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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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 malformations 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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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) | 7.7 | 1.6 (1.0–2.6) |

*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.

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