THE RELATIONSHIP BETWEEN FIRST-TRIMESTER HAEMOGLOBIN A1C AND CONGENITAL MALFORMATIONS IN WOMEN WITH TYPE 1 DIABETES MELLITUS

Summary:
A precarious glycemic control, within the first 10 pregnancy weeks, period when the organogenesis is determined, the risk of congenital malformations is increased. Thus, the existing of hyperglycemia during the first trimester of pregnancy (>150 mg/dl) results in tripling the fetal abnormalities. Fetal malformations are responsible of up to 50% of perinatal death. The aim of this study is to establish the relation between HbA1c in the first trimester of pregnancy and the congenital malformations at pregnant women with type 1 DM.

Material and method: the present study included all pregnancies in type 1 diabetic women followed at Diabetes Clinic, Emergency County Clinical Hospital, Timisoara, from 1990-2010. I have noticed differences extremely significant statistically between the average HbA1c in the studied groups (7.28 ± 0.88% in group A vs. 9.75 ± 1.85% in group B, p<0.0001). The RR of major congenital malformations from the entire sample was 4.32 bigger (confidence interval 95% of RR between 1.55 – 12) in comparison with the control sample (p=0.005, Fisher test), highly statistically significant risk. Still, the pregnancy to a patient with DM type 1 must be considered a high risk fetal pregnancy due to compromised fetal vitality in case of unsatisfactory glycemic control as well as the major risk of congenital malformations.

Keywords: diabetes mellitus, organogenesis, congenital malformations, relative risk.

Rezumat:
Un control glicemic precar, în primele 10 săptămâni de sarcină, perioadă în care se definitează organogeneza, crește riscul malformațiilor congenitale. Prezența hiperglucemiei în primul trimestru de sarcină (>150 mg/dl), determină o triplare a anomalilor fetale. Malformațiile fetale sunt responsabile de până la 50% din decesele perinatale. Scopul acestui studiu este de a determina relația dintre HbA1c din primul trimestru de sarcină și malformațiile congenitale la grăvidele cu DZ tip 1. Material și metodă: studiul de față a fost realizat pe un lot de 75 de grăvide cu DZ tip 1 aflate în evoluția Clinicii de Diabet, Nutriție și Boli Metabolice, Timișoara. Am observat diferențe semnificativ statistic între media HbA1c în loturile studiate (7.28 ± 0.88% vs. 9.75 ± 1.85%). Riscul relativ al malformațiilor congenitale fatale în întreg eșantionul a fost de 4.32 ori mai mare comparativ cu lotul marotor, risc foarte semnificativ statistic. Sarcina la gravidă cu DZ tip 1 trebuie considerată o sarcină cu mare risc fetal din cauza compromiterii vitalității fetale în cazul unui control glicemic nesatisfăcător, precum și a riscului major de apariție a malformațiilor congenitale.

Cuvinte cheie: diabet zaharat, organogeneză, malformații congenitale, risc relativ.

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INTRODUCTION

Currently, diabetes mellitus (DM) occurs in about 8% of all pregnancies, in most cases (90%) it is the gestational diabetes mellitus, and in 10% cases, there is pre-existing diabetes or, in other words, a pregnancy in women with known DM (1). Nowadays, the maternal mortality is equal to that of patients with no diabetes, and the fetal mortality has lowered from 40% during the years of ’40s to 5-8% during the years of ’70s and to 1,2-2% in specialized centres, values which are similar to those of general perinatal mortality in economical developed countries (1-1,5%) (2,3). Although maternal mortality has been reduced, the morbidity and perinatal mortality of the fetus are increasing in woman’s pregnancy with diabetes, which makes this to be considered further on as pregnancy with increased fetus risk. (4).

A precarious glycemic control, within the first 10 pregnancy weeks, period when the organogenesis is determined, the risk of congenital malformations is increased. Thus, the existing of hyperglycemia during the first trimester of pregnancy (>150 mg/dl) results in tripling the fetal abnormalities. The most frequent congenital malformations associated to pregnancy of a woman with DM type 1 are those at the level of central nervous system, heart and kidney, these having a prevalence of 25% at cases HbA1c > 10% cases. From this reason, pregnant women with type 1 DM must be informed by their physician, since the first meeting on the possibility of occurrence of this major risk which implies an unplanned pregnancy (5, 6, 7). Fetal malformations are responsible of up to 50% of perinatal death. (8).

The aim of this study is to establish the relation between HbA1c in the first trimestre of pregnancy and the congenital malformations at pregnant women with type 1 DM.

MATERIAL AND METHOD

The present study included all pregnancies in type 1 diabetic women followed at Diabetes Clinic, Emergency County Clinical Hospital, Timisoara, from 1990-2010. Fetal outcome was divided in two groups: A - pregnancies ending with healthy and B - all pregnancies ending with major congenital malformations. Major congenital malformations were defined as those who were responsible for the death of the fetus. HbA1c was measured using DCCT standardized immune-turbidimetric assay.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 5. Data are expressed as mean and standard deviation for parametric variables. Differences between groups were studied using the Student’s t-test. Pearson’s correlation coefficient (r) was used to measure the strength of the association between two variables. Fisher’s exact test was used in the analysis of contingency tables. For the statistical tests and risk estimates, the 0.05 two-tailed level of significance with a 0.95 (95%) confidence interval (CI), was considered statistically significant.

RESULTS

In the study group there were sixty-seven pregnancies ending with healthy babies and 8 major congenital malformations. The fetal congenital malformations occurred at birth, at pregnant women with type 1 DM were: complete transposition of great vessels (2 cases), tetralogy of Fallot (1 case), hypoplastic left heart syndrome (1 case), anencephaly (2 cases), caudal regression syndrome (1 case) and association between the ventricular septal defect and anorectal agenesis (1 case).

There were not noticed any differences regarding age distribution within the studied groups. These presented a normal distribution with no statistic signification for the registered differences between the two groups (26.4 ± 4.11 years in the group A vs. 26.5 ± 7.11 years in the group B, p=0.69) (Fig. 1 and no.2).

Further on, we compared the duration of DM within both groups. Thus, the average time of DM in group A was of 8.6 ± 6.09 years (the minimum limit is of 1 month and the maximum is of 22 years), and in group B of 10.8 ± 5.3 years (the minimum limit is of 3 years and the maximum of 17 years) I did not notice significant statistic differences regarding the duration of DM in the studied groups (p=0.29) (Fig. 3).

We also studied the correlation coefficient Pearson in order to assess the time influence of DM on fetal congenital malformations and I drew the right of regression. The obtained data (r=0.04, R2=0.002, confidence interval 95% of r between -0.18 and 0.26, p=0.7) does not suggests the existence of any correlation between these (Fig. 4).The average HbA1c in group A was of 7.28 ± 0.88% (the minimum limit being of 5.3% and the maximum of 11.1%, confidence interval 95% of the average between 7.06-7.49).
Fig. 1. Group A age distribution

Fig. 2. Group B age distribution

Fig. 3. Duration of type 1 DM in studied groups

Fig. 3. Correlation between time DM and fetal congenital malformations

Fig. 5. HbA1c in the first trimester of pregnancy in studied groups
In group B, the average HbA1c was 9.75 ± 1.85% (the minimum limit being of 6.9% and the maximum of 11.7%, confidence interval 95% of the average between 8.2-11.3) (Fig. 5).

I have noticed differences extremely significant statistically between the average HbA1c in the studied groups (7.28 ± 0.88% in group A vs. 9.75 ± 1.85% in group B, p<0.0001).

I have calculated the Pearson correlation coefficient in order to assess the relation between HbA1c and major congenital malformations in complicated pregnancies with type 1 DM and I drew the right os regression. Value \( r=0.39 \) suggests a moderate intensity correlation (\( R^2=0.14 \), confidence interval 95% of \( r \) between 0.16 and 0.57) and the test of \( t \) values distribution underlined an extremely significat statistically correlation (\( p=0.0009 \)) (Fig. 6).

In order to assess the relative risk (RR) of congenital malformations we have used a sample control made of 267 pregnant women with no diabetes, being observed a rate of 2.25% (n=6) major congenital malformations.

RR was determined for all pregnancy group with type 1 DM, as well as for groups of HbA1c (#6% respectively >6%). Thus, RR of major congenital malformations from the entire sample was 4.32 bigger (confidence interval 95% of RR between 1.55 – 12) in comparison with the control sample (\( p=0.005 \), Fisher test), highly statistically significant risk. A value of HbA1c # 6% was associated with a RR of major congenital malformation of 3.68 higher (confidence interval 95% of RR between 0.48 – 28) than the one encountered for the sample control (\( p=0.27 \), Fisher test), statistically unsignificant risk. RR of a major congenital malformation, to a value of HbA1c >6%, was 4.43 bigger (confidence interval 95% of RR between 1.55 – 12.7) in comparison with the group of pregnant women with no diabetes (\( p=0.007 \), Fisher test), statistically highly significant risk (Fig. 7).

**DISCUSSION**

The importance of congenital malformations within complicated pregnancies is in close relation with the precarious quality of the glycemic control (HbA1c), especially during the first weeks of pregnancy evolution, period when the organogenesis is determined (9). In this study, the average value of HbA1c from the first trimester, among all complicated pregnancies with major congenital malformations was of 9.75% for type 1 DM, of 7.28%, respectively, in uncomplicated pregnancies with
congenital malformations. The duration of DM (8.6 vs. 10.88 years) and pregnant women’s age (26.4 vs. 26.5 years) in the studied groups did not reach the limit of the statistic signification, their role for the final outcome of the pregnancy being assessed as insignificantly.

Examining the new international guides, which recommend as therapeutic objective in pregnancy associated with type 1 DM, the obtaining a normal value of HbA1c or adequate to normal (HbA1c #6%), I have estimated the relative risk of congenital malformations taking into account this value (10,11,12,13). There were consistent increases in RR of major congenital malformations with stepwise increasing levels of HbA1c. A value of HbA1c less than 6% did not differ significantly from our control group concerning the severe outcomes. As illustrated above, the risk of pregnancy loss due to major congenital malformations increased abruptly when HbA1c exceeded 6%.

A Swedish analysis which was published in 2009 was carried out for a group of 5089 pregnant women with type 1 DM in comparison with 1260207 women with no diabetes which formed the control sample, revealed a major occurrence rate of congenital malformations of 4.7% in comparison with 1.8%, for the period of 1989-2003(14).

The same conclusion is found for the Spanish population, the occurrence rate for major congenital malformations being three times bigger in both types of pre-existing DM as for general population (2%). It is also mentioned that the level of HbA1c # 7% is associated to a congenital malformation rate similar to that of pregnant women but with no diabetes (15).

The data published in the CEMACH report which includes England, The Wales and Nord Ireland, reveals the compared historical results (4.1% - 17.1%) and the present ones (4.8%) regarding the relation between type 1 DM and incidence of major congenital malformations. These values are substantially bigger than the observed ones in general population, that is 2.1% (16,17).

The study carried out by Jensen and his collaborators in the year of 2009, regarding a sample of 933 pregnant women with DM type 1, reported the occurrence of a number of 45 congenital malformations, out of which 23 were fatal, the RR of their occurrence increased when HbA1c exceeded the value of 6% and maintained its ascension gradually, depending on its value. The outcome the study reported that, in a percentage of 4.9% of congenital malformations occurred at a value of HbA1c between 6.9% - 7.8%, while 10.9% of the pathological situations were registered values of HbA1c higher than 10.4%. It is recommended that the level of HbA1c during the in the preconception period to be # 7% (18).

CONCLUSIONS

Type 1 DM was and is associated to an increased risk of major congenital malformations. In recent decades, a better understanding of the importance of glycaemic control and preconception planning has reduced their rates amongst diabetic pregnancies. The participation of the pregnant women herself, especially to maintaining the normal glycaemia during the period of organogenesis and, ideally during the entire pregnancy period, as well as for her compliance to the rhythm of periodic monitoring improves the maternal fetus diagnosis.

The family planning of pregnant women with DM type constitutes a condition, not only necessary but also compulsory, for obtaining a favourable final outcome. The pregnant women with DM type 1 must be informed by the physician, since their first meeting, about the possibility of occurrence of this major risk involved by an unplanned pregnancy. Still, the pregnancy to a patient with DM type 1 must be considered a high risk fetal pregnancy due to compromised fetal vitality in case of unsatisfactory glycemic control as well as the major risk of congenital malformations.
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