Ovarian reserve in women with type 1 diabetes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study

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Novelty Statement

- Markers of ovarian reserve such as anti-Müllerian hormone (AMH) are used in the management of fertility and prediction of menopause.

- Although women with type 1 diabetes have a high prevalence of reproductive disorders, no studies have examined whether markers of ovarian reserve are associated with randomization to intensive insulin therapy and subsequent markers of glycemic control.

- Using data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study, we found that the strongest predictor of AMH was chronologic age, and that diabetes-specific variables such as randomization to intensive therapy, insulin dose, and glycemic control were not associated with AMH concentrations.

Introduction

Anti-Müllerian hormone (AMH), originally known as Müllerian-inhibiting substance, is produced by ovarian pre-antral or "viable" follicles, declines with chronologic age, and is

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undetectable in the years before menopause [1]. A previous report noted that AMH concentrations were lower among women with type 1 diabetes compared to women without diabetes [2]. We examined the relationship between diabetes-specific variables during the Diabetes Control and Complications Trial (DCCT) and its observational follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC) study. The objective of this study was to determine whether glycemic control was associated with AMH concentrations in women with type 1 diabetes.

Participants and Methods

The DCCT and EDIC studies have been described in detail [3]. From 1983–1989, 1,441 participants (including 680 women) were randomized to intensive insulin treatment vs. conventional treatment. Participants with >15 years of diabetes duration, hypertension, nephropathy, and symptomatic ischemia and neuropathy were excluded. The DCCT ended in 1993 and 1,375 (96%) of the 1,428 surviving DCCT subjects enrolled in EDIC. At the 17th year of EDIC, 564 women (91% of surviving women) were actively participating. Natural menopause was defined as cessation of menses for at least 1 year in the absence of gynecologic surgery. Two-hundred two of the active participants were in natural menopause at year 17; women with premature ovarian insufficiency were excluded (n=6) [4] resulting in 196 women.

AMH was measured using ELISA (Beckman Coulter second generation kit) with a detection limit of 0.08 ng/ml [5]. Coefficients of variation were 8.1% at a mean concentration of 3.3 ng/ml and 4.2% at a mean concentration of 8.3ng/ml. For the purposes of this analysis, undetectable concentrations of AMH (defined as < 0.08 ng/mL) were converted to 0.04 ng/ml, halfway between 0 and 0.08 ng/ml. In a subset of 50 women, AMH was measured every other year to confirm that declines in log AMH were linear. In the remaining women, AMH was measured two times for each woman to minimize serum use. To minimize the number of zero values, AMH was measured at the earliest available EDIC year for each woman and the EDIC year closest to the 7th year prior to their final menstrual period.

Statistical Analysis

We evaluated the relationships between $_{log}$AMH concentrations (dependent variable) and covariates measured at the same EDIC year as the AMH measurement. HbA1c levels and total daily insulin dose were represented as time-weighted variables or the running arithmetic mean up the point of AMH measurement. The models adjusted for time prior to menopause and used a random intercept for each individual. To minimize overfitting, we used a forward model-building scheme. We also constructed mixed regression models that forced diabetes-specific variables including diabetes duration, intensive vs. conventional therapy, and time-weighted measures of A1c and insulin dose into the model. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Participant characteristics at EDIC baseline are shown in Table 1. AMH concentrations declined with chronologic age to undetectable levels prior to the final menstrual period. For

each year of age, women had an 8.4% reduction (95% CI −14.4%, −3.3%) in their AMH concentrations. Women who used oral contraceptives at the time of AMH assessment had lower AMH concentrations than women who were not currently using oral contraceptives (p=0.046).

When forced into regression models, diabetes-specific variables including randomization arm (p=0.39), diabetes duration (p=0.86), time-weighted A1c (p=0.34), and time-weighted insulin dose (p=0.73) were not associated with AMH concentrations. Similar results were obtained using a forward building model strategy.

Discussion

Higher serum AMH concentrations correspond with higher implantation rates after in-vitro fertilization [6] and older age at menopause [1]. Our results suggest that AMH may be used for these purposes among women with type 1 diabetes. Strengths of this report include analysis of a longitudinal prospective cohort and a well-characterized population regarding glycemic control. All EDIC participants were post-pubertal at the time of initial randomization and this limited our ability to distinguish between separate effects of age of onset vs. duration of diabetes. It is possible that a different pattern of results would be observed among women who remain premenopausal currently. Finally, detailed information on reproductive disorders was not routinely obtained, and thus information on menstrual irregularities, subfecundity, and hyperandrogenism is not known.

In conclusion, among women with type 1 diabetes, AMH concentrations decline in a manner similar to that previously reported in women without diabetes. Thus, it is possible that AMH may be used to risk-stratify women with type 1 diabetes at risk for poor reproductive outcomes in a similar manner as used in healthy populations. Future examinations should assess whether the AMH patterns observed here are confirmed in younger reproductive-age populations, and whether AMH correlates with reproductive outcomes among women with type 1 diabetes.

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References

1. Broer S, Eijkemans M, Scheffer G, van Rooij I, de Vet A, Themmen A, et al. Anti-mullerian hormone predicts menopause: a long-term follow-up study in normoovulatory women. J Clin Endocrinol Metab. 2011; 96:2532–2539. [PubMed: 21613357]

2. Soto N, Iniguez G, Lopez P, Larenas G, Mujica V, Rey R, et al. Anti-Mullerian hormone and inhibin B levels as markers of premature ovarian aging and transition to menopause in type 1 diabetes mellitus. Hum Reprod. 2009; 24:2838–2844. [PubMed: 19643804]

3. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med. 2000; 342:381–389. [PubMed: 10666428]

4. Torrealday S, Pal L. Premature menopause. Endocrinol Metab Clin N Am. 2015; 44:543–557.

5. Kumar A, Kalra B, Patel A, McDavid L, Roudebush W. Development of a second generation anti-Müllerian hormone (AMH) ELISA. J Immunol Methods. 2010; 362:51–59. [PubMed: 20801125]

6. Patrelli T, Gizzo S, Sianesi N, Levati L, Pezzuto A, Ferrari B, et al. Anti-Mullerian hormone serum values and ovarian reserve: can it predict a decrease in fertility after ovarian stimulation by ART cycles? PLoS One. 2012; 7:e44571. [PubMed: 22984527]

Table 1

Characteristics of the study population at EDIC baseline (n=196). The study population consists of women who were naturally menopausal by EDIC follow-up year 17.

Age (years)	39.8 (4.5)
Married (n, %)	133 (73.1%)
Current smoking (n,%)	41 (22.3%)
Body mass index (BMI) (kg/m^2)	26.2 (4.5)
BMI category (kg/m^2) (n, %)	
Normal (<25.0)	91 (49.5%)
Overweight (25.0–29.9)	60 (32.6%)
Obese (30.0)	33 (17.9%)
Age at final menstrual period (years)	50.8 (3.4)
Current oral contraceptive pill use (n, %)	13 (6.7%)
Primary prevention cohort (n,%)	88 (45.4%)
Intensive treatment group (n,%)	114 (58.8%)
Duration of diabetes (years)	14.3 (5.4)
HbA1c (mmol/mol) time weighted DCCT to EDIC baseline	61.7 (9.5)
HbA1c (%) time weighted DCCT to EDIC baseline	7.8 (1.2)
Time-weighted insulin dose (units/kg/day)	0.7 (0.3)

[*]Data are Mean±SD for continuous variables or n (%) for categorical variables