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

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Abstract

Background and aims: *A precarious glycemic control in the first 10 weeks of pregnancy, the period defining organogenesis, increases the risk of pregnancy loss. The aim of this study was to estimate the relationship between pregnancy loss and HbA1c values in early pregnancy in type 1 diabetic women.* ***Material and method:*** *The present study included all pregnancies in type 1 diabetic women followed at Diabetes Clinic, Emergency County Clinical Hospital, Timişoara, from 1990-2011.* ***Results:*** *The risk of pregnancy loss was significantly increased compared with the background control group. In our study the relative risk of pregancy loss increased when HbA1c exceeded 6.5%. We found a consistent increasing risk with stepwise increasing levels of HbA1c.* ***Conclusions:*** *A better glycemic control in this period and throughout the pregnancy could reduce the risk of severe adverse outcomes in type 1 diabetic pregnancies.*

key words: *diabetes mellitus, pregnancy loss, haemoglobin A1c, congenital malformations, spontaneus abortions.*

Background and Aims

Before the discovery of insulin the link between diabetes mellitus and pregnancy was a medical scarcity, the latter being considered as a pregnancy with high mortality and maternal and fetal complications risk [1]. Although the maternal mortality has been reduced, the prenatal morbidity and mortality of the fetus are still increased in the pregnancy of diabetic woman, which makes it still a pregnancy with high fetal risk [2,3].

A precarious glycemic control in the first 10 weeks of pregnancy, the period defining organogenesis, increases the risk of congenital malformations and spontaneous pregnancy loss. The frequency of fetal complications in diabetic pregnancies with an optimal glycemic control (HbA1c<6,5%) is higher than in the general population. The fetal condition depends on the severity of maternal

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hyperglycemia and on the time of the pregnancy when the exposure to this environment takes place. Every 1% increase of the HbA1c increases the risk of an unfavorable outcome with 5.5% [4,5].

The most important fetal complications are represented by: spontaneous abortion, congenital malformations, stillbirth, perinatal death, growth disorders, respiratory distress, diabetic cardiomiopathy, neonatal hypoglycemia, hyperbilirubinemia, disorders of calcium and magnesium metabolism, polycitemia etc. [6].

The woman with type 1 diabetes mellitus, before the setting of pregnancy, should be supervised by a medical team, including a diabetologist, gynecologist, general practitioner, followed by, in case of need, other specialists: an oftalmologist, nephrologist, cardiologist etc. [7]. This collaboration, the medical progresses in different fields (obstetrics, gynecology, neonatology), and an optimal glycemic control have contributed to the improve of pregnancy outcomes [8,9].

The contribution of the pregnant woman herself, especially to maintain euglycemia, during the time of organogenesis and, ideally, troughout the pregnancy, and her compliance to periodic monitoring rhythm, improves the maternal-fetal prognosis [10,11].

The aim of this study was to estimate the relationship between pregnancy loss and HbA1c values in the first trimester of pregnancy in type 1 diabetic women.

Material and Method

The present study included all pregnancies in type 1 diabetic women followed at Diabetes Clinic, Emergency County Clinical Hospital, Timişoara, from 1990-2011. Fetal outcome was divided in two groups: A – pregnancies ending with healthy babies (including those with minor non-fatal malformations) and B – all pregnancies ending with pregnancy loss. Induced abortion due to the high risk of pregnancy was not included. Data concerning maternal age, duration of diabetes mellitus (DM), first trimester BMI, White classification [12], time of the first visit, preconceptional care, HbA1c, diabetic complications, insulin regiments, number of self monitoring tests and fetal status were taken from the medical records.

Pregnancy loss was defined as spontaneous abortion, major congenital malformations, stillbirth and perinatal death. Spontaneous abortion was defined as a clinically non-induced pregnancy loss reported to occur before 24 weeks of gestation. Stillbirth is defined as death of fetus after 24 week of pregnancy. Perinatal death was defined as the combined rate of stillbirth and early mortality within 7 days of life or late mortality within 28 days. 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.

From 1990-2011 a total number of 99 type 1 pregnancies were registered. In 5 cases, due to the high maternal risk, induced abortion was performed and these cases were excluded from the study.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 5. Data are expressed as mean and standard deviation for parametric variables. Distribution of variables was investigated using a histogram and the

normality of the distribution with Kolmogorov-Smirnov test. Differences between median of the groups were studied using the Mann-Whitney test or the Student's t-test for differences between means. Pearson's correlation coefficient (r) was used to measure the strength of the association between two variables and its significance with t-distribution test. Fisher's exact test was used in the analysis of contingency tables. For the statistical tests α=0.95 significance levels was accepted and for means and risk estimates a 95% confidence interval was computed.

Results

In the study group there were sixty-seven pregnancies ending with healthy babies (Group A) and twenty-seven pregnancies terminated with fetal loss (Group B: 8 major congenital malformations, 11 spontaneous abortions, 6 stillbirth and 2 early neonatal death). The median age of group A was 25 years with a variation between 18 and 41 years. Group B had a median age of 26 years with a variation between 19 and 40 years. The main characteristics of the study group are described in Table 1.

Table 1. Characteristics of the study group.

Parameter		Group A	Group B	p
Number of pregnancies n(%)		67 (71.2%)	27 (28.8%)	
Median age (range)		25 (18-41)	26 (19-40)	NS
Diabetes Duration (yr)		8.88±6.35	10.37±6.05	NS
White classification	B	37 (55.2%)	4 (14.8%)	p<0.001
	C	18 (26.8%)	12 (44.4%)	p<0.001
	D	12 (18%)	11 (40.8%)	p<0.001
Preconceptional care	Yes	48 (71.6%)	7 (26%)	p<0.001
	No	19 (28.4%)	20 (74%)	p<0.001
First visit	<6th week	8 (12%)	3 (11.1%)	NS
	6th-12th week	34 (50.7%)	10 (37%)	p<0.001
	≥12th week	25(37.3%)	14 (51.9%)	p<0.001
Diabetic retinopathy	Yes	11 (16.4%)	13 (48.2%)	p<0.001
Diabetic nephropathy	Yes	1 (1.5%)	4 (14.8%)	p<0.001
Daily self monitoring tests	≤1	14 (20.9%)	17 (63%)	p<0.001
	2-3	26 (38.8%)	8 (29.6%)	p<0.001
	≥4	27 (40.3%)	2 (7.4%)	p<0.001
First trimester insulin dose (UI/kg/day)		0.83±0.3	0.83±0.32	NS
BMI (kg/m2)		22.5±2.83	23.8±4.35	NS

First trimester mean HbA1c in group A was 7.52±1.26% (95% CI 7.21-7.82) with a minimun value of 5.3% and maximum of 11.7% (Figure 1). In group B mean HbA1c during the first trimester of pregnancy was 8.94±1.5% (95%CI 8.34-9.53), with a minimum value of 5.6% and a maximum of 12% (Figure 2).

The difference between mean HbA1c during the first trimester in the two groups was extremely significant ($p < 0.001$) (Figure 3).

Analysing the value of HbA1c in both studied groups we found that in pregnancies ending with healthy babies, 11 (16.42%) had a HbA1c lower then 6.5%, 42 (62.69%) between 6.5-8% and 14 (20.9%) exceeded 8%.

In the pregnancies ending with fetal loss, in 1 (3.7%) pregnancy HbA1c was lower then 6.5%, in 6 (22.22%) cases HbA1c was between 6.5-8% and 20 (74.07%) had a HbA1c value greater then 8% (Figure 4).

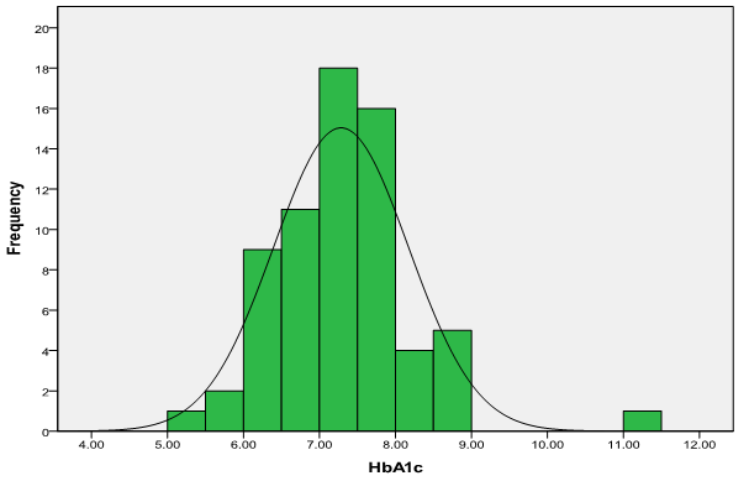

Figure 1. Group A- first trimester HbA1c distribution.

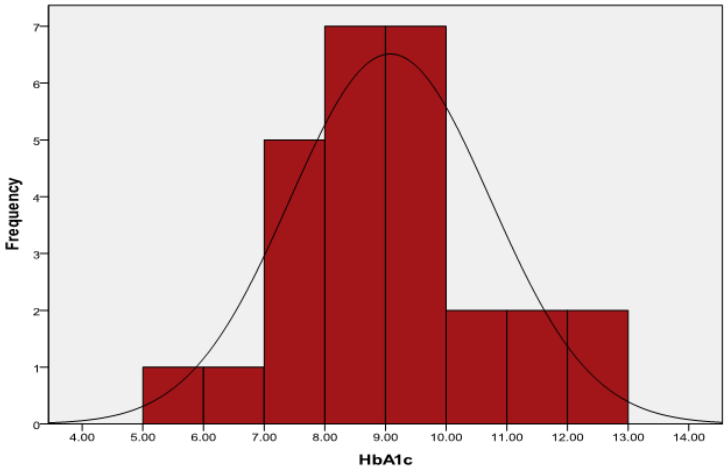

Figure 2. Group B-first trimester HbA1c distribution.

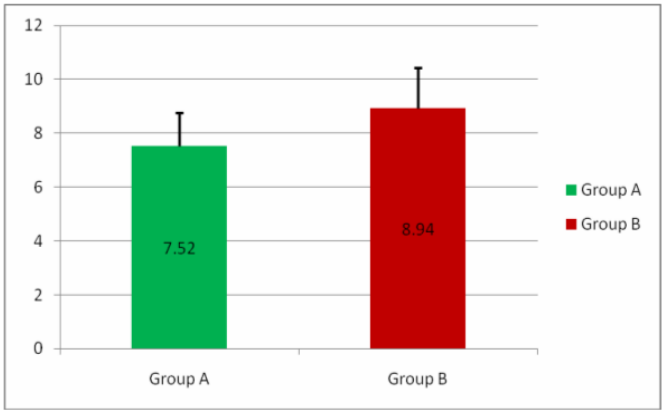

Figure 3. The difference between mean HbA1c in the study group.

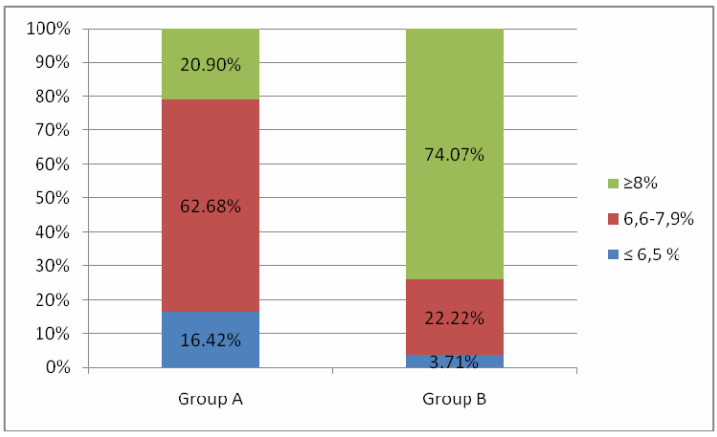

Figure 4. Prevalence of HbA1c in the study group.

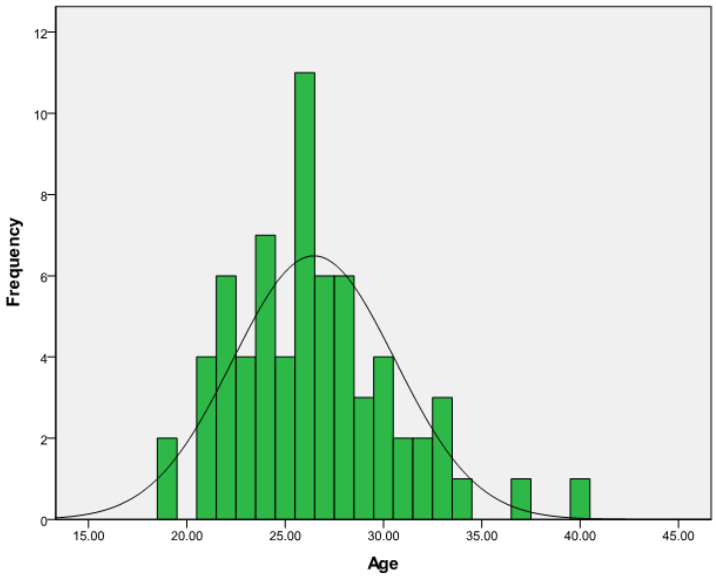

Figure 5. Group A-age distribution.

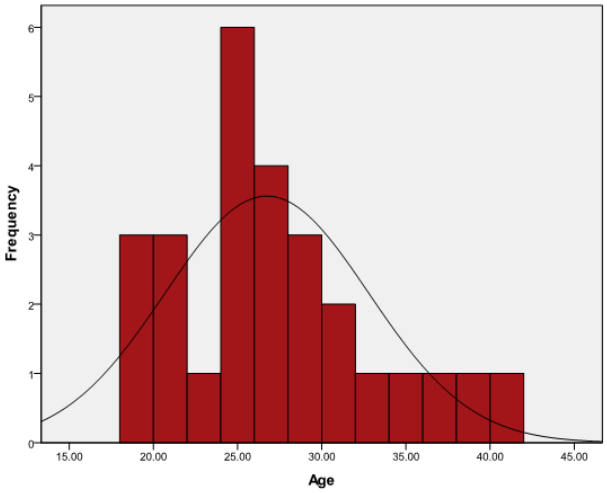

Figure 6. Group B-age distribution.

There was no difference beteween age distributions in the studied groups. Both of them had a normal distribution without a statisticaly significant difference, median age 25 vs 26, p=0.72 (Mann-Whitney test) (Figures 5,6).

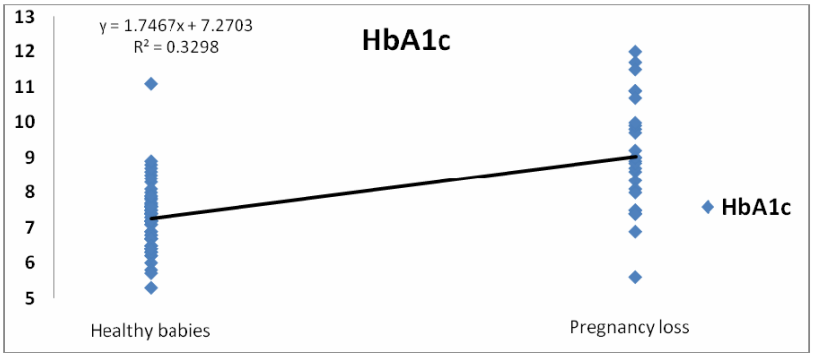

Figure 7. Correlation between first trimester HbA1c and pregnancy loss.

There was a moderate correlation between first trimester HbA1c and pregnancy loss. We found a 0.57 Pearson correlation coefficient between them (95% CI: 0.42 to 0.69; r squared= 0.32), with an extremely significant p value (p<0.001) (Figure 7).

We used a control group of 267 pregnancies without diabetes mellitus to determine the relative risk of pregnancy loss. There were no significant differences between age distributions in the two studied groups: normal pregnancies vs pregnacies complicated with type 1 diabetes mellitus (median age 25 vs 26; p=0.75 Mann-Whitney test). There was a consistent increase in the relative risk of pregnancy loss with stepwise increasing levels of HbA1c (Figure 8).

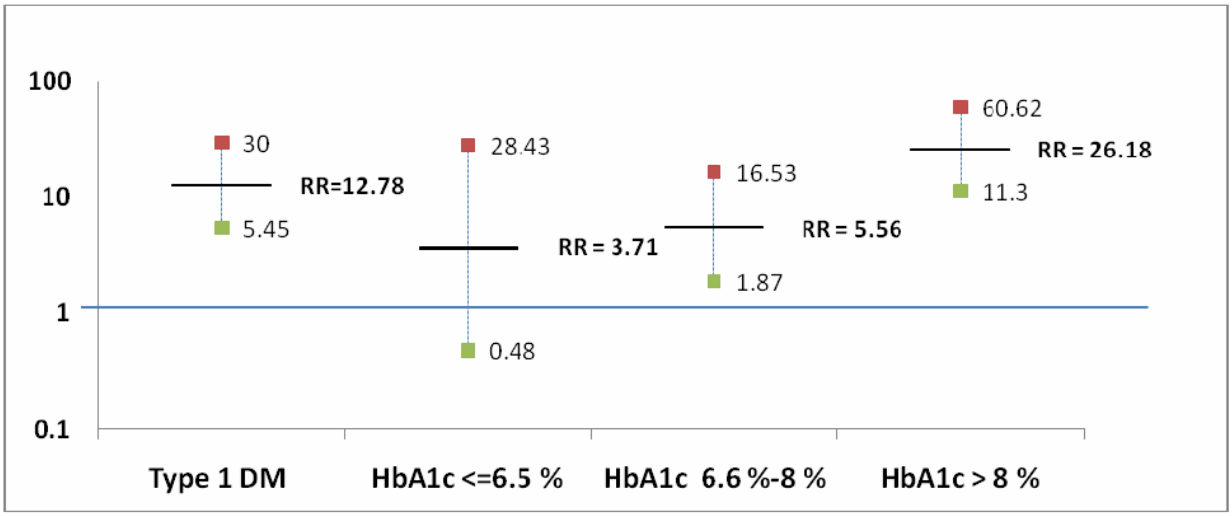

Figure 8. Relative risk of pregnancy loss.

We found a RR of pregnancy loss of 3.71 (95%CI 0.48-28.43, p=0.267) compared to the control group in pregnancies with a first trimester HbA1c lower than 6.5 %. HbA1c between 6.6-8 % was associated with a estimated RR of 5.56 (95%CI 1.87-16.53; p=0.004) compared to the control group. The RR in pregnancies with HbA1c greater then

8% was 26.1 (95%CI 11.3-60.62; p<0.001) compared to the control group. By comparing all pregnancies with diabetes mellitus with all the normal pregnancies we obtained a RR of 12.78 (95%CI 5.45-30; p<0.001).

Discussions and Conclusions

We found that pregnancies with a mean HbA1c of 7.52% had a good outcome ending with healthy babies while those in which the mean HbA1c value was 8.94% had severe outcomes ending with fetal loss. The risk of pregnancy loss in T1D pregnancies was significantly increased compared with the background control group. In our study the relative risk of pregancy loss increased when HbA1c exceeded 6.5%. We found a consistent increasing risk with stepwise increasing levels of HbA1c. A value of HbA1c less then 6.5% did not differ significantly from our control group concerning the frequency of adverse outcomes. As ilustrated above, the risk of pregnancy loss increased abruptly when HbA1c exceeded 6.5%.

HbA1c is considered the best marker for monitoring metabolic control in diabetic patients. There are evidence that a poor metabolic control during the first period of pregnancy correlates with severe pregnancy outcomes [13].

Nielsen et al. identified 573 pregnancies in 301 women with type 1 diabetes mellitus. Among them, pregnancies with a good outcome had a mean HbA1c of 7.4% while those with severe outcomes a value of 8.5%. There were 124 spontaneus abortions, 10 stillbirth, 3 neonatal death and 19 congenital malformations. He noticed that levels of HbA1c > 7% during early pregnancy corespond to an increased risk of severe outcomes [14].

A study performed by Jensen et al. on pregnancy outcomes in 933 women with type 1 diabetes mellitus found that the risk of severe outcomes was significantly higher in those cases in which peri-conceptional HbA1c exeeded 6.9%. The risk increased gradually with increasing HbA1c values [15].

Hanson et al. and Suhonen et al. studied the relation between glycemic control and the risk of congenital malformations in the offspring of type 1 diabetic women. They found out an increased risk between congenital malformation and raised HbA1c values during early pregnancy, sugesting the importance of a strict glycemic control in this period [16,17].

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