Ann. Ist. Super. Sanità, vol. 33, n. 3 (1997), pp. 307-311

Congenital malformations in infants of 517 pregestational diabetic mothers

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Summary. - To determine whether the maternal metabolic control and/or the use of hypoglycemic drugs during early gestation is associated with a risk of congenital malformations, beginning on January 1989 to December 1994, clinical data from 16 Italian centers were collected retrospectively and entered in a computerized data base: 517 pregnant women with pregestational diabetes mellitus, 362 with insulin-dependent diabetes mellitus (IDDM) (mean age 28.13 ± 4.8 years), 130 with non insulin-dependent diabetes mellitus (NIDDM) (mean age 33.01 ± 5.32 years) and 25 with impaired glucose tolerance (IGT) (mean age 32.48 ± 6.2 years). The percentage of congenital malformations in NIDDM that took oral hypoglycemic drugs was 11.6% respect to 1.4% of NIDDM that did not take hypoglycemic drugs ($p < 0.01$) and 3.7% of IDDM. Fasting blood glucose, glycosylated hemoglobin and urine keton bodies were more elevated in IDDM respect to NIDDM ($p < 0.005$). The percentage of malformations in offspring of NIDDM mothers is higher with respect to that of IDDM women, in spite of a better metabolic control.

Key words: oral hypoglycemic drugs, insulin-dependent diabetes mellitus, non insulin-dependent diabetes mellitus, pregnancy, congenital malformations.

Riassunto *(Malformazioni congenite nei figli di 517 madri con diabete pregestazionale).* - Per indagare se il compenso metabolico e/o l'uso degli ipoglicemizzanti orali durante l'embriogenesi possono influenzare la comparsa di malformazioni congenite, sono stati raccolti dal gennaio 1989 al dicembre 1994, i dati clinici provenienti da 16 centri italiani relativi a 517 donne gravide affette da diabete mellito prima del concepimento: 362 con diabete mellito insulino-dipendente (IDDM) (età media 28,13 ± 4,8 anni), 130 con diabete mellito non insulino-dipendente (NIDDM) (età media 33,01 ± 5,32 anni) e 25 con ridotta tolleranza al glucosio (IGT) (età media 32,48 ± 6,2 anni). La percentuale di malformazioni congenite nelle NIDDM che assumevano ipoglicemizzanti orali era dell'11,6% rispetto all'1,4% delle NIDDM che non prendevano ipoglicemizzanti orali ($p < 0,01$) e del 3,7% delle IDDM. I valori di glicemia a digiuno, di emoglobina glicosilata e di chetonuria sono risultati più elevati nelle IDDM che nelle NIDDM ($p < 0,005$). La percentuale di malformazioni è più elevata nelle donne NIDDM rispetto alle IDDM, anche se il controllo metabolico è migliore.

Parole chiave: ipoglicemizzanti orali, diabete mellito insulino-dipendente, diabete mellito non insulino-dipendente, gravidanza, malformazioni congenite.

Introduction

It is well known that in fetuses of insulin-dependent diabetic mellitus (IDDM) mothers, congenital anomalies are increased with respect to the general population [1-4]. On the contrary, very few reports [5, 6] exist on congenital anomalies in newborns of pre-pregnancy non insulin-dependent diabetes mellitus (NIDDM) mothers. In these patients, besides hyperglycemia, oral hypoglycemic agents can negatively influence embryogenesis, if they are taken during the first trimester of pregnancy.

The present study was conducted to determine whether the maternal metabolic control and/or the use of oral hypoglycemic drugs during early gestation is associated with a risk of congenital malformations in a large group of women affected by diabetes mellitus before pregnancy.

Patients and methods

Beginning on 1 January 1989 to 31 December 1994, clinical data from 16 Italian centers were collected retrospectively and entered in a computerized data base. 517 pregnant women with pregestational diabetes mellitus of which 362 IDDM (mean age 28.13 ± 4.8 years), 130 NIDDM (mean age 33.01 ± 5.32 years) and 25 impaired glucose tolerance (IGT) (mean age 32.48 ± 6.2 years), were studied according to National Diabetes Data Group criteria [7].

Duration and complications of maternal diabetes, body mass index, gestational age at first examination, use of sulfonylureas, biguanides and/or insulin and other drugs were considered. Cholesterol, triglyceride, glyco-

(*) With the collaboration of the Italian Diabetes and Pregnancy Study Group (for the other authors who participated in this study, see the list before the references in this article).

sylated hemoglobin, fasting and 2 h postprandial glucose levels and urin keton bodies were measured at first trimester or early in the second trimester of pregnancy. Hypoglycemia per week was also considered. The newborn's weight at delivery was evaluated. The newborns were accurately examined at birth and again after approximately one week.

Maternal and fetal complications were evaluated (abortions, intrauterine death, maternal hypertension and/or gestosis).

Before pregnancy and during the first phase of embryogenesis of NIDDM patients, 43 women were taking oral hypoglycemic drugs (sulphonilureas and/or biguanide). Some patients stopped spontaneously oral hypoglycemic agents (OHA) before coming to ambulatory. In the other ones we stopped OHA at the first visit.

The data are expressed as mean ± SD. Comparisons among the three groups of pregnant women were made using one-way analysis of variance. If a statistical difference was found between the groups, the Student-Newman-Keuls test was used to study the results of groups which differed from each other. The percentage of groups was compared by means of χ^2 test. Statistical significance was considered when the p value was less than 0.05.

Results

Table 1 shows clinical features of patients and their pregnancies. The IDDM pregnant women were younger than NIDDM and IGT pregnant women. The duration

Table 1. - Clinical features of patients and their pregnancies

	IDDM	NIDDM	IGT	p
no.	**362**	**130**	**25**	
Age (years)	28.1 ± 4.8	33.0 ± 5.3	32.5 ± 6.2	< 0.001 IDDM *vs* NIDDM-IGT
Duration of disease (years)	11.9 ± 7.3	5.7 ± 4.4	3.2 ± 4.2	< 0.001 IDDM *vs* NIDDM-IGT
Complications	27.6 %	4.1 %	0 %	< 0.005 IDDM *vs* NIDDM-IGT
BMI	22.3 ± 2.7	28.4 ± 6.3	27.3 ± 5.7	< 0.001 IDDM *vs* NIDDM-IGT
1st examination (week)	9.8 ± 6.1	11.9 ± 6.3	17.9 ± 8.2	< 0.001 IDDM *vs* NIDDM-IGT < 0.001 IGT *vs* NIDDM
Prepregnancy counselling	40 %	11 %	0 %	< 0.01 IDDM *vs* NIDDM
Abortions	10.5 %	11.6 %	5 %	< 0.05 IGT *vs* NIDDM-IDDM
Perinatal mortality	0.8 %	2.3 %	0 %	ns
Hypertension or gestosis	9 %	17 %	2 %	< 0.05 NIDDM *vs* IGT
Delivery week	36.8 ± 2.2	37.9 ± 1.8	38.1 ± 2.3	< 0.001 IDDM *vs* NIDDM-IGT
Infant birth weight (kg)	3.39 ± 0.6	3.47 ± 0.68	3.31 ± 0.64	ns

Means ± SD; IDDM: insulin-dependent diabetes mellitus; NIDDM: non insulin-dependent diabetes mellitus; IGT: impaired glucose tolerance; ns: not significant.

of disease was higher in IDDM with respect to the other two groups. 27.6% of IDDM patients had complications of diabetes (rethynopathy or nephropathy) with respect to 4.1% of NIDDM patients. The prepregnancy BMI was higher in NIDDM and IGT than in IDDM patients.

The IDDM group underwent first visit earlier than the other two groups. 40% of IDDM patients and 11% of NIDDM patients were attending to preconceptional counseling. None of IGT had prepregnancy care.

Of pregnancies examined, 10.5% of IDDM, 11% of NIDDM and 5% of IGT patients had abortions. Moreover, 9% of IDDM and 17% of NIDDM and 2% of IGT patients showed hypertension or pre-eclampsia.

Table 2 shows the metabolic parameters at first trimester or early at second trimester of pregnancy. The mean fasting blood glucose was more elevated in the IDDM patients with respect to the IGT and NIDDM group ($p < 0.001$). The blood glucose levels determined 2 h after breakfast and 2 h after lunch were higher in IDDM and NIDDM patients than in IGT patients ($p < 0.001$).

The percentage of hypoglycemia and urin keton bodies were more elevated in IDDM than in NIDDM patients ($p < 0.001$; $p < 0.05$). The glycosylated hemoglobin values were more elevated in IDDM and in NIDDM than in IGT group ($p < 0.001$).

Cholesterol and triglyceride levels were more elevated in NIDDM than in IDDM and IGT patients ($p < 0.001$). No correlation was found between the examined parameters.

Among the 324 IDDM mothers' fetuses we observed 12 congenital anomalies: cardiac, skeletal, or renal. The percentage was 3.7% (Table 3).

Among the 115 NIDDM mothers' fetuses we observed 6 congenital malformations (5.5%): of these patients, before pregnancy and during the first phase of embryogenesis, 5 were taking oral hypoglycemic agents. The interruption was between 5 and 18 week. The percentage of congenital malformations in 43 NIDDM patients that took oral hypoglycemic drugs was 11.6% with respect to 1.4% on NIDDM that did not take oral hypoglycemic drugs ($p < 0.01$) and 3.7% of IDDM patients. None of IGT women's infants had malformations.

Table 2. - Metabolic parameters at first examination

	IDDM	NIDDM	IGT	p
no.	**324**	**115**	**24**	
FBG (mg/dl)	149 ± 57	129 ± 35	117 ± 15	< 0.001 IDDM *vs* NIDDM-IGT
BG 2 h after breakfast (mg/dl)	137 ± 46	138 ± 43	112 ± 23	< 0.001 IGT *vs* IDDM-NIDDM
BG 2 h after lunch (mg/dl)	140 ± 45	141 ± 41	111 ± 19	< 0.001 IGT *vs* IDDM-NIDDM
Hypoglycemia (> 1/week)	66%	13%	0%	< 0.001 IDDM *vs* NIDDM-IGT
UKB *vs* NIDDM-IGT	15%	2%	0%	< 0.005 IDDM
HbA1c (%)	7.06 ± 1.7	6.9 ± 1.6	5.6 ± 0.7	< 0.001 IGT *vs* IDDM-NIDDM
Cholesterol (mg/dl)	180 ± 34	197 ± 37	171 ± 16	< 0.001 NIDDM *vs* IDDM-IGT
Triglycerides (mg/dl)	90 ± 43	140 ± 75	92 ± 28	< 0.001 NIDDM *vs* IDDM-IGT

Means ± SD; FBG: fasting blood glucose; BG: blood glucose; UKB: urin keton bodies; IDDM: insulin-dependent diabetes mellitus; NIDDM: non insulin-dependent diabetes mellitus; IGT: impaired glucose tolerance; ns: not significant.

Table 3. - Congenital malformations of IDDM and NIDDM mothers' fetuses

IDDM mothers' fetuses (3.7%)
- Ventricular septal defect. Botallo pervious
- Trasposition of great vessels
- Ventricular septal defect
- Pulmunar a. stenosis. Left hydronephrosis
- Left renal agenesis. Right kidney displasia
- Right ureterocele
- Ureterocele
- Multimalformed
- Diaphragmatic hernia
- Talipes equinovarum
- Somatoschisis
- Hypospadia
NIDDM mothers' fetuses (5.5%)
- Pervious oval foramen (glibenclamide: 10 weeks) *(*)*
- Interatrial septum aneurysm (association: 5 weeks) *(*)*
- Interventricular defect (no. OHA) *(*)*
- Right tibia and 4th and 5th toe agenesis (metformin: 5 weeks) *(*)*
- Hydrocephalus (association: 18 weeks) *(*)*
- Sacral agenesis (association: ?) *(*)*

(*) OHA: oral hypoglycemic agents (interruption week); IDDM: insulin-dependent diabetes mellitus; NIDDM: non insulin-dependent diabetes mellitus.

Discussion

The percentage of malformations in offspring of NIDDM mothers is higher than that of IDDM women, in spite of a better metabolic control (fasting blood glucose, hypoglycemia and ketonuria). Other factors, like maternal age and obesity or oral hypoglycemic drugs may influence organogenesis in fetuses of NIDDM mothers.

Towner *et al.* [5] found that 11.7% of 332 Latino women with NIDDM who did not participate in a preconceptional diabetes care program gave birth to infants with major congenital anomalies. The rate and types of malformations were similar to those reported in offspring of women with IDDM. The risk of major malformations increased in association with maternal glycohemoglobin concentrations early in the second trimester, but no association was identified between the risk of malformations and maternal use of sulphonylureas drugs during the first 8 weeks of gestation.

In contrast, our results may be due to the influence of oral hypoglycemic drugs, in particular biguanides, on organogenesis in fetuses of NIDDM mothers with glycosylated hemoglobin values not excessively elevated. Unfortunately no studies report the effects of oral hypoglycemic agents on embryo culture systems.

However, Freinkel and his coworkers demonstrated that glucose and b-hydroxybutyrate can act synergistically in the rat embryo culture system. Thus, when the medium is supplemented with 33.3 mM D-glucose or 8 mM DL-b-hydroxybutirate alone, neither metabolite has much effect. In contrast, the two in combination markedly reduce growth and disrupt development [8]. The same phenomenon can happen *in vivo* with fair glycemic levels and oral hypoglycemic agents that alone do not determine dysmorphogenesis but in combination can lead to malformed fetuses.

In our country the NIDDM patients are followed by general physicians and rarely respect the diet therapy. They are not educated to home glycemic monitoring. Considering that recently the age of conception has increased, and that the older age corresponds to a greater risk of onset of diabetes coupled with a high risk of congenital malformations, we strongly suggest to avoid the use of biguanides in the treatment of NIDDM patients who need to be educated before pregnancy, and monitored closely as in the case of IDDM pregnant women.

This study has been carried out with the collaboration of:

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Submitted on invitation.
Accepted on 14 February 1997.

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