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Maternal Glycemic Control in Type 1 Diabetes and the Risk for Preterm Birth

A Population-Based Cohort Study

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Background: Maternal type 1 diabetes (T1D) has been linked to preterm birth and other adverse pregnancy outcomes. How these risks vary with glycated hemoglobin (or hemoglobin A_{1c} [HbA_{1c}]) levels is unclear.

Objective: To examine preterm birth risk according to periconceptional HbA_{1c} levels in women with T1D.

Design: Population-based cohort study.

Setting: Sweden, 2003 to 2014.

Patients: 2474 singletons born to women with T1D and 1 165 216 reference infants born to women without diabetes.

Measurements: Risk for preterm birth (<37 gestational weeks). Secondary outcomes were neonatal death, large for gestational age, macrosomia, infant birth injury, hypoglycemia, respiratory distress, 5-minute Apgar score less than 7, and stillbirth.

Results: Preterm birth occurred in 552 (22.3%) of 2474 infants born to mothers with T1D versus 54 287 (4.7%) in 1 165 216 infants born to mothers without diabetes. The incidence of preterm birth was 13.2% in women with a periconceptional HbA_{1c} level below 6.5% (adjusted risk ratio [aRR] vs. women without T1D, 2.83 [95% CI, 2.28 to 3.52]), 20.6% in those with a level from 6.5% to less than 7.8% (aRR, 4.22 [CI, 3.74 to 4.75]), 28.3% in those with a level from 7.8% to less than 9.1% (aRR, 5.56 [CI, 4.84 to 6.38]), and 37.5% in those with a level of 9.1% or higher (aRR, 6.91 [CI, 5.85 to 8.17]). The corresponding aRRs for medically indicated preterm birth (n = 320) were 5.26 (CI, 3.83 to 7.22), 7.42 (CI, 6.21 to 8.86), 11.75 (CI, 9.72 to 14.20), and 17.51 (CI, 14.14 to 21.69), respectively. The corresponding aRRs for spontaneous preterm birth (n = 223) were 1.81 (CI, 1.31 to 2.52), 2.86 (CI, 2.38 to 3.44), 2.88 (CI, 2.23 to 3.71), and 2.80 (CI, 1.94 to 4.03), respectively. Increasing HbA_{1c} levels were associated with the study's secondary outcomes: large for gestational age, hypoglycemia, respiratory distress, low Apgar score, neonatal death, and stillbirth.

Limitation: Because HbA_{1c} levels were registered annually at routine visits, they were not available for all pregnant women with T1D.

Conclusion: The risk for preterm birth was strongly linked to periconceptional HbA_{1c} levels. Women with HbA_{1c} levels consistent with recommended target levels also were at increased risk.

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About 1 in 200 to 250 pregnancies are complicated by preexisting type 1 diabetes (T1D) (1). Several studies have linked T1D to preterm birth and other adverse outcomes in pregnant women (2, 3) and their offspring (3–5), but the relationship between maternal glycemic control and preterm birth is less clear (6). Preterm birth is the second most common cause of death in children younger than 5 years and is a cause of childhood morbidity (7).

In recent years, guidelines have underlined the importance of strict glycemic control, with at least 3 major organizations now recommending a target hemoglobin A_{1c} (HbA_{1c}) level less than 6.5% (<48 mmol/mol) in early pregnancy (8–10). However, because these recommendations originate from research regarding congenital malformations and large for gestational age (LGA) infants, whether such strict glycemic control prevents or reduces an excess risk for preterm birth in women with T1D is uncertain.

We linked nationwide Swedish registers to examine adverse pregnancy outcomes in 2474 singleton deliveries according to HbA_{1c} levels in mothers with T1D. The primary outcome was preterm birth. We also examined neonatal death, LGA, macrosomia, infant birth injury, hypoglycemia, respiratory distress, low Apgar score, and stillbirth.

Methods

Data Sources

Through the personal identity numbers assigned to all Swedish residents (11), we linked the following Swedish national registers: the National Diabetes Register (NDR) (12), the National Patient Register (13), the Medical Birth Register (14), the Cause of Death Register (15), and the Education Register (described in detail in the Supplement, available at Annals.org).

Study Participants

Figure 1 shows the formation of the cohort. We used the Medical Birth Register to identify all liveborn singleton births in Sweden between January 2003 and December 2014. Exclusion criteria were a missing ma-

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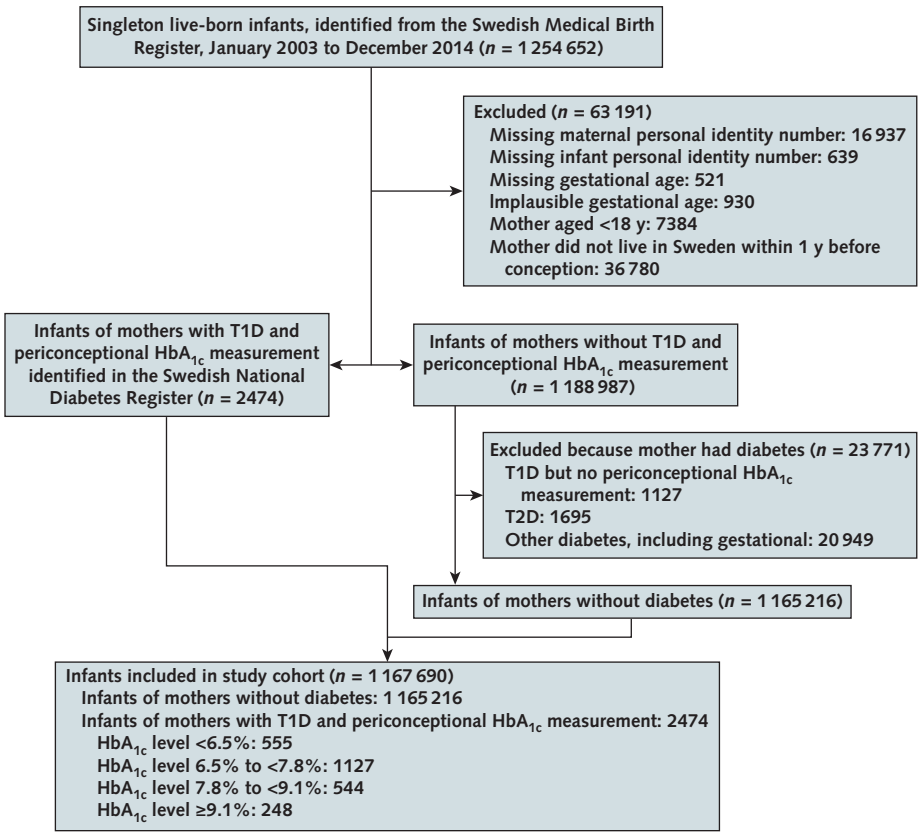
Figure 1. Design of a nationwide cohort study of the association between periconceptional HbA_{1c} levels in mothers with T1D and the risk for preterm birth, Sweden, 2003 to 2014.



HbA_{1c} = hemoglobin A_{1c} (glycated hemoglobin); T1D = type 1 diabetes.

ternal or infant personal identity number, no or improbable gestational age (≤22 weeks or >44 weeks), maternal age younger than 18 years at delivery (the NDR covers only persons aged ≥18 years), and nonresidence in Sweden the year before conception.

T1D and HbA_{1c}

We used the NDR to identify mothers with a diagnosis of T1D before conception and up to 91 days after conception and who had at least 1 registered HbA_{1c} value any time between 90 days before to 91 days after conception. For women who had 2 or more HbA_{1c} values within this 182-day interval, the latest value was used. Hemoglobin A_{1c} levels were defined in millimoles per mole according to the International Federation of Clinical Chemistry and Laboratory Medicine and converted into percentages according to the Diabetes Control and Complications Trial (16). Hemoglobin A_{1c} values were divided into 4 categories, with the lowest category reflecting the current HbA_{1c} recommendation during pregnancy and the other categories defined arbitrarily: less than 6.5%, 6.5% to less than 7.8%, 7.8% to less than 9.1%, and 9.1% or greater (corresponding to <48 mmol/mol, 48 to <62 mmol/mol, 62 to <76 mmol/mol, and ≥76 mmol/mol). Reference mothers were defined as those without diabetes of any type before conception and up to 91 days after conception, thus excluding mothers with a record of type 2 or other non–type 1 diabetes, as well as those with T1D who did not have a registered HbA_{1c} value in the periconceptional period (**Supplement Table 1**, available at Annals.org).

Preterm Birth

Preterm birth (the primary outcome measure) was defined as less than 37 completed gestational weeks. We also examined very preterm birth (<32 weeks). In addition, we distinguished between medically indicated (that is, induced birth or labor or planned cesarean section) and spontaneous preterm birth. Births starting with preterm premature rupture of the membranes also were classified as spontaneous. Gestational age and date of conception were estimated by using routine ultrasonography or, if there was no record of ultrasonography, the last menstrual period. Early second-trimester ultrasonography for determining gestational age has been used routinely in Sweden since 1990 and is performed in about 95% of pregnant women (17).

Secondary Outcomes

Neonatal death was defined as death less than 28 days after birth. Large for gestational age was defined

as a birth weight greater than 2 SDs above the sex-specific mean for gestational age (18), in line with Swedish ultrasonography-based reference curves, and macrosomia was defined as a birthweight greater than 4.5 kg. We defined low Apgar score as less than 7 points at 5 minutes. Analyses of low Apgar scores and macrosomia were based on term infants alone. Finally, we examined neonatal hypoglycemia (International Classification of Diseases, 10th Revision [ICD-10], code P70.4) and respiratory distress (ICD-10 code P22) within the first 4 months of life. Stillbirths were recorded from 28 completed gestational weeks until July 2008 and thereafter from 22 completed weeks, with the analysis based on 1 171 815 births (livebirths and stillbirths). All outcome data (including preterm birth) were retrieved from the Medical Birth Register, except for data on neonatal death, which were retrieved from the Cause of Death Register, and on infant birth injuries (ICD-10 codes P10 to P15), for which outcomes were identified from the Medical Birth Register and the National Patient Register during the first year of life.

Statistical Analysis

We estimated adjusted risk ratios (aRRs) and adjusted risk differences for adverse pregnancy outcomes on the basis of HbA_{1c} levels in women with T1D versus those without it.

Generalized linear regression was used to estimate aRRs. To account for correlations among infants born to the same mother, we used a generalized estimated equation model assuming a Poisson distribution with a log link and an exchangeable covariance matrix, where the identity of the mother was used as a cluster, resulting in robust estimates of the SE (19). The following covariates were entered into our modified Poisson regression model: calendar year of birth, maternal age, country of birth, living with a partner, education, parity, body mass index (BMI), smoking status, and diabetes-associated autoimmune diseases (for definitions, data sources, and extent of missing values, see **Supplement Table 2**, available at Annals.org). A log-binomial regression model with a robust sandwich estimator (20, 21) was tested on the data but failed to converge (a model with 5 instead of the desired 9 included covariates converged, however, for preterm birth with similar estimates for aRRs).

The adjusted risk differences—that is, the adjusted absolute differences measured in percentage points of pregnancy outcomes (such as preterm birth)—were calculated by using a marginal structural binomial regression model by estimating standardized risk differences (22). Inverse probability weights were calculated by using a logistic model including the same covariates as in the model estimating aRRs. These weights were used to estimate standardized differences in a generalized estimated equation model with a binomial distribution that had an identity link and an exchangeable covariance matrix, as well as to obtain robust estimates of the SE by using the identity of the mother as a cluster.

Mode imputation was used for country of birth, living with a partner, and education. For BMI and smoking, we used a multiple imputation regression model by fully conditional specification methods with 5 iterations (23). Variables included in the model were calendar year of birth, maternal age, country of birth, living with a partner, education, parity, BMI, maternal height, smoking status, and diabetes-associated autoimmune diseases. Regression estimates from each of the 5 sets of data were combined by using the MIANALYZE procedure in SAS, version 9.4 (SAS Institute).

We also used a logistic regression model to estimate the adjusted proportion of preterm births corresponding to HbA_{1c} levels on a continuous scale, where HbA_{1c} was included as a natural cubic spline function (with knots at HbA_{1c} levels of 6%, 7%, 8%, 9%, and 10%). The model was adjusted further for calendar year of birth, maternal age, country of birth, living with a partner, education, parity, BMI, smoking status, and diabetes-associated autoimmune diseases. Using this model, we estimated the adjusted risk for all 2474 births in the 5 sets of data from the multiple imputation procedure, and then we added a polynomial trendline (fourth degree) on all observations (for the point estimate as well as on the high and low 95% CI limit estimates).

In an additional analysis, we explored the effect of an HbA_{1c} cutoff (<6.0%) lower than the one currently recommended in the guidelines (<6.5%) on the risk for preterm birth.

Further, we examined the risk for preterm birth on the basis of alternative markers of poor glycemic control and diabetes severity, including hospitalization due to acidosis and to T1D within 365 days before conception, long-term glycemic control (average of the last 3 HbA_{1c} values), albuminuria, and estimated glomerular filtration rate (eGFR; <60 mL/min/1.73 m^2, 60 to 120 mL/min/1.73 m^2, and >120 mL/min/1.73 m^2) (see **Supplement Table 3**, available at Annals.org, for detailed information).

Finally, we calculated E-values (24) indicating the strength of association with both T1D in mothers and preterm birth that an unmeasured confounder would need to fully explain away the observed aRRs, overall and by HbA_{1c} level.

Results were considered statistically significant if the 95% CIs did not include 1.0 for risk ratios and 0 for risk differences. Data were analyzed by using SAS, version 9.4; SAS procedures used and the analyses for which they were used are described in the **Supplement** (available at Annals.org).

Ethics

This study was approved by the Regional Ethical Review Board in Stockholm, Sweden (approval 2016/1969-31). All women registered in the NDR had provided informed consent; for the population-level comparisons, the review board waived consent for this register-based study (25).

Role of the Funding Source

The funding agencies had no role in the design, conduct, and analysis of the study or in the decision to submit the manuscript for publication.

Table 1. Characteristics of Mothers of Infants Included in the Cohort, by T1D Status and HbA_{1c} Level in the Periconceptional Period*

Characteristic	No Diabetes (*n* = 1 165 216)	T1D Overall (*n* = 2474)	T1D, by HbA_{1c} Level			
			<6.5% (*n* = 555)	6.5% to <7.8% (*n* = 1127)	7.8% to <9.1% (*n* = 544)	≥9.1% (*n* = 248)
Mean age (SD), *y*	30.1 (5.1)	30.0 (4.8)	30.3 (4.5)	30.5 (4.6)	29.8 (5.1)	27.7 (5.3)
Nordic country of birth	940 624 (80.7)	2361 (95.4)	526 (94.8)	1093 (97.0)	509 (93.6)	233 (94.0)
Living with a partner	1 102 933 (94.7)	2358 (95.3)	540 (97.3)	1093 (97.0)	499 (91.7)	226 (91.1)
Year of delivery						
2003–2006	366 476 (31.5)	501 (20.3)	115 (20.7)	228 (20.2)	117 (21.5)	41 (16.5)
2007–2010	393 387 (33.8)	852 (34.4)	212 (38.2)	387 (34.3)	171 (31.4)	82 (33.1)
2011–2014	405 353 (34.8)	1121 (45.3)	228 (41.1)	512 (45.4)	256 (47.1)	125 (50.4)
Education level						
≤9 y	92 810 (8.0)	170 (6.9)	18 (3.2)	62 (5.5)	51 (9.4)	39 (15.7)
10–12 y	436 659 (37.5)	1009 (40.8)	184 (33.2)	446 (39.6)	238 (43.8)	141 (56.9)
≥13 y	635 747 (54.6)	1295 (52.3)	353 (63.6)	619 (54.9)	255 (46.9)	68 (27.4)
Parity						
0	509 820 (43.8)	1191 (48.1)	269 (48.5)	552 (49.0)	244 (44.9)	126 (50.8)
1	435 701 (37.4)	912 (36.9)	223 (40.2)	412 (36.6)	191 (35.1)	86 (34.7)
≥2	219 695 (18.9)	371 (15.0)	63 (11.4)	163 (14.5)	109 (20.0)	36 (14.5)
BMI in early pregnancy						
<18.5 kg/m^2	33 544 (2.9)	21 (0.8)	1 (0.2)	6 (0.5)	10 (1.8)	4 (1.6)
18.5 to <25 kg/m^2	696 140 (59.7)	1225 (49.5)	320 (57.7)	559 (49.6)	250 (46.0)	96 (38.7)
25 to <30 kg/m^2	300 380 (25.8)	874 (35.3)	174 (31.4)	409 (36.3)	191 (35.1)	100 (40.3)
30 to <35 kg/m^2	98 053 (8.4)	282 (11.4)	49 (8.8)	124 (11.0)	71 (13.1)	38 (15.3)
≥35 kg/m^2	37 099 (3.2)	72 (2.9)	11 (2.0)	29 (2.6)	22 (4.0)	10 (4.0)
Smoking in early pregnancy	79 820 (6.9)	172 (7.0)	21 (3.8)	48 (4.3)	47 (8.6)	56 (22.6)
Other autoimmune disease	20 246 (1.7)	262 (10.6)	54 (9.7)	114 (10.1)	64 (11.8)	30 (12.1)
Median duration of diabetes (IQR), *y*	–	16 (9–22)	13 (4–20)	17 (10–23)	17 (11–23)	16 (10–20)
Median HbA_{1c} level (IQR), %	–	7.3 (6.5–8.1)	6.1 (5.8–6.3)	7.2 (6.9–7.5)	8.3 (8.0–8.6)	9.7 (9.3–10.4)

BMI = body mass index; HbA_{1c} = hemoglobin A_{1c} (glycated hemoglobin); IQR = interquartile range; T1D = type 1 diabetes mellitus.
* Imputed data are shown for variables with missing values (**Supplement Table 2**, available at Annals.org). Values are numbers (percentages) unless otherwise indicated.

RESULTS

Background Data

Our cohort consisted of 2474 liveborn infants of 2038 mothers with T1D who had a periconceptional HbA_{1c} measurement and 1 165 216 reference infants born to 746 916 mothers without diabetes (Table 1). Among both women with and those without diabetes, the mean age at delivery was 30 years, approximately 7% smoked in early pregnancy, and 95% were living with a partner (Table 1). Compared with the reference women, those with T1D were more likely to be of Nordic origin, to be overweight or obese, and to have diabetes-related autoimmune diseases. As HbA_{1c} levels increased in T1D pregnancies, young maternal age, lower education level, higher BMI, smoking, and not living with a partner tended to be more prevalent. Characteristics of pregnant women with T1D who did not have a recorded HbA_{1c} measurement between 90 days before and 91 days after conception (who were not included in the study) were similar to those of the women included in the study (Supplement Table 4, available at Annals.org).

Preterm Birth

Of 2474 births among women with T1D, 552 (22.3%) were preterm versus 54 287 (4.7%) in 1 165 216 births among women without diabetes. The incidence of preterm birth was 13.2% for women with a periconceptional HbA_{1c} level below 6.5%, 20.6% for those with a level of 6.5% to less than 7.8%, 28.3% for those with a level of 7.8% to less than 9.1%, and 37.5% for those with a level of 9.1% or higher (Table 2). The aRRs for preterm birth associated with T1D compared with preterm birth among women without diabetes were 2.83 (95% CI, 2.28 to 3.52) for an HbA_{1c} level below 6.5%, 4.22 (CI, 3.74 to 4.75) for a level of 6.5% to less than 7.8%, 5.56 (CI, 4.84 to 6.38) for a level of 7.8% to less than 9.1%, and 6.91 (CI, 5.85 to 8.17) for a level of 9.1% or higher (Table 2). The corresponding adjusted risk differences were 7.5 (CI, 4.4 to 10.6), 14.3 (CI, 11.4 to 17.2), 24.0 (CI, 17.8 to 30.3), and 29.3 (CI, 21.6 to 36.9) percentage points. Figure 2 depicts the predicted adjusted risk for preterm birth, according to HbA_{1c} level, on a continuous scale. The association between progressively higher HbA_{1c} levels and risk for preterm birth was independent of the timing of the periconceptional HbA_{1c} measurement (Supplement Figure 1, available at Annals.org). The risk for very preterm birth also increased with increasing HbA_{1c} levels (Table 2).

Of the preterm births, 320 were medically indicated, 223 were spontaneous preterm births, and 9 could not be classified. The risk for spontaneous preterm birth among women with T1D was linked to periconceptional HbA_{1c} levels, with an incidence of 6.0% for a level lower than 6.5%, then rising to an incidence of around 10% for all HbA_{1c} level categories of 6.5% and greater (Table 2). This increased risk translated into aRRs of 1.81 (CI, 1.31 to 2.52) for HbA_{1c} levels below

6.5%, 2.86 (CI, 2.38 to 3.44) for levels of 6.5% to less than 7.8%, 2.88 (CI, 2.23 to 3.71) for levels of 7.8% to less than 9.1%, and 2.80 (CI, 1.94 to 4.03) for levels of 9.1% and higher (**Table 2**). The largest risk increase was observed for medically indicated preterm birth. The incidence of medically indicated preterm births in women with T1D increased progressively across all HbA_{1c} categories (from 6.9% for an HbA_{1c} level below 6.5% to 27.0% for a level of 9.1% or higher), corresponding to aRRs of 5.26 (CI, 3.83 to 7.22) for HbA_{1c} levels lower than 6.5%, 7.42 (CI, 6.21 to 8.86) for levels of 6.5% to less than 7.8%, 11.75 (CI, 9.72 to 14.20) for levels of 7.8% to less than 9.1%, and 17.51 (CI, 14.14 to 21.69) for levels of 9.1% and higher (**Table 2**).

In a further analysis, we explored the effect of reducing the cutoff level of the lowest HbA_{1c} category from less than 6.5% to less than 6.0% (**Supplement Table 5**, available at Annals.org). The aRR for preterm birth associated with HbA_{1c} levels below 6.0% (2.88 [CI, 2.11 to 3.93]) was similar to that observed for the under 6.5% category in the main analysis.

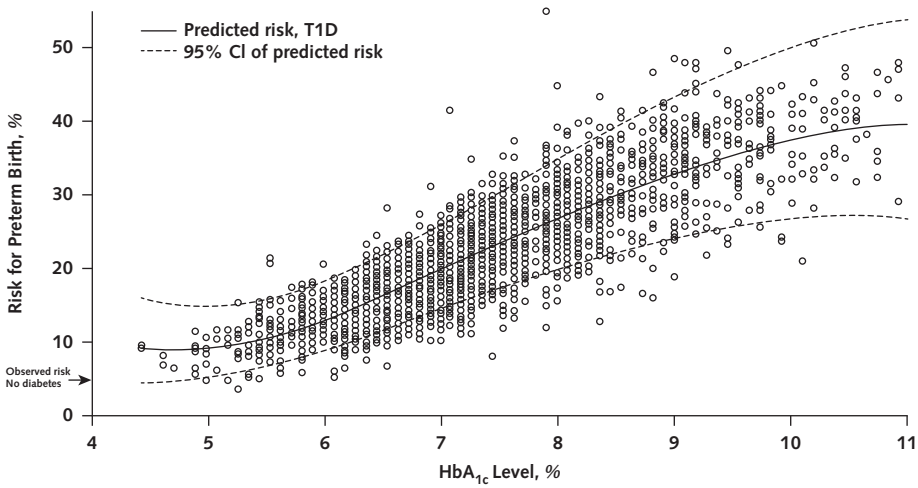
The risk for preterm birth increased according to alternative markers of poor glycemic control and diabetes severity, including long-term glycemic control, albuminuria, and eGFR (**Figure 3**). For instance, the aRR for preterm birth was 8.85 (CI, 6.61 to 11.84) in women with T1D in the lowest eGFR category (<60 mL/min/1.73 m^2).

Table 2. Association Between T1D and Risk for Preterm Birth, by HbA_{1c} Level in the Periconceptional Period

Outcome Measures	No Diabetes	T1D Overall	T1D, by HbA_{1c} Level			
			<6.5%	6.5% to <7.8%	7.8% to <9.1%	≥9.1%
Preterm birth						
Infants, *n*	1 165 216	2474	555	1127	544	248
Events, *n (%)*	54 287 (4.7)	552 (22.3)	73 (13.2)	232 (20.6)	154 (28.3)	93 (37.5)
Risk ratio (95% CI)						
Unadjusted	–	4.76 (4.40 to 5.14)	2.85 (2.29 to 3.53)	4.41 (3.92 to 4.96)	5.95 (5.19 to 6.82)	7.89 (6.71 to 9.28)
Adjusted*	–	4.52 (4.18 to 4.89)	2.83 (2.28 to 3.52)	4.22 (3.74 to 4.75)	5.56 (4.84 to 6.38)	6.91 (5.85 to 8.17)
Risk difference (95% CI), *percentage points*						
Unadjusted	–	17.7 (15.9 to 19.4)	8.7 (5.8 to 11.6)	16.0 (13.6 to 18.5)	23.3 (19.5 to 27.1)	32.4 (26.4 to 38.4)
Adjusted*	–	16.5 (14.2 to 18.7)	7.5 (4.4 to 10.6)	14.3 (11.4 to 17.2)	24.0 (17.8 to 30.3)	29.3 (21.6 to 36.9)
Very preterm birth						
Infants, *n*	1 165 216	2474	555	1127	544	248
Events, *n (%)*	7583 (0.7)	50 (2.0)	4 (0.7)	16 (1.4)	21 (3.9)	9 (3.6)
Risk ratio (95% CI)						
Unadjusted	–	3.11 (2.35 to 4.12)	1.14 (0.44 to 2.97)	2.15 (1.29 to 3.58)	5.94 (3.92 to 9.01)	5.59 (2.94 to 10.61)
Adjusted*	–	2.95 (2.23 to 3.91)	1.17 (0.45 to 3.03)	2.05 (1.23 to 3.42)	5.45 (3.58 to 8.29)	4.74 (2.49 to 9.05)
Risk difference (95% CI), *percentage points*						
Unadjusted	–	1.4 (0.8 to 2.0)	0.1 (−0.6 to 0.8)	0.8 (0 to 1.5)	3.2 (1.6 to 4.9)	3.0 (0.7 to 5.4)
Adjusted*	–	1.4 (0.7 to 2.0)	0.4 (−0.6 to 1.3)	0.5 (−0.1 to 1.2)	3.0 (1.1 to 4.9)	3.3 (0 to 6.6)
Medically indicated preterm birth						
Infants, *n*	1 164 605	2465	553	1123	541	248
Events, *n (%)*	15 103 (1.3)	320 (13.0)	38 (6.9)	118 (10.5)	97 (17.9)	67 (27.0)
Risk ratio (95% CI)						
Unadjusted	–	9.97 (8.95 to 11.10)	5.34 (3.90 to 7.32)	8.13 (6.83 to 9.69)	13.54 (11.23 to 16.31)	20.43 (16.65 to 25.07)
Adjusted*	–	9.07 (8.12 to 10.12)	5.26 (3.83 to 7.22)	7.42 (6.21 to 8.86)	11.75 (9.72 to 14.20)	17.51 (14.14 to 21.69)
Risk difference (95% CI), *percentage points*						
Unadjusted	–	11.8 (10.4 to 13.1)	5.7 (3.5 to 7.9)	9.4 (7.5 to 11.2)	16.4 (13.1 to 19.7)	25.5 (20.0 to 31.0)
Adjusted*	–	10.6 (8.9 to 12.4)	4.8 (2.6 to 7.0)	8.3 (6.2 to 10.4)	15.9 (11.0 to 20.8)	22.1 (15.8 to 28.4)
Spontaneous preterm birth						
Infants, *n*	1 164 605	2465	553	1123	541	248
Events, *n (%)*	38 573 (3.3)	223 (9.0)	33 (6.0)	110 (9.8)	54 (10.0)	26 (10.5)
Risk ratio (95% CI)						
Unadjusted	–	2.71 (2.39 to 3.08)	1.81 (1.30 to 2.51)	2.94 (2.45 to 3.52)	2.98 (2.31 to 3.84)	3.13 (2.17 to 4.51)
Adjusted*	–	2.63 (2.31 to 2.99)	1.81 (1.31 to 2.52)	2.86 (2.38 to 3.44)	2.88 (2.23 to 3.71)	2.80 (1.94 to 4.03)
Risk difference (95% CI), *percentage points*						
Unadjusted	–	5.7 (4.5 to 6.9)	2.7 (0.7 to 4.7)	6.4 (4.7 to 8.2)	6.6 (4.1 to 9.1)	7.1 (3.3 to 10.9)
Adjusted*	–	5.5 (4.0 to 7.1)	2.1 (0 to 4.1)	5.7 (3.7 to 7.6)	7.9 (3.2 to 12.6)	7.3 (1.9 to 12.7)

HbA_{1c} = hemoglobin A_{1c} (glycated hemoglobin); T1D = type 1 diabetes mellitus.
* Adjusted for calendar year, maternal age, country of birth, living with a partner, education level, parity, body mass index, smoking status, and other autoimmune disease. For 620 births (9 of which were among infants of mothers with T1D), data on how the birth started were not available, hence the sum of the medically indicated and spontaneous preterm births is lower than the total number of preterm births.

Figure 2. Predicted adjusted risk for preterm birth associated with T1D, by periconceptional levels of HbA_{1c}.



Scatter plot depicting the predicted adjusted risk for preterm birth, according to HbA_{1c} level for each individual pregnancy with T1D in the cohort, whereas the line shows the predicted adjusted risk (with 95% CI) across all pregnancies in women with T1D. The model was adjusted for calendar year, maternal age, country of birth, living with a partner, education level, parity, body mass index, smoking status, and other autoimmune diseases. HbA_{1c} = hemoglobin A_{1c} (glycated hemoglobin); T1D = type 1 diabetes.

The percentage of preterm deliveries was similar in women with T1D who had periconceptional HbA_{1c} measurements and those who did not (**Supplement Table 6**, available at Annals.org).

Secondary Outcomes in Infants

Risk for the secondary outcomes of LGA, macrosomia, hypoglycemia, respiratory distress, and low Apgar score increased with rising HbA_{1c} levels (**Figure 4**; **Supplement Table 7**, available at Annals.org), although the risk increase for these outcomes seemed to plateau at the second (6.5% to <7.8%) or third (7.8% to <9.1%) HbA_{1c} category. For instance, the risk for LGA was 3.3% among reference infants, compared with 25.6% among infants born to mothers with an HbA_{1c} level below 6.5% (aRR, 7.75 [CI, 6.72 to 8.95]), 40.5% for a level of 6.5% to less than 7.8% (aRR, 11.22 [CI, 10.37 to 12.14]), 48.4% for a level of 7.8% to less than 9.1% (aRR, 12.88 [CI, 11.69 to 14.20]), and 39.9% for a level of 9.1% or higher (aRR, 12.01 [CI, 10.23 to 14.09]). For birth injury, we observed an overall 3-fold increase of risk in infants born to mothers with T1D, independent of HbA_{1c} level. The risks for neonatal death and stillbirth, respectively, were significantly increased only at HbA_{1c} levels of 7.8% and above, although these 2 analyses were based on a small number of T1D-exposed cases.

Sensitivity Analyses

Post hoc, we conducted sensitivity analyses of all preterm birth and secondary outcomes restricted to nulliparous women. Results were consistent with those of the main analyses (**Supplement Table 8**, available at Annals.org).

E-Values: Assessing Potentially Unmeasured Confounding

We found that for the observed aRR of 4.52 (aRR for T1D overall) to be reduced to 1, the minimum strength of an unmeasured confounder would need to be 9-fold to be associated with both T1D in mothers and preterm birth. The lower limit of the CI could be shifted below 1 by an unmeasured confounder that was associated with both T1D in mothers and preterm birth by an 8.3-fold risk ratio. The corresponding minimum strength of association in HbA_{1c} levels (with the minimum risk ratio needed to shift the lower limit of the CI below 1 in parentheses) needs to be 5.1 (4.0), 8.3 (7.3), 11.4 (9.9), and 15.3 (12.9) for the categories of less than 6.5%, 6.5% to less than 7.8%, 7.8% to less than 9.1%, and 9.1% and above, respectively, for both the HbA_{1c} level in women with T1D and to preterm birth.

DISCUSSION

This nationwide population-based cohort study of more than 2400 singleton infants born to mothers with T1D showed that increasing HbA_{1c} levels were associated with progressively increased risks for preterm birth, as well as other adverse pregnancy outcomes. Most of the elevated risk for preterm birth was attributable to medically indicated preterm births, although spontaneous preterm births also increased with higher HbA_{1c} levels.

The American Diabetes Association (ADA) recommends a target HbA_{1c} level below 6.5% (<48 mmol/mol) during early pregnancy (8). This guideline focuses primarily on the prevention of congenital malformations and excessive fetal growth, measured as LGA birth. Of the 4 publications constituting the basis for the ADA recommendations (26–29), only 1 (Maresh and colleagues [27]) reports data on preterm birth. In that study, the authors did not detect an increased risk for preterm birth for HbA_{1c} levels below 6.0% at 26 weeks gestation but did report a 2.5-fold increased risk at lev-

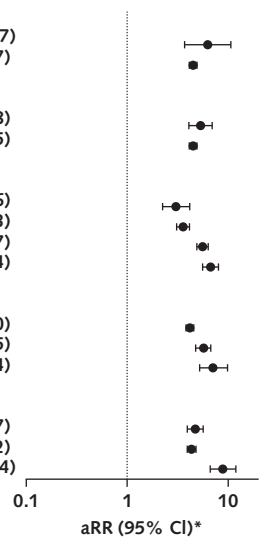
els of 6.0% to 6.5% (CI for odds ratio, 1.4 to 4.8) (27). In contrast, we observed a statistically significant aRR of 2.83 (CI, 2.28 to 3.52) for the below-6.5% category; further, the aRR was of similar magnitude and remained increased when we recategorized the lowest category to below 6.0% (aRR, 2.88 [CI, 2.11 to 3.93]), and the aRR for the category of 6.0% to less than 6.5% was 2.80 (CI, 2.11 to 3.71). These differences among studies are probably attributable to statistical power; the study by Maresh and colleagues (27) comprised 725 women, compared with 2474 in our study. Although other studies have indicated a relationship between HbA_{1c} level and preterm birth (30), most have failed to detect such a relationship, most likely because of insufficient power (31–33). Furthermore, earlier studies failed to calculate relative risks or risk differences according to HbA_{1c} level.

Poor glycemic control was linked to neonatal death, LGA, macrosomia, hypoglycemia, respiratory distress, a low 5-minute Apgar score, and stillbirth. However, for most outcomes, the risk increase seemed to plateau at the second (6.5% to <7.8%) or third (7.8 to <9.1%) HbA_{1c} category. We also observed a 3-fold increase independent of HbA_{1c} level for birth injury. We found a positive relationship between HbA_{1c} levels and stillbirth and neonatal death, but only for levels of 7.8% and above. Jensen and colleagues (28), who examined death between gestational week 25 and the first 7 days after birth, found a 2.8-fold (CI, 1.3- to 6.1-fold) increased risk in women with a periconceptional HbA_{1c} level below 6.9% and a 7.3-fold (CI, 2.5- to 19.8-fold) increased risk in the highest HbA_{1c} category (≥10.4%) compared with the general population. However, that study did not use the ADA-recommended cutoff (<6.5%) to determine whether this HbA_{1c} level is safe, nor did it adjust for potential confounders.

Although Nielsen and colleagues (26) reported an adjusted odds ratio of 30.3 (CI, 8.6 to 106) for any adverse pregnancy outcome in women with an HbA_{1c} level of 10.3% or above in the last 2 months before conception and in the first trimester versus those with a level of 7.0% or below, their study did not include stillbirth and neonatal death. Likewise, these outcomes were not included by Maresh and colleagues (27), who reported as their main finding a 4.4-fold (CI, 1.6- to 12.3-fold) increased risk for an adverse pregnancy outcome in women with an HbA_{1c} level of 7.5% or higher versus those with lower levels. Our findings of an association between progressively higher periconceptional HbA_{1c} levels and adverse pregnancy outcomes confirm earlier evidence reported by Tennant and colleagues (34), who found an increased risk for fetal and neonatal

Figure 3. Association between T1D and risk for preterm birth based on alternative measures of poor glycemic control and diabetes severity.

Measure	Infants, *n*	Events, *n* (%)	aRR (95% CI)*
No diabetes (common reference in all analyses)	1 165 216	54 287 (4.7)	–
T1D			
Hospitalization for acidosis in past year			
Yes	24	9 (37.5)	6.29 (3.71–10.67)
No	2450	543 (22.2)	4.50 (4.16–4.87)
Hospitalization for diabetes in past year			
Yes	135	42 (31.1)	5.32 (4.11–6.88)
No	2339	510 (21.8)	4.47 (4.12–4.85)
Long-term glycemic control, HbA_{1c}, %†			
<6.5	264	35 (13.3)	3.04 (2.23–4.16)
6.5 to <7.8	983	168 (17.1)	3.58 (3.10–4.13)
7.8 to <9.1	631	182 (28.8)	5.59 (4.91–6.37)
>9.1	214	80 (37.4)	6.70 (5.59–8.04)
Albuminuria			
Normoalbuminuria	2026	419 (20.7)	4.20 (3.84–4.60)
Microalbuminuria	374	106 (28.3)	5.70 (4.82–6.75)
Macroalbuminuria	74	27 (36.5)	7.13 (5.17–9.84)
eGFR, *mL/min/1.73 m²*			
>120	384	94 (24.5)	4.73 (3.94–5.67)
60–120	1916	402 (21.0)	4.31 (3.93–4.72)
<60	55	25 (45.5)	8.85 (6.61–11.84)



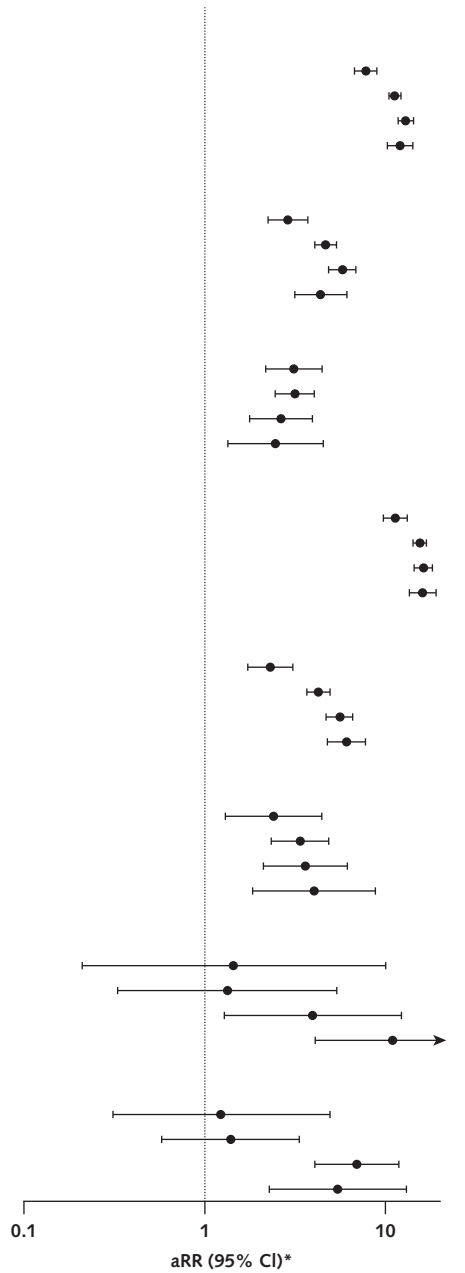
The analyses were restricted to infant–mother pairs with available data for the respective measure of glycemic control and diabetes severity. Of the 2474 mothers with T1D included in the cohort, 2092 had data on long-term glycemic control and 2355 had data on eGFR; for the other analyses, all cohort mothers had available data. The scale of the risk ratio plot is a log scale. aRR = adjusted risk ratio; eGFR = estimated glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c} (glycated hemoglobin); T1D = type 1 diabetes.

* Adjusted for calendar year, maternal age, country of birth, living with a partner, education level, parity, body mass index, smoking status, and other autoimmune diseases.

† Long-term glycemic control was defined as the mean of the last 3 HbA_{1c} measurements, with the analysis restricted to individuals with ≥3 values, each measured ≥6 mo apart.

Figure 4. Association between T1D and risk for secondary adverse pregnancy outcomes, by HbA_{1c} levels.

Outcome, by HbA_{1c} Level	Infants, *n*	Events, *n* (%)	aRR (95% CI)*
LGA			
No diabetes	1 163 085	38 058 (3.3)	–
<6.5%	547	140 (25.6)	7.75 (6.72–8.95)
6.5% to <7.8%	1089	441 (40.5)	11.22 (10.37–12.14)
7.8% to <9.1%	519	251 (48.4)	12.88 (11.69–14.20)
≥9.1%	238	95 (39.9)	12.01 (10.23–14.09)
Macrosomia†			
No diabetes	1 109 502	41 799 (3.8)	–
<6.5%	480	54 (11.3)	2.88 (2.23–3.72)
6.5% to <7.8%	890	174 (19.6)	4.65 (4.06–5.32)
7.8% to <9.1%	388	96 (24.7)	5. 76 (4.85–6.85)
≥9.1%	155	26 (16.8)	4.36 (3.14–6.07)
Birth injury			
No diabetes	1 165 216	18 918 (1.6)	–
<6.5%	555	28 (5.0)	3.10 (2.17–4.44)
6.5% to <7.8%	1127	58 (5.1)	3.15 (2.45–4.04)
7.8% to <9.1%	544	23 (4.2)	2.64 (1.77–3.94)
≥9.1%	248	10 (4.0)	2.46 (1.34–4.51)
Hypoglycemia			
No diabetes	1 165 216	25 168 (2.2)	–
<6.5%	555	135 (24.3)	11.30 (9.73–13.12)
6.5% to <7.8%	1127	402 (35.7)	15.45 (14.21–16.80)
7.8% to <9.1%	544	207 (38.1)	16.21 (14.43–18.22)
≥9.1%	248	97 (39.1)	16.03 (13.55–18.95)
Respiratory distress			
No diabetes	1 165 216	35 872 (3.1)	–
<6.5%	555	42 (7.6)	2.31 (1.73–3.07)
6.5% to <7.8%	1127	167 (14.8)	4.25 (3.68–4.91)
7.8% to <9.1%	544	106 (19.5)	5.60 (4.68–6.69)
≥9.1%	248	53 (21.4)	6.07 (4.76–7.74)
Apgar score <7 at 5 min†			
No diabetes	1 106 271	9408 (0.9)	–
<6.5%	479	10 (2.1)	2.40 (1.30–4.44)
6.5% to <7.8%	892	28 (3.1)	3.36 (2.33–4.85)
7.8% to <9.1%	385	13 (3.4)	3.61 (2.11–6.17)
≥9.1%	154	6 (3.9)	4.02 (1.84–8.79)
Neonatal death			
No diabetes	1 165 216	1595 (0.1)	–
<6.5%	555	1 (0.2)	1.44 (0.21–10.05)
6.5% to <7.8%	1127	2 (0.2)	1.34 (0.33–5.36)
7.8% to <9.1%	544	3 (0.6)	3.95 (1.28–12.23)
≥9.1%	248	4 (1.6)	10.92 (4.09–29.11)
Stillbirth			
No diabetes	1 169 315	3546 (0.3)	–
<6.5%	557	2 (0.4)	1.23 (0.31–4.92)
6.5% to <7.8%	1133	5 (0.4)	1.39 (0.58–3.33)
7.8% to <9.1%	557	13 (2.3)	6.93 (4.06–11.85)
≥9.1%	253	5 (2.0)	5.44 (2.28–13.02)



Full results, including unadjusted risk ratios, as well as unadjusted and adjusted risk differences, are shown in **Supplement Table 7** (available at Annals.org). Missing outcome data in the full cohort: LGA, 2212 deliveries; macrosomia, 1436 deliveries; Apgar score less than seven, 4670 deliveries. The scale of the risk ratio plot is a log scale. aRR = adjusted risk ratio; HbA_{1c} = hemoglobin A_{1c} (glycated hemoglobin); LGA = large for gestational age; T1D = type 1 diabetes.

* Adjusted for calendar year, maternal age, country of birth, living with a partner, education level, parity, body mass index, smoking status, and other autoimmune diseases.

† The analyses of macrosomia and Apgar score <7 were based on full-term deliveries.

death (in their case, infant death [that is, before 1 year of life]) among mothers with T1D and an HbA_{1c} level above 6.6% in the last 3 months before the last menstrual period or in the first trimester. However, our study builds on this work by reporting both absolute and risk ratios according to HbA_{1c} levels and represents T1D in the modern era.

We demonstrated that the risk for preterm birth increased with progressively higher HbA_{1c} levels in women with T1D. One potential mechanism underlying the association between increasing HbA_{1c} levels and risk for preterm birth is that hyperglycemia might induce oxidative stress, which affects nitric oxide levels, potentially influencing myometrial contraction and cer-

vical ripening (35, 36). Of note, the association between periconceptional glycemic control and preterm birth may not necessarily represent a direct effect of glycemic control on preterm birth. In fact, in the case of induced preterm birth, it probably does not represent a direct effect. Instead, the pathway from poor glycemic control to induced preterm birth may, for instance, go through LGA. This scenario would then represent an intermediate—not a confounder—because the exposure led to a decision to induce delivery prematurely, because poor glycemic control had led to LGA. The association with medically indicated preterm birth may also be driven by factors other than periconceptional HbA_{1c} in itself.

Of particular note is the finding that women meeting target HbA_{1c} levels (<6.5%) (8–10) were also at increased risk for preterm delivery, which may be explained by several factors. The possibility exists that glycemia drives a risk for preterm birth even at the currently recommended target HbA_{1c} level. However, at less than 6.0%, we found an increased risk for preterm birth that was similar in magnitude to that found at levels below 6.5%. In addition, our analysis of preterm birth risk according to HbA_{1c} levels on a continuous scale indicated that the risk remained greater than in women without diabetes, even at the lowest HbA_{1c} values. Therefore, T1D in itself may be independently linked to preterm birth, and increasing HbA_{1c} levels may add to the risk in T1D pregnancies.

The excess risk for stillbirth and neonatal death was substantially and statistically significantly increased, but in only the upper 2 HbA_{1c} categories (≥7.8%). From an international perspective, the stillbirth rates in our study are low (37). Diabetes may influence stillbirth risk through several mechanisms, including poor placentation with intrauterine growth restriction (38) but also placental abruption. Hyperglycemia in itself, but also macrosomia, may cause stillbirth (37). High maternal glucose levels induce fetal hyperinsulinemia followed by disproportionate fetal growth and, potentially, fetal hypoxia and fetal acidosis, thereby increasing the risk for stillbirth.

A major strength of the study was its access to routinely collected nationwide register data. We identified women with T1D by using the well-characterized NDR, and we used the National Patient Register and Medical Birth Register to minimize misclassification and increase specificity. Using these registers increased the generalizability of our findings. The National Patient Register has high specificity, and most diagnoses have a positive predictive value of 85% to 95% (13). The main registers used in this study—the NDR and Medical Birth Register—are of high quality (12, 14, 39). The substantial number of infants in the study allowed for high statistical power, even for more detailed analyses; for instance, we had data on 792 infants born to women with an HbA_{1c} value of 7.8% or above, compared with Maresh and colleagues, who had data on 73 infants born to women with an HbA_{1c} value of 7.5% or higher (27). This large number allowed us to calculate robust risk estimates across predefined HbA_{1c} categories. Finally, we adjusted for many potential confounders, including smoking status, BMI, education level, living with a partner, country of birth, and autoimmune diseases.

The study also had several limitations. As with all observational studies, residual confounding could not be ruled out. Only randomized trials can exclude such confounding and establish causal relationships. However, when Middleton and colleagues (40) reviewed existing trials on strict (or moderate) versus poor glycemic control and pregnancy outcome, they could identify only 3 such trials (41–43). Results from these 3 studies suggest a protective effect against adverse pregnancy outcomes in women with T1D who have strict or moderate glycemic control during pregnancy. Yet, the authors included only about 223 deliveries. In addition, randomly assigning a pregnant woman with T1D to less strict control may seem unethical, considering the consensus that strict glycemic control is optimal.

A second limitation concerns our HbA_{1c} data being registered in the NDR annually as part of routine visits. Because of timing issues, we did not have HbA_{1c} values for all pregnant women with T1D. However, our comparison with pregnant women in the NDR without a recorded HbA_{1c} value during pregnancy found no systematic differences. Thus, we can be reasonably assured that our cohort represents pregnant women with T1D in Sweden. Finally, because data on physical activity, drinking habits, and race/ethnicity were lacking, we could not consider these characteristics as covariates in our models. We also recognize that the National Patient Register may have low sensitivity for some of the autoimmune diseases used for adjustment, that BMI was based on self-reported height, and that we could not distinguish between moderate and heavy smokers in our models. We also acknowledge that T1D management may differ among countries, which may affect absolute and relative risks for preterm birth at different HbA_{1c} levels.

We investigated the association between periconceptional HbA_{1c} and risk for adverse pregnancy outcomes in women with T1D. However, some data suggest that HbA_{1c} levels later in pregnancy might be a better predictor of preterm birth (30). Murphy and colleagues (44) reported that women with an HbA_{1c} level of 6.5% or higher early in pregnancy (week 13), but who later (week 24) had a level of 6.4% or less, had lower rates of preterm birth than those with persistently higher HbA_{1c} levels. This finding underlines the importance of regulating HbA_{1c} throughout pregnancy in women with T1D.

In conclusion, in this nationwide population-based cohort study, preterm birth among women with T1D was strongly linked to periconceptional HbA_{1c} levels, although women whose HbA_{1c} levels were consistent with recommended target values also were at increased risk for preterm birth as well as other adverse pregnancy outcomes. These data are important for developing future guidelines and informing clinicians about the risks associated with poor glycemic control. However, they do not support the idea that further low-

ering the recommended HbA_{1c} level during early pregnancy (at least not to 6.0%) will eliminate the excess risk for preterm birth among women with T1D.

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Reproducible Research Statement: *Study protocol:* Available from Dr. Ludvigsson (e-mail, jonasludvigsson@yahoo.com). *Statistical code and data set:* Not available.

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