HHS Public Access

Author manuscript

Menopause. Author manuscript; available in PMC 2022 March 01.

Published in final edited form as:

Menopause. ; 28(6): 634–641. doi:10.1097/GME.0000000000001758.

Women with Type 1 Diabetes (T1D) Experience a Shorter Reproductive Period Compared with Nondiabetic Women: The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study and the Study of Women's Health Across the Nation (SWAN)

Yan Yi, MPH[1], **Samar R. El Khoudary, PhD**[1], **Jeanine M. Buchanich, PhD**[2], **Rachel G. Miller, PhD**[1], **Debra Rubinstein, MD**[1], **Karen Matthews, PhD**[1,3], **Trevor J Orchard, MBBCH**[1], **Tina Costacou, PhD**[1]

[1]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

[2]Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

[3]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

Abstract

Objective: Evidence suggests that insulin deficiency and hyperglycemia may disrupt the female reproductive system's normal function, leading to delayed menarche and premature ovarian aging. We thus compared the length of the reproductive period of women with type 1 diabetes (T1D) to women without diabetes.

Methods: Women with childhood-onset T1D (diagnosed in 1950-80) from the prospective Epidemiology of Diabetes Complications (EDC) study and non-diabetic women from the Pittsburgh site of the Study of Women's Health Across the Nation (SWAN) were studied. Exclusion criteria comprised not having reached natural menopause, hysterectomy/oophorectomy before menopause, and sex hormone therapy during the menopausal transition. Reproductive history was self-reported. The historical and Women's Ischemia Syndrome Evaluation hormonal algorithms were also used to assess menopause status.

Results: Women in the T1D cohort (n=105) were younger, more likely to be white, never smokers, with lower BMI and higher HDL-C levels (all p-values<0.05) compared with women without diabetes (n=178). After covariate adjustment, T1D women were also older at menarche (0.5-year delay, p=0.002) but younger at natural menopause (−2.0 years, p<0.0001). Women with T1D thus experienced 2.5 fewer reproductive years compared to those without diabetes (p<0.0001). These findings were restricted to the subgroup of women who were diagnosed with T1D before reaching menarche (n=80).

Corresponding Author: Tina Costacou, Ph.D. (CostacouT@edc.pitt.edu, TEL: 1-412-383-2062), University of Pittsburgh, DLR Building, 3512 Fifth Avenue, Pittsburgh, PA 15213.

Conflicts of interest: None

An abstract from this study was selected as a poster presentation in the American Diabetes Association (ADA) 80th Scientific Sessions (1633-P) and published on Diabetes 2020 Jun; 69(Supplement 1).

Conclusion: Women with T1D onset before menarche have a shorter reproductive period compared with non-diabetic women, exhibiting delayed menarche and earlier natural menopause. Factors which may be related to a shorter reproductive period in T1D should be investigated.

Keywords

type 1 diabetes; age at menarche; age at natural menopause; length of reproductive period

Introduction

Insulin plays a key role in regulating female reproductive function through its effects on both gonadotropin-releasing hormone (GnRH) neurons in the central nervous system [1] and the granulosa, thecal, and stromal components in the ovarian system [2, 3]. The impact of disruption in insulin regulation and hyperglycemia on the length of the female reproductive period has been reported separately by assessment of the two components of reproductive years: menarche and menopause. Existing epidemiological studies have shown that insulin deficiency and hyperglycemia disrupt the normal function of the female reproductive system, leading to delayed menarche in women with type 1 diabetes [4-9], especially when the onset of type 1 diabetes precedes the onset of menarche [5, 8, 9].

The evidence regarding the effect of type 1 diabetes on age at natural menopause, however, is limited and conflicting [10-13]. Natural menopause is the cessation of ovarian function and the end of a woman's reproductive life, resulting from oocyte depletion. Studying the age at natural menopause has both clinical and public health significance, as the menopause transition brings substantial physiological and metabolic changes in the human body and age at menopause is considered to be a marker of body aging and health [14]. First, early natural menopause is related to increased risk of both all-cause [15] and cardiovascular disease mortality [16, 17], with a 2% increase in age-adjusted mortality per year decline in age at natural menopause [18]. In addition, early natural menopause is associated with increased risk of atherosclerosis [19], stroke [20], cardiovascular disease [17], osteoporosis [21], and fracture [22].

The Familial Autoimmune and Diabetes (FAD) study was the first to report that women with type 1 diabetes reached natural menopause at a younger age compared with their nondiabetic sisters or unrelated control participants (41.6, 49.9, and 48.0 years respectively) [10]. However, this finding was based on a small number of women having reached menopause (n=15, 21, and 15 respectively), as the average age in this study was only 42 years [10]. The European Prospective Investigation into Cancer and Nutrition (EPIC) study also suggested that early-onset diabetes (onset between 10-20 years) was associated with earlier menopause onset (HR=1.43, 95% CI, 1.02-2.01) [11]. However, the EPIC study could not distinguish the effect of type 1 and type 2 diabetes [11]. On the contrary, mean age at natural menopause did not differ between women with type 1 diabetes and controls in the more recent Ovarian Aging in type 1 Diabetes mellitus (OVADIA) study, although the participant response rate was only ~50% [12]. Moreover, in a study from Finland, the median age at natural menopause in women with type 1 diabetes (52.5 years) did not significantly differ from that of the general Finnish population (51 years) [13]. The Finnish study used population level data rather

than individual level data for non-diabetic controls, and, thus, investigators were unable to control for confounding factors in their analysis [13].

Thus, to date, research gaps and conflicting findings persist in terms of the age at natural menopause in type 1 diabetes and no study has directly assessed the length of the reproductive period in women with this chronic disorder. Therefore, the aim of this study was to fill these research gaps by assessing the length of the reproductive years of women with type 1 diabetes from the Pittsburgh Epidemiology of Diabetes Complication (EDC) study and of women without diabetes from the Pittsburgh site of the Study of Women's Health Across the Nation (SWAN). We hypothesized that women with type 1 diabetes experience a shorter reproductive period compared with non-diabetic women.

Research Design and Methods

Study population

Eligible women with type 1 diabetes were from the Pittsburgh Epidemiology of Diabetes Complication (EDC) study. The Pittsburgh EDC Study recruited childhood-onset (<17 years) type 1 diabetes patients diagnosed, or seen within one year of diagnosis, at Children's Hospital of Pittsburgh between 1950 and 1980. Among 658 individuals who completed a baseline assessment in 1986-1988, the mean baseline age and diabetes duration were 28 years (range 8-48 years) and 19 years (range 8-37 years), respectively. These 658 participants (325 female and 333 male) were then surveyed and reexamined biennially for up to 10 years. Subsequently, biennial surveys continued up to 30 years whereas additional exams occurred at 18, 25 and 30 years of follow-up. A more detailed EDC Study description can be found elsewhere [23].

Although all the biennial surveys administered to female EDC participants included a question on the age at which menopause began, a detailed women's reproductive health questionnaire, which allowed more accurate assessment of the age at natural menopause, was first administered during the 22-year follow-up (2009-2011). Testing for plasma follicle stimulating hormone (FSH) and estradiol to help with menopausal status determination was also initiated at that time. Of 325 female participants, 128 did not complete the detailed women's reproductive health questionnaire and sex hormone tests due to loss to follow-up (n=53) or death (n=75) prior to the 22-year assessment. Of the remaining 197, 37 had not yet reached menopause and thus did not have a corresponding age at menopause by the last available follow-up, 35 had a hysterectomy/oophorectomy before menopause, and 20 received sex hormone therapy during the menopausal transition and were thus excluded from analyses. Thus, the analytic sample comprised 105 women. Sensitivity analyses were further performed including 18 EDC women who either died (n=12) prior to the 22-year assessment or did not partake in exams after 20 years (n=6) and thus had no hormone data available but had previously self-reported age at natural menopause.

Women without diabetes were from the Pittsburgh site of the Study of Women's Health Across the Nation (SWAN) and formed the comparison group. SWAN is a multi-site, longitudinal, epidemiologic study designed to examine the health of women during their menopausal transitional period and was initiated in 1996-1997. A detailed study design has

been previously published [24]. Briefly, the inclusion criteria comprised women who 1) were 42-52 years of age, 2) had experienced a menstrual period within the past 3 months, and 3) had at least one intact ovary. The SWAN Pittsburgh site included 463 women at baseline (1998), with a mean age of 45.7 years (range 44.1-47.8 years) who were followed-up annually for up to 20 years. The study design required that approximately 1/3 of the SWAN Pittsburgh cohort were black and 2/3 white. Of these 463 SWAN Pittsburgh site participants, women who developed diabetes before or during the annual follow-ups (n=74) or received hysterectomy and/or oophorectomy before menopause (n=48) were excluded from analysis. A given SWAN participant was defined as having diabetes if she met any of the following criteria: 1) using anti-diabetic medication at any visit, 2) having a fasting glucose >=126 mg/dL (while not on steroids) on 50% of at least 3 attended visits or 2 consecutive visits, or 3) having any two visits with self-reported diabetes and at least one visit with fasting glucose >=126 mg/dL (while not on steroids). Women with missing natural menopause age (n=163) due to missingness or hormone replacement therapy were also excluded from primary data analyses. Therefore, a total of 178 SWAN participants were included in the primary data analyses.

Covariate Assessment

Since EDC participants were younger at study entry compared with participants of the SWAN cohort, covariate data for women with type 1 diabetes were taken from the follow-up visit preceding menopause in which chronological age was closest to the mean baseline age (i.e., 46.0 years) in SWAN. This time point constituted the “baseline” assessment for the present analyses.

In the EDC study, survey questionnaires regarding demographic characteristics, medical history, and reproductive history were sent to participants before each clinical examination visit. During the clinical visits, body mass index (BMI) was recorded as weight in kilograms (kg) divided by height in meters squared (m^2). The waist to hip ratio (WHR) was recorded as the circumference of the waist divided by that of the hips. A random zero sphygmomanometer was used to measure blood pressure after a 5-minute rest according to the Hypertension Detection and Follow-up Program protocol [25]. Hypertension was defined as blood pressure ≥140/90 mm Hg or use of antihypertensive medications. High-density lipoprotein cholesterol (HDL-C) was measured by means of a precipitation technique (heparin and manganese chloride) with a modification of the Lipid Research Clinics method [23, 26]. Total cholesterol and triglycerides were measured enzymatically [23, 26]. Non-HDL cholesterol was computed by subtracting HDL-C from total cholesterol.

In the SWAN study, demographic characteristics, medical history, and reproductive history were derived from questionnaires administered at the baseline assessment. Age at menarche was self-reported. BMI, WHR, and hypertension were measured/defined as for the EDC study. As in EDC, HDL-C was isolated by using heparin-2M manganese chloride[27] while total cholesterol and triglycerides were analyzed by enzymatic methods (on a Hitachi 747 analyzer -Boehringer Mannheim Diagnostics, Indianapolis, Indiana)[27]. Non-HDL cholesterol was computed by subtracting HDL-C from total cholesterol.

Menopause status assessment

In the EDC study, reproductive history information, including age at menarche and menopause, was self-reported. Menopausal status was defined as follows: women <45 years reporting regular menstrual cycles were classified as pre-menopausal, whereas those >55 years with no menstrual periods for 12 months were classified as post-menopausal. Plasma FSH and estradiol were measured in women falling outside this classification, in which case the Women's Ischemia Syndrome Evaluation (WISE) hormonal and historical algorithms [28] were used to assess menopausal status. Briefly, women who 1) were >50 years, 2) had no menstrual periods for more than 6 months, and 3) had FSH >30 IU/L were classified as post-menopausal. The complete WISE algorithm for determination of menopausal status can be found elsewhere [28]. Age at natural menopause was defined as the chronological age at the time menopause was determined to have occurred.

In the SWAN study, annual assessments of menstrual bleeding patterns was used to define the following menopause transition stages: premenopausal (no change in menses regularity), early perimenopausal (menses within the prior 3 months but change in length of bleed or interbleed interval), late perimenopausal (3-11 months without menses), and natural postmenopausal (≥12 months without menses not due to surgery) [27]. For women defined as postmenopausal, their age at menopause was calculated by subtracting date of birth from date of participants' last menstrual period [29]. For those women with missing natural menopause age (n=163), a multiple imputation model (10 runs) was used to estimate their age at natural menopause by utilizing the following variables: chorological age, race, BMI, smoking status, educational level, employment status, vasomotor symptoms, bleeding patterns, sex hormone levels, history of hormone use, and prevalent disease (diabetes, cardiovascular disease, osteoporosis etc.). Those women with imputed data were included in a sensitivity analysis.

In both the EDC study and SWAN, the length of reproductive years was determined by subtracting the age at menarche from the age at natural menopause.

Statistical analyses

Univariable analyses, including two sample t-test for normally distributed continuous variables, the Wilcoxon test for non-normally distributed continuous variables, and the Chi-Squared test or Fisher's exact test for categorical variables, were performed to assess differences in baseline characteristics between EDC and SWAN female participants. General linear models and multiple imputation analyses were used to assess whether mean age at natural menopause differed between EDC women and SWAN women after adjusting for covariates. Adjustments were made for age, race, BMI, smoking status, hypertension, HDL-C, non-HDL, and the number of pregnancies when assessing age at natural menopause and the length of reproductive years. Adjustments were made for race only when assessing age at menarche as other covariates were measured after menarche. Sensitivity analyses were performed 1) including the SWAN imputed data by using multiple imputation analysis (PROC MIANALYZE in SAS) or 2) including 18 EDC women who provided self-reported age at natural menopause without sex hormone data before visit 12 thus increased the EDC sample size to 123. To address potential bias from excluding 37 EDC women who had not

yet reached menopause and whose age at menopause may be later than those partaking in the analyses, we conducted sensitivity analyses assigning the mean age at natural menopause in SWAN to these 37 women. SAS version 9.4 (SAS Institute, Cary, NC) was used for all analyses.

Results

Although covariate data for female EDC study participants were selected from a follow-up visit so that chronological age was more similar to that of non-diabetic women at SWAN baseline, women in the T1D cohort were statistically significantly younger (42.8±7.3 vs. 46.0±2.4 years, p=0.002). Their mean diabetes duration was 33.5±8.0 years and their age at diabetes onset was 9.3±3.9 years. Differences between women with and without type 1 diabetes were also observed in terms of race/ethnicity, with the vast majority (96.2%) of women in EDC being non-Hispanic white and only 3.8% being black, whereas the proportion of non-Hispanic white women in SWAN was statistically significantly lower by study design (67.4% non-Hispanic white vs. 32.6% black, p<0.0001). In addition, compared to women without diabetes, those with type 1 diabetes were less likely to smoke (never smoker: 67.3% vs. 51.4%, p=0.03), and had lower BMI (25.2 vs. 26.5 kg/m^2, p=0.01), diastolic blood pressure (65.0 vs. 70.0 mmHg, p<0.0001), total cholesterol (181.0 vs. 188.0 mg/dl, p=0.01), LDL cholesterol (100.9 vs. 115.0 mg/dl, p=0.002) and triglyceride concentrations (74.0 vs. 86.0 mg/dl, p=0.004), but higher HDL-C levels (61.0 vs. 54.0 mg/dl, p<0.0001). No other statistically significant differences were observed (Table 1).

Compared with women without diabetes, those with type 1 diabetes had a 0.6-year delay in menarche (13.2±1.7 vs. 12.6±1.5 years, p=0.003). The delay in menarche was restricted to women who were diagnosed with type 1 diabetes before reaching menarche, (n=80), among whom the age at menarche was 13.6±1.7 years (p<0.0001 compared with non-diabetic women). The age at menarche did not statistically significantly differ between women with type 1 diabetes whose diabetes onset occurred after menarche (12.2±1.2 years, n=25) and SWAN study participants (p=0.20) (Table 1).

At the last available follow-up, the mean age of women with type 1 diabetes was 58.7±6.1 years and of non-diabetic women was 64.0±3.6 years (p<0.0001). Women with type 1 diabetes were also less likely to have ever used oral contraceptives (63.5% vs. 77.5%, p=0.011) and to have been pregnant (72.4% vs. 91.0%, p<0.0001). Among those who reported at least one pregnancy (n=76, 162), the mean number of pregnancies (2.4±1.3 vs. 3.2±1.4, p=0.0001) and the mean number of live births (1.4±0.8 vs. 2.3±1.0, p<0.0001) were both lower in women with type 1 diabetes compared with women without diabetes (Table 2).

The unadjusted age at natural menopause was 2.6 years younger in women with type 1 diabetes compared to women without diabetes (49.5±4.1 vs. 52.1±2.8 years, p<0.0001) and this finding was statistically significant both among women who were diagnosed with type 1 diabetes before (p<0.0001 compared with non-diabetic women) and after (p=0.037 compared with non-diabetic women) menarche. Similarly, women with type 1 diabetes had 3.4 years shorter unadjusted length of reproductive period compared to non-diabetic women (36.2±4.4 vs. 39.6±3.2 years, p<0.0001), irrespective of whether type 1 diabetes onset

preceded (p<0.0001) or followed (p=0.03) menarche (Table 2). Similar results were obtained when analyses were conducted including 1) SWAN women with imputed menopause data (n=338) or 2) the 18 EDC women who self-reported age at menopause (n=123) (Table 2).

In multivariable analyses, the delay in age at menarche was 0.5 years (p=0.002) after adjusting for race. The difference in age at natural menopause between these two cohorts was reduced from 2.6 years (p<0.0001, unadjusted) to 2.0 years (p<0.0001, after adjusting for age, race, BMI, smoking status, hypertension, HDL-C level, having ever taken oral contraceptives, and number of pregnancies). After adjustment, type 1 diabetes was associated with 2.5 fewer reproductive years (p<0.0001). When multivariable models were stratified by menarche onset before or after type 1 diabetes onset, differences remained statistically significant only among women whose onset of type 1 diabetes occurred prior to menarche. Age at menarche (p=0.14), age at natural menopause (p=0.08) and the length of women's reproductive period (p=0.29) were not statistically significantly different between women whose menarche onset preceded type 1 diabetes development and non-diabetic women in these multivariable analyses (Table 3).

Similar results were apparent when analysis included 1) SWAN women with imputed data for age at menopause (n=336) or 2) 18 EDC women who provided self-reported age at natural menopause without sex hormone data (n=121) (Table 3). Results also did not change significantly when we assigned the mean age at natural menopause in SWAN to the 37 EDC women who had not yet reached menopause (0.4 year delay in menarche, 2.0 years earlier in natural menopause, and 2.4 fewer reproductive years in women with type 1 diabetes).

Discussion

In the current study, we found that the length of the reproductive period of women with type 1 diabetes onset prior to menarche was 2.9 years shorter (1 year delay in menarche and 1.8 years early in menopause) compared to women without diabetes, a difference that persisted after adjusting for age, race/ethnicity, BMI, smoking status, hypertension, lipid concentrations, number of pregnancies, and oral contraceptive use. However, no association between type 1 diabetes and age at menarche, age at natural menopause, and length of reproductive years was found when type 1 diabetes developed after menarche although the small sample size (n=25) may undermine the statistical power to detect a difference. Another possible explanation regarding these findings being restricted to women whose type 1 diabetes onset occurred prior to menarche may be that type 1 diabetes occurring before menarche leads to a greater disruption of the female reproductive system compared with type 1 diabetes occurring after menarche.

Previously, data from the large, international, EPIC study suggested that women with diabetes diagnosed before the age of 20 years had an earlier menopause compared with non-diabetic women, whereas women with diabetes diagnosed after the age of 50 years had a later menopause [11]. However, the EPIC study could not distinguish the effect of type 1 and type 2 diabetes and the sequence of diabetes development and menopause onset in women with a late age at diabetes [11]. The magnitude of the difference in age at natural menopause between female participants with type 1 diabetes and non-diabetic controls in

the present study (1.8 years) was far smaller than observed in the FDA study (~ 6.4 years) [10]. The reasons for this difference may relate to the very small sample size of women with type 1 diabetes in the FDA study (n=15), as well as the selection of the controls. A total of 96 healthy women and their mothers and female siblings were examined and served as controls in the FDA study, but the authors did not take into account for clustering between the diabetes cases and controls in their analysis [10]. Furthermore, selection of controls from the same household may compromise the representativeness of the control sample, although it takes into account any genetic influences[10]. On the contrary, the Finnish study failed to detect a difference in age at natural menopause by type 1 diabetes, although only population level data were available for non-diabetic controls, which prohibited adjustment for potential confounders [13]. In addition, in the Finnish study, the median age at diagnosis of type 1 diabetes (12.8 years) was very close to the median age at menarche (13 years) which means that half of the study participants were diagnosed with type 1 diabetes after menarche and investigators did not assess whether the timing of type 1 diabetes onset relative to menarche affected study findings [13]. It is thus possible that a small difference in the age at menopause was not made apparent in the entire population studied. Similarly, the OVADIA study failed to detect a difference as well, which could also be attributed to the proportion of women who were diagnosed with type 1 diabetes after menarche (mean age at diabetes onset: 28±14.2 years) as both childhood and adult onset type 1 diabetes patients were included in the OVADIA study analysis [12].

A possible mechanism underlying the observed shorter length of the reproductive years of women with type 1 diabetes may relate to the disruption of the hypothalamus-pituitary-ovary (HPO) axis function and premature ovarian aging caused by endogenous insulin deficiency, hyperglycemia and exogenous hyperinsulinemia. It is well-known that insulin receptors (IRs) are widely distributed in the central nervous system (CNS) [1] and the ovaries [2, 3]. Thus, insulin plays a key role in maintaining the normal function of the female's HPO axis, not only through its impact on the upstream component – neurons in the CNS [1] but also on the downstream component - granulosa, thecal, and stromal in the ovaries [2, 3]. In mice with a neuron-specific destruction of the insulin receptor gene, *INSR*, female mice showed impaired ovarian follicle maturation because of dysregulation of luteinizing hormone (LH) resulting from hypothalamic dysregulation [1]. In addition, restoration of the function of the IRs in the brain through genetic reconstitution experiments normalized the reproductive function of female *INSR* knockout mice [30]. Moreover, studies have suggested the presence of direct central effects of insulin on the neuroendocrine system by using primary hypothalamic cell cultures and a GnRH neuronal cell line [31, 32]. At the ovarian level, the downstream element of the HPO axis, insulin exerts influences by its gonadotropin-like function [33] or through enhancing steroidogenesis responses to gonadotropins [34-37].

Due to the important role of insulin in maintaining the normal function of the female HPO axis, the disruption in insulin regulation in women with type 1 diabetes may underlie our findings of delayed menarche and premature ovarian aging compared with general population. Meanwhile, elevated concentrations of advanced glycation end-products (AGE) caused by hyperglycemia comprise another potential mechanism for premature ovarian aging in women with type 1 diabetes. Existing studies have suggested that

the interaction between AGE and receptor for advanced glycation end-products (RAGE) triggers/accelerates oxidative stress (OxS) and inflammation, contributing to cell, tissue, and vascular damage [38, 39], and leading to the development of diabetes complications [40 41]. Although no study has directly investigated whether elevated AGE concentrations cause ovarian dysfunction in women with type 1 diabetes, it is logical to postulate that AGE/RAGE also affect the normal function of the ovaries, leading to premature ovarian aging in women with type 1 diabetes, based on their damaging effect on cells and tissues. In addition, in type 1 diabetes blood insulin levels are often increased in the systemic circulation as exogenous insulin does not go through an initial liver passage and thus avoids significant early clearance. Increased exposure of the ovary tissue to insulin might lead to excess follicle recruitment and thus accelerated depletion of the ovarian reserve due to the gonadotropic function of insulin [42].

A limitation of the present study is the different ascertainment of menopause status in the EDC study and SWAN. However, a previous study has suggested that the two algorithms (WISE and SWAN) agreed for 73% of the SWAN women for menopausal status determination, with especially high concordance for classifying postmenopausal status (30.5% of women classified as postmenopausal by SWAN algorithms and 32.7% of women classified as postmenopausal by WISE algorithm) [43]. In addition, chronological age was younger among women with type 1 diabetes at the analytic baseline. Although baseline age was included as a covariate in multivariable models, it is still possible that residual confounding may have affected study findings. A third limitation of the present analysis was the unavailability of data on reproductive health (especially hormone levels) prior to the 12th follow-up visit of the EDC study. Thus, selection or survival bias may have been introduced given that women who did not participate in assessments post 2009 due to death, dropout, or other reasons, were excluded from analyses. However, early loss due to death or ill health would also be more likely to be associated with an earlier age at menopause, again confirming the main finding. Sensitivity analyses addressing some of these limitations confirm the main finding of a younger age at natural menopause in type 1 diabetes.

Conclusion

In conclusion, our data suggest that women with type 1 diabetes have a shorter reproductive period compared with non-diabetic women, exhibiting delayed menarche and earlier natural menopause. These findings appear restricted to women who were diagnosed with T1D before reaching menarche. The present study identified the subgroup of women with type 1 diabetes who have a high likelihood of experiencing early age at natural menopause so that efforts to unearth the biologic rationale and target potential prevention practices would be better focused. Given the high likelihood of experiencing early menopause in type 1 diabetes, and the enormous impact on health associated with early menopause, further studies are needed to determine modifiable factors that contribute to early menopause to improve reproductive health in women with type 1 diabetes.

Acknowledgements

The authors would like to thank the study staff and all the women who participated in the EDC study and SWAN for their invaluable contribution and support.

Financial support:

The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study was funded by NIH grant DK34818 and the Rossi Memorial Fund.

The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, U01AG012495). The content of this article (Title: Women with Type 1 Diabetes (T1D) Experience a Shorter Reproductive Period Compared with Nondiabetic Women: The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study and the Study of Women's Health Across the Nation (SWAN)) is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH.

Reference:

1. Bruning JC, Gautam D, Burks DJ, et al. Role of brain insulin receptor in control of body weight and reproduction. Science. [Article]. 2000;289(5487):2122–5. [PubMed: 11000114]
2. Poretsky L, Grigorescu F, Seibel M, Moses AC, Flier JS. Distribution and characterization of insulin and insulin-like growth factor i receptors in normal human ovary. Journal of Clinical Endocrinology and Metabolism. [Article]. 1985;61(4):728–34. [PubMed: 2993346]
3. Poretsky L, Smith D, Seibel M, Pazianos A, Moses AC, Flier JS. Specific insulin binding sites in human ovary. Journal of Clinical Endocrinology and Metabolism. [Article]. 1984;59(4):809–11. [PubMed: 6480806]
4. Rohrer T, Stierkorb E, Grabert M, et al. Delayed menarche in young German women with type 1 diabetes mellitus: Recent results from the DPV diabetes documentation and quality management system. European Journal of Pediatrics. [Article]. 2008;167(7):793–9. [PubMed: 17763869]
5. Deltsidou A Age at Menarche and Menstrual Irregularities of Adolescents with Type 1 Diabetes. Journal of Pediatric and Adolescent Gynecology. 2010;23(3):162–7. [PubMed: 19679499]
6. Strotmeyer ES, Steenkiste AR, Foley TP Jr, Berga SL, Dorman JS. Menstrual cycle differences between women with type 1 diabetes and women without diabetes. Diabetes Care. 2003;26(4):1016–21. [PubMed: 12663566]
7. Danielson KK, Palta M, Allen C, D'Alessio DJ. The association of increased total glycosylated hemoglobin levels with delayed age at menarche in young women with type 1 diabetes. Journal of Clinical Endocrinology and Metabolism. 2005;90(12):6466–71. [PubMed: 16204372]
8. Schweiger BM, Snell-Bergeon JK, Roman R, McFann K, Klingensmith GJ. Menarche delay and menstrual irregularities persist in adolescents with type 1 diabetes. Reproductive Biology and Endocrinology. [Review]. 2011;9.
9. Harjutsalo V, Maric-Bilkan C, Forsblom C, Groop PH, FinnDiane Study G. Age at menarche and the risk of diabetic microvascular complications in patients with type 1 diabetes. Diabetologia. 2016;59(3):472–80. [PubMed: 26607636]
10. Dorman JS, Steenkiste AR, Foley TP, et al. Menopause in type 1 diabetic women: is it premature? Diabetes. 2001;50(8):1857–62. [PubMed: 11473049]
11. Brand JS, Onland-Moret NC, Eijkemans MJC, et al. Diabetes and onset of natural menopause: Results from the European Prospective Investigation into Cancer and Nutrition. Human Reproduction. [Article]. 2015;30(6):1491–8. [PubMed: 25779698]
12. Yarde F, Van Der Schouw YT, De Valk HW, et al. Age at menopause in women with type 1 diabetes mellitus: The OVADIA study. Human Reproduction. [Article]. 2015;30(2):441–6. [PubMed: 25452435]
13. Sjöberg L, Pitkäniemi J, Harjutsalo V, et al. Menopause in women with type 1 diabetes. Menopause. [Article]. 2011;18(2):158–63. [PubMed: 20881890]
14. Gold EB. The timing of the age at which natural menopause occurs. Obstetrics and gynecology clinics of North America. 2011;38(3):425–40. [PubMed: 21961711]
15. Jacobsen BK, Heuch I, Kvale G. Age at natural menopause and all-cause mortality: a 37-year follow-up of 19,731 Norwegian women. Am J Epidemiol. 2003;157(10):923–9. [PubMed: 12746245]

16. Jacobsen BK, Knutsen SF, Fraser GE. Age at natural menopause and total mortality and mortality from ischemic heart disease: the Adventist Health Study. J Clin Epidemiol. 1999;52(4):303–7. [PubMed: 10235170]
17. Hu FB, Grodstein F, Hennekens CH, et al. Age at natural menopause and risk of cardiovascular disease. Archives of internal medicine. 1999;159(10):1061–6. [PubMed: 10335682]
18. Ossewaarde ME, Bots ML, Verbeek AL, et al. Age at menopause, cause-specific mortality and total life expectancy. Epidemiology. 2005;16(4):556–62. [PubMed: 15951675]
19. Joakimsen O, Bonaa KH, Stensland-Bugge E, Jacobsen BK. Population-based study of age at menopause and ultrasound assessed carotid atherosclerosis: The Tromso Study. J Clin Epidemiol. 2000;53(5):525–30. [PubMed: 10812326]
20. Lisabeth LD, Beiser AS, Brown DL, Murabito JM, Kelly-Hayes M, Wolf PA. Age at natural menopause and risk of ischemic stroke: the Framingham heart study. Stroke. 2009;40(4):1044–9. [PubMed: 19233935]
21. Kritz-Silverstein D, Barrett-Connor E. Early menopause, number of reproductive years, and bone mineral density in postmenopausal women. American journal of public health. 1993;83(7):983–8. [PubMed: 8328621]
22. van Der Voort DJ, van Der Weijer PH, Barentsen R. Early menopause: increased fracture risk at older age. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2003;14(6):525–30.
23. Orchard TJ, Dorman JS, Maser RE, et al. Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. Diabetes. 1990;39(9):1116–24. [PubMed: 2384191]
24. Sowers MF, Crawford SL, Sternfeld B. SWAN: A multi-center, multi-ethnic, community-based cohort study of women and the menopausal transition. Menopause: Biology and Pathobiology. 2000:175–88.
25. The hypertension detection and follow-up program: Hypertension detection and follow-up program cooperative group. Preventive medicine. 1976;5(2):207–15. [PubMed: 935073]
26. Orchard TJ, Dorman JS, Maser RE, et al. Factors associated with avoidance of severe complications after 25 yr of IDDM. Pittsburgh Epidemiology of Diabetes Complications Study I. Diabetes Care. 1990;13(7):741–7. [PubMed: 2387194]
27. Thurston RC, El Khoudary SR, Sutton-Tyrrell K, et al. Vasomotor symptoms and lipid profiles in women transitioning through menopause. Obstetrics and gynecology. 2012;119(4):753–61. [PubMed: 22433339]
28. Johnson BD, Merz CN, Braunstein GD, et al. Determination of menopausal status in women: the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) Study. Journal of women's health. 2004;13(8):872–87.
29. Samargandy S, Matthews KA, Brooks MM, et al. Arterial Stiffness Accelerates Within 1 Year of the Final Menstrual Period: The SWAN Heart Study. Arterioscler Thromb Vasc Biol. 2020;40(4):1001–8. [PubMed: 31969013]
30. Okamoto H, Nakae J, Kitamura T, Park BC, Dragatsis I, Accili D. Transgenic rescue of insulin receptor-deficient mice. Journal of Clinical Investigation. [Article]. 2004;114(2):214–23.
31. Salvi R, Castillo E, Voirol MJ, et al. Gonadotropin-releasing hormone-expressing neurons immortalized conditionally are activated by insulin: Implication of the mitogen-activated protein kinase pathway. Endocrinology. [Article]. 2006;147(2):816–26. [PubMed: 16293665]
32. Pralong FP. Insulin and NPY pathways and the control of GnRH function and puberty onset. Molecular and Cellular Endocrinology. [Review]. 2010;324(1-2):82–6. [PubMed: 20138117]
33. Poretsky L, Kalin MF. The gonadotropic function of insulin. Endocrine Reviews. [Article]. 1987;8(2):132–41. [PubMed: 3301317]
34. Garzo VG, Dorrington JH. Aromatase activity in human granulosa cells during follicular development and the modulation by follicle-stimulating hormone and insulin. American Journal of Obstetrics and Gynecology. [Article]. 1984;148(5):657–62. [PubMed: 6422764]
35. Willis D, Mason H, Gilling-Smith C, Franks S. Modulation by insulin of follicle-stimulating hormone and luteinizing hormone actions in human granulosa cells of normal and polycystic

ovaries. Journal of Clinical Endocrinology and Metabolism. [Article]. 1996;81(1):302–9. [PubMed: 8550768]

36. Cara JF, Rosenfield RL. Insulin-like growth factor i and insulin potentiate luteinizing hormone-induced androgen synthesis by rat ovarian thecal-interstitial cells. Endocrinology. [Article]. 1988;123(2):733–9. [PubMed: 2969325]
37. Davoren JB, Hsueh AJW. Insulin enhances FSH-stimulated steroidogenesis by cultured rat granulosa cells. Molecular and Cellular Endocrinology. [Article]. 1984;35(2-3):97–105. [PubMed: 6428947]
38. Bodiga VL, Eda SR, Bodiga S. Advanced glycation end products: Role in pathology of diabetic cardiomyopathy. Heart Failure Reviews. [Review]. 2014;19(1):49–63. [PubMed: 23404649]
39. Ramasamy R, Schmidt AM. Receptor for advanced glycation end products (RAGE) and implications for the pathophysiology of heart failure. Current Heart Failure Reports. [Article]. 2012;9(2):107–16. [PubMed: 22457230]
40. Furth AJ. Glycated proteins in diabetes. British Journal of Biomedical Science. [Review]. 1997;54(3):192–200. [PubMed: 9499597]
41. McCance DR, Dyer DG, Dunn JA, et al. Maillard reaction products and their relation to complications in insulin-dependent diabetes mellitus. Journal of Clinical Investigation. [Article]. 1993;91(6):2470–8.
42. Poretsky L, Kalin MF. The gonadotropic function of insulin. Endocr Rev. 1987;8(2):132–41. [PubMed: 3301317]
43. Johnston JM, Colvin A, Johnson BD, et al. Comparison of SWAN and WISE menopausal status classification algorithms. Journal of women's health. 2006;15(10):1184–94.

Table 1

Characteristics of women with (EDC study) or without (SWAN study) type 1 diabetes

Characteristics at baseline	EDC		SWAN		p-value
	n		n		
Age (years)	105	42.8 (7.3)	178	46.0 (2.4)	0.002
Age at diabetes onset (years)	105	9.3 (3.9)	-	-	-
Age at menarche (years)	105	13.2 (1.7)	177	12.6 (1.5)	0.003
Limiting EDC data to women with T1D onset before menarche	80/105	13.6 (1.7)	177	12.6 (1.5)	<0.0001
Limiting EDC data to women with T1D onset after menarche	25/105	12.2 (1.2)	177	12.6 (1.5)	0.20
Non-Hispanic white women only	101/105	13.2 (1.7)	120/178	12.6 (1.5)	0.004
Data adding 18 EDC women [a]	123	13.2 (1.7)	177	12.6 (1.5)	0.0001
Diabetes duration (years)	105	33.5 (8.0)	-	-	-
Race (%)	105		178		
Non-Hispanic White	101/105	96.2	120/178	67.4	<0.0001
Black	4/105	3.8	58/178	32.6	
Marital status (%)	104		178		
Single, never married	14/104	13.5 (14)	17/178	9.6 (17)	0.47
Currently married or cohabitating	72/104	69.2 (72)	119/178	66.9 (119)	
Divorced	13/104	12.5 (13)	27/178	15.1 (27)	
Separated, Widowed, or others	5/104	4.8 (5)	15/178	8.4 (15)	
Education (%)	104		178		
High school or less	33/104	31.7 (33)	42/178	23.6 (42)	0.19
Some college or received bachelor's degree	53/104	51.0 (53)	92/178	51.7 (92)	
Graduate education beyond bachelor's degree	18/104	17.3 (18)	44/178	24.7 (44)	
BMI (kg/m^2)	105	25.2 (22.6, 28.1)	177	26.5 (23.4, 31.0)	0.01
Waist to hip ratio	94	0.81 (0.76, 0.86)	174	0.79 (0.76, 0.84)	0.28
Smoking status (%)	104		177		
Never smoker	70/104	67.3 (70)	91/177	51.4 (91)	0.03
Past smoker	17/104	16.4 (17)	48/177	27.1 (48)	
Current smoker	17/104	16.4 (17)	38/177	21.5 (38)	
Systolic blood pressure (mmHg)	105	114.0 (102.0, 124.0)	178	111.0 (104.0, 123.0)	0.84

Characteristics at baseline	EDC		SWAN		p-value
Diastolic blood pressure (mmHg)	105	65.0 (58.0, 71.0)	178	70.0 (64.0, 79.0)	<0.0001
Blood pressure medication use (%)	17/105	16.2	17/178	9.6	0.10
Lipid medication use (%)	20/105	19.1	0/178	0.0	<0.0001
Total cholesterol (mg/dl)	105	181.0 (162.0, 197.0)	177	188.0 (173.0, 214.0)	0.01
HDL-C (mg/dl)	105	61.0 (50.6, 73.0)	177	54.0 (47.0, 62.0)	<0.0001
LDL-C (mg/dl)	84	100.9 (87.0, 127.4)	176	115.0 (99.0, 137.0)	0.002
Triglycerides (mg/dl)	86	74.0 (51.0, 100.0)	177	86.0 (65.0, 122.5)	0.004

Data are means (SD), median (interquartile range) or percent.

BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; T1D: type 1 diabetes.

[a]Sensitivity analysis included 18 EDC women who provided self-reported age at natural menopause without sex hormone data prior to the 22-year assessment.

Table 2

Characteristics of women with (EDC study) or without (SWAN study) type 1 diabetes at the last available follow-up

Characteristics	EDC		SWAN		p-value
	n		n		
Age (years)	105	58.7 (6.1)	178	64.0 (3.6)	<0.0001
Diabetes duration (years)	105	49.5 (6.8)	-	-	-
Percent ever on oral contraceptives (%)	66/104	63.5	138/178	77.5	0.01
Percent ever pregnant (%)	76/105	72.4	162/178	91.0	<0.0001
Number of pregnancies	76	2.4 (1.3)	162	3.2 (1.4)	0.0001
Number of live births	76	1.4 (0.8)	155	2.3 (1.0)	<0.0001
Age at natural menopause	105	49.5 (4.1)	178	52.1 (2.8)	<0.0001
Limiting EDC data to women with T1D onset before menarche	80	49.3 (4.0)	178	52.1 (2.8)	<0.0001
Limiting EDC data to women with T1D onset after menarche	25	50.2 (4.4)	178	52.1 (2.8)	0.037
Including SWAN imputed data	105	49.5 (4.1)	341	52.1 (3.3)	<0.0001
Non-Hispanic white women only	101	49.6 (3.9)	120	52.1 (2.7)	<0.0001
Data adding 18 EDC women [a]	123	48.9 (4.7)	178	52.1 (2.8)	<0.0001
Reproductive years	105	36.2 (4.4)	177	39.6 (3.2)	<0.0001
T1D onset before menarche	80	35.7 (4.2)	177	39.6 (3.2)	<0.0001
T1D onset after menarche	25	38.0 (4.6)	177	39.6 (3.2)	0.03
Including SWAN imputed data	105	36.2 (4.4)	338	39.5 (3.0)	<0.0001
Non-Hispanic white women only	101	36.3 (4.3)	120	39.5 (3.1)	<0.0001
Data adding 18 EDC women [a]	123	35.7 (4.9)	177	39.6 (3.2)	<0.0001

Data are means (SD) or percent (n).

T1D: type 1 diabetes.

[a]Sensitivity analysis included 18 EDC women who provided self-reported age at natural menopause without sex hormone data prior to the 22-year assessment.

Table 3

Association between diabetes status and the length of reproductive period

Characteristics	Type 1 diabetes (Beta coefficient, 95%CI)	p-value
Age at menarche [b] (n=105, 177)	0.5 (0.2 to 1.1)	0.002
Limiting EDC data to women with T1D onset before menarche [b] (n=80, 177)	1.0 (0.6 to 1.4)	<0.0001
Limiting EDC data to women with T1D onset after menarche [b] (n=25, 177)	−0.5 (−1.1 to 0.2)	0.14
Data adding 18 EDC women [b] (n=123, 177) [a]	0.6 (0.2 to 1.0)	0.005
Age at natural menopause [c] (n=103, 176)	−2.0 (−2.9 to −1.0)	<0.0001
Limiting EDC data to women with T1D onset before menarche [c] (n=78, 176)	−1.8 (−2.7 to −1.0)	<0.0001
Limiting EDC data to women with T1D onset after menarche [c] (n=25, 176)	−1.0 (−2.1 to 0.1)	0.08
Including SWAN imputed data [c] (n=103, 336)	−1.8 (−2.5 to −1.0)	<0.0001
Data adding 18 EDC women [c] (n=121, 176) [a]	−1.8 (−2.5 to −1.0)	<0.0001
Reproductive years [c] (n=103, 176)	−2.5 (−3.6 to −1.5)	<0.0001
Limiting EDC data to women with T1D onset before menarche [c] (n=78, 176)	−2.9 (−3.8 to −2.0)	<0.0001
Limiting EDC data to women with T1D onset after menarche [c] (n=25, 176)	−0.7 (−1.9 to 0.6)	0.29
Including SWAN imputed data [c] (n=103, 336)	−2.3 (−3.1 to −1.5)	<0.0001
Data adding 18 EDC women [c] (n=121, 176) [a]	−2.4 (−3.2 to −1.5)	<0.0001

T1D: type 1 diabetes

[a] Sensitivity analysis included 18 EDC women who provided self-reported age at natural menopause without sex hormone data prior to the 22-year assessment.

Models were constructed among study participants with complete covariate data

[b] Model controlled for race

[c] Model controlled for baseline age, race, BMI, smoking status, blood pressure, HDL-C, non-HDL-C, number of pregnancies, and having ever taken oral contraceptives