ORIGINAL ARTICLE: REPRODUCTIVE ENDOCRINOLOGY

Risk of type 2 diabetes is increased in nonobese women with polycystic ovary syndrome: the National Health Insurance Service-National Sample Cohort Study

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Objective: To investigate the relationship between polycystic ovary syndrome (PCOS) and type 2 diabetes mellitus (T2DM) in Korean women.
Design: Longitudinal case-control study.
Setting: Not applicable.
Patient(s): PCOS patients aged 15 to 44 years (n = 1,136) and control individuals (n = 5,675), matched 1:5 by age group, income, and region of residence.
Intervention(s): Not applicable.
Main Outcome Measure(s): The occurrence of T2DM.
Result(s): In the PCOS and control groups, 15.7% and 14.4%, respectively, were obese (body mass index $\geq$25 kg/m^2). The incidence rate of T2DM was 15.84/1,000 and 5.80/1,000 person-years in the PCOS and control groups, respectively. The unadjusted hazard ratio (HR) of T2DM in women with PCOS was 2.6-fold higher than that in control individuals. Women with PCOS still had a higher HR of T2DM than did control individuals after adjustment for body mass index, family history of T2DM, physical exercise level, and total cholesterol. PCOS was significantly associated with T2DM in women both with and without obesity.
Conclusion(s): PCOS is independently associated with an increased incidence of T2DM in both obese and nonobese women. Screening for T2DM should be considered for both obese and nonobese women with PCOS in Korea. (Fertil Steril® 2020;■:■–■. ©2020 by American Society for Reproductive Medicine.)
Key Words: Diabetes mellitus, East Asia, insulin resistance, obesity, polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age, affecting 8%–13% of this population (1). Insulin resistance, together with hyperandrogenism, has been assumed to play a major role in the pathophysiology of PCOS (2). Hyperinsulinemia in PCOS, a compensatory strategy in the face of insulin resistance, could contribute to hyperandrogenism in PCOS by stimulating ovarian androgen production and decreasing serum sex hormone–binding globulin concentrations (3). The excessive androgen production associated with PCOS could contribute to an increase in visceral fat, decreased lipolysis in subcutaneous fat, and reduced insulin sensitivity in adipose tissue and skeletal muscle (4).

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The major consequence of these metabolic abnormalities, namely, increased peripheral insulin resistance with secondary abnormal insulin secretion and hyperinsulinemia, is a high and earlier incidence of impaired glucose tolerance and type 2 diabetes mellitus (5, 6). However, further research is required to elucidate the exact physiologic mechanisms underlying these relationships.

The increasing global prevalence of metabolic disorders has led to the association between PCOS and type 2 diabetes mellitus receiving particular attention in recent years (7, 8). Several epidemiologic studies have indicated that women with PCOS have an increased risk of type 2 diabetes mellitus, although most of these studies are limited by small sample sizes, cross-sectional design, nonmatched or unmatched control groups, or a clinic-based study population (5, 9–12). Only a few longitudinal community-based studies have investigated the association between PCOS and type 2 diabetes mellitus or other metabolic complications (13, 14). A recent meta-analysis reported that the incidence rate of type 2 diabetes mellitus was three-fold higher among women with PCOS than among women without PCOS (15). However, most of these studies were conducted in Western populations, mainly comprising white women (15). There is considerable ethnic variation in the manifestation of PCOS, and previous studies have reported a low body mass index (BMI) and mild hirsutism in East Asian women with PCOS compared with Western or South Asian women with PCOS (16, 17). The metabolic features of PCOS, including the risk of type 2 diabetes mellitus, in East Asian women, especially those without obesity, have not been clearly established.

The purpose of this study was therefore to evaluate the association between PCOS and type 2 diabetes mellitus in Korean women of reproductive age and to assess the effect of body weight on this association using nationwide population-based data.

MATERIALS AND METHODS

A Nationwide Representative Sample Cohort

We used the National Health Insurance Service–National Sample Cohort (NHIS-NSC) obtained from the Korean National Health Insurance Service (K-NHIS), the single medical insurer in the Republic of Korea, which is managed by the government. The majority of Korean people (97.1%) are mandatory subscribers, and the database is freely accessible to medical researchers. The NHIS-NSC was created and released by the K-NHIS in 2014 and covers health insurance claims filed between January 1, 2002, and December 31, 2013. Of the eligible population in 2002 (46,605,433 target individuals of 47,851,928 individuals constituting the entire Korean population), 1,025,340 participants (2.2% of the target population) were randomly selected by use of a systematic stratified random sampling method and were followed up until 2013 (for 12 years). The NHIS-NSC database contains demographic data, diagnosis codes, use of inpatient and outpatient services, pharmacy dispensing claims, and mortality data. More details of the cohort, including the sampling method, are described elsewhere (18). Our study protocols were approved by the official review committee of the Korean government and by the Institutional Review Board (IRB) of Korea University Anam Hospital (IRB No: 2020AN0298).

Study Population

The diagnosis of PCOS requires an inpatient or outpatient record of the International Classification of Disease, tenth revision (ICD-10) code E282 in the database. The Rotterdam 2003 criteria were used for diagnosing PCOS in South Korea during the studied period (19). We assessed the annual incidence of PCOS among women of reproductive age (15–44 years) in the entire NHIS-NSC database. We then analyzed the risk of type 2 diabetes mellitus using the following inclusion criteria: women receiving new diagnoses of PCOS between January 2003 and December 2012; age 15–44 years at the time of PCOS diagnosis; and data available on BMI, family history of type 2 diabetes mellitus, level of physical exercise, and serum total cholesterol levels from routine health checkups. Women who had received diagnoses of type 2 diabetes mellitus (ICD-10 code E11) before PCOS diagnosis were excluded. These PCOS patients were matched 1:5 with women in the cohort who had no PCOS diagnosis from 2003 to 2012 (the control group). Matching was based on age group, income group, and region of residence. The following age groups were defined: 15–19, 20–24, 25–29, 30–34, 35–39, and 40–44 years old. The income groups were categorized into 11 classes: one health aid class (class 0) and 10 employment health insurance classes divided by income quintile: class 1 (lowest income) to class 11 (highest income). Region of residence was divided into 16 areas on the basis of administrative districts. We regrouped the regions into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas. To prevent selection bias when choosing matched participants, potential control group women were sorted by use of a random number order and then selected from top to bottom. In the end, the 1:5 matching resulted in the inclusion of 1,136 PCOS patients and 5,675 control participants (Supplemental Figure 1).

Study Endpoint and Other Variables

The participants' medical histories were evaluated according to ICD-10 codes. The primary endpoint of this study was the occurrence of type 2 diabetes mellitus (ICD-10 code E11) in the PCOS and control groups. During the studied period (2003–2012), in South Korea, based on the diagnostic criteria suggested by the American Diabetes Association in 2003, patients with abnormalities in fasting glucose and oral glucose tolerance test results received diagnoses of diabetes (20). Hemoglobin A1c was used as a diagnostic method for identifying type 2 diabetes mellitus from 2009 onward (21). The following variables were compared between the PCOS and control groups: age, BMI, total cholesterol, family history of type 2 diabetes mellitus, physical exercise level, history of hypertension (ICD-10 codes I10 and I15), waist circumference, blood pressure, serum glucose level, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL)

cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transferase (GGT). BMI was categorized into four groups based on the Asia-Pacific cutoff points: underweight (<18.5 kg/m^2), normal weight (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2), and obese (≥25 kg/m^2). For statistical analyses, those in the underweight category were combined with those in the normal weight category owing to the small number of underweight women in this study. Physical exercise level was categorized according to the frequency of activity lasting at least 20 minutes per day as follows: none, one to four times per week, and more than five times per week.

Statistical Analysis

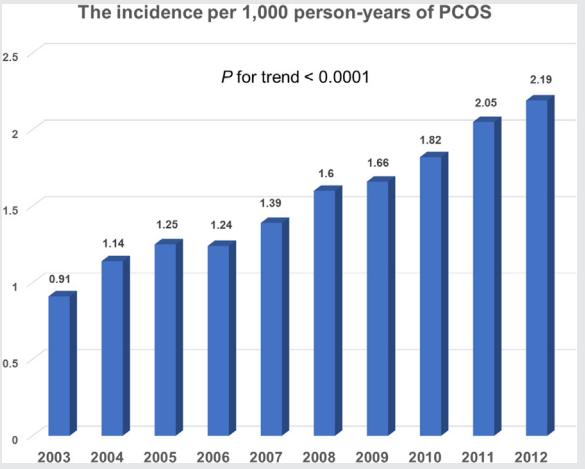
The incidence per 1,000 person-years was calculated for each year. The incidence rate for the study outcome (number of type 2 diabetes mellitus events per 1,000 person-year) was calculated from the PCOS and control groups and their subgroups at the BMI level. The incidence rate ratio for study outcome (type 2 diabetes mellitus) was computed for each BMI subgroup. To balance baseline covariates such as patient age group, income group, and region of residence between the PCOS and control groups, 1:5 greedy matching (five controls per one case) was performed by use of a nearest-neighbor algorithm. Greedy matching is a valid matching method used in observational studies; it sorts the cases and controls randomly and matches each case repeatedly with the closest controls until all cases are matched. This method has been previously described in detail (22). Continuous variables were indicated as means ± standard deviation and compared with the paired *t*-test. Categoric variables were presented as number with percentages and compared with the McNemar test. In the matched data, stratified Cox proportional hazards regression analyses for the covariates of BMI, total cholesterol, family history of type 2 diabetes mellitus, and physical exercise level were performed to evaluate the relative hazard of events between the PCOS and control groups. Kaplan-Meier curves for type 2 diabetes mellitus event were used to compare survival time between the PCOS and control groups and were tested by use of the log-rank test. For subgroup analyses, we divided the participants into obese (BMI ≥25 kg/m^2) and nonobese (BMI <25 kg/m^2) groups, and the same stratified multivariate Cox regression analyses were performed within each subgroup. Two-sided $P<.05$ was considered statistically significant. All analyses were performed with SAS version 4 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

The incidence per 1,000 person-years of newly diagnosed PCOS among the cohort population showed an increasing trend from 2003 to 2012 (P for trend <.0001) (Figure 1). Standardized difference between the PCOS and control groups after 1:5 matching for age, income, and region of residence showed that the two groups were matched appropriately (P=.0137, .0028, and .0005, respectively). The comparison of baseline characteristics between the two groups is presented in Table 1. Mean BMI, prevalence of obesity, serum total cholesterol level, physical exercise levels, body weight, waist circumference, diastolic blood pressure, fasting glucose level, LDL cholesterol, triglycerides, AST, ALT, and GGT were all significantly higher in the PCOS group than in the control group. HDL cholesterol was lower in the PCOS group than in the control group. Over a follow-up time of 144,831,677 person-years, the incidence rate of type 2 diabetes mellitus was 15.84/1,000 and 5.80/1,000 person-years (P<.001) in the PCOS and control groups, respectively.

The unadjusted hazard ratio (HR) of type 2 diabetes mellitus in women with PCOS was 2.594 (95% confidence interval [CI] 1.98–3.39) as compared with women without PCOS. The results of multivariate Cox regression analysis are presented in Table 2. After adjustment for confounding factors (BMI, family history of diabetes mellitus, physical exercise levels, and total cholesterol level), women with PCOS were found to have a higher HR (2.355 [95% CI 1.80–3.08]) of type 2 diabetes mellitus as compared with women without PCOS. The Kaplan-Meier survival curve shows the difference in the HR of type 2 diabetes mellitus between the PCOS and control group (Figure 2). Subgroup analysis showed that PCOS was significantly associated with an increased HR for type 2 diabetes mellitus in both women with and without obesity (Table 2). After adjustment for a family history of diabetes mellitus, physical exercise levels, and total cholesterol levels, obese women with PCOS had a higher HR for type 2 diabetes mellitus than did obese women without PCOS and nonobese women without PCOS (2.847 [95% CI 1.59–5.11] and 4.821 [95% CI 3.08–7.54], respectively). After adjustment for the same variables, nonobese women with PCOS also had a higher HR (2.334 [95% CI 1.72–3.18]) for type 2 diabetes mellitus than did nonobese women without PCOS.

FIGURE 1



The incidence per 1,000 person-years of PCOS among women aged 15-44 years in the Korean National Health Insurance Service sample cohort from 2003 to 2012. PCOS = polycystic ovary syndrome.

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TABLE 1

Comparison of the baseline characteristics and incidence of type 2 diabetes mellitus between polycystic ovary syndrome and control groups after 1:5 matching by age group, income group, and region of residence in the Korean National Health Insurance Service sample cohort from 2003 to 2012.

Characteristic	PCOS (n = 1,136)	Control (n = 5,675)	*P* value
Follow-up (y), median (IQR)	4.45 (2.35, 6.21)	4.61 (2.50, 6.50)	
Incidence per 1,000 person-years of type 2 DM (%)	15.84	5.80	<.0001
BMI (kg/m^2)	21.79 ± 3.9	21.06 ± 3.0	<.0001[a]
BMI group (%)			<.0001[b]
Normal	72.0	80.1	
Overweight	12.3	10.9	
Obese	15.7	9.0	
Physical exercise level (%)			.0201[b]
None	49.6	54.0	
1–4 times/wk	30.3	26.6	
≥5 times/wk	20.2	19.4	
Hypertension (%)	0.2	0.3	.0085[b]
Family history of DM (%)	10.6	9.7	.3456[b]
Waist circumference (cm)	71.8 ± 9.4	70.2 ± 7.6	<.0001[a]
Systolic BP (mm Hg)	111.8 ± 12.1	111.0 ± 11.6	.0534[a]
Diastolic BP (mm Hg)	70.6 ± 8.6	69.9 ± 8.7	.008[a]
Fasting glucose (mg/dL)	87.8 ± 13.0	86.9 ± 16.0	.0311[a]
Total cholesterol (mg/dL)	179.98 ± 32.0	175.67 ± 30.9	<.0001[a]
HDL cholesterol (mg/dL)	61.9 ± 14.0	63.7 ± 23.6	.0284[a]
LDL cholesterol (mg/dL)	102.4 ± 28.7	97.7 ± 25.9	.0019[a]
Triglycerides (mg/dL)	97.3 ± 65.7	79.8 ± 51.0	<.0001[a]
AST (IU/L)	21.2 ± 11.8	19.5 ± 11.6	<.0001[a]
ALT (IU/L)	19.3 ± 22.1	15.6 ± 18.2	<.0001[a]
GGT (IU/L)	19.7 ± 23.6	16.3 ± 11.8	<.0001[a]

Note: Data are expressed as mean values ± standard deviation, unless specified otherwise. ALT = alanine transaminase; AST = aspartate aminotransferase, BMI = body mass index, BP = blood pressure, DM = diabetes mellitus, GGT = γ-glutamyl transferase, HDL = high-density lipoprotein, IQR = interquartile range, LDL = low-density lipoprotein, PCOS = polycystic ovary syndrome.

[a] Paired *t*-test.

[b] Conditional logistic regression analysis.

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DISCUSSION

This longitudinal study using nationally representative cohort data with a 10-year follow-up time revealed that women of reproductive age with PCOS have an approximately 2.6-fold higher hazard of the development of type 2 diabetes mellitus than do women without PCOS, even after confounding factors including BMI are controlled for. It is important to note that most of our participants were not obese (BMI <25 kg/m^2), even in the PCOS group. The association between PCOS and an increased HR for type 2 diabetes mellitus remained significant in both the obese and nonobese subgroups.

Our results also indicated that the annual incidence of PCOS has increased steadily among Korean women during recent years. The Rotterdam criteria for PCOS diagnosis have been used in South Korea from 2003 onward; therefore, the increasing trend of PCOS observed in this study may not be the result of the change in diagnostic criteria or classification of PCOS. Rather, our findings indicate an association with the steady increase of prevalence of obesity, which may promote the manifestation of PCOS phenotypes, among women of reproductive age in South Korea (23). Obesity has been assumed to be associated with a more prominent manifestation of both PCOS phenotypes and type 2 diabetes mellitus, rather than acting as a direct inducer of either condition (24). In this study, women with PCOS had higher BMI than did those in the control group. The high rate of physical exercise in women with PCOS observed in this study might be due to the higher rates of obesity in these women, because it is assumed that obese women are recommended exercise for weight reduction more often than are nonobese women.

The increased incidence of type 2 diabetes mellitus in Korean women with PCOS compared with that in women without PCOS observed in this study is comparable with the findings reported in Western populations. A recent meta-analysis of studies mainly including white women showed a higher rate of type 2 diabetes mellitus among women with PCOS than in women without PCOS (relative risk, 3.00; 95% CI 2.56–3.51) (15). Furthermore, a review of data from a general practitioner research database in the United Kingdom reported a relative risk ratio of 1.9 for the development of type 2 diabetes mellitus in woman with PCOS (reference: BMI-matched control group) over a median follow-up period of 4.7 years (13).

Recent international guidelines for PCOS management recommend that glycemic status should be assessed in all women with PCOS and, in particular, the oral glucose tolerance test should be performed to assess glycemic status in women with a high risk of PCOS (including those with obesity, history of impaired fasting glucose, impaired glucose tolerance or gestational diabetes, family history of type 2 diabetes mellitus, or hypertension, or women of high-risk ethnicity) (17). However, there have been conflicting results regarding the risk of type 2 diabetes mellitus in nonobese women with PCOS. A Finnish population-based birth cohort study reported that only obese women with PCOS have an increased risk of type 2 diabetes mellitus, whereas lean women with PCOS do not have an increased risk of prediabetes or type 2 diabetes mellitus (25). By contrast, an Australian population-based cohort study reported that PCOS is independently associated with an increased incidence of type 2 diabetes mellitus among young Australian-born women and that this increased risk is present irrespective of BMI (26). According to a recent systemic review and meta-analysis, which included 22 studies selected from 7,432 searched articles, nonobese women with PCOS show an increased risk of type 2 diabetes mellitus, but this review lacked data on Asian populations (27). Our nationally representative population-based longitudinal study demonstrates that nonobese women with PCOS also face an increased HR of type 2 diabetes mellitus. Nonobese women with PCOS had a greater than two-fold higher HR of type 2 diabetes mellitus than nonobese women without PCOS. The prevalence of obesity (BMI ≥25 kg/m^2) among women with PCOS was 15.7% in the present study, whereas it has been reported to be 50% to 60% among

TABLE 2

Results of multivariate Cox regression analyses to determine hazard ratios of type 2 diabetes mellitus in women with polycystic ovary syndrome as compared with the matched control group after adjustment for confounding factors in the Korean National Health Insurance Service sample cohort from 2003 to 2012.

		Subgroup analysis	
Parameter	**Entire cohort**	**Nonobese group (BMI < 25 kg/m^2)**	**Obese group (BMI ≥25 kg/m^2)**
PCOS			
Yes	2.355 (1.799–3.082)	2.334 (1.715–3.178)	2.847 (1.586–5.109)
BMI	1.087 (1.054–1.122)	—	—
Family history of DM			
Yes	1.663 (1.18–2.344)	1.515 (0.993–2.313)	2.348 (1.237–4.457)
Physical exercise			
1–4 times/wk	0.934 (0.698 - 1.25)	0.884 (0.631–1.239)	1.27 (0.704–2.292)
≥ 5 times/wk	1.163 (0.805–1.681)	1.398 (0.943–2.074)	0.432 (0.127–1.468)
Total cholesterol	1.004 (1–1.009)	1.005(1–1.009)	1.005 (0.996–1.015)

Note: Data are presented as hazard ratios (95% confidence intervals). Statistical analysis was performed by stratified Cox proportional-hazards regression analysis. BMI = body mass index, DM = diabetes mellitus, HR = hazard ratio, PCOS = polycystic ovary syndrome.

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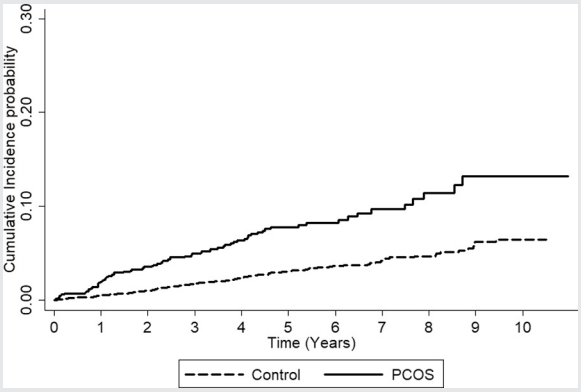
FIGURE 2



Kaplan-Meier survival curve analysis for the hazard of type 2 diabetes mellitus in the PCOS and control groups from the Korean National Health Insurance Service sample cohort from 2003 to 2012 after 1:5 matching by age group, income group, and region of residence. PCOS = polycystic ovary syndrome.

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Western women with PCOS (28). On the basis of these findings, we suggest that screening for type 2 diabetes mellitus in Korea should not be restricted to obese women with PCOS. It should also be offered to women with a normal BMI and PCOS. Early screening and regular checkups for diabetes among women with PCOS would be helpful in preventing any long-term complications related to diabetes, such as cardiovascular risks.

To the best of our knowledge, this is the first large-scale community-based longitudinal cohort study revealing an association between PCOS and an increased HR of type 2 diabetes mellitus in a cohort of East Asian women, irrespective of the presence of obesity. Unlike other clinic-based studies, our results might be better representative of the nationwide population of Korea. In contrast to previous reports from Western populations, the proportion of healthy-weight PCOS patients was high in our studied population, making our findings more applicable to East Asian women with PCOS. Furthermore, the diagnoses of PCOS and type 2 diabetes mellitus were defined on the basis of ICD-10 codes recorded by physicians rather than on the patients' self-reported data. Our study was able to adjust for important confounding factors, such as anthropometric and laboratory data of patients, which were obtained from objective measures during health checkup visits. Moreover, we used a well-matched control group, matched by age, income, and region of residence, in our analyses.

However, our study also has some limitations. First, the incidence of PCOS may be underestimated in an NHIS database because it was estimated based on physicians' diagnoses of the disease and because asymptomatic patients are less likely to visit a gynecologic clinic than are symptomatic or high-risk patients. However, both the high accessibility of the health service and the frequency of anovulatory symptoms of PCOS in South Korea might compensate for this limitation of the database. Further studies are needed to validate the incidence of PCOS in the NHIS database. Second, women with features of PCOS, such as irregular menstruation and hirsuitism, could not be excluded from the control group because data on these parameters were not available in the NHIS-NSC database. Third, the methods used for the biochemical assays were not provided in the database. Fourth, this study could not assess the diagnostic details of PCOS and diabetes encoded by the ICD system because of the characteristics of the claims database. Finally, the study could not assess insulin resistance and prediabetes status. Further longitudinal studies that include these measures may be needed to understand the mechanisms underlying our findings.

In conclusion, our nationwide population-based longitudinal study revealed that women with diagnoses of PCOS have a higher HR of type 2 diabetes mellitus than do women without PCOS, irrespective of the presence of obesity. Early

screening for type 2 diabetes mellitus may be required not only for obese women with PCOS but also for nonobese women with PCOS in East Asian countries where PCOS is characterized by a relatively low BMI. A formal assessment of glycemic status, including glucose tolerance test, should be performed for such a population. Our findings may be helpful in determining guidelines for the management of PCOS in East Asian women and in guiding physicians in treating PCOS patients with a healthy body weight.

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