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# Impact of Youth Onset Type 2 Diabetes During Pregnancy on Microvascular and Cardiac Outcomes

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## Abstract

**Aims:** To examine the impact of pregnancy on microvascular and cardiovascular measures in women with youth-onset T2D.

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All authors are members of the TODAY Study group
**Jeanie B. Tryggestad:** Conceptualized the paper, wrote the original draft, reviewed and edited subsequent drafts. **Kimberly L Drews:** Developed the analytic plan, developed tables, contributed to the original draft, reviewed and edited drafts. **Lisa Mele:** Curated the data, performed formal analyses, developed tables, reviewed and edited drafts. **Silva Arslanian:** Contributed to analytic plan, reviewed and edited subsequent drafts. **Steven D. Chernausek:** Contributed to analytic plan, reviewed and edited subsequent drafts. **Elia N. Escaname:** Contributed to analytic plan, reviewed and edited subsequent drafts. **Elvira Isganaitis:** Contributed to analytic plan, reviewed and edited subsequent drafts. **Jennifer Sprague:** Contributed to analytic plan, reviewed and edited subsequent drafts. **Megan M. Kelsey:** Conceptualized the paper, contributed to the original draft, reviewed and edited subsequent drafts.

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**Methods:** Microvascular and cardiovascular measures were compared in in a cohort of 116 women who experienced a pregnancy of ≥ 20 weeks gestation and 291 women who did not among women in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study.

**Results:** Cox regression models adjusted for participant characteristics at baseline including age, race/ethnicity, household income, diabetes duration, HbA1c (>6%), and BMI, demonstrated those who experienced pregnancy had 2.76 (1.38–5.49; p=0.004) fold increased risk of hyperfiltration (eGFR ≥ 135 ml/min/1.73m$^2$), compared to those without a pregnancy. No differences were observed in rates of retinopathy (48.9% vs. 41.1%) or neuropathy (23.3% vs. 16.3%) in women who experienced pregnancy vs. women who did not, respectively. In fully adjusted models, pregnancy did not impact changes in echocardiographic or arterial stiffness compared to changes in women who were never pregnant.

**Conclusions:** These results indicate that pregnancy increases the risk of hyperfiltration in women with youth-onset T2D, but not other micro or macrovascular complications. The rates of vascular complications are very high in youth-onset T2D potentially obscuring micro- and macrovascular changes attributable to pregnancy.

### Keywords

Microvascular; cardiovascular; Youth-Onset Type 2 Diabetes; Pregnancy

## 1 INTRODUCTION

Diabetes during pregnancy is associated with increased morbidity to the mother, and pregestational diabetes is associated with worse outcomes compared to gestational diabetes (GDM) (1, 2, 3). With increased incidence of type 2 diabetes (T2D), the proportion of women with pregestational T2D is equal to pregestational type 1 diabetes (T1D) (4). Few studies have examined the impact of pre-gestational T2D, which differs from T1D in pathophysiology, on micro- and macrovascular complications during pregnancy.

The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study was a multi-site intervention study designed to evaluate optimal diabetes therapy to maintain glycemic control which was extended as an observational study through early adulthood. Over 15 years of follow-up, 260 pregnancies were reported by 141 women with 65% of women reporting a complication during the pregnancy (5). Prior to pregnancy, 35% of the women had hypertension, 25% microalbuminuria and 7% macroalbuminuria (5) demonstrating a high rate of microvascular complications and cardiovascular risk even before pregnancy.

In prior reports of pregestational T2D diabetes, the average age at pregnancy onset ranged from 33–36 years, with a diabetes duration averaging approximately 5 years (6, 7). The TODAY study offers a unique opportunity to understand the impact of T2D on pregnancy in women who are younger with a longer duration of diabetes while also comparing diabetes-related complications and co-morbidities in women with similar age and T2D duration who have experienced a pregnancy versus not with the hypothesis being that women who experienced a pregnancy would have worse vascular outcomes.

## 2 SUBJECTS, MATERIALS, AND METHODS

The TODAY study has been previously described in detail (8). The study included 699 participants 10–17 years of age diagnosed with T2D using the American Diabetes Association criteria, with duration of 2 years or less (9). Participants were randomly assigned to one of three treatment arms, metformin alone, metformin with rosiglitazone, or metformin plus a lifestyle intervention program, and followed longitudinally for 2–6 years with the primary outcome of the trial being loss of glycemia control. The primary outcome was defined as a persistently elevated HbA1c (≥8%) over a period of 6 months or inability to wean from insulin after metabolic decompensation. Upon completion of the clinical trial, the same participants were given the option to continue in a two-phase observational study. During the first phase, participants transitioned to non-blinded, non-randomized, standard diabetes care provided by TODAY. In the second phase, all participants were transitioned to community providers but continued to have annual study visits to collect serum samples and health information data. At the start of each phase participants were reconsented and participation in the final observational study phase was not contingent on participation in the initial observational phase.

Of the 699 participants, 452 (64.7%) of the cohort were female (8) with an average duration in the study of 10.3 ± 4.5 years [Median 12 years, 7.8 (Q1) −13.7 (Q3)]. Pregnancy information, including outcome and maternal complications, was obtained prospectively from the female participants consenting to release of records from which data was abstracted for reporting of outcomes. Race and ethnicity were collected by self-report. A total of 260 pregnancy outcomes were reported by 141 of female participants (5), with 116 women having a pregnancy of at least 20 weeks gestation. No study assessments were made by the study during the pregnancy. All participants identified as pregnant during the study were referred to local providers for high-risk care.

Pregnancy was defined as gestations lasting at least 20 weeks. For outcomes during the pregnancy, all diagnoses were obtained from records review. Outcomes prior to and after pregnancy were obtained from TODAY study visits using the following methods and criteria. Microalbuminuria was defined as urine albumin/creatinine ratio greater than 30mg/g on at least two of three assessments. Macroalbuminuria was defined as one urine albumin/creatinine ratio greater than 300mg/g. The Full Age Spectrum (FAS) combined serum creatinine and cystatin C equation was used to calculate estimated glomerular filtration rate (eGFR), and hyperfiltration was defined as an eGFR ≥ 135 ml/min/1.73m$^2$ at two consecutive visits (10). Neuropathy was defined as Michigan Neuropathy Screening Instrument (MNSI) exam score > 2 or an abnormal monofilament exam (< 8 of 10 responses to light touch) on two consecutive exams (11). Fundus photography was performed (2017–2018) and graded by masked examiners at a centralized reading center (12) with eye disease defined as Early Treatment Diabetic Retinopathy Study (ETDRS) protocol grade > 20 in either eye and/or clinically significant macular edema (12). Arterial stiffness, measured twice during the trial (2013–2014 and 2018–2019), consisted of five arterial stiffness measurements: 1) carotid femoral pulse wave velocity (PWV), 2) carotid radial PWV, 3) femoral foot PWV, 4) augmentation index (AIx), and 5) brachial distensibility (BrachD) as previously described (13, 14). PWV and AIx measurements were obtained

using the SphygmoCor CPV system (AtCor Medical, Lisle, IL), and BrachD was measured using the DynaPulse 2000 (PulseMetric, San Diego, CA). Two-dimensional transthoracic echocardiograms were performed twice during the study as well (2010–2011 and 2015–2016). Women who had a pregnancy prior to the first echo or arterial stiffness assessment were excluded (Appendix B). IRB approval was obtained for the study at all clinical centers.

### 2.1 Statistical Analysis

Baseline characteristics for women who experienced a pregnancy versus not were compared using Chi-square tests for categorical variables and t-tests for continuous variables. Women with unknown pregnancy status were excluded. Pregnancies were categorized as none, one, or ≥ two. Descriptive statistics were reported as percentages for categorical variables and means ± standard deviations for continuous variables. Comparison of microvascular complications in those never vs ever pregnant was conducted using similar approaches. Microvascular events (microalbuminuria, macroalbuminuria, diabetic retinopathy, peripheral neuropathy) were aggregated to identify the first occurrence of any event.

Separate Cox proportional hazards models were used to estimate the overall risk of microalbuminuria, macroalbuminuria, hyperfiltration, neuropathy, and any microvascular event based on pregnancy status at the time of the assessment including all available data from the female participants. The assumption of proportional hazards was satisfied for each outcome. For complications not assessed annually, linear and logistic regression analysis was performed using all women who had the assessments on both occasions (ranging from 5 to 7 years apart) excluding any who had a pregnancy prior to the first assessment, as noted previously. For multivariable adjustment, covariates, selected *a priori* based on associations from other studies, were included in the models. These variables, which contained no missing values, were maternal age at baseline, race/ethnicity, household income, duration of diabetes at baseline, baseline HbA1c (>6%), and baseline BMI for events assessed annually; for those outcomes assessed only twice, the duration of diabetes at the first exam was used rather than at baseline, since time in study varied by participant. P-values <0.05 were considered significant and no adjustment for multiple testing was performed as these analyses are considered exploratory. Given the high rate of retention and the similarity in the retained cohort and those lost to follow-up, no additional adjustments for missing data were performed. All analyses were conducted using SAS Version 9.4.

## 3 RESULTS

### 3.1 Baseline Characteristics

A total of 407 female participants with complete study records were included; 116 experienced at least one pregnancy lasting 20 weeks. The mean time between pregnancy and the end of the study was 5.2 years (IQR: 3.1, 7.7 years). The mean age at first pregnancy was 20.5 ± 3.2 years. For those who experienced a pregnancy, the average duration in the study was 12.7 ± 1.69 years [median 13.0 years, 11.9 (Q1) - 13.9 (Q3)] and for those never pregnant 9.3 ± 4.84 years [median 11.1 years, 4.8 (Q1) - 13.1 (Q3)]. The women who were never pregnant had a shorter time in the study due to the loss of follow-up in these women. Women experiencing pregnancy had lower household income (p=0.002) and were

marginally older (p=0.05) at baseline (Table 1). They were also more likely be classified as non-Hispanic Black or American Indian compared to women without a pregnancy. Loss of glycemic control and BMI were similar between the two groups and between those who experienced one vs. multiple pregnancies. Prior to the first pregnancy, glycemic failure was evident in 53/116 (45.7%) of women who experienced a pregnancy. As reported previously, almost 74% of the women who experienced a pregnancy required insulin therapy during the pregnancy, and 32% of the women had a HbA1c >8% at some point during the pregnancy (5).

### 3.2 Microvascular Complications

Of the 397 women with complete data, 237 (59.7%) experienced a microvascular complication during TODAY. Overall, microvascular complications were common regardless of pregnancy status (Table 2). Women with a pregnancy had higher rates of microvascular complications compared those who did not (74.3% vs 53.9%, p<0.001); however, when evaluating the timing of diagnosis in relation to pregnancy and adjusting for maternal age, race/ethnicity, household income, duration of diabetes, high baseline HbA1c (>6%), and BMI, although the rates of microvascular complications were higher in women who had a pregnancy, it did not reach statistical significance (hazard ratio 1.47 [95% CI: 0.96–2.26] p=0.08). Number of pregnancies did not impact the risk for microvascular complications examining the linear trend for multiple pregnancies (1.58 [95% CI: 0.76–3.30] p=0.22 for two or more pregnancies versus none).

**3.2.1 Nephropathy—**Rates of hyperfiltration, microalbuminuria, and macroalbuminuria were higher in women who experienced a pregnancy than women who did not in unadjusted comparisons. (Table 2) In Cox regression models adjusted for characteristics as above, the women who experienced a pregnancy had a 2.76 (95% CI: 1.38–5.49, p=0.004) increased risk of hyperfiltration after their pregnancy compared to nulliparous women. (Table 2) While 20% of the women who experienced a pregnancy developed preeclampsia, there was no difference in rates of hyperfiltration (53.9% vs. 63.8% in those that did versus did not p=0.54). After adjustment, the rates of micro- and macroalbuminuria were no longer significant. The median and interquartile range for the timing of the development of nephropathy after pregnancy are as follows: macroalbuminuria – 285 days (126–1255), microalbuminuria – 549 days (129–1607.5), and hyperfiltration – 375 days (302–935.5).

**3.2.2 Retinopathy—**In the fully adjusted models, there were no differences in retinopathy between those who experienced a pregnancy compared to those who had not (odds ratio 1.24 [95%CI: 0.61–2.50] p=0.55). Rates of retinopathy were higher for women who required insulin therapy during pregnancy compared to women who did not (56.1% and 26.7%, respectively, p=0.04), but this association was not significant after adjustment (odds ratio 2.04 [95% CI: 0.29–14.3] p=0.47). Since retinopathy was only assessed twice, the median and interquartile range for the time between the first pregnancy and subsequent retinopathy evaluation was 1354 (633–2064) days.

**3.2.3 Neuropathy—**In the fully adjusted regression models, there were no differences in neuropathy observed between those who experienced a pregnancy versus not (hazard ratio

1.34 [95%CI: 0.73–2.44] p=0.35). The median and interquartile range for the timing of the development of peripheral neuropathy after pregnancy was 1,203 days (605–1872).

### 3.3 Cardiovascular Measures

In both unadjusted and adjusted models, no differences were observed between women who experienced pregnancy versus never pregnant regarding changes between the echocardiographic measures (Table 3). As echocardiograms were only assessed twice, the median and interquartile range for the time between the first pregnancy and subsequent echocardiogram evaluation was 758 (379–1141) days.

Experiencing pregnancy resulted in significantly lower mean change between the two assessments of pulse wave velocity (PWV) carotid – radial measurement (p=0.024); however, this was not significant after adjustment (Table 4). No additional differences in vascular measures were noted. As PWV was only assessed twice, the median and interquartile range for the time between the first pregnancy and subsequent PWV evaluation was 915.5 (264–1304.5) days.

## 4 DISCUSSION

Women with youth-onset T2D experiencing pregnancy have increased risk of hyperfiltration after pregnancy, but no increased risk of other micro- or macrovascular complications as compared to nulliparous women of similar age and diabetes duration. As presented previously, in TODAY, 60% of all the participants experienced at least one microvascular complication in the 15 years of follow-up (15). Within the TODAY female sub-cohort, 59.7% of the women experienced a microvascular complication. Microvascular complications are linked to glycemic control (16). Loss of diabetes control was experienced by 45.7% of the women in TODAY prior to their first pregnancy which may account for the high rates of microvascular complications in women within TODAY. With very high rates of microvascular complications even prior to pregnancy, screening for microvascular complications should occur pre-conception or very early in gestation. The aggressive management of glycemia and microvascular complications in youth-onset T2D may reduce the higher rates of hyperfiltration noted after pregnancy.

Glomerular filtration rate (GFR) increases in pregnancy by as much as 50% due to lower net oncotic pressure and increased renal size (17). Hyperfiltration is an early marker of nephropathy in diabetes resulting from increase in renal size and alterations in filtration pressure (18). In TODAY, the baseline prevalence of hyperfiltration was 12.3% with a 14-year cumulative incidence of 49.2% with a trend toward a higher incidence in females (19). Thus, the additional stressor of pregnancy on the kidney may explain the higher risk for hyperfiltration seen in TODAY women following pregnancy; however, the hyperfiltration was not noted until 1 year after the pregnancy.

Similar to nephropathy, rates of retinopathy in TODAY were high and related to loss of glycemic control (15); however, pregnancy did not increase this risk. In a cohort of older women with T2D (average age 33 years, average diabetes duration 3 years) and baseline HbA1c of 6.4%, progression of retinopathy between 10 and 28 weeks gestation

was observed in 11% of the cohort and associated with duration of diabetes and insulin therapy prior to the pregnancy (20). In TODAY, more women developed retinopathy who were prescribed insulin during their pregnancy; however, this difference was no longer evident after controlling for multiple covariates suggesting that diabetes control and duration affected the development of retinopathy rather than the use of insulin per se during pregnancy. It is important to note that retinal exams were not conducted during pregnancy in TODAY, and timing between the retinopathy exam and the pregnancy varied among participants, so a transient progression of retinopathy could have been missed.

In TODAY, neuropathy rates were high, with a cumulative incidence of 32% (15). In the EURODIAB Prospective Complications Study, pregnancy was not associated with an increased incidence of neuropathy in women with T1D (21), but little is known about the relationship between pregnancy and neuropathy in T2D. With very high rates of microvascular complications in TODAY, the significant risk of microvascular disease from youth-onset T2D in general may supersede any additive risk of pregnancy.

As in microvascular disease, pregnancy did not affect arterial stiffness or echocardiographic findings. This contrasts with findings in GDM which has been associated with increases in arterial stiffness compared to pregnancies without diabetes (22, 23, 24). While in TODAY no increased stiffness was noted in women who experienced a pregnancy, the time between the pregnancies and the measurements varied. Thus, the TODAY study measures may have occurred too close to the pregnancy to detect changes, and studies that are specifically designed to assess the effect of pregestational diabetes on post-partum cardiovascular outcomes are needed. Additionally, no differences in echocardiographic findings were observed in women in TODAY who experienced a pregnancy. Again, the time frame between the echocardiogram and the pregnancy was variable, thus small changes during the pregnancy could be missed with limited ability to detect changes not seen until years after the pregnancy.

This study has several strengths. Microvascular complications were assessed routinely and in a systematic fashion. The study also included women of similar age and diabetes duration for a comparison group. Some limitations are acknowledged. Pregnancy outcomes are a secondary analysis for the study; thus no data was collected on the women during their pregnancy. As measurements of glycemia and micro- and macrovascular complications were not obtained during the pregnancy, the ability to see transient changes that may resolve at the end of pregnancy are limited. Some outcomes such as retinal exams, pulse wave velocity and echocardiography were only collected twice during the study making changes over time difficult to interpret. Hyperfiltration measures were not available on all participants related to sample availability. Finally, the number of women who experienced more than one pregnancy was relatively small and limits conclusions that can be drawn about the effect of multiple pregnancies on diabetes complications.

In conclusion, women with youth-onset T2D experiencing pregnancy seem to have an increased risk of hyperfiltration after pregnancy, but no increased risk of other micro- or macrovascular complications as a result of pregnancy as compared to nulliparous women of similar age and diabetes duration in the short term. The rates of microvascular complications

specifically were very high in both the women that did and did not experience a pregnancy potentially obscuring any changes attributable to pregnancy.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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### CONFLICTS OF INTEREST:

SA receives research funding from NovoNordisk and Eli Lily consulting fees from Societe des Produits Nestle SA, honoraria for lectures from Sanofi, and participation on a data safety monitoring board or advisory board from NovoNordisk, Eli Lily, and AstraZeneca. MG receives or, over the past three years, has received research funding from Diurnal, Neurocrine Biosciences, Novo Nordisk, and Spruce Biosciences; royalties from UpToDate and McGraw Hill; consulting fees from Adrenas Therapeutics, Eton Pharmaceuticals, Gilead Sciences, Neurocrine Biosciences, NovoNordisk, and Spruce Biosciences; honoraria for lectures from Pfizer and Spruce Biosciences; payment for expert testimony; support for attending meetings from Pfizer and Spruce Biosciences; and participation on a data safety monitoring board or advisory board from Ascendis Pharma, Eton Pharmaceuticals, Neurocrine Biosciences, NovoNordisk, and Pfizer. MG has also had leadership roles in the Pediatric Endocrine Society, CARES Foundation, and the MAGIC Foundation. JS receives research funding from Eli Lily. MMK receives research funding from Rhythm Pharmaceuticals, Boehringer Ingelheim, and Janssen. All other authors have nothing to report.

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**Highlights:**

- Microvascular complications in type 2 diabetes during pregnancy are inconsistent.
- Women with youth onset T2D have higher rates of hyperfiltration after pregnancy.
- Risk for micro- or macrovascular complications was not increased after pregnancy.
- Complications are high in youth with T2D, but pregnancy did not increase the risk.

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**Table 1.**

Demographic and baseline metabolic characteristics of participants by ever pregnant (Never/Experienced Pregnancy) and number of pregnancies (None, 1, 2+)

| | | | | Number of Pregnancies | | | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **Never Pregnant (n=291)** | **Experienced Pregnancy (n=116)** | **p-value** | **No Pregnancy (n=291)** | **One Pregnancy (n=67)** | **≥ Two Pregnancies (n=49)** | **p-value** |
| ***Baseline Characteristics*** | | | | | | | |
| Age (years) | 13.6 ± 2.1 | 14.0 ± 2.0 | 0.05 | 13.6± 2.1 | 13.6± 1.9 | 14.6 ± 1.9 | 0.005 * |
| Diabetes Duration (months) | 8.1 ± 6.0 | 8.0 ± 6.3 | 0.65 | 8.1 ± 6.0 | 8.6 ± 6.6 | 7.1 ± 5.7 | 0.48 * |
| Race/ethnicity (%) | | | <0.001 | | | | 0.001 |
| Black non-Hispanic | 32.7 | 39.7 | | 32.7 | 44.8 | 32.7 | |
| Hispanic | 39.9 | 30.2 | | 39.9 | 29.9 | 30.6 | |
| White non-Hispanic | 21.3 | 15.5 | | 21.3 | 13.4 | 18.4 | |
| None of the above | 6.2 | 14.7 | | 6.2 | 11.9 | 18.4 | |
| *American Indian* | *3.8* | *14.7* | | *3.8* | *11.9* | *18.4* | |
| *Asian non-Hispanic* | *2.4* | *0* | | *2.4* | *0* | *0* | |
| Household income (%) | | | 0.002 | | | | 0.007 |
| <$25000 | 37.7 | 51.5 | | 37.7 | 54.1 | 47.6 | |
| $25000–49999 | 33.2 | 36.9 | | 33.2 | 32.8 | 42.9 | |
| ≥$50000 | 29.1 | 11.7 | | 29.1 | 13.1 | 9.5 | |
| Loss of Diabetes Control (%) | 42.6 | 45.7 | 0.57 | 42.6 | 49.3 | 40.8 | 0.86 * |
| BMI (kg/m$^2$) | 34.5 ± 7.7 | 34.9 ± 6.6 | 0.31 | 34.5 ± 7.7 | 34.9 ± 6.1 | 34.8 ± 7.3 | 0.71 |
| ***End of Study Characteristics*** | | | | | | | |
| Age (years) | 26.8 ± 2.5 | 27.4 ± 2.3 | 0.05 | 26.8 ± 2.5 | 27.0 ± 2.2 | 28.0 ± 2.4 | 0.004 * |
| Duration in Study (years) | 9.3 ± 4.8 | 12.7 ± 1.7 | <0.001 | 9.3 ± 4.8 | 12.8 ± 1.8 | 12.7 ± 1.6 | <0.001 * |

* P-value based on linear trend

**Table 2.**

Microvascular Complications: Rates for never versus experienced pregnancy and risk associated with pregnancy (unadjusted and adjusted)

| | Rates of Complications* | | | Risk Assessment† | | | |
|---|---|---|---|---|---|---|---|
| **Complication** | **Never Pregnant** | **Experienced Pregnancy** | **p-value** | **Model** | **Never Pregnant** | **Experienced Pregnancy** | **p-value** |
| Macroalbuminuria | 22/291 (7.6) | 18/116 (15.5) | 0. 015 | Unadjusted | Ref | 1.45 (0.62 – 3.39) | 0.40 |
| | | | | Adjusted | Ref | 1.49 (0.57 – 3.89) | 0.42 |
| Microalbuminuria | 102/291 (35.1) | 53/116 (45.7) | 0.046 | Unadjusted | Ref | 0.94 (0.53 – 1.68) | 0.84 |
| | | | | Adjusted | Ref | 1.17 (0.63 – 2.17) | 0.62 |
| Hyperfiltration | 101/218 (46.3) | 53/84 (63.1) | 0.009 | Unadjusted | Ref | 1.82 (0.96 – 3.47) | 0.07 |
| | | | | Adjusted | Ref | 2.76 (1.38 – 5.49) | 0.004 |
| Diabetic Retinopathy | 62/151 (41.1) | 44/90 (48.9) | 0.24 | Unadjusted | Ref | 1.47 (0.86 – 2.53) | 0.16‡ |
| | | | | Adjusted | Ref | 1.24 (0.61 – 2.50) | 0.55‡§ |
| Peripheral Neuropathy | 47/289 (16.3) | 27/116 (23.3) | 0.10 | Unadjusted | Ref | 1.43 (0.82 – 2.52) | 0.21 |
| | | | | Adjusted | Ref | 1.34 (0.73 – 2.44) | 0.35 |
| Microvascular Disease// | 153/284 (53.9) | 84/113 (74.3) | <0.001 | Unadjusted | Ref | 1.50 (1.01 – 2.23) | 0.05 |
| | | | | Adjusted | Ref | 1.47 (0.96 – 2.26) | 0.08 |

*Data shown represents n/N and (%) based on the number of participants with the data sufficient to determine whether or not the event occurred among the female participants in TODAY. Participants with missing data for outcomes are excluded.

†Data shown represents hazard ratios and 95% confidence intervals for Cox regression models unless otherwise indicated. Models were adjusted for maternal age at baseline, race or ethnicity, household income, duration of diabetes at baseline, baseline high HbA1c (>6%), and baseline BMI.

‡Odds ratios and 95% confidence intervals based on logistic regression models.

§Model was adjusted for maternal age at baseline, race or ethnicity, household income, duration of diabetes at initial eye exam, baseline high HbA1c (>6%), and baseline BMI.

//Microvascular disease is the composite of microalbuminuria, macroalbuminuria, diabetic retinopathy, and peripheral neuropathy.

Ref – reference group for all risk assessment models is never pregnant

**Table 3.**

Changes in Echocardiography measures by pregnancy status between the two exams and adjusted regression results between change in echocardiography outcome measure and pregnancy status.

| | Never Pregnant | | | Experienced Pregnancy | | | Adjusted Regression Results | |
|---|---|---|---|---|---|---|---|---|
| | | *Baseline* | *Follow-up* | | *Baseline* | *Follow-up* | | |
| **Echocardiography Outcome** | ***N*** | ***Mean ± SD*** | ***Mean ± SD*** | ***N*** | ***Mean ± SD*** | ***Mean ± SD*** | **β (95% CI)** | **p-value** |
| LV mass | 150 | 139.3 ± 35.7 | 142.4 ± 35.7 | 48 | 139.1 ± 35.8 | 147.0 ± 43.0 | 8.8 (−1.5 – 19.1) | 0.09 |
| LV mass h (g/m) | 150 | 36.7 ± 8.8 | 37.2 ± 8.7 | 48 | 36.1 ± 9.1 | 38.0 ± 9.9 | 2.5 (−0.20 – 5.2) | 0.07 |
| LV wall thickness | 151 | 0.34 ± 0.07 | 0.34 ± 0.06 | 48 | 0.34 ± 0.06 | 0.34 ± 0.05 | 0.0009 (−0.02 – 0.03) | 0.94 |
| TAPSE Systolic Dimension (cm) | 145 | 2.2 ± 0.3 | 2.2 ± 0.3 | 45 | 2.1 ± 0.3 | 2.2 ± 0.3 | 0.03 (−0.11 – 0.17) | 0.66 |
| LV ejection fraction [*] | 151 | 67.7 ± 5.9 | 67.0 ± 5.7 | 48 | 69.6 ± 5.3 | 67.9 ± 5.4 | −0.03 (−1.9 – 1.9) | 0.98 |
| LA internal dimension (cm) | 146 | 3.6 ± 0.5 | 3.6 ± 0.5 | 42 | 3.6 ± 0.5 | 3.6 ± 0.5 | −0.04 (−0.19 – 0.10) | 0.54 |
| Mitral valve lateral Em [†] | 148 | 16.9 ± 4.4 | 14.4 ± 3.0 | 47 | 17.4 ± 4.1 | 14.1 ± 3.3 | −0.07 (−0.16 – 0.02) | 0.10 |
| Mitral valve lateral E/Em | 148 | 5.9 ± 1.8 | 6.5 ± 1.7 | 47 | 6.0 ± 2.1 | 6.9 ± 2.1 | 0.42 (−0.23 – 1.07) | 0.20 |

Experienced pregnancy for these results is defined as having a first pregnancy of at least 20 weeks between the first and second echocardiography evaluations. Women who experienced a pregnancy before the first evaluation or after the second evaluation may be classified as having experienced a pregnancy for other outcomes. Summary data are presented as mean ± standard deviation.

Results for multivariable linear regression models were adjusted for maternal age at baseline, race or ethnicity, household income, duration of diabetes at baseline echocardiogram, baseline high HbA1c (>6%), and baseline BMI.

[*] Regression model included baseline value of the outcome as a covariate

[†] Data were log transformed to approximate normality

TAPSE – Tricuspid annular plane systolic excursion

Em – early diastolic annular velocity

E/Em – ratio of early transmitral flow velocity to the early diastolic annular velocity

**Table 4.**

Changes in arterial stiffness measures by pregnancy status between the two exams and adjusted regression results examining change in arterial stiffness outcome measure and pregnancy status.

| Arterial Stiffness Outcome | Never Pregnant | | | Experienced Pregnancy | | | Adjusted Regression Results | |
|---|---|---|---|---|---|---|---|---|
| | | *Baseline* | *Follow-up* | | *Baseline* | *Follow-up* | | |
| | *N* | *Mean ± SD* | *Mean ± SD* | *N* | *Mean ± SD* | *Mean ± SD* | β (95% CI) | p-value |
| PWV Carotid – Femoral (m/s) | 92 | 6.1 ± 1.0 | 6.7 ± 1.8 | 29 | 6.5 ± 1.3 | 7.3 ± 2.1 | 0.08 (−0.55 – 0.70) | 0.81 |
| PWV Carotid – Radial (m/s)* | 89 | 7.3 ± 1.0 | 8.7 ± 1.8 | 26 | 8.2 ± 1.2 | 8.9 ± 2.1 | 0.15 (−0.73 – 1.03) | 0.74 |
| PWV Femoral – Foot (M/s) * | 68 | 8.4 ± 2.2 | 9.3 ± 3.0 | 24 | 8.1 ± 2.4 | 9.5 ± 2.0 | 0.83 (−0.19 – 1.85) | 0.11 |
| Aix (%) | 117 | 10.9 ± 10.5 | 16.5 ± 9.7 | 35 | 8.9 ± 12.6 | 15.4 ± 10.1 | 0.88 (−2.68 – 4.45) | 0.62 |
| Brach D (mm/mm Hg) | 112 | 6.0 ± 1.3 | 6.2 ± 1.4 | 37 | 6.0 ± 1.3 | 6.2 ± 1.2 | 0.005 (−0.52 – 0.53) | 0.99 |

Experienced pregnancy for these results is defined as having a first pregnancy of at least 20 weeks between the first and second arterial stiffness evaluations. Women who experienced a pregnancy before the first evaluation or after the second evaluation may be classified as having experienced a pregnancy for other outcomes. Summary data are presented as mean ± standard deviation.

Results for multilinear regression models were adjusted for maternal age at baseline, race or ethnicity, household income, duration of diabetes at time of baseline PWV measures, baseline high HbA1c (>6%), and baseline BMI.

*Regression model includes baseline value of the outcome as a covariate