Peri-Conceptional A1C and Risk of Serious Adverse Pregnancy Outcome in 933 Women With Type 1 Diabetes

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OBJECTIVE — To study the association between peri-conceptional A1C and serious adverse pregnancy outcome (congenital malformations and perinatal mortality).

RESEARCH DESIGN AND METHODS — Prospective data were collected in 933 singleton pregnancies complicated by type 1 diabetes.

RESULTS — The risk of serious adverse outcome at different A1C levels was compared with the background population. The risk was significantly higher when peri-conceptional A1C exceeded 6.9%, and the risk tended to increase gradually with increasing A1C. Women with A1C exceeding 10.4% had a very high risk of 16%. Congenital malformation rate increased significantly at A1C above 10.4%, whereas perinatal mortality was increased even at A1C below 6.9%.

CONCLUSIONS — These results support recent guidelines of preconceptional A1C levels <7% in women with type 1 diabetes.

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Recently, guidelines for management of pregnancy in women with pregestational diabetes have recommended pregestational A1C values <7.0% (1,2) and <6.1% (3). Previous studies have reported information of early A1C including 116–691 pregnancies (4–10). We aimed to study whether there is a threshold value for peri-conceptional A1C 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 1993–1999, 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 prepregnancy counseling, but only 58% attended this (11). A dose of 400 μg folic acid was recommended in early pregnancy. All patients gave informed consent, and the local ethics committees approved the study.

Inclusion criteria were as follows: delivery after 24 completed weeks (n = 1,215) 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 preconceptional A1C, whereas first-trimester A1C 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 A1C 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 nonpregnant subjects (5.4 ± 1.0% [mean ± 2 SD]) was used for reference. Correction was made in ~50% by multiplying A1C with a correction factor (mean of reference values for the standard assay divided by mean of the reference values for the given assay). The z scores were derived from the standard assay. Corresponding z scores and A1C values are shown in Table 1.

Perinatal mortality was intrauterine death at >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% CIs. The χ^2 test was used for comparing outcomes at different A1C levels.

RESULTS

— Participants were 28.6 ± 4.8 years old with a prepregnancy BMI of 23.6 ± 3.5 kg/m^2; duration of diabetes was 12.3 ± 7.9 years, and time for admission was 9.6 ± 3.5 weeks (means ± SD). All women were Caucasian. A total of 71 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 peri-conceptional A1C compared to the background population are presented in Table 1. The risk was increased when A1C exceeded 6.9% and tended to increase gradually with increasing A1C. Congenital

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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-conceptional glycemic control*

A1C (%)*	*z* score (SD > mean)	Number 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 ± 2 SD) in the nondiabetic background population. †Significantly higher than background population at significance level of 0.05. RR, relative risk.

malformation rate increased significantly at A1C above 10.4%, whereas perinatal mortality was increased even at an A1C 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-conceptional A1C. Denmark is a small country with an overall consensus on prenatal care, and with the central validation of the A1C analysis, we find our results representative and valid.

We used a reference based on A1C values outside pregnancy, and although A1C 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 A1C *z* scores <3 (A1C 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 A1C threshold exists above the upper normal range. The risk of congenital malformation at A1C *z* scores above 10 (A1C 10.4%) was fourfold and significantly increased compared with the background population. Perinatal mortality was increased also when *z* score was <3, most likely reflecting the well-known fact that factors other than hyperglycemia, such as smoking, nephropathy, preeclampsia, preterm delivery, and A1C in late pregnancy, affect 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 A1C 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 first trimester A1C without any threshold value. Hanson et al. (7) examined 532 women with type 1 diabetes and 222 control subjects, demonstrating a significant increase in congenital malformation and spontaneous abortion at A1C *z* scores >8.

The risk of the composite serious adverse outcome among diabetic women in our study was higher than in the background population when peri-conceptional A1C *z* scores exceeded three, but again, it cannot be ruled out that the risk at A1C *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 A1C *z* score >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 prepregnancy care have significantly lower A1C levels than nonattenders (13), indicating that improved prepregnancy 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 A1C *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 preconceptional A1C levels <7% in women with type 1 diabetes, emphasizing the importance of prepregnancy counseling.

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