

# Menarchal Timing in Type 1 Diabetes Through the Last 4 Decades

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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.

**RESEARCH DESIGN AND METHODS** — This work consisted of 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 type 1 diabetes ( $12.69 \pm 0.08$  vs.  $13.22 \pm 0.12$  years, mean  $\pm$  SE,  $P < 0.001$ ). Age at menarche was later in both adolescent girls and adult women with type 1 diabetes diagnosed before menarche ( $12.82 \pm 1.16$  and  $13.7 \pm 2.23$  years) than for individuals diagnosed after menarche ( $12.12 \pm 1.25$  and  $12.65 \pm 1.38$  years,  $P < 0.001$  for both). Age at menarche was then examined by decade of type 1 diabetes diagnosis (1970–1979, 1980–1989, 1990–1999, and 2000–2009). Age at menarche significantly declined over the 4 decades ( $P = 0.0002$ ). However, the delay in menarche among girls diagnosed with type 1 diabetes before menarche compared with 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 premenarche).

**CONCLUSIONS** — Age at menarche has declined over the past 4 decades among girls with type 1 diabetes, but a delay in age at menarche remains among individuals diagnosed before menarche compared with individuals diagnosed after menarche.

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Previous studies have demonstrated that the age of menarche is still delayed in girls with type 1 diabetes (1–5). However, none have compared age of menarche of young adolescents with type 1 diabetes with adult women with type 1 diabetes to see if the delay in menarche has decreased over the past several decades. Though there is conflicting evidence as to whether the age at menarche in the general population has remained the same (6) or has declined (7), there has been little research done to look at the effects of type 1 diabetes on menarchal timing since the completion of the landmark Diabetes Control and Complications Trial (DCCT) (8), which led to

widespread use of intensive diabetes treatment. The purpose of this study was to compare age at menarche by decade of diabetes diagnosis, to examine the temporal trends in age at menarche in type 1 diabetes.

## RESEARCH DESIGN AND METHODS

Adolescent subjects were recruited from the pediatric clinic at the Barbara Davis Center for Childhood Diabetes. We enrolled females of all ethnicities between the ages of 11 and 24 years of age, and individuals who had at least one menstrual period were included in the analysis. Subjects with any renal, respiratory, or cardiac disease and any

other chronic disease besides type 1 diabetes were excluded from the study. Subjects with a preexisting diagnosis of Hashimoto's thyroiditis were included if their initial diagnosis was made by close surveillance and if they had a longstanding history of being clinically and biochemically euthyroid. The study took place between November 2008 and May 2009. The clinical diabetes type assigned by the health care provider was obtained from the medical records and categorized as type 1 diabetes if the provider assignment was type 1, type 1a, 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 subjects. The age of diagnosis of type 1 diabetes 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 type 1 diabetic women between ages 19 and 55 years as part of the Coronary Artery Calcification in Type 1 Diabetes study. Inclusion criteria for participants with diabetes were diagnosis before the age of 30 years or positive antibodies or a clinical course consistent with type 1 diabetes, insulin therapy within 1 year of diagnosis, and longstanding diabetes (mean duration 24 years, range 4–52). 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 2002 and March 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 type 1 diabetes 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.

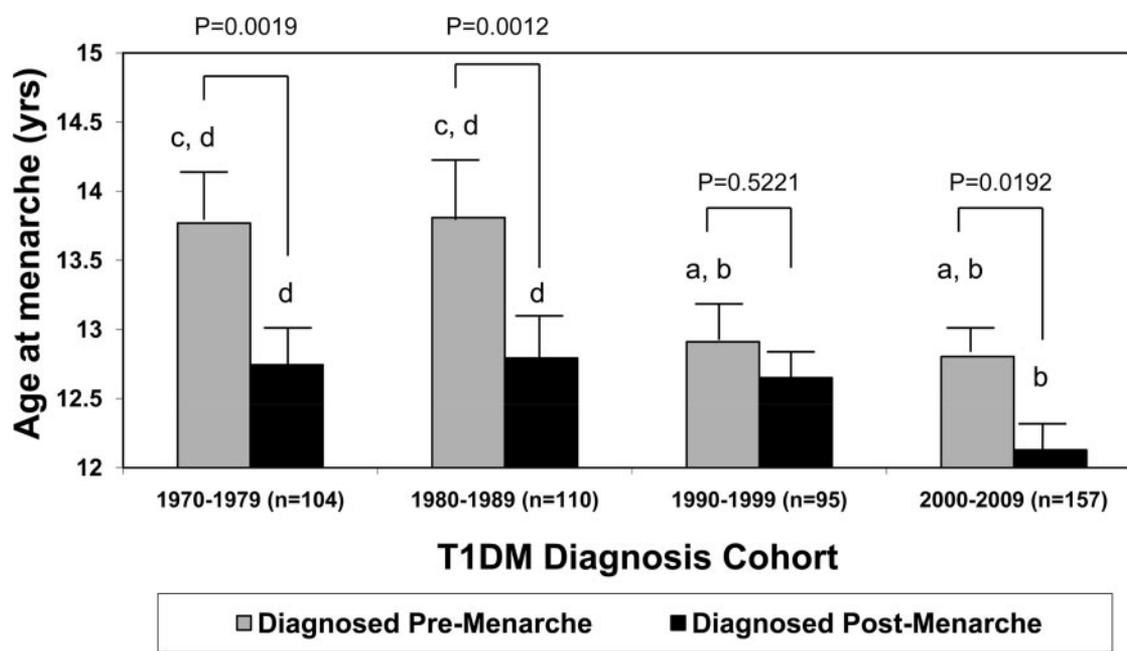
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**Figure 1**—Age at menarche by type 1 diabetes (T1DM) diagnosis year. <sup>a</sup> $P < 0.05$  for comparison with 1970–1979 cohort, <sup>b</sup> $P < 0.05$  for comparison with 1980–1989 cohort, <sup>c</sup> $P < 0.05$  for comparison with 1990–1999 cohort, <sup>d</sup> $P < 0.05$  for comparison with 2000–2009 cohort.

### 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 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  $\pm$  SE. An independent samples *t* test was used to test the difference in age at menarche between individuals who developed type 1 diabetes before menarche and individuals who developed type 1 diabetes after menarche. Four cohorts were formed based on the year of type 1 diabetes diagnosis: 1970–1979, 1980–1989, 1990–1999, and 2000–2009. Multivariate ANOVA was used to examine age at menarche by these type 1 diabetes diagnosis cohorts and by diagnosis of type 1 diabetes before versus after menarche.

**RESULTS**— Of the 228 adolescent females with type 1 diabetes, 185 participants had diabetes onset before menarche and 43 were diagnosed with type 1 diabetes after menarche. The overall mean age of menarche among adolescent females

with type 1 diabetes was  $12.69 \pm 0.08$  years. Girls who developed diabetes before menarche had an average age of menarche of  $12.81 \pm 0.09$  years compared with  $12.17 \pm 0.19$  years ( $P = 0.0015$ ) in individuals who developed diabetes after menarche. The delay between individuals diagnosed with type 1 diabetes before menarche and individuals diagnosed after menarche was  $0.69 \pm 0.20$  years in adolescent girls.

In the cohort of adult women participating in the Coronary Artery Calcification in Type 1 Diabetes study, the mean age at the follow-up examination was  $42.8 \pm 0.53$  years. The overall mean age of menarche among adult females with type 1 diabetes was  $13.22 \pm 0.12$  years. Women who developed diabetes before menarche ( $n = 155$ ) had an average age of menarche of  $13.7 \pm 2.23$  years compared with  $12.65 \pm 1.38$  years ( $P < 0.0001$ ) in girls who developed diabetes after menarche ( $n = 135$ ). The delay in menarche between individuals diagnosed with type 1 diabetes before menarche compared with individuals diagnosed after menarche was  $1.1 \pm 0.22$  years in adult women.

Age at menarche was then examined by decade of type 1 diabetes diagnosis, as shown in Fig. 1. Women who were diagnosed with type 1 diabetes before 1970 ( $n = 52$ ) were excluded, since 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 type 1 diabetes before menarche (13.32 years [95% CI 13.13–13.52]) compared with girls diagnosed with type 1 diabetes after they had already gone through menarche (12.58 years [12.31–12.85],  $P < 0.0001$ ), 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 type 1 diabetes diagnosis overall ( $P = 0.0002$ ). This decline in age at menarche from 1970–1979 to 2000–2009 was only significant among girls who were diagnosed with type 1 diabetes before menarche (0.97 years [0.47–1.46],  $P = 0.0001$ ) and not among girls with menarche before the diagnosis with type 1 diabetes (0.62 years [–0.08 to 1.32],  $P = 0.08$ ). However, there was no significant interaction between decade of type 1 diabetes diagnosis and premenarchal versus postmenarchal diagnosis of type 1 diabetes on age at menarche ( $P = 0.41$ ).

**CONCLUSIONS**— This study reveals that the age at menarche has significantly declined over the past 40 years in girls with type 1 diabetes, 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 before 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 analogs 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 A1C in children, adolescents, and young adults with type 1 diabetes 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 type 1 diabetes (15,16). Thus, improved glycemic control is also likely contributing to the decline in age at menarche.

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 type 1 diabetes report a younger age at menarche than girls who were diagnosed in prior decades. Also, the delay between individuals diagnosed with type 1 diabetes before menarche and individuals diagnosed after menarche is trending to be less in adolescent girls than in adult women with type 1 diabetes. Besides the well-reported decrease in micro- and macrovascular complications associated improved treatment of type 1 diabetes, reproductive potential may also have improved. However, a delay in menarche of >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

B.S. researched data, wrote the manuscript, contributed to the discussion, and revised and edited the manuscript. G.J.K. and J.K.S.-B. 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. There was no other editorial assistance of a colleague in the preparation of the manuscript.

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