Polycystic ovary syndrome is a risk factor for diabetes and prediabetes in middle-aged but not elderly women: a long-term population-based follow-up study

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Objective: To study the incidence rate and hazard ratios of diabetes and prediabetes between women with PCOS and healthy subjects.
Design: Prospective population-based study.
Setting: Not applicable.
Patient(s): Women with PCOS (n = 178) and eumenorrheic, nonhirsute, healthy women as controls (n = 1,524), all followed for a median time of 12.9 years.
Intervention(s): None.
Main Outcome Measure(s): Incidence rate and hazard ratios of diabetes and prediabetes between women with PCOS and healthy controls.
Result(s): We analyzed the participants on two pathways. First, for detecting new diabetes mellitus (DM) events, we selected participants who were free of DM at baseline (n = 39). Second, for detecting new pre-DM events, we selected participants who were free of pre-DM and DM at baseline (n = 222) from the baseline population. The rest of the population were included for final analysis to calculate the incidence rates and hazard ratio of diabetes and prediabetes events. The incidence rates of diabetes were 12.9 and 4.9 per 1,000 person-years for PCOS and controls, respectively. This incidence rate in women younger than 40 with and without PCOS was 13.4 and 4.2, respectively. The adjusted hazard ratio (HR) for women ≤40 was 4.9 (95% confidence interval [CI], 2.5–9.3). There were no statistically significant differences between the two groups studied after age 40. The incidence rates of prediabetes were 29.7 and 25.9 per 1,000 person-years for PCOS and healthy women, respectively. The incidence rate in women younger than 40 with and without PCOS was 30.3 and 23.9, respectively. The adjusted HR for women ≤40 years, 1.7 (95% CI, 1.1–2.6), disappeared after age 40.
Conclusion(s): These data suggest that routine screening for diabetes in prevention strategies does not need to be emphasized for PCOS patients at late reproductive ages if they have not been affected by glucose intolerance up to that point. (Fertil Steril® 2017;108: 1078–84. ©2017 by American Society for Reproductive Medicine.)
Key Words: Diabetes, incidence, PCOS, prediabetes, population-based cohort study

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Polycystic ovary syndrome (PCOS) is the one of the most common endocrine disorders among reproductive-aged women (1), with a prevalence of between 5% and 18% reported by recent studies (2). Although the exact underlying mechanism of PCOS remains largely unclear, it is presumed to be complex and multifactorial. The hormone imbalance created by a combination of hyperandrogenism and/or insulin resistance plays an important role in the pathophysiology of PCOS. As such, genetic and environmental factors contributing to hormone disturbances combine with other factors, including obesity, ovarian dysfunction, and hypothalamic pituitary abnormalities, to contribute to the etiology of PCOS (3, 4).

It has been suggested that some diabetes risk factors including insulin resistance, impaired fasting glucose, obesity, and central obesity are more common among women with PCOS than in the general female population. This led to the hypothesis that women with PCOS also have an elevated risk of diabetes mellitus (DM). In this respect, it is well-documented that the prevalence of impaired glucose tolerance and diabetes is increased in women with PCOS compared with healthy controls (5, 6), and this was further confirmed by a meta-analysis showing that women with PCOS had an elevated prevalence of impaired glucose tolerance and DM in studies that both did and did not match for body mass index (BMI) (7).

Despite the extensive data on prevalence, few studies have addressed the incidence of prediabetes and diabetes in this population (8–11). Morgan et al. (11) reported that during a median follow-up period of 4.7 years, women with PCOS had an approximately three times increased risk of type 2 diabetes compared with age- and BMI-matched general population controls (11). Most of their evidence was derived from tertiary-based settings and most likely did not include the milder phenotypes of PCOS (8–11); also their results were not compared with control groups (8) or used heterogeneous diagnostic criteria with a short follow-up period (8, 10). Therefore, we compared the incidence and the risk of diabetes and prediabetes among women with PCOS and healthy controls using data from a long-term, prospective, population-based study.

MATERIALS AND METHODS

The ethics review board of the Research Institute for Endocrine Sciences approved the study proposal, and written informed consent was obtained from all participants. This study was conducted among reproductive-aged women who had participated in the Tehran Lipid and Glucose Study (TLGS), a large-scale, long-term, population-based prospective study initiated in 1998 to explore the prevalence and risk factors of noncommunicable diseases (also known as chronic diseases), which tend to be of long duration and are the result of a combination of genetic, physiologic, environmental, and behaviors factors. The main types of noncommunicable diseases studied are cardiovascular diseases (heart attacks and stroke), cancers, chronic respiratory diseases (chronic obstructive pulmonary disease and asthma), and diabetes. In the TLGS, 15,005 people aged $\geq$3 years were invited to participate. Data on different risk factors for noncommunicable diseases, demographic variables, and reproductive and obstetrics histories were collected during face-to-face interviews conducted every 3 years by trained staff. Every follow-up visit included a comprehensive questionnaire, information on general anthropometrics, a physical examination, and collection of blood samples. A detailed description of the TLGS has been published elsewhere (12).

Study Population

For the present study, after the baseline examination of reproductive-aged women, 18 to 49 years old, who had attended at least one follow-up visit up to March 31, 2010, we excluded the women who had undergone a hysterectomy or bilateral oophorectomy, who were menopausal or pregnant, or who had a history of endocrine disorders, including Cushing's syndrome, congenital adrenal hyperplasia, or androgen-secreting neoplasm, hyperprolactinemia, thyroid disease, or any corticosteroid usage (n = 82). We also excluded women if they had a menstrual irregularity (n = 52) or hyperandrogenism (n = 310). The remaining participants (n = 1,702) were divided into two study groups as follows: women with PCOS (n = 178) and healthy, eumenorrheic, nonhirsute control women (n = 1,524).

We analyzed the remaining participants in two pathways. First, for detecting new DM cases (DM events), we selected participants from the baseline population who were free of diabetes at baseline, and we excluded those with DM (n = 39). Second, for detecting new pre-DM cases (pre-DM event), we selected participants from the baseline population who were free of prediabetes and diabetes at baseline, thus excluding those with DM and pre-DM (n = 222). The rest of population were included for the final analysis to calculate the incidence rates and hazard ratios (HR) of diabetes and prediabetes events (Fig. 1).

Physical and Biochemical Measures

Using a standard questionnaire, face-to-face interviews were conducted with all participants to collect data on their demographic status, smoking, medication, and familial and personal history of diseases. Details of the anthropometrics and blood pressure data as well as biochemical measurements were published previously elsewhere (12, 13). Measurements of dehydroepiandrosterone sulfate (DHEAS), total testosterone (TT), and androstenedione (A4) were obtained by enzyme immunoassay (EIA) (Diagnostic Biochem Canada). Sex hormone-binding globulin (SHBG) was measured by immunoenzymometric assay (Mercodia). All enzyme-linked immunosorbent assay tests were performed using the Sunrise ELISA Reader (Tecan). The free androgen index (FAI) was calculated using the formula [TT (nmol/L) $\times$ 100/SHBG (nmol/L)]. The intra-assay and interassay coefficients of variation for TT were 3.6% and 6.0%, respectively; for DHEAS were 1.9% and 3.2%, respectively; for SHBG were 1.1% and 4.1%, respectively; and for A4 were 2.2% and 3.5%, respectively.

Outcome and Term Measures

We used the U.S. National Institutes of Health consensus criteria for the diagnosis of PCOS, which includes menstrual irregularities due to oligo/anovulation and either biochemical

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