Title: Incident Diabetes Complications among Women with type 1 diabetes based on Parity

Short Running Title: Pregnancy in T1D

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Abstract (150/150)

Objectives: To assess risk factors and incidence of diabetes complications in women with type 1 diabetes (T1D) based on parity.

Research Design/Methods: Data were collected from women (16-40 years old) in the T1D Exchange completing pregnancy/childbirth questionnaires during 2011-13 and 2016-18. Incidence of risk factors and diabetes complications were compared between women with a first pregnancy at/within 1-year of enrollment (n=28) and never pregnant women by year 5 (n=469).

Results: There was a trend for lower HbA1c (adjusted p=0.14) and higher rates of overweight/obesity, triglyceride/HDL>2, log (triglyercide/HDL), and hypertension among parous women compared with nulliparous women. There were no significant differences in rates of advanced nephropathy, albuminuria or cardiovascular disease.

Conclusions: Four-5 years after delivery, parous women with T1D tended to have lower HbA1c levels despite higher body mass indices and more frequent adverse lipid profiles and hypertension compared with nulliparous women. Further studies based on these trends are warranted.

Keywords: type 1 diabetes mellitus; pregnancy; parity; risk factors; diabetes complications; humans

Introduction/Background

Pregnancies associated with diabetes are at high-risk for diabetes complications [1,2]. Nearly half of women with diabetes develop or have progression of existing retinopathy during pregnancy [3]. The incidence of gestational hypertensive disorders is higher in women with pre-existing diabetes compared to women without diabetes during gestation [4,5]. Importantly, the impact of gestational hypertensive disorders (such as preeclampsia, gestational hypertension, HELLP syndrome [hemolysis, elevated liver enzymes, and low platelets]) can extend beyond pregnancy, as those diagnosed with these conditions are at a two-fold increased risk for cardiovascular disease (CVD) more than 2 decades after the pregnancy [4]. Nephropathy can develop or worsen during gestation[6,7]. Furthermore, renal function can decline to the point of end-stage renal disease after development of a gestational hypertensive disorder [8,9].

Many studies have focused on sex-differences in type 1 and type 2 diabetes complication rates, but have neglected to take parity into account [10-12]. Other studies, conducted exclusively in women, have focused on the incidence of one type of complication during gestation instead of adopting a broader approach to risk assessment [3-6,8,9]. Moreover, the long-term effects of parity on complications remains elusive. For example, in pregnancies without diabetes there are two predominant changes in lipid metabolism: 1) early gestational accumulation of fat and lipid maternal depots and 2) maternal hyperlipidemia with breakdown of adipose tissue in the last third of the pregnancy [13]. In pregnancies associated with type 1, type 2, or gestational diabetes, there is abnormal lipid metabolism [13-15], even with maternal euglycemia [16], that reverses after delivery [15]. Yet, the long-term implications for cardiovascular health in women who have adverse lipid profiles during pregnancy, especially in those who do not develop preeclampsia, remains indefinable.

The T1D Exchange Network and Clinic Registry collected prospective data on parity status and the rates of onset of multiple diabetes complications over time. We compared incidence rates of diabetes complications and their risk factors in women without complications at baseline over a 5-year period in women with a first pregnancy at baseline/Year 1 compared with those never pregnant throughout the observation period.

Research Design and Methods

The T1D Exchange Clinic Network includes over 80 US-based pediatric and adult endocrinology practices providing specialized diabetes care that enrolled over 35,000 individuals with type 1 diabetes (T1D). Each clinic received approval from a local institutional review board (IRB). Informed consent was obtained according to IRB requirements. Data were collected for the registry's central database from the participant's medical record and by having the participant or parent complete a comprehensive questionnaire, details on T1D Exchange Clinic Registry participant eligibility criteria, the informed consent process, and data collection have been published previously [17]. Data (questionnaires, medical data from charts) were collected from more than 26,000 children and adults with T1D enrolled between September 2010 and December 2012. Core data were updated annually from medical record data extraction. One year after enrollment (referred to as Year 1) and approximately five years after enrollment (April 2016 through April 2018; referred to as Year 5), female participants ≥16 years of age completed a questionnaire regarding pregnancy, child birth, and menstruation history.

This report includes data from 497 female clinic registry participants between 16 and 40 years of age at study enrollment who completed the pregnancy and childbirth portions of the questionnaires administered at enrollment, Year 1 and Year 5 with no pregnancy reported prior to

study enrollment. Sex, race/ethnicity, insurance status, and pregnancy status were collected through comprehensive participant questionnaires. Information about age, duration of diabetes, body mass index (BMI; height and weight), use of insulin pump, use of continuous glucose monitoring (CGM), albuminuria status, low-density lipoprotein (LDL) level, high-density lipoprotein (HDL) level, triglycerides, blood pressure, diagnosis of hypertension, and glycated hemoglobin A1c (HbA1c) level obtained as part of usual care were collected from medical records.

Nephropathy was defined as presence of one or more of the following: report of renal failure, kidney transplant, glomerular filtration rate (GFR) <60 mL/min on medical chart; or estimated GFR calculated using the CKD-Epi equation [18] from clinic-reported serum creatinine values <60 mL/min. Albuminuria was defined as two consecutive albumin/creatinine ratios or two of the past three measurements ≥30 mcg/mg as reported on the data collection form. Neuropathy was defined as a report of one or more of the following from medical chart data extraction: neuropathy, autonomic neuropathy, peripheral neuropathy. Cardiovascular disease was defined as a report of one or more of the following from the medical chart: coronary artery disease, coronary atherosclerosis, arteriosclerotic heart disease, hypertensive heart disease, congenital heart disease, congenital heart disease NOS, heart failure, congestive heart failure, cardiac failure congestive, cardiac failure, myocardial infarction, acute myocardial infarction, non-ST segment elevation myocardial infarction, heart murmur, cardiac murmur, ischemic cardiomyopathy, cardiomyopathy, arrhythmia, cardiac arrhythmia, or peripheral vascular disease.

Statistical Methods

Among the 497 participants who met criteria for inclusion in the analysis, pregnancy status was grouped as either: a) first pregnancy at enrollment or Year 1 (N=28), or b) never pregnant by

Year 5 (N=469) based on participant report. Participants were excluded from specific analyses if the outcome of interest was experienced at/prior to enrollment or Year 1. Multivariable linear regression was used to assess the association between HbA1c and pregnancy cohort and between blood pressure and pregnancy cohort. Multivariable logistic regression was used to assess the association between binary outcomes (occurrence of nephropathy by Year 5, occurrence of albuminuria at Year 5, neuropathy by Year 5, cardiovascular disease by Year 5, LDL >2.5 mmol/l (>100 mg/dL) at Year 5, triglyceride/HDL >2 at Year 5, log (triglyceride/HDL) >0.3 at Year 5, BMI ≥25 kg/m^2 at Year 5, diagnosis of hypertension at Year 5) and pregnancy cohort. Triglyceride to HDL ratios have been associated with incident CVD and all-cause mortality [19], which is why we chose to include them in this analysis.

Results are expressed as means ± standard deviations for normally distributed variables or medians (interquartile range (IQR)) for non-normally distributed variables. To account for possible confounding, the following covariates were assessed for association with each outcome through bivariate analysis and selection models: age at enrollment, diabetes duration at enrollment, race/ethnicity, insurance status at enrollment, use of insulin pump at enrollment, use of CGM at enrollment, BMI z-score at enrollment [20], and clinic site. If an association with an outcome was present, the covariate was included in the model for that outcome. The adjusted covariates for each outcome are detailed in the table footnotes.

Data analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). In view of multiple comparisons, only p-values <0.01 were considered suggestive of a true association. All p-values are two-sided.

Results

There were 28 women who reported being pregnant at enrollment or Year 1 who had data available at Year 5; 2 (7%) women were excluded from the nephropathy analysis for experiencing nephropathy at/prior to enrollment or Year 1, 1 (3%) woman was excluded from the CVD analysis, and 3 (11%) women were excluded from the neuropathy analysis. Among the 28 participants with first pregnancy at baseline/Year 1, the mean age at baseline was 28±4 years old, median diabetes duration was 17 (8, 21) years, 82% were non-Hispanic White, 81% had private insurance, mean BMI z-score was 0.14±0.81, 54% were using CGM, 67% were using an insulin pump, and mean HbA1c was 52±16.4 mmol/l (6.9%±1.5%).

By Year 5, there were 469 women who reported never being pregnant (including miscarriages and still births); 53 (11%) were excluded from the nephropathy analysis for experiencing nephropathy at/prior to enrollment or Year 1, 7 (1%) were excluded from the CVD analysis, and 22 (5%) were excluded from the neuropathy analysis. In this never pregnant by Year 5 cohort, the mean age at baseline was 22±5, median duration was 11 (6, 16) years, 87% were non-Hispanic White, 84% had private insurance, mean BMI z-score was 0.44±0.85, 16% were using CGM, 68% were using an insulin pump, and mean HbA1c was 64±15.4 (8.0%±1.4%). Additional characteristics are described in Table 1.

There was a trend for lower HbA1c five years after study enrollment in the cohort with first pregnancy at baseline/Year 1 compared with the never pregnant by Year 5 group (56±14.2 mmol/l [7.3%±1.3%] versus 63±15.3 mmol/l [7.9%±1.4%], P=0.14 adjusted for age at baseline, race/ethnicity, and BMI at baseline; Table 2). Occurrence of nephropathy, albuminuria, and cardiovascular disease within five years after study enrollment was low, with no events in the cohort with first pregnancy at baseline/Year 1 and 2%, 6%, and <1%, respectively in the never

pregnant by Year 5 group (Table 2). Occurrence of neuropathy by Year 5 also was infrequent, with 4% and 3% experiencing an event in the cohort with first pregnancy at baseline/Year 1 and never pregnant by Year 5 groups, respectively. While not statistically significant, frequency of some cardiovascular risk factors at Year 5 was higher in the cohort with first pregnancy at baseline/Year 1 compared to the cohort who was never pregnant by Year 5: BMI ≥25 kg/m^2 (80% vs 63%; adjusted P=0.28), triglyceride/HDL >2 (33% vs 21%; adjusted P=0.85), log(triglyceride/HDL) >0.3 (53% vs 46%; adjusted P=0.31), and diagnosis of hypertension (18% vs 10%); adjusted P=0.23) (Table 2).

Discussion

In the T1D Exchange Clinic Registry, women without nephropathy, albuminuria, and cardiovascular disease at baseline who became pregnant did not have increased rates of these diabetes complications 5 years after delivery compared to women who were never pregnant, despite the fact that the cohort was older and had a longer duration of diabetes. While there were trends showing clinically meaningful lower A1C levels, higher BMIs, higher rates of adverse lipid profiles, and higher rates of hypertension in previously pregnant women compared to never pregnant women, none of these factors reached statistical significance.

Diabetes (types 1 and 2) confers a greater risk of CVD for women with the condition compared with men [10,11] and CVD risk factors disproportionately increase for women with diabetes over time compared to men with diabetes [21]. It is known that gestational hypertensive disorders increase the risk for CVD later in life [4,5]. However, it is unclear how much parity alone and parity associated with gestational hypertensive disorders account for these sex differences. While we did not see differences in CVD rates between parous and nulliparous women, this was a young cohort. Some differences in CVD risk factors, such as BMI and adverse lipid profiles,

suggest a trend towards worse CVD risk factors based on parity; yet, our sample size of pregnant women without outcomes of interest at baseline was low and could have potentially mitigated our ability to detect a true difference. The higher proportion of parous women being overweight/obese, compared to nulliparous women, is not surprising. Hill and colleagues conducted a systematic review, where 24 studies found an association between parity and gestational weight gain while only 9 did not, and 5 studies found that gestational weight gain events predicted maternal obesity [22].

Incident advanced nephropathy and albuminuria were low in both of our cohorts. Advanced nephropathy includes end-stage renal disease (ESRD), the risk of which increases with increased diabetes duration. Costacou and Orchard examined cumulative kidney complication risks over 50 years in cohorts diagnosed with T1D between 1950-64 and 1965-80 [23]. ESRD incidence declined in the more recently diagnosed cohort compared to the cohort diagnosed 1950-64 with all T1D duration categories (20 years, 30 years, 40 years, and 50 years, $p<0.0001$), but increased with duration of diabetes [23]. ESRD affected 5.5% of people with T1D for 20 years duration [23]. Thus, it is not surprising that our cohorts with predominantly <20 years duration of diabetes have low incident rates of advanced renal disease.

This study has several strengths. This was a prospectively followed cohort of women with T1D, rather than a retrospective chart review. The cohort of never pregnant women followed over 5 years was large. Lab values associated with diabetes complications were collected in real-time. Multiple diagnostic codes were used to determine incident advanced renal disease. All pregnancies, including miscarriages and still births, were confirmed by patients in self-reports.

Despite the size and breadth of the T1D Exchange Clinic Network, this study has several limitations. The sample size of women with a pregnancy at baseline was small. Unfortunately, our

data collection forms and questionnaires did not capture information about nulliparous women who were unsuccessful in becoming pregnant, despite trying to conceive, which could influence some risk factors, such as for CVD in women with premature ovarian insufficiency or polycystic ovarian syndrome. Similarly, we did not have a rigorous method to collect data on retinopathy status or on the development or worsening of existing diabetes complications during pregnancy. Instead, data was extracted at the baseline/Year 1 time-point and compared to the Year 5 follow up data, allowing for a rather large cohort of women who were never pregnant over the 5 years of data collection to be included in this analysis. It is also possible other confounding variables could explain some of the trends reported. All pregnancies, including miscarriages and still births, were confirmed by patients in self-reports.

To ascertain risk factors for complications, lab values associated with diabetes complications were collected. Additionally, multiple diagnostic codes were used to determine incident advanced renal disease. Nevertheless, some women may have developed a complication that regresses after delivery, which may lead them to neglect to report the event on the questionnaires. However, these diabetes related complications developed during gestation that have regress may still increase risks of future complications later in life. Most importantly, our follow-up time period was limited to 5 years and in a young cohort. Thus, it may take a longer duration of time to see diabetes complications develop after a pregnancy.

In conclusion, some risk factors for CVD appeared to be slightly increased in parous women compared to nulliparous women with T1D who did not have CVD at the baseline assessment of the observation period. Advanced nephropathy and CVD rates were similar between parous and nulliparous women with T1D in the T1D Exchange. More studies are needed to

determine if parity alone, or parities associated with complications, increase the risk for diabetes complications later in life.

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Table 1. Participant Baseline Characteristics

	Pregnant at Baseline/Year 1 N=28	Never Pregnant by Year 5 N=469
Age (years) – *mean ± std*	28 ± 4	22 ± 5
Diabetes duration (years) – *median (IQR)*	17 (8, 21)	11 (6, 16)
Race/ethnicity – *n(%)*		
White Non-Hispanic	23 (82%)	407 (87%)
Black Non-Hispanic	0	14 (3%)
Hispanic or Latino	4 (14%)	34 (7%)
Other race/ethnicity	1 (4%)	14 (3%)
Insurance status[a] – *n(%)*		
Private	21 (81%)	356 (84%)
Other insurance	5 (19%)	62 (15%)
No insurance	0	8 (2%)
Body mass index z-score[ab] – *mean ± std*	0.14 ± 0.81	0.44 ± 0.85
CGM use [a] – *n(%)*	15 (54%)	70 (16%)
Insulin pump use [a] – *n(%)*	18 (67%)	301 (68%)
HbA1c [a] – mmol/l (%) *mean ± std*	52±16.4 (6.9±1.5)	64±15.3 (8.0±1.4)
LDL[a] – mmol/l (mg/dl) *mean ± std*	2.3±0.8 (91 ± 31)	2.4±0.6 (94 ± 27)
HDL[a] – mmol/l (mg/dL)*mean ± std*	1.7±0.3 (66 ± 12)	1.5±0.4 (61 ± 16)
Triglycerides[a] – mmol/l (mg/dL) *median [IQR]*	0.8 [0.6, 1.2] (76 [61, 115])	0.8 [0.6, 1.2] (76 [58, 109])
Systolic blood pressure (mm Hg) – *mean ± std*	113 ± 11	116 ± 11
Diastolic blood pressure (mm Hg) – *mean ± std*	71 ± 8	71 ± 8

IQR = interquartile range (25th and 75th percentiles) | std = standard deviation

CGM = continuous glucose monitoring

[a]Insurance status missing for 45 participants (2 in the pregnant group and 43 in the never pregnant group); body mass index information missing for 74 participants (11 pregnant and 63 never pregnant); use of CGM missing for 23 participants in the never pregnant group; use of insulin pump missing for 25 participants (1 pregnant and 24 never pregnant); HbA1c missing for 30 participants in the never pregnant group; LDL missing for 92 participants (4 pregnant and 88 never pregnant); HDL information missing for 99 participants (9 pregnant and 90 never pregnant); triglycerides missing for 113 participants (10 pregnant and

103 never pregnant); systolic blood pressure missing for 21 participants (2 pregnant and 19 never pregnant); diastolic blood pressure missing for 21 participants (2 pregnant and 19 never pregnant)

[b]Body mass index z-score adjusted for age and sex

Table 2. Association between Complications at/by Year 5 and Pregnancy Status

	Pregnancy at Baseline/ Year 1* N=28	Never Pregnant by Year 5 N=469	P-value**
Nephropathy[a] by Year 5 - *n(%)*	0	10 (2%)	NA
Albuminuria[b] at Year 5 – *n (%)*	0	21 (6%)	NA
Neuropathy[c] by Year 5 – *n (%)*	1 (4%)	13 (3%)	NA
Cardiovascular disease[d] by Year 5 – *n (%)*	0	2 (<1%)	NA
Cardiovascular Risk Factors at Year 5:			
HbA1c – mmol/l (%) *mean ± std*	56±14.2 (7.3% ± 1.3%)	63±15.3 (7.9% ±1.4%)	0.14
LDL >2.5 mmol/l (>100 mg/dL) – *n(%)*	5 (28%)	104 (38%)	0.87
Triglyceride/HDL >2 – *n(%)*	5 (33%)	52 (21%)	0.85
Log(Triglyceride/HDL) >0.3 – *n(%)*	8 (53%)	113 (46%)	0.31
BMI ≥25 kg/m^2 – *n(%)*	20 (80%)	245 (63%)	0.28
Systolic blood pressure (mm Hg) – *mean ± std*	118 ± 15	118 ± 12	0.63
Diastolic blood pressure (mm Hg) – *mean ± std*	74 ± 8	74 ± 9	0.90
Diagnosis of Hypertension – *n(%)*	5 (18%)	49 (10%)	0.23

Std = standard deviation | BMI = body mass index | HDL = high-density lipoprotein | LDL = low-density lipoprotein

*First pregnancy at baseline/year 1

**Number of events too low to calculate p-value for nephropathy, albuminuria, neuropathy, cardiovascular disease. P-value for HbA1c at year 5 calculated from multivariable linear regression adjusted for age at baseline, race/ethnicity, and BMI at baseline. P-value for LDL>100 mg/dL calculated from a multivariable logistic regression model adjusted for LDL, insurance status, and BMI at baseline. P-value for triglyceride/HDL >2 from a multivariable logistic regression model adjusted for diabetes HDL at baseline, triglyceride at baseline, duration at baseline and BMI at baseline. P-value for log(triglyceride/HDL)>0.3 from a multivariable logistic regression model adjusted for HDL at baseline, triglyceride at baseline, age, diabetes duration and BMI at baseline. P-value for BMI≥25 kg/m^2 from a multivariable logistic regression model adjusted for age and BMI at baseline. P-value for systolic blood pressure from multivariable linear regression models adjusted for blood pressure at baseline, BMI at baseline, and clinic site. P-value for diastolic blood pressure from multivariable linear regression models adjusted for blood pressure at baseline, race/ethnicity, and clinic site. P-value for diagnosis of hypertension from a multivariable logistic regression model adjusted for hypertension at baseline, baseline age and BMI at baseline.

[a]Nephropathy defined as presence of any of the following: 1) report of renal failure, kidney transplant, glomerular filtration rate (GFR) <60 mL/min on medical chart data extraction, 2) estimated GFR (calculated) <60 mL/min

[b]Albuminuria defined as report of 2 consecutive albumin/creatinine ratios (ACRs) ≥30 mcg/mg or 2 out of the past 3 measurements as reported from medical chart data extraction

[c]Neuopathy defined as >1 of the following: 1) report of neuropathy on case report form, 2) record in medical chart of: autonomic neuropathy, peripheral neuropathy, or neuropathy

[d]Cardiovascular disease defined as record from medical chart data extraction of >1 of the following: coronary artery disease, coronary atherosclerosis, arteriosclerotic heart disease, hypertensive heart disease, congenital heart disease, congenital heart disease NOS, heart failure, congestive heart failure, cardiac failure congestive, cardiac failure, myocardial infarction, acute myocardial infarction, non-ST segment elevation myocardial infarction, heart murmur, cardiac murmur, ischemic cardiomyopathy, cardiomyopathy, arrhythmia, cardiac arrhythmia, or peripheral vascular disease