Type 1 Diabetes Mellitus and Pregnancy- Time Trends and Delivery Outcomes in Women With Concurrent Chronic Hypertension

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Type 1 Diabetes Mellitus and Pregnancy-
Time Trends and Delivery Outcomes in Women with Concurrent Chronic Hypertension

by

Sarit Helman

A Dissertation Submitted to the Faculty of Harvard Medical school
in Partial Fulfillment of
the Requirements for the Degree of Master of Medical Sciences in Clinical
Investigation (MMSCI)

Harvard University
Boston, Massachusetts
April 2019

Area of Concentration: Type 1 Diabetes in Pregnancy
Project Advisors: Dr. Tamarra James-Todd, Dr. Florence Brown

We have reviewed this thesis, it represents work done by the author under our
guidance/ supervision
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Low Prevalence of Small for Gestational Age in Women with Concurrent Type 1 Diabetes and Chronic Hypertension in Pregnancy

Abstract

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Finally, I am thankful to my dear family.
Overview of the thesis papers

The Joslin Diabetes Center and Beth Israel Deaconess Medical Center diabetes and pregnancy Program is a program that offers optimal pre-conception and prenatal care for women with type 1 diabetes. Our research is based on data collected from over 700 pregnancies that occurred in this Program over the past 14 years. The data were collected from the two facilities and integrated to create one of the largest datasets of pregnant women with type 1 diabetes in the US.

The first part of the thesis is describing time trends in pregnancy-related outcomes among women with type 1 diabetes mellitus, between the years 2004-2017. We aimed to examine time trends in pre-pregnancy maternal characteristics, treatment and glucose control measures, along with pregnancy- and delivery outcomes among US women with type 1 diabetes. Evaluating time trends for pregnancy and delivery outcomes could provide valuable information for this high-risk US population, with respect to program needs and high-priority areas for clinical care and services.

The second part of the thesis concentrate on a subset of the former study population of women with type 1 diabetes and medically treated chronic hypertension (cHTN) and comparing their pregnancy and delivery outcomes to women with type 1 diabetes and no cHTN. Currently, there are limited data to define optimal blood pressure (BP) targets in pregnancies complicated by type 1 diabetes and cHTN. Our study evaluates the pregnancy and delivery outcomes, particularly birth weight measures, comparing women with type 1 diabetes who have cHTN to those without cHTN. Of importance, recent guideline changes may impact treatment with consequences for adverse pregnancy outcomes. In this study, utilizing the previous criteria for cHTN treatment with anti-hypertensive pharmacotherapy to target BP 110-129/65-79 mmHg throughout
pregnancy, we note the importance of reconsidering previous guidelines as a better standard for this unique population with comorbid conditions.
Time Trends in Pregnancy-Related Outcomes among Women with Type 1 Diabetes Mellitus, 2004-2017

Running title: Time trends in pregnant women with type 1 DM

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Abstract

**Objective:** To examine time trends in US pregnant women with type 1 diabetes mellitus for maternal characteristics and pregnancy outcomes: maternal pre-pregnancy body mass index and gestational weight gain; treatment factors: glycemic control, insulin pump and continuous glucose monitor (CGM) use; and delivery outcomes: gestational age at delivery, birth weight and mode of delivery.

**Research Design and methods:** We abstracted clinical data from the medical records of 700 pregnant women seeking care at the Joslin and Beth Israel Deaconess Medical Center Diabetes in Pregnancy Program from 2004-2017. Eligible women were ≥18 years old, had a singleton pregnancy, had clinically diagnosed type 1 diabetes mellitus and delivered a live birth during this time period. For each time period, means and percentages were calculated. P-values for trend were calculated using linear and logistic regression.

**Results:** From 2004-2017, the use of insulin pumps and CGMs increased from 50% to 72.7%, and 0% to 39.9%, respectively (p<0.001). HbA1c in each trimester was unchanged across the analysis period. The prevalence of nephropathy decreased from 4.8% to 0% (p=0.002). Excessive gestational weight gain increased (p=0.01). Gestation length also increased (p=0.01), as did vaginal deliveries (p=0.03). There were no change in birth weight percentiles over time (p=0.77). and the percentage of neonates with macrosomia and large for gestational age (LGA) neonates also remained unchanged.

**Conclusion:** Obstetric guideline changes may have improved gestation length and mode of delivery; however, other outcomes need more attention, including excessive gestational weight gain, macrosomia, and LGA.
Introduction

The prevalence of type 1 diabetes mellitus in pregnancy has almost doubled in the past few decades in the US (1). Of concern, numerous studies show that maternal and fetal complications, such as perinatal mortality and fetal macrosomia, are substantially higher in women with type 1 diabetes than in women from the general population (2, 3). In addition, pregnancies complicated by type 1 diabetes have a higher prevalence of cesarean section, preterm birth, and macrosomia and incur higher health care costs than pregnancies complicated by type 2 diabetes and gestational diabetes (4). Optimization of glycemic control before and during pregnancy in women with type 1 diabetes is critical for improving pregnancy and delivery outcomes (5).

Interestingly, concurrent with the increase in type 1 diabetes prevalence, there have been rapid advances in technology for the purpose of improving glycemic control, including insulin pumps and continuous glucose monitors (CGM). However, it is unclear how widely technology to treat type 1 diabetes has been adopted for use in pregnancy or whether this has had any impact on pregnancy and delivery outcomes.

Several studies, conducted outside the US, have examined time trends in pregnancy-related outcomes among women with type 1 diabetes. Two Scandinavian studies which looked at the preconception period found increases in pre-pregnancy body mass index (BMI) over a 10-20 year time span (2, 6); while other studies did not show increases in BMI during the same time period (7-9). Preconception improvements in glycemic control were noted in one study, while others showed either deterioration or similar glycemic control levels (6, 10, 11). Studies of trends in glycemic control during pregnancy demonstrated conflicting results with deterioration in a study from Finland but improvement in a study from the United Kingdom (6, 11). Differences in
these studies may be attributed to differences in population characteristics and health care delivery. Other European and Canadian studies have evaluated trends in delivery outcomes such as preterm births, cesarean deliveries, and birth weight finding increases in these outcomes over time. These studies also show that macrosomia remained higher than in the general population and did not change over time (6, 10, 12, 13). While findings from these studies suggest the need for further evaluation, to our knowledge no study has specifically assessed time trends in pregnancy, treatment and delivery outcomes among women with type 1 diabetes in a US population.

Therefore, we aimed to examine time trends in pre-pregnancy maternal characteristics, treatment and glucose control measures, along with pregnancy and delivery outcomes among US women with type 1 diabetes. With rapid advances in technology to treat type 1 diabetes, including the introduction of CGMs and the increasing use of insulin pumps, evaluating time trends for pregnancy and delivery outcomes could provide insights about this high-risk US population.

**Research design and Methods**

**Study population and eligibility**

Clinical data were abstracted from the medical records of pregnant women with type 1 diabetes seeking care at the Joslin Diabetes Center and Beth Israel Deaconess Medical Center (BIDMC) Diabetes in Pregnancy Program. Eligible women had clinically diagnosed type 1 diabetes, were 18 years or older with a singleton live birth pregnancy and delivered at BIDMC in the time period of 2004 through 2017. We included women who had multiple pregnancies as well.
Pre-pregnancy maternal characteristics and treatment factors

We evaluated maternal pre-pregnancy characteristics, including age (continuous) and ethnicity (white or nonwhite). Pre-pregnancy weight and height were measured at the first prenatal clinic visit, prior to 14 weeks’ gestation. BMI was calculated as weight in kilograms per height in meters squared, and women were categorized as follows: underweight at <18.5 kg/m², normal at 18.5-24.9 kg/m², overweight at 25-29.9 kg/m², and obese at ≥30 kg/m² (14). In addition, we abstracted data on the albumin-creatinine ratio (ACR) recorded at the first prenatal visit up to six months prior to the last menstrual period. Normal ACR was defined as <30 mg/g. Microalbuminuria was defined as 30-299 mg/g and macroalbuminuria as ≥300 mg/g (15). Data on mode of glucose management were abstracted as either multiple daily injections or insulin pump use based on first prenatal visit. In addition, information on use of CGMs was taken from the medical records of the first prenatal visit.

Pregnancy glycemic control and weight gain measures

Pregnancy glycemic control was evaluated using HbA1c values that were assessed in each trimester. Recommended levels of HbA1c were defined as lower than 6.5% (48 mmol/mol) in the first trimester, and lower than 6.0% (42 mmol/mol) for the second and third trimesters (16).

Gestational weight gain was calculated by subtracting the initial weight measured at the first prenatal visit from the weight measured in the third trimester. Excessive weight gain was assessed according to the revised recommendation of the Institute of Medicine (IOM), that account for maternal pre-pregnancy BMI (17). Weight gain velocity was calculated by dividing the total weight gain by the gestational age at delivery.
**Delivery outcomes**

Data on delivery mode, gestational age at birth, and birth weight were obtained from the medical records. We evaluated vaginal versus cesarean deliveries based on delivery records. Gestational age was based on last menstrual period and assessed as a continuous variable. In addition, preterm delivery was defined as <37 weeks gestation and early preterm birth was defined as <32 weeks gestation (18). Birth weight was evaluated continuously, and birthweight percentiles were adjusted for infant sex, gestational age, maternal height, weight, parity, and ethnicity using the Grow Customized weight centile calculator (19). Birth weight was evaluated categorically as well, as 1) macrosomia; or 2) large for gestational age (LGA). Macrosomia was defined as birth weight greater than 4000g. Infants with birth weight > 90th percentile were classified as LGA; those with birth weight below the 10th percentile were classified as small for gestational age (SGA). Infants with birth weight between the 10th and 90th percentile were considered as appropriate for gestational age (AGA).

**Statistical analysis**

We calculated means and standard deviation for continuous variables and percentages for categorical variables. To calculate trends over time, the study cohort was divided into three groups: the first group included women who delivered in 2004-2008 and numbered 214 pregnancies; the second group delivered in 2009-2012 and numbered 215 pregnancies; and the third group delivered in 2013-2017 and numbered 271 women.

Linear regression was used, evaluating each time period as an indicator variable and assessing the pregnancy, treatment, and delivery outcomes as continuous variables. Logistic regression was used to evaluate the association between each time period and categorical outcome variables. All tests were two-tailed and p-values for trend over time were calculated, with p < 0.05 as
statistically significant time trend. All models were unadjusted. Given that 188 women had more
than one pregnancy within this dataset and thus had correlated data, we performed two forms of
sensitivity analyses. The first included only the first pregnancy within the dataset for each
woman and the second included only the primiparous women. For the first analysis, a total of
512 women were included and for the second sensitivity analysis 368 women were included. All
models were re-run within these restricted datasets. All analyses were performed using R version
3.3.2 (2016-10-31) and Stata/IC 15.1.

Results

**Pre-pregnancy maternal characteristics and treatment factors**

In the years from 2004 through 2017, there were 700 pregnancies that met the eligibility criteria
in 512 women with type 1 diabetes. The pre-pregnancy maternal characteristics across the three
evaluated time windows, together with p for trends, are presented in Table 1. During the study
period, changes in mean maternal age and the prevalence of primiparous were negligible. The
mean BMI and the prevalence of obesity remained the same, although there was a possible trend
towards an increase in obesity over time. The prevalence of nephropathy decreased during the
study period, with ACR greater than 300 at 4.8% in 2004-2008 to 0 % in 2013-2017 (p for
trend=0.002). The use of insulin pumps increased from 50.0% in 2004-2008 to 58.1% in 2009-
2012, and to 72.7% in 2013-2017 (p<0.001). The use of CGMs also increased significantly with
no use at the beginning of the study period to 2.2% in 2009-2012 and 39.9% in 2013-2017
(p<0.001).

**Pregnancy glycemic control and weight gain measures**

In Table 2, we present the mean values of HbA1c during pregnancy. When analyzed
continuously, there were no differences between the 3 groups for any trimester. In addition, we
examined the percentage of women who reached the recommended levels of HbA1c in each trimester (<6.5% [48 mmol/mol] in the first trimester, and <6.0% [42 mmol/mol] for the second and third trimester), with a similar percentage of women reaching the recommendation across all time periods.

Overall, mean gestational weight gain remained unchanged across each of the time periods (Table 2). However, when assessed categorically based on IOM guidelines that account for pre-pregnancy BMI, the percentage of women with excessive gestational weight gain increased significantly with 16.3% gaining excessive weight in 2004-2008 and 26.2% in 2013-2017 (p=0.02). When evaluating weight gain velocity, no significant differences were seen over time.

**Delivery outcomes**

Table 3 presents delivery outcomes. The average gestational age at delivery lengthened from 37.0 weeks in 2004-2008 to 37.1 weeks in 2009-2012 and 37.4 weeks in 2013-2017 (p=0.03). However, preterm birth did not change significantly over time for either measure (gestational age <37 weeks or <32 weeks). Birthweight increased over the study period but it was not statistically significant, however, birth weight percentiles did not change over time and the prevalence of macrosomia and LGA remained high but did not change significantly over time. The prevalence of SGA did not change over time as well and remained low. Vaginal deliveries increased from 21.1% in 2004-2008 to 24.2% in 2009-2012, and 29.6% in 2013-2017 (p=0.03).

**Sensitivity analysis**

The results of the sensitivity analyses are presented in Tables 1-6 in the supplementary materials. By restricting the dataset, we eliminated correlated data in two different ways. The first analysis included only the first pregnancy for each woman in the dataset. As expected, maternal age was younger and decreased in the sensitivity analysis subgroups especially in the 2009-2012 and
2013-2017 (p=0.005), and the prevalence of primiparous increased significantly (p<0.001). The increase in the use of insulin pumps and CGMs and the decrease in the prevalence of nephropathy remained significant. Glucose control results were similar to the full dataset, with no difference between the subgroups during pregnancy and the increase in excessive weight gain during pregnancy remained significant as well (p=0.03). Finally, we found similar results for no change in birth weight, prevalence of macrosomia, LGA and SGA and preterm deliveries. We found weaker p values for the increase in vaginal deliveries and gestational age at delivery, possibly due to limited power attributed to smaller sample size. The second analysis included only primiparous women in all time periods. There was a significant decrease in maternal age (30.9 years in 2004-2008 vs. 29.5 years in 2013-2017, p=0.03). There were no other differences noted between this analysis and the former analysis.

Discussion

Our study sought to focus on quantifying maternal variables and selected delivery outcomes, such as maternal BMI, gestational weight gain and birth weight, that have been possibly more intractable over time despite technological advances in diabetes management. We found significant time trends in several pre-pregnancy maternal characteristics, treatment measures and pregnancy and delivery outcomes. First, while pre-pregnancy anthropometry factors remained the same nephropathy decreased. Second, the percentage of women who use insulin pumps and CGMs increased dramatically between 2004 and 2017. There were no changes in glycemic control based on mean trimester-specific HbA1c levels across pregnancy. Third, the percentage of women with type 1 diabetes, who gained excessive gestational weight increased significantly. Fourth, gestational age at delivery increased and the percentage of cesarean
deliveries decreased. However, birth weight, the prevalence of preterm birth, as well as LGA and fetal macrosomia did not change over the study period.

During the study period, there were significant changes in glucose management that include an increase in the use of insulin pumps and CGMs. Previous studies examining the efficacy of these techniques showed conflicting results (20-24). We did not demonstrate any changes in mean HbA1c levels before and during pregnancy and the percentage of women with higher than recommended levels of HbA1c during pregnancy remained fairly high at 60-70%. This inconsistent attainment of HbA1c targets is worrisome since poor glycemic control is known to increase adverse perinatal outcomes (25; 26). It had been observed that HbA1c is too blunt a tool to detect important improvements in glucose in pregnancy and that CGM analysis is far better at giving this information in pregnancy (27). However, as in the CONCEPTT trial, HbA1c may not fully reflect glycemic control, including time spent in target range (21). Possible explanations for our results could be that the users of insulin pumps and CGMs might have had more severe forms of diabetes to begin with or that self-adjustment of insulin dosing may be more challenging during pregnancy (20). A recent study demonstrated that the prevalence of LGA is higher in insulin pump users than those who use multiple daily injections and this may be mediated by excess weight gain in pregnancy (28). Moreover, it is possible that the lack of improvement in glycemic control, as reflected by HbA1c, might be due to a false sense of reassurance for individual patients using these newer technologies, with less concern about counting carbohydrates and pre-bolusing before meals.

Despite the fact that we did not find a significant change over time for trimester-specific HbA1c, the prevalence of nephropathy decreased significantly. In pregnancy, diabetic nephropathy is associated with several adverse outcomes in pregnancy including hypertensive disorders, preterm
deliveries, intrauterine growth restriction, and stillbirth (25). Of interest, within this population this trend may have started prior to the start of the present study, as earlier studies in late 1970s and 1980s at the Joslin Diabetes Center reported nephropathy prevalence of 9.6% and 14% compared to our 0% for the 2013-2017 time period (29; 30). This decrease in the prevalence of diabetic nephropathy may indicate improvements in glycemic control that preceded the start of the present study’s time period or the increasing use of renin angiotensin system blocking medications in our population with micro albuminuria, in the years leading up to pregnancy.

A pre-pregnancy factor that complicates all pregnancies is obesity, as it is an important risk factor for perinatal complications (2; 31). We did not find significant change in maternal BMI, although there was a suggestive increase. However, we did find a significant increase in the percentage of women with gestational weight gain that exceeded the IOM recommendations, based on their pre-pregnancy BMI. The prevalence of excessive gestational weight gain was reported to be 47% of the general population pregnant women and is associated with several adverse outcomes such as hypertensive disorders, cesarean delivery and macrosomia, which are complications that are more prevalent in women with type 1 diabetes (32-34). The increase in the prevalence of women with excessive gestational weight gain by BMI category could be attributed to the possible increasing prevalence of pre-pregnancy obesity in this population, with gestational weight gain categories relying on pre-pregnancy BMI to determine excessive, adequate, or inadequate weight gain during pregnancy. Specifically, the prevalence of obesity in this study population increased from 16.8% in 2004-2008 to 22.2% in 2013-2017. In fact, most of the women who had excessive gestational weight gain were categorized as obese, with only 18% of women with normal BMI gaining excessive weight based on IOM guidelines compared to 72% of obese women. Thus, it may be important to consider strategies for communicating
appropriate weight gain for a somewhat increasingly obese population of women with type 1 diabetes.

During the study period, there were several changes in obstetrical practice, including a change in the approach for the timing for induction of labor for women with type 1 diabetes. Traditionally, the goal of induction of labor for women with type 1 diabetes was the prevention of stillbirth and macrosomia along with the complications associated with these conditions (35). According to current recommendation made by the American College of Obstetrics and Gynecology delivery is no longer induced prior to 39 weeks gestation unless glucose control is suboptimal, or maternal or fetal complications accrue (5; 36). This change could have influenced our study results towards longer gestational age at delivery and higher birth weights in the latter time periods. In fact, a randomized control trial conducted two decades ago corroborates these findings, with women having higher birth weight babies in the expectant management group compared to the induction of labor group (37). We found a decrease in cesarean deliveries in the present study, as opposed to other studies that examined trends in pregnancy outcomes in women with type 1 diabetes (9, 12). Guidelines regarding labor management have changed in recent years as a concerted effort is being made to reduce the cesarean section rate in all obstetric populations. The definition of labor dystocia has been revisited with more generous definitions of arrested labor, fetal heart rate interpretation has been standardized, and breech versions and vaginal births after cesarean are offered more frequently. All of these measures are employed more uniformly with the intention of decreasing the cesarean section rate nationwide (38).

The sensitivity analyses that were conducted excluded recurrent pregnancies or included only primiparous women, therefore eliminated the correlation between the different observations. There were no substantial differences between our main analysis and the sensitivity analyses,
indicating the validity of the main analysis. A few outcomes in our analysis showed a near significant p value (birth weight in the main analysis). As p values are effected from the effect size as well as the sample size we acknowledge that these results may reveal a trend that could not be evident due to small sample size. Larger sample size allows measuring more precise means and proportions. This is particularly true for the results in the sensitivity analyses that had near significant p values (Gestational age at delivery and vaginal deliveries in the sensitivity analyses).

This study has several limitations. First, this study was conducted in a single site, and therefore may not be generalizable to other study populations. However, the Joslin Diabetes Center has a large catchment area and is located in Massachusetts where in 2006 a law mandated that residents obtain a minimum level of insurance coverage which could be free or subsidized based on earnings, allowing for improved health care access (39). Second, we evaluated time trends descriptively using each time period as the predictor, therefore the different maternal characteristics or treatment modalities were not considered confounders and could not be adjusted for in this descriptive analysis. Third, this dataset was not created for research purposes and consequently, we did not have reliable data on the duration of diabetes.

Percentage of missing data is shown in supplement Table 4. We acknowledge that there is missing data for BMI and gestational weight gain. The missing data is noted more often in the earlier years of this study when height and weight were not as rigorously recorded as they are now. In addition, some 1st trimester missing data (HbA1c, weight) were due to presenting after the first trimester of pregnancy. However, we found no differences in birth weight, birth weight percentiles and gestational age at delivery in pregnancies missing BMI compared to not missing BMI data. Further, 82%-99% of our data was complete and we were able to evaluate a variety of
pre-pregnancy, pregnancy, treatment, and delivery related outcomes across more than a decade within a single clinic. Fourth, we recorded the CGM use only at the beginning of the study, however, the effectiveness of CGM in pregnancies with type 1 diabetes appears to come from continuous wear and usage in pregnancy, rather than intermittent usage. This data recorded at the start, may not mean it was used consistently throughout pregnancy. Finally, the presence of anemia could possibly impact HbA1c levels in this pregnant population. We did not include hemoglobin levels as a part of this study; while clinically used to evaluate glycemic control, results of HbA1c should be interpreted with caution (40).

Despite these limitations, this study has several strengths. The main strength of our study is that it is one of the largest datasets of women with type 1 diabetes in the US. Furthermore, the study evaluates more than a decade of data allowing detection of time trends in a high-risk population. The data includes information on maternal pre-pregnancy characteristics, treatment and glycemic control measures during pregnancy, and pregnancy and delivery outcomes. Finally, this is the first study to examine time trends in pregnant women with type 1 diabetes living in the US.

In conclusion, over the last ~15 years, rapid technological changes have occurred with a significant increase in the use of insulin pumps and CGM. In addition, changes in obstetrical guidelines also occurred. With this, certain pregnancy and delivery-related outcomes improved, including increased gestational age and decreased cesarean delivery. However, other pregnancy-related outcomes have been adversely impacted, including increases in the prevalence of excessive gestational weight gain and no improvements in infant birth weight measures. As such, this study may provide some insight into adverse outcomes that may need to have focused attention for improving pregnancy health in women with type 1 diabetes. Future studies will be
aimed at evaluating associations between maternal characteristics, treatment modalities and glycemic control with delivery outcomes in this population.
### Table 1. Pre-pregnancy maternal characteristics in women with type 1 diabetes over 14 years of follow-up

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<tr>
<td>Age (years) (n=679)</td>
<td>31.7±5.2</td>
<td>31.9±5.4</td>
<td>32.0±5.5</td>
<td>31.3±4.7</td>
<td>p=0.19</td>
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<tr>
<td>White Ethnicity (n=700)</td>
<td>601 (85.8)</td>
<td>184(85.9%)</td>
<td>182 (84.6%)</td>
<td>235 (86.7%)</td>
<td>p= 0.80</td>
</tr>
<tr>
<td>Primiparous (n=695)</td>
<td>368 (52.9%)</td>
<td>112(52.3%)</td>
<td>119 (56.4%)</td>
<td>137 (50.7%)</td>
<td>p= 0.67</td>
</tr>
<tr>
<td>BMI (kg/m²) (n=577)</td>
<td>26.74±5.3</td>
<td>26.45±5.13</td>
<td>26.64±4.99</td>
<td>26.99±5.54</td>
<td>p=0.31</td>
</tr>
<tr>
<td>*Obesity (n=577)</td>
<td>117 (20.2%)</td>
<td>26 (16.8%)</td>
<td>35 (20.6%)</td>
<td>56 (22.2%)</td>
<td>p=0.19</td>
</tr>
<tr>
<td>Pump use (n=652)</td>
<td>405 (62.1%)</td>
<td>83 (50.0%)</td>
<td>125 (58.1%)</td>
<td>197 (72.7%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>† CGM use (n=652)</td>
<td>111 (17%)</td>
<td>0 (0%)</td>
<td>5 (2.2%)</td>
<td>106 (39.9%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>‡ Nephropathy (n=597)</td>
<td>16 (3%)</td>
<td>9 (4.8%)</td>
<td>7 (4.1%)</td>
<td>0 (0%)</td>
<td>p=0.002</td>
</tr>
</tbody>
</table>

Data are counts (percentages) or means ± SD. P values were calculated for trend. *Obesity defined as BMI≥30, † CGM= continuous glucose monitoring, ‡Nephropathy defined as albumin creatinine ratio ≥300. § Across all time periods. Analysis of 700 pregnancies in 512 women. Numbers may not sum up to 700 due to missing data on maternal characteristics.
Table 2. Glucose control and gestational weight gain in women with type 1 diabetes during pregnancy over 14 years of follow-up

<table>
<thead>
<tr>
<th></th>
<th>2004-2008 (n=214)</th>
<th>2009-2012 (n=215)</th>
<th>2013-2017 (n=271)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c % 1st trimester (n=636)</td>
<td>7.01 ± 1.31</td>
<td>6.88 ± 1.14</td>
<td>6.98 ± 1.05</td>
<td>p=0.83</td>
</tr>
<tr>
<td>HbA1c mmol/mol 1st trimester (n=636)</td>
<td>53±9.89</td>
<td>52±8.6</td>
<td>53±8</td>
<td>p=0.35</td>
</tr>
<tr>
<td>HbA1c&lt;6.5% 1st trimester (n=636)</td>
<td>72 (37.3%)</td>
<td>72 (37.9%)</td>
<td>84 (33.2%)</td>
<td>p=0.35</td>
</tr>
<tr>
<td>HbA1c % 2nd trimester (n=660)</td>
<td>6.37± 0.94</td>
<td>6.24 ± 0.79</td>
<td>6.26 ± 0.74</td>
<td>p=0.20</td>
</tr>
<tr>
<td>HbA1c mmol/mol 2nd trimester (n=660)</td>
<td>46±6.8</td>
<td>45±6.3</td>
<td>45±6</td>
<td>p=1.00</td>
</tr>
<tr>
<td>HbA1c&lt;6.0% 2nd trimester (n=660)</td>
<td>70 (34.0%)</td>
<td>77 (38.5%)</td>
<td>87 (34.3%)</td>
<td>p=0.97</td>
</tr>
<tr>
<td>HbA1c % 3rd trimester (n=648)</td>
<td>6.38 ± 0.79</td>
<td>6.31 ± 0.81</td>
<td>6.29 ± 0.68</td>
<td>p=0.18</td>
</tr>
<tr>
<td>HbA1c mmol/mol 3rd trimester (n=648)</td>
<td>46±5.6</td>
<td>45±5.8</td>
<td>45±5</td>
<td>p=0.97</td>
</tr>
<tr>
<td>HbA1c&lt;6.0% 3rd trimester (n=648)</td>
<td>60 (29.6%)</td>
<td>59 (31.1%)</td>
<td>76 (29.8%)</td>
<td>p=0.28</td>
</tr>
<tr>
<td>Gestational weight gain (lbs.) (n=585)</td>
<td>20.38 ± 10.33</td>
<td>19.11 ± 9.34</td>
<td>21.31 ± 10.91</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Excessive weight during pregnancy (n=527)</td>
<td>23 (16.3%)</td>
<td>23 (15.4%)</td>
<td>62 (26.2%)</td>
<td>p=0.01</td>
</tr>
</tbody>
</table>

Data are means ± SD or n (%). p values were calculated for trend. ‡ Maternal HbA1c data were available for N = 636 in the first trimester, N = 660 in the second trimester, and N = 648 in the third trimester. † Target HbA1c value were <6.5% (48 mmol/mol) in the first trimester and <6.0% (42 mmol/mol) in the second and third trimester. Numbers may not sum up to 700 due to missing data on glucose control and weight gain measures.
Table 3. Delivery outcomes in women with type 1 diabetes over 14 years of follow-up

<table>
<thead>
<tr>
<th></th>
<th>2004-2008 (n=214)</th>
<th>2009-2012 (n=215)</th>
<th>2013-2017 (n=271)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (kg) (n=697)</td>
<td>3.63 ± 0.74</td>
<td>3.62 ± 0.73</td>
<td>3.75 ± 0.78</td>
<td>p=0.07</td>
</tr>
<tr>
<td>Birth weight percentile (n=697)</td>
<td>82.0 ± 24.9</td>
<td>79.4 ± 25.8</td>
<td>82.4 ± 25.1</td>
<td>p=0.77</td>
</tr>
<tr>
<td>Macrosomia (n=697)</td>
<td>67 (31.5%)</td>
<td>65 (30.2%)</td>
<td>100 (37.2%)</td>
<td>p=0.16</td>
</tr>
<tr>
<td>LGA (n=696)</td>
<td>121 (56.8%)</td>
<td>113 (52.8%)</td>
<td>166 (61.7%)</td>
<td>p=0.24</td>
</tr>
<tr>
<td>SGA (n=696)</td>
<td>7 (3.3%)</td>
<td>6 (2.8%)</td>
<td>5 (1.9%)</td>
<td>p=0.32</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks) (n=698)</td>
<td>37.0 ± 2</td>
<td>37.1 ± 2</td>
<td>37.4 ± 2</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Preterm deliveries before 37 weeks (n=698)</td>
<td>61 (28.6%)</td>
<td>54 (25.2%)</td>
<td>63 (23.2%)</td>
<td>p=0.18</td>
</tr>
<tr>
<td>Preterm deliveries before 32 weeks (n=698)</td>
<td>4 (1.9%)</td>
<td>3 (1.4%)</td>
<td>4 (1.5%)</td>
<td>p=0.74</td>
</tr>
<tr>
<td>Vaginal deliveries (n=698)</td>
<td>45 (21.1%)</td>
<td>52 (24.2%)</td>
<td>80 (29.6%)</td>
<td>p=0.03</td>
</tr>
</tbody>
</table>

Data are counts (percentages) or means ± SD. p values were calculated for trend *LGA= large for gestational age, SGA= small for gestational age. Analysis of 700 pregnancies in 512 women. Numbers may not sum up to 700 due to missing data on delivery outcomes.
Supplementary materials

Supplemental Table 1. Pre-pregnancy maternal characteristics in women with type 1 diabetes over 14 years of follow-up among first pregnancy in dataset (n=512 women)

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong> (n=497)</td>
<td>30.9±5.3</td>
<td>31.7±5.6</td>
<td>31.1±5.6</td>
<td>30.1±4.7</td>
<td>p=0.005</td>
</tr>
<tr>
<td><strong>White Ethnicity</strong> (n=512)</td>
<td>433 (84.5%)</td>
<td>159 (85.4%)</td>
<td>128 (84.2%)</td>
<td>146 (83.9%)</td>
<td>p=0.90</td>
</tr>
<tr>
<td><strong>Primiparous</strong> (n=510)</td>
<td>368 (72%)</td>
<td>112 (60.2%)</td>
<td>119 (78.8%)</td>
<td>137 (79.2%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong> (n=419)</td>
<td>26.6±5.3</td>
<td>26.43±5.32</td>
<td>26.62±5.17</td>
<td>26.78±5.47</td>
<td>p=0.56</td>
</tr>
<tr>
<td>*<strong>Obesity</strong> (n=419)</td>
<td>79 (18.8%)</td>
<td>23 (16.9%)</td>
<td>23 (18.9%)</td>
<td>33 (20.5%)</td>
<td>p=0.43</td>
</tr>
<tr>
<td><strong>Pump use</strong> (n=464)</td>
<td>267 (52.1%)</td>
<td>67 (48.6%)</td>
<td>85 (55.9%)</td>
<td>115 (66.1%)</td>
<td>p=0.002</td>
</tr>
<tr>
<td><strong>† CGM use</strong> (n=464)</td>
<td>70 (15%)</td>
<td>0 (0%)</td>
<td>4 (2.6%)</td>
<td>66 (37.9%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>‡ Nephropathy</strong> (n=425)</td>
<td>13 (3%)</td>
<td>7 (4.4%)</td>
<td>6 (5.1%)</td>
<td>0 (0%)</td>
<td>p=0.03</td>
</tr>
</tbody>
</table>

Data are counts (percentages) or means ± SD. P values were calculated for trend. *Obesity defined as BMI≥30, † CGM= continuous glucose monitoring, ‡Nephropathy defined as albumin creatinine ratio ≥300. Analysis of 512 women.
**Supplemental Table 2.** Glucose control and weight gain during pregnancy in women with type 1 diabetes over 14 years of follow-up among first pregnancy in dataset (n=550 women)

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>HbA1c % 1st trimester (n=457)</td>
<td>7.02 ± 1.31</td>
<td>6.86 ± 1.21</td>
<td>7.02 ± 1.18</td>
<td>p=0.98</td>
</tr>
<tr>
<td>HbA1c mmol/mol 1st trimester (n=457)</td>
<td>53±9</td>
<td>52±8</td>
<td>53±8</td>
<td></td>
</tr>
<tr>
<td>HbA1c&lt;6.5% 1st trimester (n=457)</td>
<td>61 (36.7%)</td>
<td>54 (40.9%)</td>
<td>56 (35.2%)</td>
<td>p=0.79</td>
</tr>
<tr>
<td>HbA1c % 2nd trimester (n=483)</td>
<td>6.38 ± 0.99</td>
<td>6.25 ± 0.89</td>
<td>6.28 ± 0.81</td>
<td>p=0.31</td>
</tr>
<tr>
<td>HbA1c mmol/mol 2nd trimester (n=483)</td>
<td>46±7</td>
<td>45±6</td>
<td>45±6</td>
<td></td>
</tr>
<tr>
<td>HbA1c&lt;6.0% 2nd trimester (n=483)</td>
<td>64 (35.8%)</td>
<td>60 (42%)</td>
<td>53 (32.9%)</td>
<td>p=0.62</td>
</tr>
<tr>
<td>HbA1c % 3rd trimester (n=475)</td>
<td>6.36 ± 0.78</td>
<td>6.25 ± 0.71</td>
<td>6.25 ± 0.74</td>
<td>p=0.21</td>
</tr>
<tr>
<td>HbA1c mmol/mol 3rd trimester (n=475)</td>
<td>46±6</td>
<td>45±6</td>
<td>45±5</td>
<td></td>
</tr>
<tr>
<td>HbA1c&lt;6.0% 3rd trimester (n=475)</td>
<td>55 (31.1%)</td>
<td>47 (35.1%)</td>
<td>57 (34.8%)</td>
<td>p=0.47</td>
</tr>
<tr>
<td>Gestational weight gain (lbs.) (n=430)</td>
<td>20.4 ± 10.4</td>
<td>19.6 ± 9.9</td>
<td>21.065 ± 12</td>
<td>p=0.57</td>
</tr>
<tr>
<td>Excessive weight during pregnancy (n=381)</td>
<td>20 (16.1%)</td>
<td>20 (18.7%)</td>
<td>41 (27.3%)</td>
<td>p=0.03</td>
</tr>
</tbody>
</table>

Data are means ± SD or n (%). p values were calculated for trend. ‡ Maternal HbA1c data were available for N = 457 in the first trimester, N = 483 in the second trimester, and N = 475 in the third trimester. † Target HbA1c value were <6.5% (48 mmol/mol) in the first trimester and <6.0% (42 mmol/mol) in the second and third trimester. Numbers may not sum up to 512 due to missing data on glucose control and weight gain measures.
**Supplemental Table 3.** Delivery outcomes in women with type 1 diabetes over 14 years of follow-up among first pregnancy in dataset (n=550 women)

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (kg) (n=509)</td>
<td>3.58 ± 0.75</td>
<td>3.57 ± 0.70</td>
<td>3.60± 0.78</td>
<td>p=0.74</td>
</tr>
<tr>
<td>Macrosomia (n=509)</td>
<td>55 (29.7%)</td>
<td>41 (27.0%)</td>
<td>49 (28.5%)</td>
<td>p=0.79</td>
</tr>
<tr>
<td>*LGA (n=509)</td>
<td>105 (56.6%)</td>
<td>77 (51.0%)</td>
<td>107 (62.2%)</td>
<td>p=0.29</td>
</tr>
<tr>
<td>†SGA (n=509)</td>
<td>7 (3.8%)</td>
<td>2 (1.3%)</td>
<td>5 (2.9%)</td>
<td>P=0.60</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks) (n=510)</td>
<td>36.6 ± 2</td>
<td>37.2 ± 2</td>
<td>37.3 ± 2</td>
<td>p=0.05</td>
</tr>
<tr>
<td>Preterm deliveries before 37 weeks (n=510)</td>
<td>55 (29.7%)</td>
<td>39 (25.8%)</td>
<td>44 (25.3%)</td>
<td>p=0.34</td>
</tr>
<tr>
<td>Preterm deliveries before 32 weeks (n=510)</td>
<td>4 (2.2%)</td>
<td>2 (1.3%)</td>
<td>4 (2.3%)</td>
<td>p=0.93</td>
</tr>
<tr>
<td>Vaginal deliveries (n=510)</td>
<td>40 (21.6%)</td>
<td>40 (26.3%)</td>
<td>52 (30.1%)</td>
<td>p=0.07</td>
</tr>
</tbody>
</table>

Data are counts (percentages) or means ± SD. P values were calculated for trend. *LGA= large for gestational age, †SGA= small for gestational age
**Supplemental Table 4.** Pre-pregnancy maternal characteristics in primiparous women with type 1 diabetes over 14 years of follow-up (n=368 women)

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (n=361)</td>
<td>30.9±5.5</td>
<td>30.4±5.6</td>
<td>29.5±4.6</td>
<td>p=0.03</td>
</tr>
<tr>
<td>White Ethnicity (n=)</td>
<td>159 (85.4%)</td>
<td>128 (84.2%)</td>
<td>146 (83.9%)</td>
<td>p=0.90</td>
</tr>
<tr>
<td>BMI (kg/m²) (n=310)</td>
<td>26.65±5.38</td>
<td>26.51±4.94</td>
<td>27.02±5.37</td>
<td>p=0.57</td>
</tr>
<tr>
<td>*Obesity (n=310)</td>
<td>16 (19.0%)</td>
<td>17 (17.5%)</td>
<td>29 (22.5%)</td>
<td>p=0.49</td>
</tr>
<tr>
<td>Pump use (n=342)</td>
<td>45 (52.3%)</td>
<td>70 (58.8%)</td>
<td>93 (67.9%)</td>
<td>p=0.02</td>
</tr>
<tr>
<td>† CGM use (n=342)</td>
<td>0 (0%)</td>
<td>4 (3%)</td>
<td>59 (43%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>‡ Nephropathy (n=310)</td>
<td>4 (4.1%)</td>
<td>4 (4.2%)</td>
<td>0 (0%)</td>
<td>p=0.05</td>
</tr>
</tbody>
</table>

Data are counts (percentages) or means ± SD. P values were calculated for trend. *Obesity defined as BMI≥30, † CGM= continuous glucose monitoring, ‡Nephropathy defined as albumin creatinine ratio ≥300
**Supplemental Table 5.** Glucose control and weight gain during pregnancy in primiparous women with type 1 diabetes over 14 years of follow-up (n=368 women)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c % 1st trimester (n=334)</strong></td>
<td>6.98 ±1.39</td>
<td>6.90 ±1.25</td>
<td>6.96 ±1.11</td>
<td>p=0.92</td>
</tr>
<tr>
<td><strong>HbA1c&lt;6.5% 1st trimester (n=334)</strong></td>
<td>39 (39.4%)</td>
<td>43 (40.6%)</td>
<td>46 (35.7%)</td>
<td>p=0.54</td>
</tr>
<tr>
<td><strong>HbA1c % 2nd trimester (n=347)</strong></td>
<td>6.31 ±0.96</td>
<td>6.23 ±0.90</td>
<td>6.24 ±0.73</td>
<td>p=0.58</td>
</tr>
<tr>
<td><strong>HbA1c&lt;6.0% 2nd trimester (n=347)</strong></td>
<td>39 (35.8%)</td>
<td>51 (45.1%)</td>
<td>39 (31.2%)</td>
<td>p=0.42</td>
</tr>
<tr>
<td><strong>HbA1c % 3rd trimester (n=339)</strong></td>
<td>6.34 ±0.77</td>
<td>6.26 ±0.72</td>
<td>6.23 ±0.68</td>
<td>p=0.22</td>
</tr>
<tr>
<td><strong>HbA1c&lt;6.0% 3rd trimester (n=339)</strong></td>
<td>31 (29.0%)</td>
<td>35 (33.7%)</td>
<td>42 (32.8%)</td>
<td>p=0.55</td>
</tr>
<tr>
<td><strong>Gestational weight gain (lbs.) (n=312)</strong></td>
<td>19.5±9</td>
<td>20.2 ± 10</td>
<td>21.4±12</td>
<td>p=0.18</td>
</tr>
<tr>
<td><strong>Excessive weight during pregnancy</strong></td>
<td>12 (15.4%)</td>
<td>19 (22.4%)</td>
<td>36 (29.8%)</td>
<td>p=0.02</td>
</tr>
</tbody>
</table>

Data are means ± SD or n (%). p values were calculated for trend. ‡ Maternal HbA1c data were available for n = 334 in the first trimester, n = 347 in the second trimester, and n = 339 in the third trimester. † Target HbA1c value were <6.5% (48 mmol/mol) in the first trimester and <6.0% (42 mmol/mol) in the second and third trimester. Numbers may not sum up to 368 due to missing data on glucose control and weight gain measures.
Supplemental Table 6. Delivery outcomes in primiparous women with type 1 diabetes over 14 years of follow-up (n=368 women)

<table>
<thead>
<tr>
<th></th>
<th>2004-2008 (n=112)</th>
<th>2009-2012 (n=119)</th>
<th>2013-2017 (n=137)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (kg) (n=366)</td>
<td>3.503±0.8</td>
<td>3.568±0.7</td>
<td>3.606±0.8</td>
<td>p=0.28</td>
</tr>
<tr>
<td>Birth weight percentile (n=365)</td>
<td>77.8±3</td>
<td>77.2±3</td>
<td>77.2±3</td>
<td>p=0.87</td>
</tr>
<tr>
<td>Macrosomia (n=366)</td>
<td>33 (29.7%)</td>
<td>32 (26.9%)</td>
<td>40 (29.4%)</td>
<td>p=0.98</td>
</tr>
<tr>
<td>LGA (n=365)</td>
<td>57 (51.4%)</td>
<td>56 (47.5%)</td>
<td>69 (50.7%)</td>
<td>p=0.95</td>
</tr>
<tr>
<td>SGA (n=365)</td>
<td>6 (5.4%)</td>
<td>3 (2.5%)</td>
<td>3 (2.2%)</td>
<td>p=0.17</td>
</tr>
<tr>
<td>Gestational age at delivery (weeks) (n=366)</td>
<td>37.0±2</td>
<td>37.4±2</td>
<td>37.5±2</td>
<td>p=0.08</td>
</tr>
<tr>
<td>Preterm deliveries before 37 weeks (n=366)</td>
<td>32 (28.8%)</td>
<td>28 (23.7%)</td>
<td>32 (23.4%)</td>
<td>p=0.34</td>
</tr>
<tr>
<td>Preterm deliveries before 32 weeks (n=366)</td>
<td>3 (2.7%)</td>
<td>2 (1.7%)</td>
<td>3 (2.2%)</td>
<td>p=0.80</td>
</tr>
<tr>
<td>Vaginal deliveries (n=366)</td>
<td>20 (18%)</td>
<td>33 (27.7%)</td>
<td>39 (28.7%)</td>
<td>p=0.06</td>
</tr>
</tbody>
</table>

Data are counts (percentages) or means ± SD. P values were calculated for trend. *LGA= large for gestational age, †SGA= small for gestational age
Supplemental Table 7. Numbers of missing data in the different time periods

<table>
<thead>
<tr>
<th></th>
<th>2004-2008 (n=214)</th>
<th>2009-2012 (n=215)</th>
<th>2013-2017 (n=271)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>59(27%)</td>
<td>45(20%)</td>
<td>19(7%)</td>
</tr>
<tr>
<td>Age</td>
<td>1(0.5%)</td>
<td>14(6%)</td>
<td>6(2%)</td>
</tr>
<tr>
<td>ACR</td>
<td>28(13%)</td>
<td>46(21%)</td>
<td>29(10%)</td>
</tr>
<tr>
<td>HbA1c tri 1</td>
<td>21(9%)</td>
<td>25(11%)</td>
<td>18(6%)</td>
</tr>
<tr>
<td>HbA1c tri 2</td>
<td>8(4%)</td>
<td>15(7%)</td>
<td>17(6%)</td>
</tr>
<tr>
<td>HbA1c tri 3</td>
<td>11(5%)</td>
<td>25(11%)</td>
<td>16(6%)</td>
</tr>
<tr>
<td>Gestational weight gain</td>
<td>37(17%)</td>
<td>52(24%)</td>
<td>26(9%)</td>
</tr>
<tr>
<td>Birth weight</td>
<td>1(0.5%)</td>
<td>0</td>
<td>1(0.4%)</td>
</tr>
<tr>
<td>Gestational age at delivery</td>
<td>0</td>
<td>1(0.5%)</td>
<td>1(0.4%)</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td>2(0.9%)</td>
<td>1(0.5%)</td>
<td>1(0.4%)</td>
</tr>
</tbody>
</table>
References

Low Prevalence of Small for Gestational Age in Women with Concurrent Type 1 Diabetes and Chronic Hypertension in Pregnancy

Short title: SGA in type 1 diabetes and chronic hypertension

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Abstract

Objective: To evaluate birth weight and other delivery outcomes among women with type 1 diabetes with and without chronic hypertension (cHTN), with cHTN treatment targeting blood pressure (BP) 110-129/65-79 mmHg.

Research Design and methods: Clinical data were abstracted from medical records of 516 pregnancies among 393 women seeking prenatal care at Joslin Diabetes Center and Beth Israel Deaconess Medical Center’s Diabetes in Pregnancy Program (2004-2017). Means and percentages were calculated, along with t test or χ² test. We used linear regression to compare birth weight percentiles in women with type 1 diabetes and cHTN to those with type 1 diabetes and no cHTN.

Results: Type 1 diabetes and cHTN co-occurred in 51 (7.3%) of pregnancies. Per trimester, BP values were higher in pregnancies with type 1 diabetes and cHTN compared to pregnancies with type 1 diabetes and no cHTN (p<0.001). In pregnancies with type 1 diabetes and cHTN, women were older (33.4 vs. 31.6 years, p=0.01) and had greater prevalence of nephropathy (10.4% vs. 1.8% p<0.001). Gestational age at delivery and birth weight were lower in the cHTN group (36.5 weeks vs. 37.4 weeks, p=0.03) and (3482g vs. 3722g, p=0.03, respectively). There were no differences in birth weight percentiles and small for gestational age (SGA) was rare in both groups (2% vs. 1.7%, p=0.9).

Conclusion: SGA was rare in pregnancies complicated by type 1 diabetes and cHTN, even when BP targets were 110-129/65-79 mmHg. These findings may provide reassurance for reestablishing lower BP targets rather than adopting recent higher targets of 120-160/80-105 mmHg followed by ACOG (2013) and ADA (2017).
Introduction

The prevalence of chronic hypertension (cHTN) in pregnancy in women with type 1 diabetes ranges from 2%-11%, and is defined as blood pressure (BP) ≥140 mmHg systolic or ≥90 mmHg diastolic that precedes pregnancy, that is present before the 20th week of pregnancy or persists longer than 12 weeks postpartum (1-4). Severe BP is defined as ≥160 mmHg systolic or ≥100 mmHg diastolic (3). Both type 1 diabetes and cHTN are independent risk factors for adverse maternal and fetal outcomes and the combination of them increases the risk of preeclampsia, cerebrovascular complications, acute renal failure, pulmonary edema, stillbirth, preterm delivery and poor fetal growth (4-7). These complications highlight the importance of controlling cHTN and diabetes during pregnancy in women with type 1 diabetes, while taking into consideration maternal and fetal risks and benefits. However, there are limited data to define optimal BP targets in pregnancies complicated by type 1 diabetes and cHTN.

In 2008, The American Diabetes Association (ADA) technical review and the summary of recommendations recommended BP targets 110-129/65-79 mmHg. These corresponded to the 50-97.5 percentiles for BP in normal pregnancy, addressed the U-shaped relationship between blood pressure and adverse pregnancy outcomes, and were consistent with the recommended BP targets in patients with preexisting diabetes, who were not-pregnant to reduce the risk of micro and macro-vascular complications (8-10).

Historically, there has been concern that lower BP values will reduce the perfusion of the intervillous space of the placenta (11, 12). This is a particular concern with cHTN, as it is thought to accelerate placental aging and cause preeclampsia (13-15). Antihypertensive therapy has been shown to be associated with restricted fetal growth by adversely affecting placental
perfusion in pregnant women with cHTN in several studies (16-19). Consequently, the ADA recommended targets to be changed in 2017. The updated BP targets are 120-160/80-105 mmHg to match “reasonable” American College of Obstetrics and Gynecology (ACOG) guidelines from 2013 “in the interest of optimizing long-term maternal health and minimizing impaired fetal growth” (20, 21). The most recent ACOG Practice Bulletin on Chronic Hypertension in Pregnancy does not specify the BP targets for women with type 1 diabetes and cHTN, other than generally recommending that they should be lower than the above targets (22). Thus, it is important to present data that clarifies the risks of restricted fetal growth of defined BP targets in women with type 1 diabetes and cHTN while avoiding severe maternal hypertension and its consequences.

Our retrospective cohort study evaluates the prevalence of SGA in women with and without cHTN among women with type 1 diabetes. In addition, we assessed the association of cHTN with other pregnancy and delivery outcomes in women with co-existent type 1 diabetes and cHTN treated with anti-hypertensive pharmacotherapy to target BP 110-129/65-79 mmHg throughout pregnancy.

**Methods**

**Study population**

We previously performed a retrospective cohort study of 700 pregnancies derived from 512 women with type 1 diabetes seeking prenatal care and who delivered at the Joslin Diabetes Center and Beth Israel Deaconess Medical Center’s Diabetes in Pregnancy Program from 2004-2017 (manuscript under review). The inclusion criteria for the entire cohort were: clinically diagnosed type 1 diabetes and being 18 years or older with a singleton live birth pregnancy.
For the present study we identified a group with medically-treated cHTN defined as being treated with anti-hypertensive medication either prior to pregnancy or in the first trimester of pregnancy (type 1 diabetes cHTN group; n=51 pregnancies in 35 women). Within the rest of pregnancies (n=649), we excluded pregnancies with no available BP data during pregnancy (n=184) and then identified pregnancies with type 1 diabetes without cHTN defined as women who had normal BP values in one or more trimesters of pregnancy and were not treated with antihypertensive medication (type 1 diabetes and no cHTN group; n= 465 pregnancies in 358 women). See Supplemental Figure 1. The study was approved by the Committee for Human Subjects at Joslin Diabetes Center.

Most type 1 diabetes and cHTN pregnancies were treated with one medication (n=47): nifedipine (n=21), labetalol (n=15), alpha methyl dopa (n=6), metoprolol (n=5), diltiazem (n=4), or verapamil (n=1). Four were treated with 2 medications combining nifedipine with either labetalol, metoprolol or methyl dopa and methyl dopa with diltiazem. None were treated with 3 or more medications. All data were abstracted from the medical records.

**Birth weight and birth weight for gestational age measures**

Neonatal outcomes included birth weight, birth weight percentiles, and gestational age at delivery. Because of differences in gestational age at delivery, we prespecified use of customized birth weight percentiles (gestation-related optimal weight) that adjust for infant sex and gestational age as well as maternal height, weight, parity, and race/ethnicity to calculate the birth weight percentile (23). Infant birth weights >90th percentile and <10th percentile were referred as large for gestational age (LGA) and small for gestational age (SGA), respectively. Infant birth weights between the 10th and 90th percentile were referred as appropriate for gestational age (AGA).
Maternal covariates

Data on maternal characteristics were abstracted from medical records. Specifically, information on maternal age, use of insulin pump, and antihypertensive medications were collected from the first prenatal visit. BMI and the presence of nephropathy were collected from the first prenatal visit or up to 6 months prior to the last menstrual period. Nephropathy was defined as urine albumin/creatinine ratio ≥300. In addition, maternal BP values at 4 time points in pregnancy: the first visit in the 1st, 2nd, 3rd trimesters and the last visit prior to delivery were collected. Preeclampsia was also abstracted for the cHTN group from medical records.

Statistical analysis

We calculated means and conducted t-tests to evaluate mean differences in birth weight, birth weight percentiles, along with maternal characteristics and pregnancy outcomes (i.e. maternal age, 1st trimester BMI trimester-specific blood pressures, and gestational age at delivery) comparing women with concurrent type 1 diabetes and cHTN to those with type 1 diabetes and no cHTN. In addition, we calculated frequencies and percentages, along with χ2 test to evaluate differences between the prevalence of SGA, AGA, LGA, along with other pregnancy and delivery outcomes (i.e. insulin pump use during pregnancy, maternal obesity, nephropathy, delivery type, and preterm birth).

We used multivariable linear regression to predict the association between cHTN and birth weight percentile among women with type 1 diabetes. Due to the rare occurrence of SGA, we could not use multivariable linear regression to evaluate the association between cHTN and SGA in this population. All analyses were performed using R version 3.3.2 (2016-10-31) and Stata/IC 15.1.
Results

Type 1 diabetes and cHTN occurred in 51 (7.3%) of 700 pregnancies (n=35 women) (Figure 1 supplemental materials). Maternal characteristics are presented in Table 1. Women with type 1 diabetes and cHTN, were older (33.4 vs. 31.6 p=0.01), suggestively more likely to be obese at the time of pregnancy (33.3% vs. 20.7% p=0.06) and were more likely to have diabetic nephropathy (10.4% vs. 1.8%, p<0.001).

Table 2 shows the mean BP values in mmHg in both groups. BP values were significantly higher in pregnancies with type 1 diabetes and cHTN compared to type 1 diabetes and no cHTN in each of the trimesters (p<0.001) (Figure 1). For women in the type 1 diabetes and cHTN group, mean BPs were 128/76 in the first trimester; 122/72 in the second trimester; 124/76 in the third trimester; 137/82 prior to delivery. Fifteen (29.4%) of the pregnancies with type 1 diabetes and cHTN were complicated by preeclampsia according to the ACOG criteria (24). Only 4 pregnancies (7.8%) were complicated by severe BP values of systolic BP>160 mmHg and none had diastolic BP>110 mmHg.

There were significant differences in gestational age at delivery (36.5 weeks vs. 37.4 weeks, p=0.03) and birth weight (3482g vs. 3722g, p=0.03) between women with type 1 diabetes who had cHTN and those that did not have cHTN. Interestingly, there were no differences in birth weight percentile adjusted for infant sex, gestational age, maternal height, weight, parity, and ethnicity. Notably there were no differences in the prevalence of SGA between the groups with only one case in the cHTN group and 8 cases in the no cHTN group (2.0% vs. 1.7%, p=0.9). Prevalence of AGA and LGA were similar in both groups. In addition, when adjusted for maternal age and BMI there was no association between cHTN and birth weight percentiles. (β=-7.9, 95% CI -17.4, 1.5).
The prevalence of preterm birth before 37 weeks was higher in the cHTN group (37.3% vs 23.3% p=0.03). Fewer women with type 1 diabetes and cHTN delivered vaginally compared to women with type 1 diabetes and no cHTN (8.2% vs. 26.5%, p=0.004). (Table 3).

**Discussion**

In the present study, we found SGA to be rare in type 1 diabetes pregnancies, despite accounting for maternal characteristics, including maternal weight, height, race/ethnicity, and parity. No differences were seen in birth weight percentiles for gestational age between women with type 1 diabetes with and without cHTN. This finding is particularly noteworthy in women with type 1 diabetes and cHTN treated to BP targets 110- 129/65-79 mmHg with anti-hypertensive medications. Yet, despite treatment with anti-hypertensive medications to these BP targets, the BP values in pregnancies with type 1 diabetes and cHTN remained higher in all trimesters than BP values in pregnancies with type 1 diabetes and no cHTN. Women with type 1 diabetes and cHTN tended to be older than women with type 1 diabetes and no cHTN and had higher prevalence of nephropathy and were more likely to have a cesarean delivery.

Previous retrospective studies have shown supportive evidence of low prevalence of infants with SGA under tight BP control to <135/85 mmHg in women with diabetes during pregnancy. The first study included pregnancies complicated by type 1 diabetes and microalbuminuria or diabetic nephropathy and showed no SGA in the microalbuminuria group with tight BP control compared to historic controls of similar demographics (25). The second study assessed the prevalence of pregnancy-related hypertensive disorders in women with type 1 and type 2 diabetes treated with anti-hypertensive therapy to target BP <135/85 mmHg. There was a 3% prevalence of concomitant cHTN in women with type 1 diabetes and no significant difference in the prevalence
of SGA between the treated cHTN group compared to women with normal blood pressure or gestational hypertension or preeclampsia (26).

There are no randomized control trials (RCTs) evaluating anti-hypertensive targets in pregnancies complicated by type 1 diabetes and cHTN. In women with hypertension but no diabetes, the Control of Hypertension in Pregnancy (CHIPS) study aimed to compare outcomes in women with less tight control of diastolic 100 mmHg versus tight control of diastolic 85 mmHg (27). While the CHIPS study aimed for a 15mm Hg difference in diastolic BP, they only achieved a 5mmHg difference in BP. Thus, the less tight control group had a mean BP of 138.8(+/-0.5)/89.9(+/-0.3) mm Hg and the tight control had a BP of 133.1 (+/-0.3) /85.3 (+/-0.3) mmHg. The study found a non-significant trend towards SGA in the tight control group but a significantly higher frequency of severe maternal hypertension in the less-tight control group (27). Secondary analysis of the CHIPS data looking at only those randomized at <18 weeks gestation, demonstrated increased risk of preterm deliveries at 37 week and 34 weeks, as well as severe maternal hypertension in the less tight control group but higher prevalence of SGA in the tighter control group (28). However, the finding of SGA that was demonstrated in women with cHTN, but no diabetes treated to target tight control in CHIPS, may be of less concern in a population of women with type 1 diabetes and cHTN.

The determination of optimal BP targets during pregnancy must consider maternal and fetal benefits and risks. Since there is not enough information about type 1 diabetes concurrent with cHTN in pregnancy, we must extrapolate from other populations without type 1 diabetes. Of concern when doing these extrapolations is that pregnant women with type 1 diabetes and cHTN are at increased risk of microvascular complications such as retinopathy and nephropathy as well as cardiovascular and all-cause mortality (29-31). Neonates delivered to women with type 1
diabetes and no cHTN are at increased risk of LGA (32). It is worth noting that in our study, we saw similar—and high prevalence—of LGA in the pregnancies of women with type 1 diabetes with and without cHTN. With respect to the fetal growth restriction in the presence of cHTN, data from the present study indicate negligible concern in pregnancies of women with type 1 diabetes.

This study has several limitations. First, we were limited by the small numbers of pregnancies complicated by type 1 diabetes and chronic hypertension (n=51). This may have led to type 2 error with respect to the SGA outcome. However, the similar birth weight percentiles in the two groups and extremely rare occurrence of SGA, regardless of cHTN status suggests that SGA may not be a major issue for women with type 1 diabetes. Second, we used a strict definition of chronic hypertension, restricting to those who were treated with medications for cHTN. That said, we did not see a significant difference in SGA, even with this greater contrast between women with type 1 diabetes with and without cHTN. Third, the study is based at a single clinic located in Boston, MA and may not be generalizable to other geographic or clinical settings. However, the clinic cares for a large U.S. population of pregnant women with type 1 diabetes, providing standard treatment of cHTN in this population.

Despite these limitations, the study has several strengths. First, BP targets were consistently defined over the 14 years of duration. Second, the analytic study population had detailed information about pregnancy and deliveries, including data on 1\textsuperscript{st}, 2\textsuperscript{nd}, and 3\textsuperscript{rd} trimester systolic and diastolic BP measures, as well as detailed information on gestational age, birth weight, and birth weight percentiles. In addition, data were available on delivery type, 1\textsuperscript{st} trimester BMI, and type of diabetes treatment and cHTN medication use. Third, to our knowledge, this is among the
largest studies of women with type 1 diabetes with and without cHTN, where we are able to compare pregnancy outcomes.

In conclusion, given the low prevalence of SGA in our population and similar birth weight percentiles in the offspring of women with type 1 diabetes with and without cHTN, our findings may support the use of the CHIPS tight blood pressure targets of BP of 133.1 (±/-0.3) /85.3 (+/-0.3) mmHg or prior ADA targets 110-129/65-79 mmHg for women with concurrent type 1 diabetes and cHTN. The finding of severe maternal hypertension, demonstrated in the less tight arm of the CHIPS study, is a serious concern for women with preexisting diabetes, who are at risk of end organ damage from hypertension. The current targets recommended by the ADA 120-160/80-105 mm were implemented to reduce the risk of SGA. However, this proposed risk reduction may not be warranted in this population, with the present study findings, showing very rare occurrence of SGA and similar birth weights across women with type 1 diabetes, regardless of their cHTN status. Thus, if our findings are replicated, these results suggest that the present targets may be too high and could put women with type 1 diabetes at unnecessary risk.
Tables

Table 1. Maternal characteristics for pregnant women with type 1 diabetes and cHTN compared to pregnant women with type 1 diabetes and no cHTN.

<table>
<thead>
<tr>
<th></th>
<th>Overall cohort n=516</th>
<th>Type 1 diabetes with and without cHTN n=51</th>
<th>Type 1 diabetes and no cHTN n=465</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years (n=500)</td>
<td>31.8± 4.4</td>
<td>33.4 ± 4.3</td>
<td>31.5 ± 5.0</td>
<td>p=0.02</td>
</tr>
<tr>
<td>Primiparity (n=513)</td>
<td>271 (52.5%)</td>
<td>24 (47.1%)</td>
<td>247 (53.1%)</td>
<td>p=0.41</td>
</tr>
<tr>
<td>White ethnicity (n=454)</td>
<td>441 (85.5%)</td>
<td>45(88.2%)</td>
<td>396(85.2%)</td>
<td>p=0.55</td>
</tr>
<tr>
<td>BMI kg/m² (n=458)</td>
<td>26.9± 5.6</td>
<td>28.4 ± 5.7</td>
<td>26.8 ± 5.3</td>
<td>p=0.08</td>
</tr>
<tr>
<td>*Obesity (n=458)</td>
<td>100 (21.8%)</td>
<td>14 (33.3%)</td>
<td>86 (20.7%)</td>
<td>p=0.06</td>
</tr>
<tr>
<td>Insulin pump use (n=514)</td>
<td>345 (67.1%)</td>
<td>37 (75.5%)</td>
<td>308 (66.2%)</td>
<td>p=0.19</td>
</tr>
<tr>
<td>Nephropathy (n=447)</td>
<td>12 (2.7%)</td>
<td>5 (10.4%)</td>
<td>7 (1.8%)</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

(First column n=number of pregnancies for which data is available for the combined groups. Maximum n=516.) Data are percentages or means ± SD. *Obesity defined as BMI≥30,
Table 2. Mean blood pressure (BP) values in pregnant women with type 1 diabetes with and without cHTN

<table>
<thead>
<tr>
<th></th>
<th>Type 1 diabetes and cHTN n=51</th>
<th>Type 1 diabetes and no cHTN n=465</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP first trimester</td>
<td>128±9</td>
<td>114±12</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP first trimester</td>
<td>76±8</td>
<td>69±8</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP second trimester</td>
<td>122±11</td>
<td>113 ± 12</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP second trimester</td>
<td>72±8</td>
<td>67 ± 7</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP third trimester</td>
<td>124±9</td>
<td>114 ± 12</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP third trimester</td>
<td>76±10</td>
<td>69 ± 7</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

n=number of pregnancies. All measurements are in mmHg, mean ± SD. BP values were available in all 51 women with cHTN during pregnancy and in 394 women without cHTN in the first trimester, 453 in the second trimester and 451 in the third trimester.
Table 3. Birth weight and other delivery outcomes in pregnant women with type 1 diabetes with and without cHTN.

<table>
<thead>
<tr>
<th></th>
<th>Type 1 diabetes and cHTN n=51</th>
<th>Type 1 diabetes and no cHTN n=465</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at delivery (n=515)</td>
<td>36.5 ± 2</td>
<td>37.4 ± 2</td>
<td>p=0.03</td>
</tr>
<tr>
<td>Birth weight kg (n=514)</td>
<td>3.482 ± 0.7</td>
<td>3.722 ± 0.7</td>
<td>p=0.03</td>
</tr>
<tr>
<td>Birth weight percentiles (n=514)</td>
<td>76±28</td>
<td>82±25</td>
<td>p=0.10</td>
</tr>
<tr>
<td>*SGA (n=513)</td>
<td>1 (2%)</td>
<td>8 (1.7%)</td>
<td>p=0.89</td>
</tr>
<tr>
<td>† AGA (n=513)</td>
<td>23(45%)</td>
<td>186(40.2%)</td>
<td>p=0.52</td>
</tr>
<tr>
<td>‡ LGA(n=513)</td>
<td>27 (53%)</td>
<td>269 (58.1%)</td>
<td>p=0.41</td>
</tr>
<tr>
<td>Vaginal Delivery (n=515)</td>
<td>5 (9.8%)</td>
<td>130 (26.5%)</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Preterm birth before 37 weeks (n=515)</td>
<td>18 (35.3%)</td>
<td>108 (23.3%)</td>
<td>p=0.06</td>
</tr>
<tr>
<td>Preterm birth before 32 weeks (n=515)</td>
<td>1 (2.0%)</td>
<td>5 (1.1%)</td>
<td>p=0.58</td>
</tr>
</tbody>
</table>

n= number of pregnancies. (First column n=number of pregnancies for which data is available for the combined groups. Maximum n=516.) Data are percentages or means ± SD. *SGA= small for gestational age, † AGA appropriate for gestational age, ‡ LGA= large for gestational age,
Figure 1. Boxplots of blood pressure (BP) values in pregnant women with type 1 diabetes with and without cHTN in four different time points of pregnancy.

The boxplots display the distribution of the BP data as minimum (bottom whisker), first quartile (bottom line), median (middle line), third quartile (top line), and maximum (upper whisker). Dots represent outliers.

*BP values for the last prenatal visit were available only for the cHTN group.
Supplemental Figure 1. Flow chart of study population identification and selection of analytic sample of women with type 1 diabetes with and without cHTN.

700 pregnancies of women with type 1 diabetes with and without cHTN (100%)

51 pregnancies with type 1 diabetes and cHTN (7.3%)

649 pregnancies with type 1 diabetes and no cHTN (92.7%)

465 pregnancies with type 1 diabetes and no cHTN

184 pregnancies with no extractable BP data were excluded from the analytic dataset

cHTN=chronic hypertension, BP= blood pressure. The analytic dataset compares 51 pregnancies with concurrent type 1 diabetes and cHTN to 465 pregnancies with type 1 diabetes and no cHTN.
References

23. Gestation network. [article online], Available from https://www.gestation.net/cc/about.htm. Accessed April 7, 2019
Summary and conclusions

The prevalence of pregnant women with type 1 diabetes is increasing worldwide while maternal and neonatal complications are still substantially higher in this population. This highlights the unmet need to dedicate resources to studying and gaining deeper understanding of the factors contributing to this. Our studies provide useful and practical insights about this high-risk population of women with type 1 diabetes during pregnancy. In the first paper, we found significant time trends in several pre-pregnancy maternal characteristics, treatment measures and pregnancy and delivery outcomes. We described no changes in glycemic control during the study period and a dramatic increase in the percentages of women using insulin pumps and CGMs at the same time period. We also described an increase in the percentage of women with type 1 diabetes, who gained excessive gestational weight. Finally, we described increase in gestational age at delivery and the percentage of vaginal deliveries. However, birth weight and the prevalence of LGA and fetal macrosomia did not change over the study period.

These observations will be the basis of our subsequent analyses exploring the associations between the different variables and hopefully gaining better understudying of how to improve glycemic control and delivery outcomes.

We concluded that, over the last ~15 years, rapid technological changes have occurred with a significant increase in the use of insulin pumps and CGM. In addition, changes in obstetrical guidelines also occurred. With this, certain pregnancy and delivery-related outcomes improved, including increased gestational age and decreased cesarean delivery. However, other pregnancy-related outcomes have been adversely impacted, including increases in the prevalence of excessive gestational weight gain and no improvements in infant birth weight measures. As
such, this study may provide some insight into adverse outcomes that may need to have focused attention for improving pregnancy health in women with type 1 diabetes.

In the second study, we found SGA to be rare in type 1 diabetes pregnancies. This finding is particularly noteworthy in women with type 1 diabetes and cHTN treated to BP targets 110-129/65-79 mmHg with anti-hypertensive medications. Yet, despite treatment with anti-hypertensive medications to these BP targets, the BP values in pregnancies with type 1 diabetes and cHTN remained higher in all trimesters than BP values in pregnancies with type 1 diabetes and no cHTN. Women with type 1 diabetes and cHTN tended to be older than women with type 1 diabetes and no cHTN and had higher prevalence of nephropathy and were more likely to have a cesarean delivery.

We concluded that given the low prevalence of SGA in our population and similar birth weight in women with type 1 diabetes with and without cHTN, our findings may suggest the need to utilize the CHIPS tight blood pressure targets of BP of 133.1 (=/-0.3)/85.3 (+/-0.3) mmHg or prior ADA targets 110-129/65-79 mmHg. The finding of severe maternal hypertension, demonstrated in the less tight arm of the CHIPS study, is a serious concern for women with preexisting diabetes, who are at risk of end organ damage from hypertension. The current targets recommended by the ADA 120-160/80-105 mm were implemented to reduce the risk of SGA. However, this proposed risk reduction may not be warranted, if the present study findings, showing very rare occurrence of SGA and similar birth weights across women with type 1 diabetes, regardless of their cHTN.
Discussion and perspectives
Both studies had several limitations. First, these studies were conducted in a single site, and therefore may not be generalizable to other study populations. Second, this dataset was not created for research purposes and consequently there were some missing values. Limitation specific to the first study is that we evaluated time trends descriptively and did not adjust for potential confounders, however this study’s findings might alert us to look for further directions to subsequent investigations. A limitation specific to the second study is that the study was limited by small numbers of pregnancies complicated by type 1 diabetes and cHTN. Despite these limitations, these studies have several strengths. The main strengths are that it is one of the largest datasets of women with type 1 diabetes in the US. Furthermore, the studies evaluate more than a decade of data allowing detection of time trends and provided detailed information about pregnancy and delivery outcomes. Finally, the first study is the only study to examine time trends in pregnant women with type 1 diabetes living in the US.

There are several interesting and clinically significant future directions that we are planning to explore. We would like to investigate the associations between maternal characteristics, glycemic control and treatment modalities with different delivery outcomes. We would also like to explore the associations between maternal characteristics and treatment modalities with glycemic control.

A different direction would be to look at the long-term health outcomes of women with type 1 diabetes and cHTN treated to the targets that we specify and the long-term outcomes in their offspring’s as well. Together, this body of research provides critical information about the state
of pregnancy health and treatment of an important concurrent condition among an understudied, but high-risk population, women living with type 1 diabetes.