, ma più elevata di neonati LGA (25.9% vs 14.3%), senza differenza fra i gruppi A e B. Nelle AMTGG trattate non si è registrata macrosomia, e il tasso di LGA è risultato inferiore alle non trattate (11.5% vs 30.2%). In conclusione, in presenza di AMTGG si registra una tendenza alla eccessiva crescita fetale, controllabile con trattamento dietetico e monitoraggio clinico-metabolico.

**Parole chiave:** alterazioni minori della tolleranza glucidica in gravidanza, macrosomia, LGA, screening del diabete gestazionale.

### Introduction

There is now general agreement, among both diabetologists and obstetricians [1-3], on the utility of universal screening, diagnosis and treatment of overt forms of gestational diabetes mellitus (GDM).

This is due, in part, to the high rates of perinatal mortality and morbidity encountered in the past in pregnancy complicated by undetected or untreated GDM [4-6] and, on the other hand, to the persistence of an excess risk for perinatal complications (namely macrosomia), reported in more recent studies, concerning treated forms of the disease [7].

Consensus is still lacking, however, on the approach to be adopted in front of minor alterations of glucose tolerance in pregnancy (minor degrees of glucose intolerance, MDGI), comprising several clinical situations characterized by a glycometabolic status intermediate between normality and overt GDM.

A univocal definition of this nosological category is actually hindered by the lack of uniformity on diagnostic criteria for GDM still existing among various centers. Most published data [8-12] refer to diagnostic procedures based on NDDG criteria for 100 g OGTT [13], where MDGI are identified with: a) abnormal 50 g challenge test followed by normal OGTT; b) OGTT with one

abnormal value; c) impaired gestational glucose tolerance (IGGT), with 2 h plasma glucose level 120 to 164 mg/dl. Other authors, using 75 g OGTT WHO criteria [14], or 100 g OGTT Amankwah criteria [15], also focused on women with glycemic values exceeding normal limits, without reaching diagnostic threshold for GDM [16].

In spite of this diagnostic heterogeneity, in many reports these clinical situations seem correlate with an increased rate of adverse obstetrical and perinatal outcomes, in terms of cesarean sections, length of gestation, excessive fetal growth with subsequent neonatal macrosomia.

Only few data [17], however, are relevant to MDGI classified according to more selective Carpenter and Coustan's criteria [18], recently adopted in Italy [2] and in other countries: due to lower glycemic thresholds requested for the diagnosis of GDM, this borderline group results characterized by even milder metabolic abnormalities.

As far as the general management strategy subsequent to diagnosis is concerned, little is known about the effect of metabolic control on perinatal outcome of pregnancies complicated by MDGI: actually most women are still left untreated and reassured after a non-pathological diagnostic test.

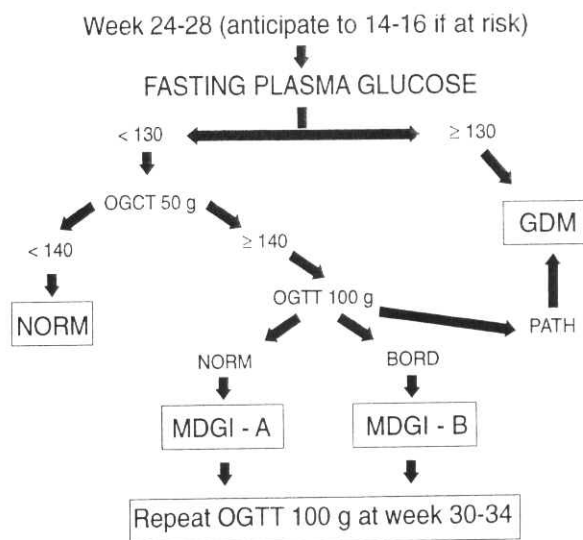
This attitude, while offering us a unique opportunity to get insight into the natural history of glucose intolerance in pregnancy, should be re-evaluated if a more active approach to treatment proves useful in reducing perinatal morbidity. In fact, Langer *et al.* [10] and Berkus and Langer [11] reported positive results of diet and insulin treatment in women with one abnormal OGTT value; both studies, however, evaluated OGTT according to NDDG diagnostic criteria, less selective than Carpenter and Coustan's criteria.

The aim of the present study was therefore double: a) to evaluate the impact on pregnancy outcome of forms of MDGI diagnosed by Carpenter and Coustan's OGTT criteria (now extensively used in many countries, Italy included, where they are recommended by diabetologic and obstetric scientific societies); b) to study the value of a program of dietary treatment and regular metabolic monitoring, in reducing perinatal risks in pregnancies complicated by these metabolic abnormalities.

## Methods

### Screening protocol

Study subjects were recruited through a screening procedure performed at our Diabetic Center from 1989 to 1995. In this period more than 1200 pregnant women were screened for carbohydrate intolerance, following a protocol illustrated in Fig. 1. For those with standard risk factors for the disorder, the screening was performed



**Fig. 1.** - Screening protocol for glucose intolerance in pregnancy used in the present study. On the basis of Carpenter and Coustan's criteria OGTT was classified as normal (NORM) when all values were within the normal range, borderline (BORD) when only one value resulted above the normal range, pathological (PATH) when two or more values resulted above the normal range. Two categories of minor degrees of glucose intolerance in pregnancy (MDGI) were considered: abnormal OGCT followed by normal OGTT (MDGI-A), and abnormal OGCT followed by borderline OGTT (MDGI-B).

from 14 to 16 week of gestation; women with a normal screening test were re-tested from 24 to 28 week, when all women without risk factors were also tested.

The screening procedure consisted of a 50 g oral glucose challenge test (OGCT), with a 1 h glycemic cut-off set at 140 mg/dl. Positive-screened women underwent a confirmatory 100 g OGTT within 7 days, evaluated by NDDG diagnostic criteria, as modified by Carpenter and Coustan (normal values: 95-180-155-140 mg/dl).

### Classifications and subjects

We considered as having MDGI all women presenting one of these characteristics at screening:

- elevated OGCT, followed by normal OGTT (group A);
- OGTT with only one value exceeding normal values (group B).

In the study period, 144 screened women met above mentioned criteria for MDGI, but only 112, with complete maternal, obstetrical and neonatal data available were considered in the study.

Group A resulted composed of 49 women, group B of 63 women.

Of the 63 group B subjects, 22 (34.9%) had the abnormal value at time 0 min, 31 (49.2%) after 1 h, 6 (9.5%) after 2 h, and only 4 (6.3%) after 3 h.

A control group of 112 BMI- and age-matched, randomly selected pregnant women, normal at screening, was also considered.

The results of the challenge test in MDGI as a group was  $151.7 \pm 10.4$  mg/dl, significantly higher than in control subjects ( $125 \pm 10.0$  mg/dl), whereas no difference was found between A ( $153.6 \pm 11.7$  mg/dl) and B ( $149.9 \pm 9.9$  mg/dl) subgroups.

The clinical characteristics of studied subjects are summarized in Table 1.

MDGI and control women were similar for age, parity, BMI; the test was performed at about the same period in the 2 groups; there was a difference, although non significant, in the percentage of women presenting standard risk factors for GDM.

No significant differences were found between the A and B subgroups of MDGI.

### Management

The type of management adopted with these women changed in the course of the study period, so that two different models of clinical approach are recognizable.

In the first period of the study, from 1989 to 1993, all MDGI women were reassured after testing, and were given no special care, diet or insulin therapy. From January 1994 on, because of preliminary observations on perinatal morbidity in this group, all diagnosed MDGI women were given dietary advice (25-30 kcal/kg/day), and entered an out-patient management protocol which involved visits every 2 weeks, with evaluation of main clinical parameters (weight, blood pressure, etc.), and measurement of fasting and 2 h post-prandial glycemic levels, HbA1c, and fructosamine. Glycemic targets were set at the same level as for GDM:  $< 90$  mg/dl fasting,  $< 120$  mg/dl post-prandial.

When we compared treated (T) and non-treated (NT) MDGI women, they resulted almost identical for age ( $30.6 \pm 4.3$  vs  $30.9 \pm 3.8$  years), BMI ( $24.2 \pm 5.6$  vs  $24.1 \pm 4.1$  kg/m<sup>2</sup>); differences were present as far as gravidity (51.1% primiparous in NT, 34.6% in T) and percentage of subjects at risk (50.0% in NT, 69.2% in T) are concerned.

### Analysis of data

In the evaluation of pregnancy outcome, newborns weighing  $\geq 4000$  g at birth were classified as "macrosomes"; newborns with weight at birth  $\geq 90$ th percentile were classified as large for gestational age (LGA).

Statistical analysis was performed using the t test for continuous variables, and the  $\chi^2$  test for discontinuous variables.

Statistical significance was set at  $p < 0.05$ .

### Results

Looking at the pregnancy outcome (Fig. 2), MDGI women, as a group, regardless of the type of management received, showed a rate of macrosomia, and cesarean section, similar to control subjects; also gestational age and mean birth weight (not reported here) were similar; no cases of low APGAR score (less than 7) were found. On the other hand, a statistically significant higher rate of LGA infants was found in the MDGI patients (without difference between group A and B) than in the control subjects.

The effect of therapeutic intervention in MDGI (that is in the treated group, T, followed from 1994 on) on metabolic control resulted in a clear-cut improvement obtained in both fasting (from  $86.9 \pm 10.1$  mg/dl at diagnosis, to  $75.0 \pm 9.6$  mg/dl, mean from diagnosis to delivery) and post-prandial glycemia (from  $109.2 \pm 10.5$  to  $91.3 \pm 12.3$  mg/dl), while HbA1c and fructosamine remained unchanged (from  $4.1 \pm 0.5$  to  $4.3 \pm 0.5\%$ , and from  $2.27 \pm 0.4$  to  $2.24 \pm 0.4$  mmol/l, respectively).

A comparison with non-treated MDGI and with normal subjects had to be limited to the evolution of fasting glycemia, the only glycometabolic index available in these groups. As a consequence of therapeutic intervention, an evident decrease of fasting glycemia (from  $86.9 \pm 10.1$  mg/dl at diagnosis to  $76.0 \pm 9.8$  mg/dl at delivery) occurred in the treated group, resulting in values at delivery lower than in NT patients, and even lower than in control women.

**Table 1.** - Maternal clinical characteristics according to study groups

|                          | MDGI-A<br>no. 49 | MDGI-B<br>no. 63 | MDGI-all<br>no. 112 | Controls<br>no. 112 |
|--------------------------|------------------|------------------|---------------------|---------------------|
| Age (years)              | $30.6 \pm 3.4$   | $30.7 \pm 4.8$   | $30.6 \pm 4.2$      | $29.8 \pm 4.2$      |
| Primiparous (%)          | 51.0             | 44.4             | 47.3                | 45.5                |
| BMI (kg/m <sup>2</sup> ) | $23.1 \pm 4.4$   | $25.0 \pm 5.7$   | $24.2 \pm 5.2$      | $23.6 \pm 4.4$      |
| Week of test             | $27.6 \pm 3.5$   | $29.7 \pm 3.3$   | $28.7 \pm 3.5$      | $27.2 \pm 3.3$      |
| At risk (%)              | 44.9             | 61.9             | 54.5                | 45.5                |

When the pregnancy outcome in T and NT groups were compared, in the treated group no macrosomic babies were found, and the percentage of LGA newborns resulted significantly lower (11.5% in T, 30.2% in NT); on the contrary, the rate of cesarean sections was similar in the two groups (26.9% in T, 29.1% in NT).

## Discussion

Many reports suggest that also minor degrees of glucose intolerance in pregnancy, like overt GDM, are associated with increased perinatal morbidity, namely excessive fetal growth resulting in abnormally high rates of LGA newborns [8-12, 15]. This finding, relevant to pregnant women presenting a borderline metabolic situation when evaluated by classic NDDG diagnostic criteria [13], is here confirmed in a population of MDGI classified on the basis of Carpenter and Coustan's criteria [18], in use in Italy and other countries [2].

Actually, our data show that also the very mild metabolic abnormality identified by means of this more restrictive diagnostic procedure is characterized by an incidence of LGA babies significantly higher than in normal pregnancies. No difference is found, in this regard, between women with type A (abnormal 50 g challenge test, followed by normal OGTT) and type B alteration (only one abnormal value in OGTT). This apparently disagrees with previous data of Berkus and Langer [11] signaling a worse pregnancy outcome in type B patients; because of the modification occurred in interpretative criteria, however, the metabolic

derangement identified in type B patients has become milder than before, so that the two groups are now very similar.

The confirmed finding of an excessive perinatal risk consequent to MDGI, raises the problem of the therapeutic approach to be held in front of this nosographic entity: our results strongly support the utility of treatment, based on dietary regimen and regular metabolic monitoring starting at diagnosis.

Compared with untreated subjects observed in the first period of our study, the MDGI group followed in years 1994-95 with diet and frequent clinical and metabolic controls presented a net improvement in pregnancy outcome, resulting in normalization of the incidence of macrosomic and LGA newborns.

In conclusion, our findings support the hypothesis that, when considering glycometabolic homeostasis in pregnancy, a dichotomous separation between normality and GDM is no more maintainable. Indeed, also when new, more restrictive parameters for diagnosing GDM are adopted, an intermediate area of minor glycemic intolerance is recognizable, still conditioning excessive fetal growth and augmented incidence of LGA newborns.

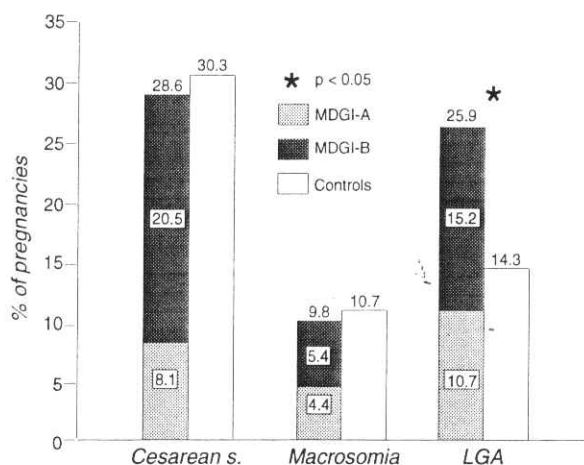
As these perinatal complications may be effectively prevented or minimized by simple and non-invasive therapeutic measures, the non-interventionist attitude usually adopted in the past towards MDGI appears at present no longer acceptable.

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**Fig. 2.** - Pregnancy outcome (incidence of cesarean section, macrosomia, LGA newborns) in women with MDGI and in control subjects. The MDGI population is also divided in groups A and B, according to the type of metabolic alteration.

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