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).

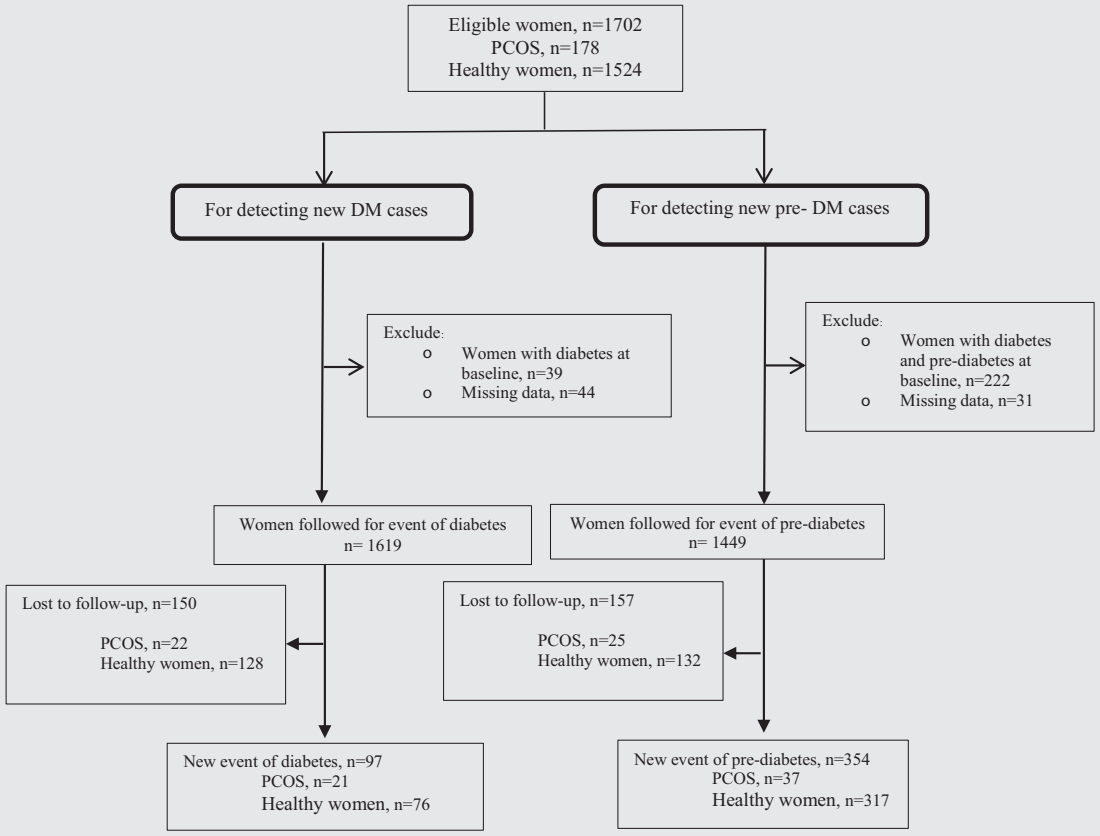
Physical and Biochemical Measures

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

FIGURE 1



Study flowchart. DM = diabetes mellitus; pre-DM = prediabetes mellitus; PCOS = polycystic ovary syndrome.

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or clinical evidence of hyperandrogenism, after exclusion of other known related disorders such as hyperprolactinemia and thyroid or adrenal disorders (14). Oligomenorrhea was assessed using a self-reported, standardized questionnaire. Women were asked about the length and regularity of their menstrual cycles, and those who indicated either regular or irregular menstrual cycles $\geq$34 days or those who had history of eight or fewer menstrual cycles in a year were considered to fulfill the criteria for oligomenorrhea.

The clinical manifestations of hyperandrogenism included hirsutism, acne, and androgenic alopecia. The presence of hirsutism was determined using a standardized modified Ferriman-Gallwey scoring system. Acne was scored based on its number, type, and distribution. The examiner was one of the main investigators who had been trained in a 1-month observer course at the PCOS clinic under supervision of a single endocrinologist.

Biochemical hyperandrogenism was evaluated as an elevated serum level of one or more androgens above the 95th percentile, including TT = 0.89 ng/mL, A4 = 2.9 ng/mL, DHEAS = 179 μg/dL, and FAI = 5.39, calculated from selected healthy, nonhirsute, eumenorrheic TLGS women (13). Physical activity was defined using the Lipid Research Clinic questionnaire (15) and was categorized as light, moderate, or strenuous activity levels.

The occurrence of newly diagnosed diabetes or prediabetes in the women with PCOS and controls was considered the primary outcome and was defined according to the following definitions. Diabetes was defined according to the American Diabetes Association criteria as fasting plasma glucose $\geq$126 mg/dL, or 2-hour plasma glucose $\geq$200 mg/dL, or using medications for a previous diagnosis of DM (16). Prediabetes referred to those with impaired fasting glucose where the fasting plasma glucose levels were 100–125 mg/dL; or impaired glucose tolerance where the 2-hour plasma glucose values in the oral glucose tolerance test (OGTT) were 140–199 mg/dL (16). The frequency of screening for each event was every 3 years.

Statistical Analysis

Continuous variables were assessed for normality using the one-sample Kolmogorov-Smirnoff test and are presented as mean ($\pm$standard deviation) and/or median and interquartile ranges, as appropriate. Categorical variables are expressed as percentages. The baseline characteristics were compared between the two groups using independent *t* tests, chi-square test, and Mann-Whitney *U* test based on specific normality distribution.

The event date for the incidence cases for both outcomes was defined as the midtime between the date of the follow-up visit at which the outcome was first diagnosed and the most

recent follow-up visit before the diagnosis; for those with a negative event (censored subjects), the time was the interval between the first and the last observation dates. The incidence density of each outcome was calculated per 1,000 person-years of follow up among the women with PCOS and the controls. The cumulative incidence of each outcome was estimated by the Kaplan-Meier method and was compared between cases and controls by the log-rank statistic.

Univariate and multiple Cox proportional hazards regression with age as the time scale were used to estimate the adjusted HR of developing outcomes in relation to PCOS. In this model, the baseline hazard assumes that each subject's observed risk period started at birth, and it was not adjusted for age truncation. The proportional hazards assumption of the univariate and multivariate Cox models were assessed by the Schoenfeld residual test and graphically by log (log); neither of them have not confirmed this assumption (Fig. 2A and B). Hence, extended Cox proportional hazards regression with age as the time scale was used. These hazard ratios were computed separately for $\leq$40 years and >40 years with heavyside functions, a model that allows step functions and thus provides constant hazard ratios within different age intervals. These ages were selected based on an examination of the cumulative hazard curves. In this respect, the cumulative hazard curve showed that the difference in hazards between the women with PCOS and the healthy women was diluted in diabetes and had a crossing pattern in prediabetes after the age of 40.

Baseline fasting blood sugar and BMI, physical activity, and family history of diabetes were evaluated for confounding factors. All statistical tests were two-tailed, and $P<.05$ was considered statistically significant. The Statistical Package for Social Sciences (SPSS version 16; SPSS Inc.) and STATA software (version 12; STATA Inc.) were used for data analysis.

RESULTS

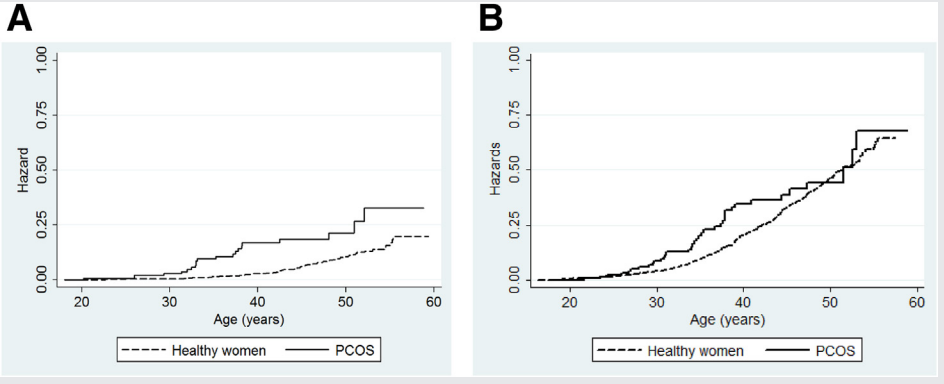
The characteristics of the study groups at the beginning of the study are presented in Table 1. Compared with the healthy controls, the women with PCOS were more likely to be younger: 26.4 ± 8.5 years versus 28.9 ± 8.6 years ($P=.001$). The mean BMI and waist circumference of the women in the PCOS and healthy groups were similar: 26.1 ± 5.1 versus 25.4 ± 4.7 ($P=.062$) and 82.8 ± 12.5 versus 81.7 ± 11.7 ($P=.281$), respectively. Moreover, there were no statistically significant differences between the two groups in terms of waist–hip ratio, waist-to-height ratio, lipids, blood pressure, or glucose profile. At the initiation of the study, the prevalence of the comorbidities of prediabetes and diabetes was similar between the women with PCOS and the healthy women.

The median follow-up time for the current analysis was 12.9 years (range: 1.98–15.79 years). The cumulative percentage of follow-up years is presented in Supplemental Table 1 (available online). The number of women in the prediabetes and diabetes group based on fasting criteria, glucose challenge, and medication is presented in Supplemental Table 2 (available online).

Among the 1,619 women with normal or impaired glucose levels at baseline, 150 women (22 PCOS and 128 healthy) were lost to follow up, and 21 PCOS cases (12.9 per 1,000 person years; 95% CI, 8.4–19.7) and 76 healthy women (4.9 per 1,000 person years; 95% CI, 3.9–6.2; $P=.0004$) developed DM over 16,925.3 person-years of follow up. However, the incidence rate of diabetes per 1,000 person years among the women aged $\leq$40 years with PCOS or healthy controls was 13.4 (95% CI, 8.6–20.8) and 4.2 (95% CI, 3.2–5.4), respectively ($P=.0001$). Also, from among 1,449 participants who were free of prediabetes and diabetes at baseline, 157 women (25 PCOS and 132 healthy women) were lost to follow up, and 37 PCOS cases (29.7 per 1,000 person years; 95% CI, 21.5–41) and 317 healthy women (25.9 per 1,000 person years; 95% CI, 23.2–29; $P=.433$) developed pre-DM. In this respect, the incidence rate of pre-DM per 1,000 person years among women aged $\leq$40 years with PCOS or healthy controls was 29.7 (95% CI, 21.5–41) and 25.9 (95% CI, 23.2–29), respectively ($P=.194$).

Table 2 contains the estimated unadjusted and adjusted HR for developing DM and pre-DM by PCOS status. Using the extended Cox model, women aged $\leq$40 years with

FIGURE 2



Kaplan-Meier hazard estimates in incidence rates in women with polycystic ovary syndrome and healthy women. Age is used as the time scale. (**A**) Women with diabetes. (Log-rank test, $P=.001$.) (**B**) Women with prediabetes. (Log-rank test, $P=.057$.)

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TABLE 1

Baseline characteristics of case and control groups.

Characteristic	PCOS (n = 178)	Control (n = 1,524)	*P* value
Age (y)	26.4 (8.5)	28.9 (8.6)	.001[a]
BMI (kg/m^2)	26.1 (5.1)	25.4 (4.7)	.062
WC (cm)	82.8 (12.5)	81.7 (11.7)	.281
WHR	0.80 (0.07)	0.80 (0.07)	.802
WHtR	0.52 (0.08)	0.51 (0.07)	.319
SBP (mm Hg)	107.5 (11.7)	108 (12.1)	.272
DBP (mm Hg)	73.1 (9.4)	72.9 (9.2)	.812
TC (mg/dL)	189.9 (44.1)	186.8 (40.04)	.337
TG (mg/dL)[b]	106 (78.7–160.2)	100.0 (73–149)	.75
HDL-C (mg/dL)	44.5 (11.2)	44.4 (10.5)	.975
LDL-C (mg/dL)	119.4 (36.7)	118.2 (34.4)	.667
FBS (mg/dL)	87.2 (9.1)	88.2 (17.2)	.217
BS-2HPP (mg/dL)	107.8 (30.7)	106.3 (35.0)	.617
Prediabetes[c]	22 (12.4)	161 (10.5)	.447
Diabetes[c]	2 (1.1)	37 (2.4)	.084
Family history of diabetes[c]	51 (28.6)	366 (24.01)	.167
Physical activity[c]			.339
Low	92 (51.6)	822 (53.9)	
Moderate	28 (15.7)	248 (16.2)	
High	58 (32.5)	454 (29.7)	

Note: Data presented as mean (±standard deviation) unless otherwise indicated. Independent *t* tests, chi-square test, and Mann-Whitney test were used as appropriate. BMI = body mass index; BS-2HPP = 2-hour postprandial blood sugar; DBP = diastolic blood pressure; FBS = fasting blood sugar; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride; WC = waist circumference; WHR = waist-to-hip ratio; WHtR = waist-to-height ratio.
[a] Statistically significant result ($P<.05$).
[b] Median, 25%–75%.
[c] Number and percentage.

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PCOS had a higher risk of developing DM in the unadjusted model (unadjusted HR 6.6; 95% CI, 3.6–12.2; $P=.001$), even after multiple adjustments for potential confounders related to DM (multiple adjusted HR 4.9; 95% CI, 2.5–9.3; $P=.001$). But there were no statistically significant differences between two study groups after the age of 40.

Regarding pre-DM, women aged ≤40 years with PCOS had a higher risk of developing pre-DM in the unadjusted model (unadjusted HR 1.9; 95% CI, 1.3–2.8; $P=.001$), even after multiple adjustments for the potential confounders related to DM (multiple adjusted HR 1.7; 95% CI, 1.1–2.6; $P=.005$). But there were no statistically significant differences between two study groups after the age of 40.

DISCUSSION

In our long-term, prospective, population-based study to evaluate the incidence rate and risk of pre-DM and diabetes outcomes comparing women with PCOS and healthy controls, the findings confirm that the risk of developing diabetes and prediabetes in young women with PCOS is 4.9 and 1.7 times higher, respectively, than in the general female population after adjustment for potential related confounders. In contrast, those hazard differences between PCOS and controls disappeared in their late reproductive years, although studies with larger sample sizes are still recommended to show whether these risks reemerge later in life.

These findings also suggest that reproductive-aged women with PCOS are more clinically affected by glucose intolerance and subsequent diabetes. However, if these women do not receive a diagnosis of pre-DM or DM, the risk of ongoing pre-DM and subsequent DM in later life may be the same as for women who do not have PCOS.

This result is partly in accordance with the limited prospective studies that have evaluated the incidence of type 2 diabetes in women with PCOS (8–11,17). Three small studies have investigated the conversion rate of normal glucose tolerance to type II diabetes, and showed that conversion is accelerated in women with PCOS (8–10). In an age- and BMI-matched controlled study of 21,734 women with PCOS followed for a mean of 4.7 years, Morgan et al (11) found a three time greater, statistically significantly higher risk of type 2 diabetes among women with PCOS compared with controls (11). However, because of the short-term follow-up period in these studies, they have limited power to identify the risk difference for early and late reproductive ages.

In a 21-year, age-matched, controlled, follow-up study (up to the late postmenopausal period), Schmidt et al. (18) reported that women with PCOS have no increased risk of acquiring diabetes and that the statistically significant difference in the prevalence of diabetes in women with PCOS compared with healthy controls disappeared during the postmenopausal period (18). Their results are in accordance our findings, but they reported on the prevalence of DM and we assessed the incidence, so our results are not directly comparable.

The available evidence supporting the statistically significantly increased incidence rate of diabetes among women

TABLE 2

Unadjusted and multiple adjusted hazard ratios of incident outcomes by PCOS status.

	PCOS (n = 178)		Healthy women (n = 1,524)		Unadjusted		Multiple adjusted	
Outcome	Yes	No	Yes	No	HR (95% CI)	*P* value	HR (95% CI)[a]	*P* value
Diabetes	21	132	76	1,240				
≤40 y	17	78	27	571	6.6 (3.6–12.2)	.001	4.9 (2.5–9.3)	.001
>40 y	4	54	49	669	1.0 (0.3–2.8)	.953	0.8 (0.3–2.3)	.737
Prediabetes	37	92	317	846				
≤40 y	30	59	175	472	1.9 (1.3–2.8)	.001	1.7 (1.1–2.6)	.005
>40 y	7	33	142	374	0.6 (0.1–1.35)	.240	0.5 (0.2–1.2)	.174

Note: Extended Cox proportional hazards regression with age as the time scale were used for analysis. CI = confidence interval; HR = hazard ratio; PCOS = polycystic ovary syndrome.
[a] Baseline fasting blood sugar and body mass index, physical activity, and family history of diabetes were evaluated for confounding.

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with PCOS is insufficient, but it may be explained by the following mechanisms. The majority of women with PCOS have defects in insulin sensitivity secondary to the postbinding defect in insulin signaling in target tissues (19–21), as well as defects in insulin secretion secondary to pancreatic β-cell secretory dysfunction (20), which contribute to insulin resistance, compensatory hyperinsulinemia, and impaired glucose tolerance/diabetes. There is also increasing evidence that the hyperandrogenemia in women with PCOS could augment glucose intolerance by stimulating chronic low-grade inflammation independent of obesity (22, 23). In addition, the higher prevalence of obesity and android obesity among women with PCOS (24) could play a synergistic role in insulin resistance and hyperglycemia (25). Furthermore, there is emerging evidence suggesting that "fetal reprogramming" may be one of the underlying pathogenic mechanisms of insulin resistance in PCOS. Accordingly, rat experiments have shown that prenatal exposure to androgens during the embryonic period could induce PCOS and metabolic disturbances in PCOS and promote their aggravation during adulthood (26, 27).

However, the findings from our long-term prospective study show that the risk of DM and pre-DM in women with PCOS may be ameliorated over time. It is assumed that these women are more likely to modify their lifestyle with various interventions, including diet and exercise, metformin therapy, and bariatric surgery for highly selected individuals. Women without PCOS also may develop with more central obesity and obesity, which may diminish any difference in glucose intolerance between the two groups. Thus, the risk of dysglycemia in women with PCOS in later life may be lower than initially anticipated (28, 29).

In our study, all the women were untreated at baseline although it is standard protocol to counsel PCOS patients in exercise and lifestyle modification, which may improve their insulin sensitivity. However, adjustments in lifestyle are hard to maintain because their overall impact may decline after a few years (30). Moreover, women with PCOS experience longer reproductive life spans because of their later age at menopause and lower conception rates, which leads to extended exposure to endogenous estrogen and may possibly affect the risk of dysglycemia (31, 32).

In addition, it has been suggested that an important factor in assessing cardiometabolic risk for women with PCOS is the PCOS phenotype (33). Women with the severe phenotype of PCOS have more menstrual irregularity, hyperandrogenism, total and central obesity, and insulin resistance, which increases their risk for developing diabetes as compared with women who have milder phenotypes of PCOS. The population-based setting of our study allowed us to recruit women with the milder phenotypes of PCOS, which may have a weaker association with insulin resistance.

It is well documented that the comorbidities associated with PCOS are age dependent. That is, the serum concentration of androgen in women may decrease over time due to ovarian aging or reduced secretion by the adrenal glands. Similarly, serum insulin levels decline with age in women with PCOS (34), which may be associated with a decrease in insulin resistance and the incidence of diabetes.

Finally, it should be noted that most of the evidence that supports the increased prevalence of dysglycemia among women with PCOS has been derived from cross-sectional, observational, retrospective, or short-term prospective studies (35, 36) that had small sample sizes (18), no non-PCOS control groups (37), inappropriate diagnostic criteria (17), or inappropriate control of confounders (38), or clinical studies that may have recruited women with severe phenotypes of PCOS who were referred for treatment (39).

Our study has a number of strengths. It was a long-term, prospective, population-based study of a cohort of women with PCOS and controls, possibly demonstrating more accurate results and facilitating the assessment the incidence of DM and pre-DM across time. Moreover, as an ongoing study, it allowed us to monitor the participants for further events. Using the standardized and precise definition of PCOS, the presence of the non-PCOS control group and adjustments for potential related confounders for each outcome were other strengths of our study that helped us achieve valuable results. Also, we used both of impaired fasting glucose and impaired glucose tolerance to define pre-DM and diabetes, which could reliably select those patients. In addition, the population-based setting of the study helped us recruit the milder phenotype of PCOS, which has increased our ability to generalize the results to general female populations.

Nevertheless, our study also had its limitations. We defined PCOS based on the narrower U.S. National Institutes of Health criteria as opposed to the new Rotterdam criteria for PCOS, and this potentially limited the diagnosis of PCOS. It has been argued that these different definitions may not have similar risks of long-term metabolic morbidities (40). Also, we did not compare the different PCOS phenotypes, which may have potentially affected our results. In addition, despite their importance we did not measure lifestyle modifications such as changes in dietary habits, which possibly had an effect on adverse PCOS outcomes, but assessing nutritional status with adequate precision can be difficult.

CONCLUSIONS

In our large, population-based study with a long-term follow-up period, the incidence and risk of diabetes and pre-DM were higher than in the general female population, although these risks disappeared in the late reproductive period. The women with PCOS may not be at additional risk for ongoing pre-DM and DM as compared with the non-POCS population. These data suggest that routine screening for diabetes does not need to be emphasized in prevention strategies for PCOS patients at late reproductive ages if they have not already experienced glucose intolerance during this period.

REFERENCES

1. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril 2016;106:6–15.
2. Tehrani FR, Simbar M, Tohidi M, Hosseinpanah F, Azizi F. The prevalence of polycystic ovary syndrome in a community sample of Iranian population: Iranian PCOS prevalence study. Reprod Biol Endocrinol 2011;9:39.
3. Behboudi-Gandevani S, Ramezani Tehrani F, Rostami Dovom M, Farahmand M, Bahri Khomami M, Noroozzadeh M, et al. Insulin resistance

in obesity and polycystic ovary syndrome: systematic review and meta-analysis of observational studies. Gynecol Endocrinol 2016;32:343–53.
4. Merkin SS, Phy JL, Sites CK, Yang D. Environmental determinants of polycystic ovary syndrome. Fertil Steril 2016;106:16–24.
5. Vrbikova J, Cifkova R, Jirkovska A, Lanska V, Platilova H, Zamrazil V, et al. Cardiovascular risk factors in young Czech females with polycystic ovary syndrome. Hum Reprod 2003;18:980–4.
6. Yildiz BO, Bozdag G, Yapici Z, Esinler I, Yarali H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. Hum Reprod 2012;27:3067–73.
7. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 2010;16:347–63.
8. Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care 1999;22:141–6.
9. Norman RJ, Masters L, Milner CR, Wang JX, Davies MJ. Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. Hum Reprod 2001;16:1995–8.
10. Legro RS, Gnatuk CL, Kunselman AR, Dunaif A. Changes in glucose tolerance over time in women with polycystic ovary syndrome: a controlled study. J Clin Endocrinol Metab 2005;90:3236–42.
11. Morgan CL, Jenkins-Jones S, Currie CJ, Rees DA. Evaluation of adverse outcome in young women with polycystic ovary syndrome versus matched, reference controls: a retrospective, observational study. J Clin Endocrinol Metab 2012;97:3251–60.
12. Azizi F, Ghanbarian A, Momenan AA, Hadaegh F, Mirmiran P, Hedayati M, et al, Tehran Lipid and Glucose Study Group. Prevention of non-communicable disease in a population in nutrition transition: Tehran Lipid and Glucose Study phase II. Trials 2009;10:5.
13. Tehrani FR, Rashidi H, Azizi F. The prevalence of idiopathic hirsutism and polycystic ovary syndrome in the Tehran Lipid and Glucose Study. Reprod Biol Endocrinol 2011;9:144.
14. Zawadzki J, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine FP, Merriam GR, editors. Polycystic ovary syndrome. Boston: Blackwell Scientific; 1992:377–84.
15. Ainsworth BE, Jacobs DR Jr, Leon AS. Validity and reliability of self-reported physical activity status: the Lipid Research Clinics questionnaire. Med Sci Sports Exerc 1993;25:92–8.
16. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2013;36(Suppl):S67–74.
17. Boudreaux MY, Talbott EO, Kip KE, Brooks MM, Witchel SF. Risk of T2DM and impaired fasting glucose among PCOS subjects: results of an 8-year follow-up. Curr Diab Rep 2006;6:77–83.
18. Schmidt J, Landin-Wilhelmsen K, Brännström M, Dahlgren E. Cardiovascular disease and risk factors in PCOS women of postmenopausal age: a 21-year controlled follow-up study. J Clin Endocrinol Metab 2011;96:3794–803.
19. Brennan K, Huang A, Azziz R. Dehydroepiandrosterone sulfate and insulin resistance in patients with polycystic ovary syndrome. Fertil Steril 2009;91:1848–52.
20. Goodarzi MO, Korenman SG. The importance of insulin resistance in polycystic ovary syndrome. Fertil Steril 2003;80:255–8.
21. Cho LW, Randeva HS, Atkin SL. Cardiometabolic aspects of polycystic ovarian syndrome. Vasc Health Risk Manag 2007;3:55–63.
22. Ding E, Song Y, Manson J, Rifai N, Buring J, Liu S. Plasma sex steroid hormones and risk of developing type 2 diabetes in women: a prospective study. Diabetologia 2007;50:2076–84.
23. Duleba AJ, Dokras A. Is PCOS an inflammatory process? Fertil Steril 2012;97:7–12.
24. Escobar-Morreale HF, Luque-Ramírez M, González F. Circulating inflammatory markers in polycystic ovary syndrome: a systematic review and metaanalysis. Fertil Steril 2011;95, 1048–58.e1–2.
25. Carmina E, Bucchieri S, Esposito A, Del Puente A, Mansueto P, Orio F, et al. Abdominal fat quantity and distribution in women with polycystic ovary syndrome and extent of its relation to insulin resistance. J Clin Endocrinol Metab 2007;92:2500–5.
26. Tehrani FR, Noroozzadeh M, Zahediasl S, Piryaei A, Hashemi S, Azizi F. The time of prenatal androgen exposure affects development of polycystic ovary syndrome-like phenotype in adulthood in female rats. Int J Endocrinol Metab 2014;12:e16502.
27. Noroozzadeh M, Tehrani FR, Sedaghat K, Godini A, Azizi F. The impact of prenatal exposure to a single dose of testosterone on insulin resistance, glucose tolerance and lipid profile of female rat's offspring in adulthood. J Endocrinol Invest 2015;38:489–95.
28. Tomlinson J, Millward A, Stenhouse E, Pinkney J. Type 2 diabetes and cardiovascular disease in polycystic ovary syndrome: what are the risks and can they be reduced? Diabet Med 2010;27:498–515.
29. Tehrani FR, Montazeri SA, Hosseinpanah F, Cheraghi L, Erfani H, Tohidi M, et al. Trend of cardio-metabolic risk factors in polycystic ovary syndrome: A population-based prospective cohort study. PLoS One 2015;10:e0137609.
30. Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. Fertil Steril 2009;92:1966–82.
31. Heianza Y, Arase Y, Kodama S, Hsieh SD, Tsuji H, Saito K, et al. Effect of postmenopausal status and age at menopause on type 2 diabetes and prediabetes in Japanese individuals: Toranomon Hospital Health Management Center Study 17 (TOPICS 17). Diabetes Care 2013;36:4007–14.
32. Tehrani FR, Solaymani-Dodaran M, Hedayati M, Azizi F. Is polycystic ovary syndrome an exception for reproductive aging? Hum Reprod 2010;25:1775–81.
33. Moran LJ, Norman RJ, Teede HJ. Metabolic risk in PCOS: phenotype and adiposity impact. Trends Endocrinol Metab 2015;26:136–43.
34. Brown ZA, Louwers YV, Fong SL, Valkenburg O, Birnie E, de Jong FH, et al. The phenotype of polycystic ovary syndrome ameliorates with aging. Fertil Steril 2011;96:1259–65.
35. Bhattacharya SM. Polycystic ovary syndrome and abnormalities in glucose tolerance. Int J Gynaecol Obstet 2009;105:29–31.
36. Cheung L, Ma R, Lam P, Lok I, Haines C, So W, et al. Cardiovascular risks and metabolic syndrome in Hong Kong Chinese women with polycystic ovary syndrome. Hum Reprod 2008;23:1431–8.
37. Gambineri A, Patton L, Altieri P, Pagotto U, Pizzi C, Manzoli L, et al. Polycystic ovary syndrome is a risk factor for type 2 diabetes. Diabetes 2012;61:2369–74.
38. Stepto NK, Cassar S, Joham AE, Hutchison SK, Harrison CL, Goldstein RF, et al. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic–hyperinsulaemic clamp. Hum Reprod 2013;28:777–84.
39. Lankarani M, Valizadeh N, Heshmat R, Peimani M, Sohrabvand F. Evaluation of insulin resistance and metabolic syndrome in patients with polycystic ovary syndrome. Gynecol Endocrinol 2009;25:504–7.
40. Roe AH, Dokras A. The diagnosis of polycystic ovary syndrome in adolescents. Rev Obstet Gynecol 2011;4:45–51.