

Peri-conceptual HbA1c and risk of serious adverse pregnancy outcome in 933 women with type 1 diabetes

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Objectives: To study the association between peri-conceptual HbA1c and serious adverse pregnancy outcome (congenital malformations and perinatal mortality).

Methods: Prospective data collection in 933 singleton pregnancies complicated by type 1 diabetes.

Results: The risk of serious adverse outcome at different HbA1c levels was compared to the background population. The risk was significantly higher when peri-conceptual HbA1c exceeded 6.9%, and the risk tended to increase gradually with increasing HbA1c, and women with HbA1c exceeding 10.4% had a very high risk of 16%. Congenital malformation rate increased significantly at HbA1c above 10.4% whereas perinatal mortality was increased even at HbA1c below 6.9%.

Conclusions: These results support recent guidelines of pre-conceptual HbA1c levels below 7% in women with type 1 diabetes.

Recently, guidelines for management of pregnancy in women with pre-gestational diabetes have recommended pre-gestational HbA1c values below 7.0% (1, 2) and 6.1% (3). Previous studies have reported information of early HbA1c including 116 to 691 pregnancies (4-10). We aimed to study whether there is a threshold value for periconceptional HbA1c in women with type 1 diabetes below which the risk of serious adverse pregnancy outcome (congenital malformation and perinatal mortality) is not increased.

RESEARCH DESIGN AND METHODS

During 1993-99 pregnancies in women with type 1 diabetes were prospectively reported from eight centers to a central registry in the Danish Diabetes Association (11). Evaluated by alternative local data sources the coverage was 75-93% and clinical data showed no differential selection. Standard guidelines included pre-pregnancy counseling, but only 58% attended this (11). Four-hundred microgram folic acid was recommended in early pregnancy. All patients gave informed consent, and the local ethic committees approved the study.

Inclusion criteria were: delivery after 24 completed weeks (n=1215) or termination before 24 weeks because of ultrasound verified malformations (n=3). Multiple and recurrent pregnancies were excluded leaving 933 pregnancies. Of these 784 had complete data on pre-conceptional HbA1c while 1st trimester HbA1c was used as a surrogate in 149 cases. Background population data were based on 70.089 deliveries recorded by the Danish Health Board in 1995 (11).

Four different local HbA1c-assays were prospectively subjected to centralized quality control: Mono-S® HPLC-method, Boehringer Mannheim Tinaquant®, Roche Unimate® and Abbott IMx®. A standard assay (Mono-S) based on non-pregnant

subjects: $5.4\% \pm 1.0$ (mean \pm 2 SD) was used for reference. Correction was made in about 50% by multiplying HbA1c with a correction factor (mean of reference values for the standard assay divided by mean of the reference values for the given assay). Z-scores were derived from the standard assay. Corresponding z-scores and HbA1c values are shown in table 1.

Perinatal mortality was intrauterine death > 24 weeks or death during the first 7 days of life. Major congenital malformations were those responsible for death, causing a significant future handicap or requiring major surgery while minor congenital malformations comprised the remainder (8). Congenital malformations were assessed during hospital stay.

Data were analyzed by STATA 9.0 (Stata Corporation®) and are given as percent or relative risk and 95% confidence intervals. Chi-square test was used for comparing outcomes at different HbA1c levels.

RESULTS

Participants were 28.6 ± 4.8 years old with pre-pregnancy body mass index of 23.6 ± 3.5 kg/m²; duration of diabetes 12.3 years \pm 7.9 and time for admission 9.6 ± 3.5 weeks (mean \pm SD). All women were Caucasians. Seventy-one infants had serious adverse outcome: (45 congenital malformations including 23 major) and 31 perinatal deaths (5 with major malformations).

The relative risks of serious adverse outcome at increasing levels of periconceptional HbA1c compared to the background population are presented in table 1. The risk was increased when HbA1c exceeded 6.9% and tended to increase gradually with increasing HbA1c. Congenital malformation rate increased significantly at HbA1c above 10.4% whereas perinatal mortality was increased even at HbA1c below 6.9%.

CONCLUSIONS

To our knowledge, the present study is the largest prospective population-based study in pregnant women with type 1 diabetes with information of peri-conceptual HbA1c. Denmark is a small country with overall consensus on prenatal care and with the central validation of the HbA1c analysis we find our results representative and valid.

We used a reference based on HbA1c values outside pregnancy; and although HbA1c has been shown to decline during pregnancy (12) this is not until later stages of gestation.

The 3.9% risk of infants with congenital malformations in diabetic women with HbA1c z-scores below 3 (HbA1c 6.9%) did not differ significantly from the 2.8% background population risk. This can be due to a true biologic relationship but could also be explained by lack of power (only 21%), since the study was not designed to specifically address this association. It is therefore still possible that no safe HbA1c threshold exists above the upper normal range. The risk of congenital malformation at HbA1c z-scores above 10 (HbA1c 10.4%) was 4-fold and significantly increased compared to the background population. Perinatal mortality was increased also when z-score was <3 most likely reflecting the well-known fact that other factors than hyperglycemia such as smoking, nephropathy, preeclampsia, preterm delivery and HbA1c in *late* pregnancy affects perinatal mortality.

Suhonen et al. (9) studied 709 offspring of type 1 diabetic women and found an increased risk of congenital malformations at slightly raised HbA1c values (z-scores of 2.0-5.9). Analyzing 573 type 1 diabetic pregnancies Nielsen et al. (5) reported a dose-dependent association between the risk for adverse pregnancy outcome (abortion, stillbirth, neonatal death or major congenital malformation) and 1st trimester HbA1c without any threshold value. Hanson et al. (7)

examined 532 women with type 1 diabetes and 222 controls demonstrating a significant increase in congenital malformation and spontaneous abortion at HbA1c z-scores above 8.

The risk of the composite serious adverse outcome among diabetic women in our study was higher than in the background population when peri-conceptual HbA1c z-scores exceeded 3 but again: it cannot be ruled out that the risk at HbA1c z-scores <3 would have been significantly increased in a larger study. As illustrated in table 1 the risk of serious adverse outcome increased abruptly at HbA1c z-score above 10 suggesting three levels of risk: z-score <3 (low risk); z-score 3-10 (intermediate risk) and z-score ≥ 10 (high risk). Women attending pre-pregnancy care have significantly lower HbA1c levels than non-attenders (13) indicating that improved pre-pregnancy glycemic control is the target for reducing the risk of serious adverse diabetic pregnancy outcomes. The experience of many clinicians dealing with planning of pregnancy in women with type 1 diabetes is that HbA1c z-score <3 is often obtainable and associated with a limited number of mild hypoglycemic episodes.

In conclusion: The results of this study support a recommendation of pre-conceptual HbA1c levels below 7% in women with type 1 diabetes emphasizing the importance of pre-pregnancy counseling.

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Table 1. Serious adverse outcomes (congenital malformations and/or perinatal mortality) in offspring of women with type 1 diabetes and background population according to peri-conceptual glycemic control.

HbA1c (%) [*]	Z-score (SD's > mean)	No. of patients	Congenital malformations (%)	RR (95% CI) vs. Background population	Perinatal mortality (%)	RR (95% CI) vs. Background population	Serious adverse outcome (%)	RR (95% CI) vs. Background population
≥ 10.4	≥ 10	55	10.9	3.9 (1.8-7.8) †	5.5	7.3 (2.5-19.8) †	16.3	4.7 (2.5-8.1) †
8.9-10.3	7.0-9.9	128	3.9	1.4 (0.6-3.1)	6.3	8.3 (4.2-15.9) †	7.8	2.2 (1.2-3.9) †
7.9-8.8	5.0-6.9	182	5.0	1.8 (0.9-3.3)	3.3	4.4 (2.0-9.4) †	7.7	2.2 (1.3-3.6) †
6.9-7.8	3.0-4.9	284	4.9	1.8 (1.0-2.9)	2.8	3.8 (1.9-7.3) †	7.7	2.2 (1.5-3.3) †
<6.9	<3.0	284	3.9	1.4 (0.8-2.4)	2.1	2.8 (1.3-6.1) †	5.6	1.6 (1.0-2.6)
Background population (N=70.089)			2.8	1.0	0.75	1.0	3.5	1.0

* Standard reference 5.4 ± 1.0 (mean \pm 2 SD) in the non-diabetic background population. † significantly higher than background population at significance level of 0.05. Relative risk (RR) is given with 95% confidence intervals (95% CI).