

A class of diabetes in mother, glycemic control in early pregnancy and occurrence of congenital malformations in newborn infants

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Summary

The study compares an occurrence rate of congenital malformations in newborn infants of mothers with insulin dependent diabetes (IDDM) and newborns of healthy mothers and mothers with pregnancy diabetes (GDM). This paper evaluates the influence of stage of advancement (a class) of diabetes in the mother and its control during early pregnancy on a rate of congenital malformations in the fetus. We have taken a group of 170 neonates of mothers with IDDM. The control group was 56 newborn infants of mothers with GDM and 26,368 newborn infants of healthy women. We found 11.2% of congenital malformations in newborn infants of mothers with IDDM, compared to 1.8% of ones in the newborn infant population of mothers with GDM and 2.2% in the population of healthy mothers. The occurrence rate of congenital malformations in offspring of diabetic mothers with IDDM was 5-times higher than in the general population of newborn infants of healthy and also mothers with GDM. A risk of major birth defect occurrence in the fetus was directly proportional to the grade of the blood glucose level control in mothers during the I trimester of pregnancy, but the presence of diabetic angiopathy (classes D-H) had a significant influence on the occurrence rate of major birth defects in the fetus only in metabolic imbalance cases.

Key words: Congenital malformations; Diabetes; Fetus; Newborn infant; Pregnancy.

Introduction

Birth defects are found in 2-3% of newborn infants of the general population [2, 12]. The risk of the occurrence of congenital malformations in newborn infants in the population of diabetic mothers is 2 to 7.9 times higher than among newborn infants of healthy mothers [3]. The most important cause in the development of embryopathy related to diabetes, is damage of a yolk-sac, which is very susceptible to teratogenic factors and the extent of the damage depends on the number of these factors, their concentrations and exposure time [22, 24]. The best known and the most proven teratogenic factor in diabetes is hyperglycemia.

A specificity of D-glucose activity and its concentration on the development of many abnormalities in the developing embryo, has been proven in studies by Reece *et al.* [25] and Freinkel *et al.* [8]. Other factors that may damage cells of developing embryos are: keto-bodies [8], oxygen free radicals [6], hypoglycemia [29], somatomedin inhibitors [27]. Such factors like deficiencies of arachidonic acid, myoinositol, vit. A and E, zinc, are also thought to be conducive to the development of abnormalities during organogenesis [5, 6, 22, 23, 28].

Material and Methods

We have examined and taken into consideration a group of 170 newborn infants of mothers with IDDM, classes B-H, born

between the 24th and the 40th week of gestation at the First Dept. of Obstetrics and Gynecology of II Medical Faculty, Medical Academy of Warsaw in the period from 1986 to 1996. A control group consisted of 56 newborn infants of mothers with GDM (class G) and 26,368 newborn infants of healthy mothers born at our Clinical Dept. during the same time. In order to find a correlation between occurrence rate of congenital malformations in newborn infants and the stage of advancement of diabetes in the mothers, we decided to divide a group of infants of mothers with IDDM into two subgroups: one consisting of 86 (50.6%) newborn infants of diabetic mothers without angiopathy (classes B and C) and another - including 84 (49.4%) newborn infants of diabetic mothers with angiopathy (classes D, R, F, RF and H).

To assess the influence of the grade of blood glucose level in diabetic mothers in early pregnancy on the occurrence rate of congenital malformations in their infants, patients were divided into two groups depending on the result of HbA_{1c} analysis taken in I trimester of pregnancy. The diabetes control criteria were based on HbA_{1c} concentration values in blood according to the European IDDM Policy Group [7].

The first group included 109 newborn infants of diabetic mothers with well-controlled blood glucose levels in early pregnancy (HbA_{1c} ≤ 7.5% in the first trimester of pregnancy). The second group included 61 newborn infants of diabetic mothers with metabolic imbalances in early pregnancy (HbA_{1c} > 7.5% in the first trimester of pregnancy).

Among the newborn infants of mothers with class B and C diabetes, 65 (75.6%) infants were included in the first group and in the second group 21 (24.4%). Among newborn infants of mothers with classes D-H diabetes (presence of angiopathy) in the first group (well-controlled blood glucose levels during organogenesis) there were only 44 (52.4%) newborn infants but in the second group - 40 (47.6%). Fig. 1 shows the respective classes of maternal diabetes (B-C and D-H) in separated groups

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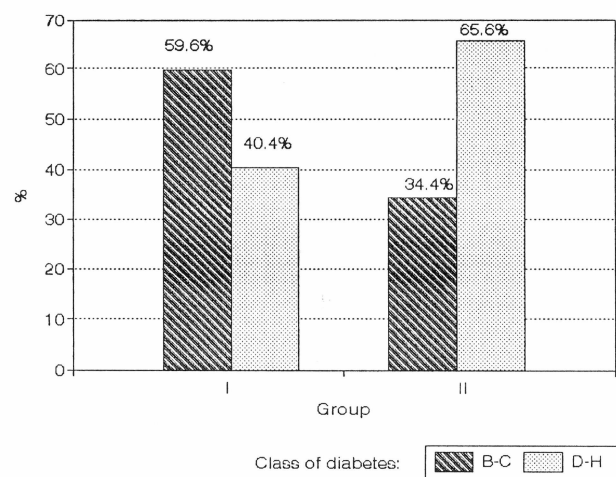


Figure 1. — Groups of examined newborn infants and stage of advancement of diabetes in the mothers.

of controlled (I) and uncontrolled (II) diabetes during organogenesis.

Diagnosis of congenital malformations was carried out on the basis of clinical examination and procedures such as echocardiography (congenital heart diseases), ultrasonography (kidney abnormalities), radiology (bones and skeleton abnormalities), or pathology in newborn infants who died. A differentiation of major or minor congenital malformations was done according to Reece's *et al.* [23] classification. Statistical analysis of examined material was carried out with the Chi-square test.

Results

In the examined 170 newborn infants of mothers with IDDM, in 19 (11.2%) different congenital malformations were found, including 15 (8.8%) major birth defects. In 4 cases syndromes of multiple-organ congenital malformations were found. In 14 newborn infants congenital heart disease (single or connected with another abnormalities) was diagnosed.

In order to find out whether insulin-dependent maternal diabetes is an essential risk factor in the occurrence of congenital malformations in the fetus, analysis of the occurrence rate of birth defects was carried out in the group of newborn infants of mothers with IDDM by comparing them to newborn infants of mothers with GDM and healthy mothers - the results are presented in Table 1.

In the group of examined newborn infants of diabetic mothers with IDDM, congenital malformations occurred 5 times more frequently than in the group of newborn infants of mothers with pregnancy diabetes and healthy mothers ($p < 0.0001$).

The assessment of the influence of the blood glucose level in diabetic mothers during I trimester of pregnancy on the occurrence of major and minor congenital malformations in the fetus was carried out in the group of mothers with well-controlled (I) and improperly-controlled (II) blood glucose levels. The results are presented in Table 2.

Table 1. — Occurrence of congenital malformations in newborn infants of diabetic mothers with IDDM compared to newborn infants of diabetic mothers with GDM and newborn infants of healthy mothers - born between 1986 and 1996 at the I Dept. of Obstetrics and Gynecology of the II Medical Faculty, Medical Academy of Warsaw.

Newborn infants of	Total number of newborn infants	Newborn infants with congenital malformations N.	%
Mothers with IDDM	170	19	11.2 ⁽¹⁾
Mothers with GDM	56	1	1.8 ⁽²⁾
Healthy mothers	26,368	573	2.2 ⁽³⁾
Statistical significance		1-2	$p < 0.0001$
		1-3	$p < 0.0001$
		2-3	(ns)

Table 2. — Occurrence of congenital malformations in newborn infants of mothers with IDDM in the examined groups

Number of newborn infants		GROUPS		p
		I HbA _{1c} ≤ 7.5 %	II HbA _{1c} > 7.5 %	
Total		109	61	
Major congenital Malformations	N. (%)	3 (2.8)	12 (19.7)	<0.005
Minor congenital Malformations	N. (%)	2 (1.8)	2 (3.3)	ns

As has been presented in Table 2, the occurrence rate of major congenital malformations in newborn infants of mothers with improper control of blood glucose levels during early pregnancy was 7 times higher than in the group of mothers with well-controlled blood glucose levels ($p < 0.005$). A significant relation between diabetes control in mothers during organogenesis and the number of newborn infants with minor congenital malformations was not found.

We also estimated the occurrence rate of major congenital malformations in newborn infants in relation to the serum HbA_{1c} concentrations in mothers in the first analysis.

We have proven that the rate of infants with major birth defects was greater when HbA_{1c} concentrations in the mother were higher during early pregnancy, reaching up to 40% when the HbA_{1c} value was above 10.1%.

To investigate a relation between the stage of clinical advancement of diabetes in the mother and the occurrence of congenital malformations (major and minor) in their infants, an evaluation of the occurrence rate of malformations was done in newborn infants of mothers with classes B-C and D-H diabetes (see Table 4).

Statistical analysis has shown an essential relation between the stage of advancement (the class) of diabetes in the mother and the rate of newborn infants with major congenital malformations ($p < 0.05$). The rate of newborn infants with minor congenital malformations in the group of diabetic mothers without angiopathy (classes B and C) and with angiopathy (classes D-H) was almost the same (2.3% and 2.4%).

Table 3. — Occurrence of major congenital malformations in newborn infants in relation to HbA_{1c} serum concentrations in mothers in the I trimester of pregnancy

Number	% HbA _{1c} in mothers in the I trimester of pregnancy			
	≤ 7.5	7.6÷8.8	8.9÷10.1	> 10.1
Examined mothers	109	31	20	10
Newborn infants with major congenital malformations (%)	N 3 (2.8)	4 (12.9)	4 (20.0)	4 (40.0)

Table 4. — Occurrence of congenital malformations in newborn infants in relation to the stage of advancement of diabetes in the mother

Class of diabetes	Total number of newborn infants	Newborn infants with congenital malformations - N. (%)	
		major	minor
B - C	86	4 (4.7)	2 (2.3)
D - H	84	11 (13.1)	2 (2.4)
Statistical significance		p<0.05	ns

Table 5. — Occurrence of major congenital malformations in newborn infants and grade of metabolic control in different classes of diabetes in mothers

Number	CLASS OF DIABETES			
	B - C % HbA _{1c}		D - H % HbA _{1c}	
	≤ 7.5	> 7.5	≤ 7.5	> 7.5
Mothers 65	65	21	44	40
Newborn infants with major congenital malformations (%)	2 ⁽¹⁾ (3.0)	2 ⁽²⁾ (9.5)	1 ⁽³⁾ (2.3)	10 ⁽⁴⁾ (25.0)
Statistical significance	1-2	ns	1-3 (ns)	3-4 <0.01

As was mentioned previously (in Material and Methods) a metabolic imbalance during early pregnancy was found in 24.4% mothers with classes B and C diabetes and as much as 47.6% in mothers with class D-H diabetes ($p < 0.01$). Consequently, we decided to analyze whether the higher rate of newborn infants with congenital malformations in the group of mothers with classes D-H diabetes depended on the presence of angiopathy, or may be linked to metabolic imbalance during early pregnancy. The estimation of the occurrence rate of major congenital malformations in the fetus in the respective classes in relation to control of diabetes in the mothers is presented in Table 5.

A significant relation between improper control of blood glucose levels in diabetic mothers with angiopathy and the rate of newborn infants with major congenital malformations was revealed ($p < 0.01$). It also was found that in cases with well-controlled blood glucose levels the presence of diabetic angiopathy in the mother did not

affect the occurrence rate of congenital malformations in their infants. In the well-controlled maternal diabetes in early pregnancy groups, the occurrence rate of congenital malformations in newborn infants of mothers with class D-H (2.3%) did not differ from the rate in the group of class B-C diabetes (3.0%) and there was no statistical difference between the above-mentioned rates and the occurrence rates of congenital malformations in newborn infants of mothers with GDM (1.8%) and healthy mothers (2.2%).

Discussion

The occurrence rate of congenital malformations in newborn infants of mothers with IDDM, has been reported to be between 2 and 13% [1, 11, 12, 13, 15]. According to the data of Bank of Technological Resources for Diagnosis and Management of Diabetes the rate of congenital malformations in newborn infants of mothers with IDDM born in Poland in the period from 1986 to 1995 was 7% [14].

In the examined group of newborn infants of mothers with class B-H diabetes (acc. White), the rate of infants with congenital malformations (11.2%) was 5 times higher than in infants of healthy mothers (2.2%). The relation between elevated concentrations of maternal HbA_{1c} in the serum in early pregnancy and the occurrence of malformations in the fetus has been demonstrated in the studies of many authors [17, 19, 30] but one of the first to show that congenital malformations in fetuses of diabetic women with IDDM were probably linked with metabolic control in the period of organogenesis, was Leslie [16]. The results of our studies have revealed a similar relation.

Major congenital malformations were found in 2.8% of infants of 109 mothers with HbA_{1c} concentrations ≤ 7.5% in the I trimester of pregnancy and in 19.7% of the infants of 61 mothers with HbA_{1c} concentrations > 7.5% in early pregnancy.

Evaluation of the occurrence risk of major congenital malformations in the fetus in relation to HbA_{1c} concentrations in the I trimester of pregnancy was done by researchers from Joslin Clinic in a population of 451 women with IDDM [10].

In our studies we have obtained comparable results. The occurrence rate of major congenital malformations in the examined group of newborn infants increased from 2.8% with HbA_{1c} ≤ 7.5% to 40% with HbA_{1c} > 10.1% in the mother's serum in the first analysis.

Investigating the occurrence rate of congenital malformations in the examined group of infants in relation to the stage of advancement of diabetes in the mother we have found, that in the group of newborn infants of diabetic mothers with a complication like angiopathy, the rate of major congenital malformations (13.1%) was 3 times higher than in the group of infants of diabetic mothers without vascular complications (4.7%). The relation between the occurrence rate of congenital malformations in the fetus and maternal diabetes with angio-

pathy has been confirmed by Pedersen [21] and Miodownik [20]. Moreover, Pedersen has found that the most serious congenital malformations in the fetus, mainly of the heart, CNS and skeletal system, occur more often in diabetic mothers with angiopathy [21]. In our research all newborn infants with lethal congenital malformations were from mothers with class D, R and RF diabetes.

The high rate of congenital malformations in newborn infants of mothers with class D-H diabetes (13.1%) in our opinion are related to the fact, that as much as 47.6% of diabetic women with angiopathy have had improper metabolic control in early pregnancy compared to 24.4% of women with class B-C diabetes. Probably, it is a result of introducing principles of functional insulin-therapy in young women with early-diagnosed diabetes as if they were in a period of pregnancy planning, whereas women who have had diabetes for many years often have been treated according to principles of so-called "old-fashioned" diabetology, based on only one or two injections of insulin in 24 hours.

Damm and Molsted-Petersen [4] have found that the presence of diabetic microangiopathy has no influence on the development of congenital malformations in the fetus in a situation when mothers with advanced diabetes have been well prepared for the pregnancy period with optimal blood glucose level control.

The results of our studies have revealed that in conditions of well-controlled blood glucose levels in mothers ($HbA_{1c} \leq 7.5\%$) in early pregnancy, the presence of diabetic angiopathy did not affect the occurrence of congenital malformations in their infants, and the rate (2.3%) did not differ from the occurrence rate (2.2%) in infants of healthy mothers. On the contrary, in conditions of improper control of blood glucose levels during organogenesis ($HbA_{1c} > 7.5\%$) the rate (25%) of newborn infants with major congenital malformations of mothers with class D-H diabetes was 2.5 times higher than the rate (9.5%) of infants of mothers with class B-C diabetes.

We have not found a relation between the stage of advancement or control of maternal diabetes and the occurrence of the minor congenital malformations in the fetus. In both groups of mothers with good and improper control of the blood glucose level, the rate of newborn infants with minor congenital malformations is comparable (1.8% and 3.3%) and in infants of mothers with class B-C diabetes (2.3%) and D-H (2.4%) is almost equal.

Different results have been reported by Rosenn *et al.* [26] in a group of infants of diabetic mothers with improper control of blood glucose levels in early pregnancy. Minor congenital malformations of the genitourinary system in 18.1% were found. They have stated that the occurrence of these malformations depended only on high concentrations of HbA_{1c} in the I trimester of pregnancy.

The rate (1.8%) of newborn infants with congenital malformations of mothers with pregnancy diabetes (class G) is comparable with the rate (2.2%) of newborn infants of mothers without diabetes.

In Poland the rate of congenital malformations in newborn infants of mothers with GDM is 1.2% [14].

McCarter *et al.* [18] have also considered that there is no increased risk of development of congenital malformations in the fetus of women when the diabetes appeared during pregnancy, unless it was undiagnosed IDD before pregnancy.

There is the generally accepted opinion that congenital malformations in the fetus create a remarkable problem in the clinical pathology of pregnancy complications of insulin-dependent diabetes. But correct metabolic control in diabetic women, especially many months before pregnancy is planned, is the essential factor in the prevention of these malformations [4, 9, 13, 17, 30].

Our studies have revealed, that in conditions of correct blood glucose level controls in mothers in early pregnancy, the rates of newborn infants with congenital malformations of diabetic mothers with class B-C (3%) and D-H (2.3%) are comparable to the rate (2.2%) of newborn infants with these malformations in healthy mothers.

The results of our research, lead us to draw the following conclusions:

- 1) The occurrence rate of congenital malformations among the offspring of mothers with insulin-dependent diabetes is 5-times higher than in a population of healthy mothers.
- 2) Pregnancy diabetes does not determine an increased risk of occurrence of congenital malformation in the fetus.
- 3) The risk of occurrence of major congenital malformations is proportional to the blood glucose level in the mother in the I trimester of pregnancy.
- 4) The presence of diabetic angiopathy in mothers has a significant influence on the occurrence rate of major congenital malformations in the fetus only under conditions of metabolic imbalance.
- 5) A correlation between the grade of diabetic control, diabetic class of the mother and the occurrence rate of minor congenital malformations in the fetus has not been found.

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