Menarchal Timing in Type 1 Diabetes through the Last Four Decades

Running Title: Menarche timing Type 1 Diabetes by Decade

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Objective- We sought to examine whether age at menarche has changed over the past 4 decades by comparing age at menarche by year of diagnosis with type 1 diabetes (T1DM).

Research Design and Methods- This was a cross sectional study of age at menarche in two cohorts: adolescents (ages 11-24 years, n=228), and adults (ages 19-55 years, n=290, enrolled in the Coronary Artery Calcification in Type 1 Diabetes study).

Results- The adolescent cohort reported a younger age of menarche than the adult women with TIDM (12.69 ± 0.08 years vs. 13.22 ± .12 yrs, mean± SE , P< 0.001). Age at menarche was later in both adolescent girls and adult women with T1DM diagnosed prior to menarche (12.82 ± 1.16 and 13.7 ± 2.23, mean± SE) than for those diagnosed after menarche (12.12 ± 1.25 and 12.65 ± 1.38, mean± SE, P<0.001 for both). Age at menarche was then examined by decade of T1DM diagnosis (1970-79, 1980-89, 1990-99, and 2000-09). Age at menarche significantly declined over the four decades (P=0.0002). However, the delay in menarche among girls diagnosed with T1DM before menarche compared to those diagnosed after menarche was also significant across all decades (P<0.0001), and did not change significantly over time (P=0.41 for interaction of cohort and diagnosis pre-menarche).

Conclusions- Age at menarche has declined over the past 4 decades among girls with T1DM, but a delay in age at menarche among those diagnosed prior to menarche compared to those diagnosed after menarche remains.
or type 1b diabetes (9). A total of 234 subjects were enrolled in the study, and complete data on age at menarche and age at diagnosis were available for 228. The age of diagnosis of T1DM was not available in four subjects and two subjects, both 15 years of age, had not yet started their menstrual periods. These six subjects were excluded from analysis. There were 23 subjects with stable, treated hypothyroidism included in the analysis.

We also recruited 293 TIDM women between ages 19 and 55 years as part of the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study. Inclusion criteria for participants with diabetes were diagnosis before the age of 30 yr or positive antibodies or a clinical course consistent with T1DM; insulin therapy within 1 yr of diagnosis; and long-standing diabetes (mean duration 24 yr, range 4-52 yr). Despite the use of these entrance criteria, it is possible that some women had type 2 diabetes. Participants completed a baseline examination between March 2000 and April 2002, and a follow-up examination between December of 2002 and March of 2005. Participants self-reported their reproductive history, including age at menarche, at the follow-up examination. Complete data were available for age at menarche and age at T1DM diagnosis for 290 of the 293 study participants.

Study approval was obtained from the institutional review board at the University of Colorado Denver and participants provided written informed consent and assent, if appropriate, at enrollment.

**Questionnaires.** Age of the first menstrual period and menstrual cycle pattern and length were obtained by self-report using a questionnaire adapted from the National Health and Nutrition Examination Survey (NHANES) reproductive health questionnaire (10). Subjects were asked to recall their age at the time of their first menstrual period. Probing questions were asked to help the subjects if they had difficulty remembering the exact age, such as remembering the season, grade or proximity to a birthday.

**Statistical Analysis.** Data are presented as mean ± standard error. An independent samples t-test was used to test the difference in age at menarche between those who developed T1DM before menarche and those who developed T1DM after menarche. Four cohorts were formed based on the year of T1DM diagnosis: 1970-79, 1980-89, 1990-99, and 2000-2009. Multivariate ANOVA was used to examine age at menarche by these T1DM diagnosis cohorts and by diagnosis of T1DM before vs. after menarche.

**RESULTS**

Of the 228 adolescent females with T1DM, 185 participants had diabetes onset prior to menarche and 43 were diagnosed with T1DM after menarche. The overall mean age of menarche among adolescent females with T1DM was 12.69 ± 0.08 years. Girls who developed diabetes before menarche had an average age of menarche of 12.81 ± 0.09 years compared to 12.17 ± 0.19 years (p = 0.0015) in those who developed diabetes after menarche. The delay between those diagnosed with T1DM prior to menarche and those diagnosed after menarche was 0.69 ± 0.20 years in the adolescent girls.

In the cohort of adult women participating in the CACTI study, the mean age at the follow-up examination was 42.8 ± 0.53 years. The overall mean age of menarche among adult females with T1DM was 13.22 ± 0.12 years. Women who developed diabetes before menarche (n=155) had an average age of menarche of 13.7 ± 2.23 years compared to 12.65 ± 1.38 years (P<0.0001) in those who developed diabetes after menarche (n=135). The delay in menarche between those diagnosed with T1DM prior to menarche compared to those diagnosed after menarche was 1.1 ± 0.22 years in the adult women.
Age at menarche was then examined by decade of T1DM diagnosis, as shown in Figure 1. Women who were diagnosed with T1DM prior to 1970 (n=52) were excluded, as there was not a full decade of data available and only a small number of study participants were diagnosed in this time frame. The age at menarche was significantly older among females diagnosed with T1DM prior to menarche (13.32 [95% CI = 13.13-13.52] years) compared to girls diagnosed with T1DM after they had already gone through menarche (12.58 [95% CI = 12.31-12.85] years, P<0.0001), with an overall mean delay in menarche of 0.74 years (95% CI = 0.41 – 1.08). Age at menarche declined significantly by decade of T1DM diagnosis overall (P=0.0002). This decline in age at menarche from 1970-79 to 2000-09 was only significant among girls who were diagnosed with T1DM prior to menarche (0.97 years, 95% CI = 0.47 – 1.46, P=0.0001), and not among girls with menarche prior to the diagnosis with T1DM. (0.62 years, 95% CI = -0.08 – 1.32, P=0.08). However, there was no significant interaction between decade of T1DM diagnosis and pre vs. post-menarchal diagnosis of T1DM on age at menarche (P=0.41).

**DISCUSSION**

This study reveals that the age at menarche has significantly declined over the past 40 years in girls with T1DM, but a delay in menarche persists. Our data also support the lack of a significant decline in age of menarche in girls with menarche occurring prior to the diagnosis of type 1 diabetes, similar to reports that the age of menarche in the general population has remained the same over this time period (6), rather than reports of a declining age of menarche (7). Studies have shown that the development of rapid and long acting insulin analogues, and initiation of insulin pump therapy has helped improve overall glycemic control (11-13) and that there has been an improvement in metabolic control as reflected by HbA1c in children, adolescents and young adults with T1DM over the last 10 years (14). Improvements in metabolic control have already been shown to have decreased the frequency of serious complications such as proliferative retinopathy, nephropathy, and cardiovascular disease seen in patients with T1DM (15-16). Thus, the decline in age at menarche is most likely also being contributed to by improved glycemic control.

There were some limitations to our study. There is the potential for recall bias with the use of self reported questionnaires. However, the age of menarche is thought to be reliable by recall since it is usually a date that is well remembered (17).

In conclusion, more recently diagnosed girls with T1DM report a younger age at menarche than those who were diagnosed in prior decades. Also, the delay between those diagnosed with T1DM prior to menarche and those diagnosed after menarche is trending to be less in adolescent girls than in adult women with T1DM. Besides the well reported decrease in micro and macrovascular complications associated improved treatment of T1DM, reproductive potential may also have improved. However, a delay in menarche of over 8 months remains, despite improved diabetes management. More research is needed in this area so that the etiology and consequences of delayed age at menarche in this population can be better understood.

**Author contributions:** Both Dr. Georgeanna J Klingensmith and Dr. Janet Snell-Bergeon contributed to the discussion and revisions and edits of the manuscript. Both are employed by the University of Colorado and work for the Barbara Davis Center for Childhood Diabetes. Dr. Bahareh Schweiger researched data, wrote manuscript, contributed discussion and revised and edited
the manuscript. There was no other editorial assistance of a colleague in the preparation of the manuscript.

REFERENCES


Figure 1. Age at Menarche by T1DM Diagnosis Year.

a p<0.05 for comparison with 1970-1979 cohort, b p<0.05 for comparison with 1980-1989 cohort, c p<0.05 for comparison with 1990-1999 cohort, d p<0.05 for comparison with 2000-2009 cohort.