Age at Menarche and Risk of Gestational Diabetes Mellitus: A Prospective Cohort Study Among 27,482 Women

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OBJECTIVE

Examine the association between age at menarche and risk of gestational diabetes mellitus (GDM).

RESEARCH DESIGN AND METHODS

A prospective cohort study of 42,109 eligible pregnancies from 27,482 women in the Nurses' Health Study II.

RESULTS

The adjusted risk ratios for GDM across the age at menarche categories (≤11, 12, 13, and ≥14 years) were 1.34 (95% CI 1.14–1.58), 1.13 (0.97–1.31), 1.11 (0.95–1.29), and 1.00 (referent; *P* for trend = 0.0005), respectively. Analysis of the mediating effect indicated that 42.1% (*P* = 0.0007) of the association was mediated through prepregnancy BMI.

CONCLUSION

These findings suggested that earlier menarche was significantly associated with an increased risk of GDM. This association was largely mediated through prepregnancy excessive body adiposity.

Gestational diabetes mellitus (GDM) is one of the most common pregnancy complications, affecting ~2–7% of all pregnancies in the U.S. (1). Identifying women who are at high risk of GDM has important public health and clinical significances. Menarche is an indicator of pubertal onset and the beginning of reproductive life in women. Although early menarche has been associated with risk factors for GDM, such as insulin resistance (2,3) and obesity (4–6), the association between age at menarche and risk of GDM has yet to be investigated. The objective of this study was to examine the association between menarche timing and GDM risk, and the extent to which the association is mediated through prepregnancy obesity.

RESEARCH DESIGN AND METHODS

The Nurses' Health Study II, initiated in 1989, is an ongoing prospective cohort of U.S. female nurses. For the current study, the final sample included 27,482 women (42,109 eligible pregnancies) who did not have diabetes and other major chronic diseases at baseline or prior to GDM, and were observed until 2001 (after which most women had passed the reproductive age).

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GDM events were identified based on self-reported information and updated every 2 years. A previous validation study (7) demonstrated a high validity of self-reported diagnosis of GDM in this cohort (94% of women who reported to have GDM were confirmed by a physician review based on a medical record review). Age at menarche was defined as the age of the first menstruation and was collected in 1989 (baseline questionnaire).

Age at menarche was grouped into a categorical variable (≤11, 12, 13, and ≥14 years of age) to ensure adequate sample size in each age category. Log-binomial models were performed to estimate the risk ratio (RR) and 95% CI of GDM associated with age at menarche, with generalized estimating equations assuming a similar within-person correlation across two or more pregnancies for a single woman. Multivariate regression models were applied to control for potential confounding factors. The mediating effect was evaluated by calculating the mediation proportion that represents the proportion for excess risk of GDM that can be attributed to a mediator.

RESULTS

We documented 1,404 pregnancies complicated by GDM (346 were recurrent GDM) among 27,482 women (92% were Caucasian). The mean age at menarche was 12.6 ± 1.5 years, and the median was 12.0 years. In general, women with an earlier age at menarche had a lower birth weight, a larger body size at age 5 and 10 years, a greater BMI at age 18 years, and a greater weight gain since age 18 years (Supplementary Table 1). Moreover, they were more likely to be overweight or obese before pregnancy, to have a higher BMI at 18 years of age and before the index pregnancy, and to gain more weight since 18 years of age than women with older ages at menarche. Early menarche was significantly associated with an increased risk of GDM (Table 1). After adjusting for age, race/ethnicity, and family history of diabetes, pregnancies among women with menarche at ≤11 years of age had a 39% increased risk of GDM (RR 1.39, 95% CI 1.19–1.63) compared with pregnancies among women with menarche at 14 years of age (referent) (multivariate model 1). The association did not change, and the trend remained significant with additional adjustment for women's birth weight, and somatotype at ages 5 and 10 years (*P* for trend = 0.0003; multivariate model 2), suggesting that the association between age at menarche and GDM is not confounded by intrauterine and childhood adiposity before the onset of menarche. After further adjustment for adulthood lifestyle factors (i.e., alcohol consumption, smoking status, Alternate Healthy Eating Index 2010, total physical activity, marital status, and oral contraceptive use in model 3), the RRs across the menarche categories (≤11, 12, 13, and ≥14 years of age) were 1.34 (95% CI 1.14–1.58), 1.13 (0.97–1.31), 1.11 (0.95–1.29), and 1.00 (referent; *P* for trend = 0.0005; multivariate model 3), respectively, indicating that the association is independent of adulthood lifestyle factors.

To further understand how body weight/adiposity after the onset of menarche impacts the menarche-GDM association, we tested the results by adding adolescent and adulthood BMIs into the multivariate models. Additional adjustment for BMI at 18 years of age did not materially change the results. The association, however, was substantially attenuated and became statistically insignificant after further adjustment of prepregnancy BMI (data not shown). We further calculated the proportions of effects mediated through prepregnancy BMI. The estimated proportion for excess risk of GDM was 42.1% (95% CI 17.9–66.3, *P* = 0.0007) for prepregnancy BMI, indicating that prepregnancy BMI was a mediator for the associations between age at menarche and GDM risk.

CONCLUSIONS

Two major findings were observed from this prospective study of 42,109 pregnancies among 27,482 women. First, earlier menarche was significantly associated with an increased risk of GDM, independent of established risk factors, such as age, parity, family history of diabetes, smoking, oral contraceptive use, physical activity, birth weight, and childhood adiposity. Second, the association between age at menarche and GDM risk might be partly mediated through prepregnancy obesity.

We were aware of one previous study that examined the relationship between age at menarche and GDM among 3,419 women (185 GDM events), and reported no association. Our findings provide new evidence that earlier menarche is associated with GDM and are generally in agreement with several recent large cohort studies (8–13) in which earlier menarche was significantly associated with an increased risk of type 2 diabetes in middle- to old-aged adults. The precise mechanism by which early age at menarche may increase the risk of GDM is not clear. Early menarche has been associated with risk factors for GDM such as excessive prepregnancy obesity (4–6) and insulin resistance (2,3). In the current study, the observed association was substantially attenuated

Table 1—Relative risk (95% CI) of GDM according to age at menarche among 42,109 pregnancies in the Nurses' Health Study II (1,404 GDM events)

Age at menarche	GDM (events/pregnancies)	Multivariate model 1	Multivariate model 2	Multivariate model 3
≤11 years	361/8,730	1.39 (1.19–1.63)	1.36 (1.16–1.60)	1.34 (1.14–1.58)
12 years	405/12,335	1.13 (0.97–1.32)	1.13 (0.97–1.31)	1.13 (0.97–1.31)
13 years	381/11,980	1.10 (0.95–1.29)	1.11 (0.95–1.29)	1.11 (0.95–1.29)
≥14 years	257/9,064	Reference	Reference	Reference
P for trend		<0.0001	0.0003	0.0005

Data are reported as RR (95% CI), unless otherwise indicated. Model 1, covariates include age (continuous), family history of diabetes (yes, no), and race/ethnicity (Caucasian, African American, Asian American, Hispanic, other); Model 2, covariates include those in model 1, birth weight (<5.5, 5.5–6.9, 7.0–8.4, 8.5–10.0, or >10.0 pounds), somatotype at age 5 years (1, 2, 3, 4, 5+), and somatotype at age 10 years (1, 2, 3, 4, 5+); and Model 3, covariates include those in model 2, and alcohol consumption (4 categories, grams/day), smoking status (4 categories), Alternate Healthy Eating Index 2010 (quintiles), total physical activity (quintiles of METs/week), marital status (yes vs. no), and oral contraceptive use (yes vs. no).

after adjusting for prepregnancy BMI. The estimated proportion of risk of GDM that was mediated by prepregnancy BMI was 42.1%, suggesting that prepregnancy adiposity may play an important role in mediating this association. Other pathways might also be implicated in the association between age at menarche and GDM. Earlier age at menarche was associated with adulthood higher estrogen levels and lower serum sex hormone–binding globulin levels among women (14). High plasma estradiol and testosterone and/or low sex hormone–binding globulin levels were also associated with a higher risk of GDM (15), independent of adiposity. Therefore, it is plausible that age at menarche may be related to GDM risk through its association with hormonal changes. Future studies to investigate the underlying mechanisms are warranted.

In summary, earlier age at menarche was associated with an elevated risk of GDM. A large proportion, but not all, of this association was mediated through excessive adiposity before pregnancy. Early age at menarche might represent another risk factor for the early identification of girls who are at increased risk of the development of GDM in adulthood.

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