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Serum anti-Müllerian hormone concentration in women with polycystic ovary syndrome and type 1 diabetes mellitus

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ABSTRACT

Purpose. A single prior study conducted in Chilean women has shown that women with type 1 diabetes mellitus (T1DM) and polycystic ovary syndrome (PCOS) have a normal serum anti-Müllerian hormone (AMH) concentrations despite polycystic ovarian morphology. As it is not clear why women with PCOS + T1DM would not have an elevated concentrations of AMH, we hypothesize that women with T1DM and PCOS have a similar hormonal profile and serum AMH levels as is observed in classic PCOS.

Methods. We studied 89 women: 37 with T1DM (16 with PCOS + T1DM, 21 with T1DM/no-PCOS), 36 with PCOS (PCOS) and 16 healthy women (control group) matched for age and body mass index (BMI). A clinical examination, determination of serum AMH and sex hormones, and an ultrasonographic evaluation of the ovaries were performed for all study participants.

Results. Serum AMH concentrations were significantly higher in women with PCOS + T1DM than in those with T1DM/no-PCOS ($p < 0.001$) and was not different between both PCOS groups (PCOS vs PCOS + T1DM). Ovarian volume and ovarian follicle count did not differ between women with PCOS + T1DM and PCOS. The number of ovarian follicles was higher in patients with PCOS + T1DM and PCOS versus the control ($p = 0.007$, $p < 0.001$) and versus cases of T1DM/no-PCOS ($p < 0.001$, $p < 0.001$, respectively). Cross-sectionally, AMH concentrations correlated positively with luteinizing hormone (LH) ($r = 0.4$; $p < 0.001$), testosterone ($r = 0.2$, $p = 0.02$), ovarian volume ($r = 0.4$, $p < 0.001$) and follicle count ($r = 0.7$, $p < 0.001$). In both groups, PCOS + T1DM and PCOS, AMH was related to LH ($r = 0.5$; $p = 0.036$; $r = 0.3$; $p = 0.031$) and to

Abbreviations: AES, Androgen Excess Society; AFC, antral follicle count; AMH, anti-Müllerian hormone; BMI, body mass index; CSII, continuous subcutaneous insulin infusion; E_2, estradiol; FAI, free androgen index; FSH, follicle stimulating hormone; HbA1c, glycosylated hemoglobin; LH, luteinizing hormone; MDI, multiple daily insulin injections; NIH, National Institutes of Health; OGTT, oral glucose tolerance test; O-V, O-FN, O-D, volume, follicle number and follicle diameter summarized for both ovaries; PCOM, polycystic ovarian morphology; PCOS, polycystic ovary syndrome; ROC, receiver operating characteristic; SHBG, sex hormone binding globulin; T, testosterone; T1DM, type 1 diabetes mellitus; TGF β, transforming growth factor β; WHR, waist to hip ratio.

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ovarian follicle number (r = 0.7; p < 0.001; r = 0.4; p = 0.006). In multivariate logistic regression analysis, serum AMH was the only predictor of PCOS in T1DM women (OR = 1.73; 95% CI 1.07-2.79, p = 0.023).

Conclusions. Women with T1DM and PCOS have a similar hormonal profile and serum AMH concentrations as observed in classic PCOS.

1. Introduction

Polycystic ovary syndrome is the most common endocrine disorder among women of reproductive age with a prevalence between 6 and 10% based on the U.S. National Institutes of Health (NIH) criteria and about 15% according to the Rotterdam criteria [1]. Women with PCOS are prone to develop metabolic and reproductive complications. A recently published study showed that the presence of adolescent oligomenorrhea predicts PCOS and metabolic complications (metabolic syndrome, disturbances of glucose metabolism) in the third decade of life [2]. In type 1 diabetes mellitus (T1DM), the prevalence of PCOS is increased and varies depending on the diagnostic criteria used – 18.8% according to the NIH, 36.8% according to the Androgen Excess Society (AES), 14.3% according to the Japanese Society of Obstetrics and Gynecology and 40.5% according to the Rotterdam criteria [3–6].

The reason for the higher prevalence of PCOS among T1DM women is not clearly understood. It has been suggested that exogenous insulin, administered to T1DM women in supraphysiologic doses, enhances LH effect on theca cells, resulting in higher androgen secretion, which increases recruitment and growth of antral follicles [7,8]. According to the published data, the most common phenotype of PCOS in T1DM women is the occurrence of clinical hyperandrogenism with polycystic ovarian morphology (PCOM) or clinical hyperandrogenism with PCOM and oligo-anovulation [3,9]. Hirsutism is usually less severe in these patients, which may be explained by normal sex hormone binding globulin (SHBG) concentrations and, consequently, a lower free androgen index (FAI) [10,11]. Increased ovarian volume and number of follicles have been observed in 54.8% of adult women with T1DM in comparison to only 13% of age-matched healthy controls [4].

A well-recognized biomarker of ovarian reserve is anti-Müllerian hormone (AMH). It is a homodimeric glycoprotein and member of the transforming growth factor β family (TGF-β), which is secreted by the granulosa cells of pre-antral and early antral ovarian follicles. It plays an important role in follicle growth, acting as an inhibitor of primordial follicle recruitment, and decreases sensitivity of granulosa cells to follicle stimulating hormone (FSH) by inhibiting aromatase expression [12]. Serum AMH is 2–4 fold higher in women with PCOS than in healthy women [13]. The serum concentrations of AMH reflect the number of small antral follicles. It has been reported that AMH expression in granulosa cells declines as the diameter of normal antral follicles reaches around 8 mm [14]. Using a serum AMH level of >35 pmol/L (or >5 ng/mL) for the definition of PCOM in the diagnosis of PCOS, as a more sensitive and specific marker than follicle count in ultrasonographic examination, has been proposed. However, it should be mentioned that, so far, there is no standardization for measurement of serum AMH concentrations and the use of AMH as a surrogate for PCOM is under discussion [15,16]. To date, it has been shown that adult women with PCOS and T1DM have normal AMH concentrations, despite an elevated number of 2–9 mm follicles in the ovaries [9]. In one study, prepubertal girls with T1DM were found to exhibit an elevated AMH concentrations, which progressively decreased during puberty and in the Tanner stages 4–5 was lower than that observed in controls [17].

Even though all women with T1DM are treated with exogenous insulin, they do not all fulfill criteria for PCOS. This indicates that there are other factors, beyond the influence of insulin, that are involved in the pathogenesis of PCOS in women with T1DM. So far, there has only been one study published from the Chilean population suggesting that adult women with PCOS + T1DM have normal AMH concentrations and enlarged ovarian follicles, thus a different picture of PCOS in T1DM women. As it is not clear why women with PCOS + T1DM would display different characteristics of PCOS, we hypothesize, in contrary to this previous study, that women with T1DM and PCOS have a similar hormonal profile and serum AMH levels as in classic PCOS.

The aim of our study was to evaluate serum AMH concentrations, hormonal profile and ultrasonographic characteristics of the ovaries in adult Caucasian women with PCOS and T1DM in comparison to nondiabetic women with PCOS, those with T1DM without PCOS and healthy controls matched for BMI and age.

2. Materials and Methods

2.1. Subjects

The study groups consisted of 16 women with PCOS and T1DM (PCOS + T1DM) with a mean diabetes duration of 12.5 years, 21 women with T1DM/no-PCOS with a mean diabetes duration of 8 years, 36 women with PCOS (PCOS) and 16 healthy women (control) matched for age and BMI. The patients with T1DM were recruited from diabetes outpatient clinics in Bialystok and from the Department of Endocrinology, Diabetology and Internal Medicine of the Medical University of Bialystok. The patients with PCOS attended Endocrinology and Gynecology Clinics or the Department of Endocrinology, Diabetology and Internal Medicine of the Medical University of Bialystok. The healthy control subjects were recruited mainly from medical staff and students. Regarding the past reproductive history, 3 women in the T1DM + PCOS group had been pregnant. Two of them had successfully delivered children and 1 had a miscarriage. In the PCOS group, 2 out of 36 women had been pregnant. One of them had delivered a child successfully and the other one had