HbA_{1c} in Early Diabetic Pregnancy and Pregnancy Outcomes

A Danish population-based cohort study of 573 pregnancies in women with type 1 diabetes

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OBJECTIVE — To assess the association between first-trimester HbA_{1c} (A1C) and the risk of adverse pregnancy outcomes in type 1 diabetic pregnancies.

RESEARCH DESIGN AND METHODS — We identified all pregnant diabetic women in a Danish county from 1985 to 2003. A1C values from first trimester were collected, and pregnancy outcome was dichotomized as good (i.e., babies surviving the 1st month of life without major congenital abnormalities) and adverse (i.e., spontaneous and therapeutic abortion, stillbirth, neonatal death, or major congenital abnormalities detected within the 1st month). The prevalence of adverse outcomes was calculated according to quintiles of A1C. We computed receiver operating characteristic and lowess curve estimates and fitted logistic regression models to calculate prevalence odds ratio while adjusting for confounding by White class and smoking status.

RESULTS — Of 573 pregnancies, 165 (29%) terminated with adverse outcomes. The prevalence of adverse outcomes varied sixfold from 12% (95% CI 7.2–17) in the lowest to 79% (60–91) in the highest quintile of A1C exposure. From A1C levels >7%, we found an almost linear association between A1C and risk of adverse outcome, whereby a 1% increase in A1C corresponded to 5.5% (3.8–7.3) increased risk of adverse outcome.

CONCLUSIONS — Starting from a first-trimester A1C level slightly <7%, there is a dose-dependent association between A1C and the risk of adverse pregnancy outcome without indication of a plateau, below which the association no longer exits. A1C, however, seems to be of limited value in predicting outcome in the individual pregnancy.

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Elevated HbA_{1c} (A1C) is associated with increased risk of adverse pregnancy outcomes (e.g., abortion, stillbirth, and congenital abnormalities) (1–4). However, a level of A1C below which further improvement will carry no benefit for the fetus has not been defined. According to several studies (5–7), there seems to be a fairly broad range (up to around 10 SDs above the reference level) of acceptable metabolic control around conception over which the risk of adverse fetal outcome does not rise. In contrast to this concept of a relatively wide range of acceptable A1C values, Suhonen et al. (8) found that even a slightly raised A1C level was positively associated with an increased risk of major congenital abnormalities. We likewise found no indication of such an A1C threshold level, but our risk estimates were imprecise due to a small number of adverse outcomes (9). Low levels of A1C can only be achieved at the cost of an increased risk of hypoglycemic episodes, which are often feared by both patients and doctors (10,11). Therefore, it is of interest to establish whether there exists an A1C threshold, below which further reduction will not improve fetal prognosis.

The aim of our study was *1*) to assess the clinical utility of first-trimester A1C level in predicting adverse pregnancy outcome and *2*) to determine whether there is a threshold below which there is no association between A1C and the risk of adverse pregnancy outcome, taking into account the potential impact of White class and smoking habits.

RESEARCH DESIGN AND METHODS

— We conducted a population-based cohort study of women with type 1 diabetes whose pregnancies ended between 1 January 1985 and 31 December 2003. All women resided in North Jutland County, Denmark, with a population of 500,000.

We first identified all women residing in the county having ever obtained a diagnosis of diabetes or gestational diabetes (ICD 8:249.xx, 250.xx, or 634.74; ICD 10:E10.x, E11.x, or O24.x) recorded in the county's hospital discharge registry. This registry was established in 1976 and records all hospital discharge diagnoses since 1980. Starting from 1994, outpatient contacts also have been recorded. We identified all discharge records among these women with diagnoses of either birth or spontaneous, elective legal, or therapeutic abortion. Medical records were reviewed to extract data on women's age, smoking habits, duration of diabetes, White class (12), A1C values in the last 2 months before conception and at different periods in pregnancy, baby's vital status at birth, and congenital abnormalities. No women were referred to hospitals outside the county. We included only women with pregestational type 1 diabetes with A1C values recorded in the first trimester; women who requested a legal abortion before the end of the 12th gestational week were excluded.

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Abbreviations: ROC, receiver operating characteristic.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Management of pregnant diabetic women

Hospital care of pregnant women with diabetes has been centralized at the Department of Obstetrics at Aalborg Hospital in collaboration with the Department of Endocrinology (13). All pregnant women routinely are offered regular and free appointments in outpatient clinics conducted by a few obstetricians and endocrinologists with special interest in diabetes and pregnancy. Our aim has been to obtain an A1C level as low as possible. All diabetic women with first contact to the department before 12th gestational week had ultrasonographic pregnancy dating in the first trimester. If this dating differed from gestational length based on last menstrual cycle by more than 7 days, the ultrasound dating was used to define conception. Routine ultrasound scan to detect nuchal translucency was performed between the 11th and 14th gestational week; malformation scan was performed between the 16th and 20th week and repeated between the 21th and 24th week.

Maternal metabolic control

Analysis of A1C routinely has been available in the county since 1982. Since 1985, A1C has been analyzed according to the standards used in the Diabetes Control and Complications Trial with an essentially unchanged analytical methodology (14). Reference A1C values in our nondiabetic population are 4.5–6.0%, and at an A1C level of 5.4% the SD was 0.13% and the coefficient of variation 2.45%.

Data on A1C values were collected from hospital records and, since 1997, also from a computerized database at the Department of Clinical Chemistry, which stores all A1C analyses countywide. For the study analyses, we used all available A1C values in the last 2 months before conception and in the first trimester. If more than one measurement was available in the same period, the median value was used.

Examination of newborns

All newborns were observed at the neonatal unit at the Department of Pediatrics as long as deemed necessary but for at least 24 h. They all were examined according to a standardized checklist by a pediatrician at delivery, on the 1st day after birth, and before discharge from the hospital (15). Congenital abnormalities were classified as *1*) lethal, *2*) major (requiring surgery or causing lasting disability), and *3*) minor (causing no lasting disability), but only lethal and major congenital abnormalities were included in the present analyses. Finally, we abstracted newborn's hospital records for data on mortality and morbidity diagnosed within the 1st month of life.

Categorization of outcome

Pregnancy outcomes were dichotomized into "good" (i.e., babies surviving the 1st month of life without detected congenital abnormalities) and "adverse" (i.e., composed of spontaneous and therapeutic abortion, stillbirth, neonatal death, or major congenital abnormalities detected within the 1st month of life). Additionally, we defined an outcome subgroup in which the impact on the fetus of maternal metabolic control in early pregnancy is considered to be most pronounced. This subgroup, termed "early adverse," included spontaneous and therapeutic abortions and lethal and major congenital abnormalities. Finally, we compared outcomes of pregnancies with and without A1C values available from the first trimester.

Statistical analyses

Prediction analyses. We first cross tabulated the study variables and outcomes. Then, we computed the prevalence of adverse and early adverse outcomes according to five levels of maternal A1C exposure defined as quintiles of A1C, as recorded in the first trimester in pregnancies terminating with adverse or early adverse outcomes. Receiver operating characteristic (ROC) curves with stepwise increments of 0.5% A1C from ≤5.0 to ≥12.0% were calculated to quantify sensitivity and specificity of various levels of A1C exposure for the prediction of adverse outcome.

Explanatory analyses. We used lowess curve estimates to assess the association between A1C and the risk of adverse or early adverse pregnancy outcome (16). We then fitted multiple logistic regression models to compute prevalence odds ratios (ORs), as estimates of relative risks, adjusted for potential confounding by maternal White class (B-C [reference] and D-F) and smoking status (yes/no). The estimates from both the crude and adjusted analyses are shown with approximate 95% CIs using the Wald approximation. These analyses were then repeated with A1C included in the models as a continuous variable. To assess the potential impact of missing A1C values, we conducted sensitivity analyses in which missing values were imputed with A1C values ranging from 6.0 to 10%.

Prediction and explanatory analyses were first performed in the entire cohort of pregnancies (n = 573) and then repeated in a subcohort where each woman contributed only her first recorded pregnancy in the study period (n = 301). In addition, analyses were repeated in pregnancies with available A1C values from the last 2 months before conception (n = 354). The latter pregnancies were all found to be included in the cohort with first-trimester values, and the data are thus not shown separately. Student's t test was used for comparisons of A1C values in various outcome categories. We used version 9.0 SE of Stata software for all analyses. The study was approved by the regional ethics committee (file no. 2-16-4-5-95).

RESULTS

Descriptive data

We identified 573 pregnancies registered in 301 women with type 1 diabetes in the study period. The distribution of pregnancies according to White class was B: 181 (32%), C: 180 (31%), D: 115 (20%), and F: 97 (17%). Ninety women with gestational and 28 with type 2 diabetes were not included in the study. We retrieved first-trimester A1C values for 474 (83%) pregnancies, leaving 99 (17%) without data on maternal metabolic control. Pregnancies without available A1C values were more likely to end with an adverse outcome than were pregnancies with A1C data available: relative risk 3.3 (95% CI 2.6–4.1) (Table 1). Of the entire cohort of 573 pregnancies, 165 (29%) had adverse outcome and 148 (26%) had early adverse outcome (Table 1). In the subcohort of 301 first pregnancies, the corresponding figures were 81 (27%) and 66 (22%).

The adverse pregnancy outcomes consisted of spontaneous abortion (n = 124), therapeutic abortion (n = 9), stillbirth (n = 10), neonatal death (n = 3), and congenital abnormalities (n = 19). Minor congenital abnormalities were suspected or found in 20 babies. In pregnancies with available data on glycosylated hemoglobin, mean A1C values were 7.4% (95% CI 7.3–7.5) in pregnancies terminating with a good outcome (n = 376) compared with 8.5% (8.2–8.9) in pregnancies ending with an adverse outcome (n = 98).

Table 1—*Number of pregnancies in each category of pregnancy outcome and of pregnancies with and without data on first-trimester A1C*

	Total number of pregnancies	Pregnancies with data on A1C	Pregnancies without data on A1C	Relative risk of adverse and early adverse outcome
n	573	474	99	—
Good outcome	408 (71) (67–75)	376 (79) (76–83)	32 (32) (24–42)	—
Adverse outcome	165 (29) (25–33)	98 (21) (17–25)	67 (68) (58–76)	3.3 (2.6–4.1)
Early adverse outcome	148 (26) (22–30)	85 (18) (15–22)	63 (64) (54–72)	3.6 (2.8–4.6)

Data are *n* (%) (95% CI) or relative risk (95% CI) of adverse and early adverse outcome for pregnancies without versus with recorded first-trimester A1C.

Prediction analyses

The prevalence of pregnancies terminating with an adverse outcome increased from 12% in the lowest to 79% in the highest category of A1C exposure (Table 2).

The ROC curve for an adverse pregnancy outcome as a function of A1C value for all pregnancies is shown in Fig. 1. The areas under the ROC curves are 0.69 (95% CI 0.63–0.76) for an adverse and 0.71 (0.64–0.77) for an early adverse outcome. In the subcohort of first pregnancies, the results were identical (curves not shown). Among pregnancies with A1C values >10% ($n = 34$), we found 21% (10–37) with good pregnancy outcome, while 15% (8–26) of pregnancies with first-trimester A1C values <6.0% ($n = 55$) terminated with an adverse outcome.

Explanatory analyses

The lowess curve estimates are seen in Fig. 2. From an A1C level of slightly <7.0%, there was a consistently positive and almost linear association between increasing A1C levels and the risk of adverse pregnancy outcome. Note that the lowess curve estimates should be interpreted with caution at the extremes of exposure range, due to low number of pregnancies and to the inherent characteristics of the model.

The prevalence odds ratios for adverse and early adverse outcome according to quintiles of glycosylated hemoglobin are shown in Table 2. We found an increasing risk of both types of adverse

Table 2—*Prevalence and prevalence odds ratios with 95% CIs for adverse and early adverse outcome in quintiles of first-trimester A1C exposure level for all pregnancies and separately for first pregnancies*

			Entire cohort ($n = 573$)			Subcohort ($n = 301$)	
	Good outcomes (*n*)	Adverse outcomes (*n*)	Prevalence of adverse outcome	Crude	Adjusted	Crude	Adjusted
Dependent variables for adverse pregnancy outcome							
1st quintile A1C: ≤7.0% (ref.)*	153	20	12 (7.6–17)	1 (—)	1 (—)	1 (—)	1 (—)
2nd quintile A1C: 7.1–7.8%	93	19	17 (11–25)	1.6 (0.8–3.1)	1.8 (0.8–3.9)	1.4 (0.6–3.4)	1.2 (0.4–3.5)
3rd quintile A1C: 7.9–8.9%	87	20	19 (12–27)	1.8 (0.9–3.5)	2.1 (1.0–4.5)	2.3 (0.9–5.9)	2.3 (0.8–7.1)
4th quintile A1C: 9.0–10.2%	38	20	35 (24–47)	4.0 (2.0–8.2)	4.2 (1.8–9.7)	2.6 (1.0–6.4)	2.0 (0.6–6.3)
5th quintile A1C: ≥10.3%	5	19	79 (60–91)	29.1 (9.8–86.4)	30.3 (8.6–106)	19.3 (5.2–71.4)	16.0 (3.2–78.9)
White class B-C (ref.)					1 (—)		1 (—)
White class D-F					1.1 (0.6–1.9)		1.5 (0.7–3.3)
Nonsmoking (ref.)					1 (—)		1 (—)
Smoking					1.1 (0.6–2.0)		0.9 (0.4–2.0)
Dependent variables for early adverse pregnancy outcome							
1st quintile A1C: ≤7.2% (ref.)†	178	18	9 (5.6–14)	1 (—)	1 (—)	1 (—)	1 (—)
2nd quintile A1C: 7.3–7.9%	77	17	18 (12–27)	2.2 (1.1–4.5)	2.7 (1.2–6.1)	1.6 (0.6–4.3)	1.4 (0.4–5.1)
3rd quintile A1C: 8.0–9.0%	87	16	16 (10–24)	1.8 (0.9–3.7)	2.2 (0.9–5.1)	2.7 (1.0–7.6)	3.5 (1.0–12.1)
4th quintile A1C: 9.1–10.2%	29	17	37 (25–51)	5.8 (2.7–12.5)	6.7 (2.8–16.5)	2.3 (0.8–6.5)	1.9 (0.5–7.9)
5th quintile A1C: ≥10.3%	5	17	77 (57–90)	33.6 (11.1–101)	35.0 (9.5–129)	48.1 (8.9–259)	70 (6.6–742)
White class B-C (ref.)					1 (—)		1 (—)
White class D-F					0.9 (0.5–1.7)		1.2 (0.4–3.1)
Nonsmoking (ref.)					1 (—)		1 (—)
Smoking					1.1 (0.6–2.0)		0.7 (0.3–2.0)

Data are OR (95% CI) except for prevalence of adverse outcome, which are % (95 % CI). Maternal White class and smoking are included in the adjusted analyses. The quintile values refer to cutoff values defined among adverse (*) and early adverse (†) outcomes in the entire cohort.

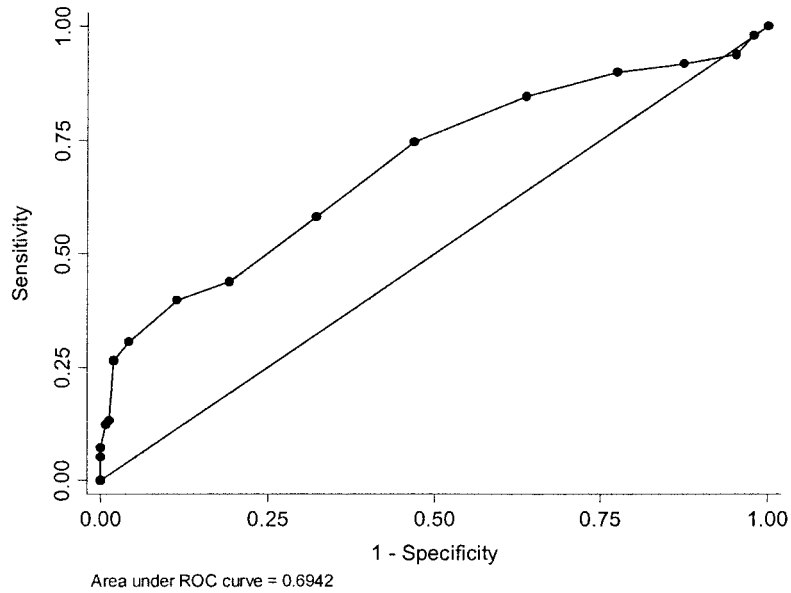

Figure 1—*ROC curve of adverse pregnancy outcome according to first-trimester A1C values based on 376 pregnancies with good outcome and 98 pregnancies with adverse outcome. Incremental level of A1C exposure was 0.5%, which equals 16 categories. Area under the ROC curve: 0.69 (95% CI 0.63–0.76). Solid straight line represents no association. Line with black circles represents association seen in actual dataset.*

outcomes with each incremental step in A1C exposure. In the subcohort of first pregnancies, the same tendency could be seen, though the estimates had wider CIs due to the reduced number of outcomes. Including White class and smoking in the models did not materially change the relative risk estimates.

When A1C was included as a continuous explanatory variable into the logistic regression model, a 1% increase in A1C corresponded to a 5.5% (95% CI 3.8–7.3) increase in prevalence odds ratio of having an adverse outcome and 6.1% (4.2–8.0) of having an early adverse pregnancy outcome.

In the sensitivity analyses, we imputed various levels of A1C in 99 pregnancies without A1C values. The prevalence odds ratio of adverse outcome was reanalyzed at each level of imputation with A1C as a continuous explanatory variable. At an A1C imputation level of 7%, the prevalence odds ratio of adverse outcome was 3.0 (95% CI 1.6–4.4), and the association gradually became stronger for all higher imputed values of A1C. Essentially identical associations were found when analyzing the 354 pregnancies with A1C values available from last 2 months before conception.

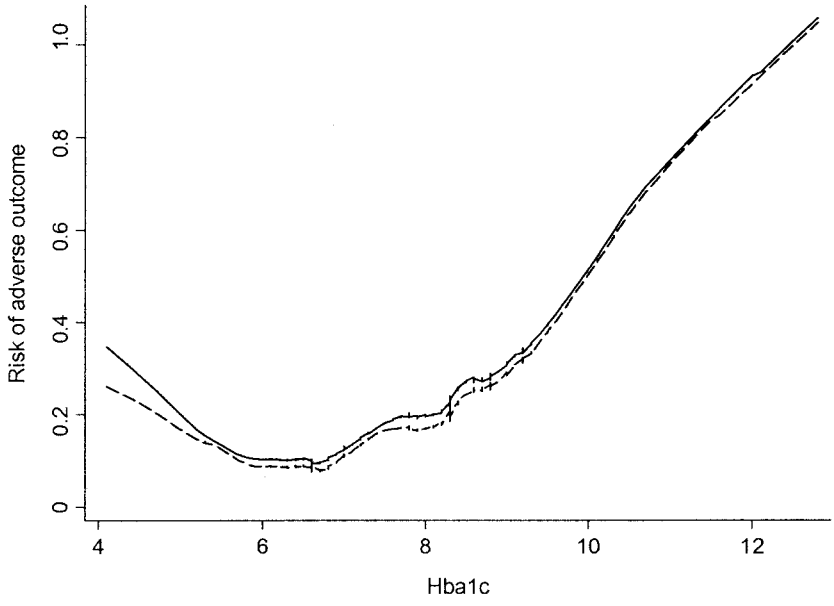

Figure 2—*Relation between first-trimester A1C level and pregnancy outcome using the lowess model with bandwidth of 0.5. Full line depicts adverse and broken line early adverse outcome. Based on 376 pregnancies with good outcomes and 98 pregnancies with adverse outcomes.*

CONCLUSIONS — We found a sixfold increase in the risk of adverse pregnancy outcome in women with A1C levels in the highest quintile, compared with women who had A1C levels in the lowest quintile in the first trimester. We observed a monotone increase in risk when A1C levels exceeded 7% equivalent to 1% above the upper limit in our reference population. Pregnancies without A1C data had a threefold increased risk of adverse outcome.

A1C values were missing in 17% of the pregnancies. Unknown factors determining the availability of A1C values in 474 pregnancies could bias our analyses. But the associations remained significant even if all 99 missing A1C values were replaced with values as low as 7%. Thus, the sensitivity analysis suggests that our results are robust.

The higher risk of adverse outcome in pregnancies without available first-trimester A1C values indicates that our study considered a group of pregnant diabetic women with better-than-average metabolic control. The observed associations likely would become stronger if all pregnant diabetic women could be included.

It would be optimal to estimate the association between maternal metabolic control and specific outcomes with presumably common etiology (e.g., early and late spontaneous abortion, congenital abnormalities, stillbirth, and peri- and neonatal mortality). However, very large cohorts are required to assess such specific associations, as each of these adverse outcomes are rare. At the same time, the composite adverse outcome considered here is clinically relevant as it addresses the question frequently posed by pregnant women: "What are the chances of this pregnancy leading to a birth of a healthy baby?"

Though an unknown part of the observed association could be due to confounding from other maternal diseases, medication use, or consumption of coffee

and alcohol, given the magnitude and the dose-dependent nature of the observed association, it appears unlikely that it could solely be ascribed to unmeasured confounding (17). In the first pregnancy subcohort, the associations essentially followed the same patterns as seen in the entire cohort.

Greene et al. (5) found no statistically significant association between first-trimester A1C level and risk of major malformations until A1C values reached ≥12 SDs above reference, although data suggested a trend toward a positive association at lower levels of A1C. Our use of lowess curves, however, is less likely to produce bias and to distort the results by post hoc definition of exposure categories (18). Kitzmiller et al. (6) reported a gradual and increasing association between maternal A1C and risk of congenital abnormalities, but due to low number of outcomes (12 major congenital abnormalities in 110 pregnancies) the association did not reach statistical significance at the lower levels of exposure. Based on ROC curves, our results are similar to those by Rosenn et al. (7), reporting an A1C level ≥13% (7.5 SDs above the normal mean) as a cutoff value for predicting abortion or congenital abnormality. However, the sensitivity of this threshold value was only ~44%, and we therefore do not believe that this threshold is clinically useful. In contrast, Suhonen et al. (8) found a threefold increased risk of major malformations at A1C levels from 2 to 6 SDs above reference in a series of 660 pregnancies. Due to a higher number of outcomes, both Suhonen et al's and our study obtain a greater precision in risk estimates.

The ROC curve is a useful analytical tool graphically presenting the relation between sensitivity and specificity at various levels of A1C. The slope of the ROC curve runs almost parallel to the diagonal line, indicating low ability to predict outcome. It therefore seems impossible to define a single specific level of A1C as the optimal cutoff value. Despite a sixfold increase in risk of adverse outcome from the lowest to the highest quintile of A1C level, we find that these values are of limited value in predicting outcome in the individual pregnancy. In the highest quintile, ~21% of the pregnancies had a good outcome and, conversely, 15% of the pregnancies with first-trimester A1C values within our reference range terminated with an adverse outcome. The fetus may only be vulnerable to the teratogenic effect of hyperglycemia during a short time window, and A1C may not reflect actual excursions in blood glucose at that specific time (19).

Increasing levels of first-trimester glycosylated hemoglobin starting from values slightly <7% show a dose-dependent association with the risk of adverse pregnancy outcome. Above this level, we do not find any indication of a plateau beyond which the association no longer exits. The specificity and sensitivity of A1C is relatively low, making A1C measurements an imprecise tool in predicting adverse outcome in the individual pregnancy.

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