Original Article

Incidence of Diabetes Mellitus in Thai Women with Polycystic Ovary Syndrome

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Objective: To determine the incidence and risk factors of type 2 diabetes mellitus (T2DM) in Thai women with Polycystic Ovary Syndrome (PCOS).

Materials and Methods: A retrospective cohort study in PCOS women diagnosed according to the Rotterdam Criteria was conducted. All PCOS women registered who had no T2DM at the visit were recruited in the present study. According to the protocol, these women were assigned to have a 75 g oral glucose tolerance test done every two years unless T2DM was found.

Results: One hundred fourteen PCOS women were included in the present study. Age, body mass index, and waist circumference were 27.4±5.4 years, 24.8±6.1 kg/m^2, and 77.7±16.2 cm, respectively. In the normal glucose tolerance (NGT) group (n=82), the incidence of T2DM was 1.2% (1 out of 82) and 3.1% (2 out of 64) at 2- and 4-year follow-up. Women with NGT converted to non-DM abnormal glucose tolerance (AGT) in 18.3% and 15.6% at 2- and 4-year follow-up. In the non-DM AGT group, the incidence rates of T2DM were 18.8% (6 out of 32) and 21.7% (5 out of 23) at 2- and 4-year follow-up. Obesity and non-DM AGT were the important risk factors for developing T2DM with OR of 4.2 (95% CI 1.2 to 14.6) and 8.9 (95% CI 2.5 to 31.0), respectively.

Conclusion: The current retrospective cohort study determined the overall incidence of T2DM was 12.3% (14 out of 114) of 4-year follow-up. Non-DM AGT and obesity were the important risk factors for conversion to T2DM.

Keywords: Abnormal glucose tolerance, Incidence, Risk factors, PCOS, Type 2 diabetes mellitus

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Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in reproductive age women. These women can be characterized by anovulation with abnormal menstruation, hyperandrogenism, and polycystic ovary[1]. There are three sets of the diagnostic criteria for PCOS commonly used nowadays, including the National Institutes of Health (NIH)[2], the Rotterdam[3], and the Androgen Excess Society & PCOS Society criteria[4]. Prevalence of PCOS was 11.9% in the Australian community sample diagnosed by the Rotterdam criteria[5]. Prevalence was lower in Asian population, about 5.6%, from a large community based-study in China[6] and 5.3% in Thai university adolescents[7]. Although the etiology of the disorder is unclear, it is recognized that insulin resistance (IR) and compensatory hyperinsulinemia are the keys of pathophysiology[8].

With these regards, PCOS women are at risk of abnormal glucose tolerance (AGT). Prevalence of type 2 diabetes mellitus (T2DM) and impaired glucose tolerance (IGT) in American women with PCOS diagnosed by the NIH criteria was 10% and 35%[9]. This phenomenon was quite similar in the Asian women with PCOS. Prevalence of AGT in Indian women with PCOS using the Rotterdam criteria was 36.3% including 6.3% T2DM and 30% impaired fasting glucose (IFG) and/or IGT[10]. In Thai women with PCOS diagnosed by the Rotterdam criteria, prevalence of T2DM, IFG, IGT, and IFG plus IGT was 10%, 5.3%, 21.2%, and 9.4%, respectively[11].

In addition, PCOS women have a higher chance to develop glucose intolerance in the future. In

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particular, the women with IGT are at higher risk to convert to T2DM[9,12]. Evidence showed that the annual conversion rates from normal glucose tolerance (NGT) to AGT and T2DM were 8.1% and 1.2%, respectively in PCOS women[13]. More recently, a long-term population-based follow-up studies showed incidence rates of T2DM were significantly higher in PCOS women than non-PCOS controls[14,15]. These studies of incidence rates were mostly conducted for Western PCOS women and only one report of Asian women with PCOS[16] has been published. Therefore, the authors undertook a retrospective cohort study to define the incidence of AGT in Thai women with PCOS.

Materials and Methods

The present study was approved by the Ethical Clearance Committee on Human Rights Related to Researches Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital, Mahidol University. Data from the medical records and electronic forms of all women with PCOS that consecutively attended and registered at the Reproductive Endocrinology Unit between June 2004 and December 2011 were reviewed and analyzed. The diagnosis of PCOS was based on the Rotterdam consensus criteria[3]. The diagnosis was established when there were two or more of the followings, 1) abnormal menstruation, oligomenorrhea (cycle lasting longer than 35 days), or amenorrhea (absence of menstrual cycle in the past 6 months), 2) any sign of clinical hyperandrogenism such as acne, seborrhea, and hirsutism (Ferriman-Gallwey score $\geq$8)[17], and 3) typical ultrasonic appearance of bilateral polycystic ovaries with 12 or more follicles of 2 to 9 mm in diameter. All diseases that mimic PCOS, including hypothalamic amenorrhea, premature ovarian failure, thyroid dysfunction, hyperprolactinemia, Cushing's syndrome, and hormone producing ovarian tumor were excluded.

According to the authors' PCOS management guideline, all women with PCOS had their menstrual pattern and clinical manifestations reviewed, received physical examination, and underwent anthropometric and metabolic measurements after the diagnosis of the disease. All women with PCOS had a 75-g oral glucose tolerance (OGTT) performed at 8.00 to 10.00 am after three days 300-g carbohydrate/day diet and at least 10 to 12 hours overnight fasting. Blood samples for glucose were obtained at 0 and 120 minutes. According to the authors' protocol, the PCOS women who had no T2DM at the initial work-up would repeat the 75-g OGTT in the next two years, and every two years thereafter if a negative result for T2DM was obtained. Other laboratory tests for hormonal and metabolic parameters were not done.

To diagnose AGT, the American Diabetes Association criteria[18] were used. AGT is composed of IFG, IGT and T2DM. The definition is as followed:

1. IFG: fasting glucose (FG) of 100 or more and less than 126 mg/dL
2. IGT: 2-hour post-load glucose (2-hPG) of 140 or more and less than 200 mg/dL
3. T2DM: FG of 126 mg/dl or more and /or 2-hPG 200 mg/dL or more

All women who did not have T2DM diagnosed at the initial visit were included in the present study. PCOS women who took progestins or oral contraceptive pill (OCP) were also included. Excluded were women who had metabolic syndrome (MS) and needed treatment, received insulin sensitizer such as metformin, and got pregnant at the time of follow-up, as well as lost follow-up.

Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared. Obesity was defined as BMI of 25 kg/m^2 or more and central obesity as waist circumference (WC) of 80 cm or more. To compare variables between groups, unpaired t-test, chi-square test, and Mann-Whitney-U test were used where appropriated. A logistic regression analysis was used to define risk factors for developing T2DM. The factors which had p-value less than 0.1 were included in the analysis. All data analyses were performed using SPSS version 18. A p-value less than 0.05 was considered statistically significant.

Results

One hundred sixty-six PCOS women consecutively registered at the division during the studied period were included in this study. Sixteen women were diagnosed as T2DM at the first visit. The remaining 150 women were recruited in the present study. Thirty-six women were excluded from the study, of these, five women were diagnosed as MS needed treatment, 15 women got pregnant, and 16 women did not attend at the first follow-up (at 2-year follow-up). Therefore, 114 PCOS women were included and analyzed (Figure 1, Table 1). These women had no history of taking metformin or other insulin sensitizers. Of these 114 women, 82 were NGT, and 32 were non-DM AGT including IFG, IGT, or IFG-IGT (Figure 1).

At the first follow-up (at 2-year follow-up), T2DM were found in seven (6.1%) women. Of these,

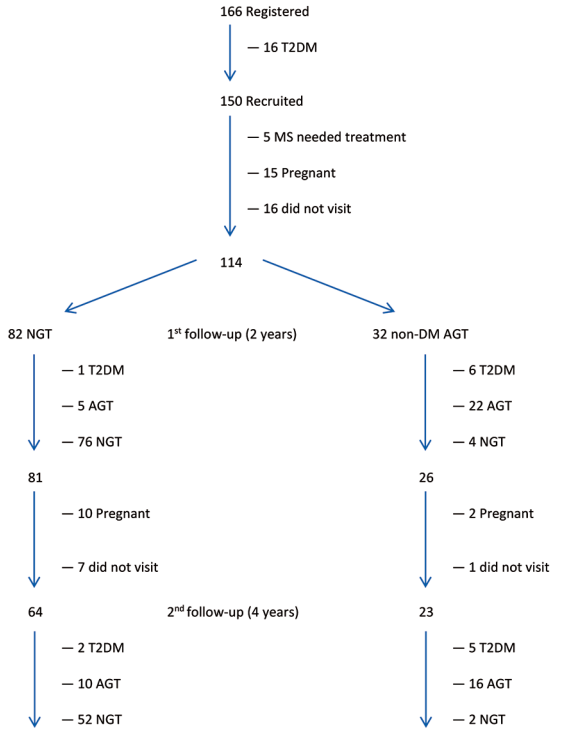

Figure 1. Flow chart showing number of PCOS women recruited, excluded, and included; and of women with T2DM detected.

PCOS=polycystic ovary syndrome; T2DM=type 2 diabetes mellitus; MS=metabolic syndrome; NGT=normal glucose tolerance; AGT=abnormal glucose tolerance

Table 1. The baseline clinical characteristics of women with polycystic ovary syndrome (n=114)

Parameters	n (%)
Age (year), Mean±SD	27.4±5.4
BMI (kg/m^2), Mean±SD	24.8±6.1
Obesity	43 (37.7)
Family history of DM	32 (28.1)
Waist (cm), Mean±SD	77.7±16.2
Waist ≥80 cm	55 (48.2)
W/H ratio, Mean±SD	0.84±0.05
Menarche (year), Mean±SD	13.61±1.95
Menstruation	
Oligomenorrhea	56 (49.1)
Amenorrhea	58 (50.9)
Hyperandrogenism	
Acne	79 (69.3)
Seborrhea	75 (65.8)
Hirsutism	27 (23.7)

BMI=body mass index; DM=diabetes mellitus; W/H ratio=waist/hip ratio; SD=standard deviation

six out of 32 (18.8%) were in the non-DM AGT group, while one out of 82 (1.2%) in the NGT group. Twenty-two out of 32 remained AGT, and four out of 32 regressed to NGT in the non-DM AGT group. In the NGT group, five out of 82 (18.3%) women developed to non-DM AGT.

During the two to four years of follow-up, 10 women in the NGT group and two women in the non-DM AGT group got pregnant, seven and one woman in the NGT and the non-DM AGT groups, respectively, were lost to follow-up. Therefore 87 women, 64 in the NGT and 23 in the non-DM AGT groups were included and analyzed in the second time of follow-up (at 4-year follow-up). Of 23 women with AGT, five (21.7%) were diagnosed as T2DM, 16 remained AGT, and two converted to NGT. In the NGT group, two (3.1%) developed to T2DM and 10 (15.6%) converted to non-DM AGT.

The overall incidence of T2DM was 12.3% (14 out of 114) assessed over four years. The incidence rates were 34.4% and 3.7% in the non-DM AGT and NGT groups, respectively. In the NGT group, the incidence rate of non-DM AGT was 18.3% (15 out of 82). Therefore, the annualized incidence rates of T2DM were 8.6% and 0.9% developed from the non-DM AGT and NGT groups.

The non-DM status and obesity were important risk factors of converting to T2DM (Table 2, 3). The odds ratio (OR) of non-DM status and obesity were 8.9 (95% CI 2.5 to 31.0) and 4.2 (95% CI 1.2 to 14.6), respectively (Table 3).

Discussion

IR plays a cardinal role of pathophysiology and clinical features of PCOS. Studies using the euglycemic-hyperinsulinemic clamp, the gold standard method of IR measure, have recently demonstrated that PCOS women have 27% worse insulin sensitivity than non-PCOS women[19]. In fact, insulin regulates glucose homeostasis by actions on many organs. It stimulates glucose uptake in skeletal muscle and adipose tissue, and suppresses hepatic glucose production[20]. IR is an impairment of insulin action on these organs leading to decrease in skeletal and adipocyte glucose uptake, and increase hepatic glucose production[20]. Therefore, women with PCOS are at risk of AGT including T2DM. Not only could

Table 2. Comparison of the baseline variables between PCOS women with and without T2DM

Factor	Without T2DM (n=100) Mean±SD	With T2DM (n=14) Mean±SD	p-value
Age (year)	27.3±5.4	28.8±5.7	0.328
BMI (kg/m^2)	24.6±6.5	26.0±3.7	0.455
BW (kg)	60.6±15.5	66.1±9.2	0.196
Waist (cm)	76.7±11.9	79.0±9.0	0.641
Obesity, n (%)	33 (33.0)	10 (71.4)	0.023
Non-DM AGT, n (%)	22 (22.0)	10 (71.4)	0.001

PCOS=polycystic ovary syndrome; T2DM=type 2 diabetes mellitus; BMI=body mass index; BW=body weight; Non-DM AGT=non-diabetes mellitus abnormal glucose tolerance; SD=standard deviation

Table 3. Risk factors for developing type 2 diabetes mellitus using logistic regression

Factors	DM group n (%)	Non-DM group n (%)	OR	95% CI	p-value
Non-DM AGT					
AGT	10 (71.4)	22 (22.0)	8.9	2.5 to 31.0	0.001
NGT	4 (28.6)	78 (78.0)	1		
Obesity					
BMI ≥25 kg/m^2	10 (71.4)	33 (38.4)	4.2	1.2 to 14.6	0.023
BMI <25 kg/m^2	4 (28.6)	53 (61.6)	1		

DM=diabetes mellitus; AGT=abnormal glucose tolerance; BMI=body mass index; OR=odds ratio; CI=confidential interval

AGT be prevalently found, PCOS women also have a chance to develop AGT in the future.

Studies of conversion to T2DM in PCOS women have been reported. The studies included small numbers of PCOS women using the NIH criteria. They had no protocol of regular time to follow-up. However, they showed an annualized incidence rates of T2DM at 8.7% from IGT and 1.3% to 2.0% from NGT[12,13]. Celik et al[21] demonstrated that two out of six PCOS women with IGT diagnosed by the Rotterdam criteria converted to T2DM, therefore, the annualized incidence rate was 10.4%. Recently, a long-term prospective study in 255 Italian women with PCOS diagnosed by the NIH criteria showed that the incidence rate of T2DM was 1.05 per 100 person-years[14]. Another long-term population-based follow-up study in Iran has shown incidence rate of T2DM of 12.9 per 1,000 person-years of 178 PCOS women by the NIH criteria compared to 4.9 per 1,000 person-years of 1,524 controls[16]. More recently, the incidence rate of developed T2DM of eight per 1,000 person-years of 18,477 PCOS women compared to two per 1,000 person-years of 54,680 controls after 11 years of follow-up has been reported from a survey of Danish national population of women with PCOS diagnosed by the Rotterdam criteria[15]. These studies were conducted in Europe[14,15,21,22], Australia[12], and the USA[23,24]. Until now, only one publication from the Middle East of Asia has been reported[16]. Evidence showed that risk of AGT was different across different ethnic groups[25]. Asian and American PCOS women have a higher risk for AGT, whereas European women have lesser risk[25]. Thai women with PCOS had a higher risk with high prevalence of AGT including T2DM[11]. It is likely that Thai women with PCOS are at higher risk of development of T2DM.

The current study did not include PCOS women who took metformin. Metformin reduced serum glucose through increasing insulin effect without increasing insulin secretion as well as decreasing hepatic glucose production[26]. It could prevent and delay the development of T2DM. Included in the current study were PCOS women who took progestins and/or OCP with the fact that both progestins and OCP have no effects on glucose metabolism[15,27,28]. Results in annualized incidence rates of 8.6% and 0.9% developed from the non-DM AGT and NGT groups, respectively in the current study were comparable

to the other reports using both the NIH[12,13] and the Rotterdam criteria[21]. It does not seem appropriate to compare the rates between PCOS women with the different criteria. However, there has not been a report comparing the incidence rates between two criteria in the same population of PCOS. In the NIH criteria, hyperandrogenism has to be one of two criteria, however, it is unnecessary in the Rotterdam criteria. A part of PCOS women with the Rotterdam criteria who do not have hyperandrogenism are categorized as the milder phenotype that may have less metabolic abnormality[29,30]. Nevertheless, evidence from the study of IR has shown that IR was not different between PCOS women by the NIH and the Rotterdam criteria assessed in the same populations[19]. Evidence has shown that IR and abnormal metabolic features in PCOS are not related to reproductive phenotype[31]. PCOS women with hyperandrogenism did not differ in abnormal glucose metabolism when compared to those without hyperandrogenism[31]. In addition, a hospital-based observation study of 2,635 Chinese PCOS women showed that there were no differences in IR, prevalence of T2DM and non-DM AGT when compared between four phenotypes composing of subgroups with and without hyperandrogenism according to the Rotterdam criteria[32]. Rubin et al[15] demonstrated that there were no differences in incidence rates of T2DM between the four phenotypes of PCOS women diagnosed by the Rotterdam criteria. It is possible that incidence rates of AGT are similar in PCOS women when compared between both criteria. Included in the current study were PCOS women using the Rotterdam criteria where two-third of women had clinical hyperandrogenism presenting as acne and about 24% as hirsutism. Most recently, acne has been accepted as one of clinical manifestation of hyperandrogenism[33]. One-third of PCOS women in the current study without clinical hyperandrogenism were categorized as milder phenotype. The annualized incidence rates of T2DM of the current study were quite similar to those using the NIH and the Rotterdam criteria, which were 8.7% to 10.4% from IGT[12,21] and 0.9% to 1.3% from NGT[12,13,21].

The current study showed that non-DM AGT was the most important risk factor for developing T2DM compared within PCOS women. The PCOS women with non-DM AGT had almost nine times higher risk than those with NGT to convert to T2DM. The other work was quite similar[12]. The rate of conversion to T2DM from IGT was 54%, whereas it was 8% from NGT in the work of Norman et al[12]. In another report, the baseline fasting glucose (10 mg/dl increase) was an independent risk factor of development to T2DM in PCOS with the hazard ratio of 1.52 (95% CI 1.01 to 2.29)[14]. Rubin et al[15] also showed that PCOS women who developed T2DM had higher glucose, both fasting and 2-hPG levels, than PCOS women without development of T2DM. However, when comparing PCOS women with non-PCOS controls, there were contradicting data on the risk of the baseline AGT[15,16]. Kazemi Jaliseh et al[16] demonstrated that there was no difference in FG and 2-hPG levels, and prevalence of non-DM AGT including IFG and IGT between both groups. By contrast, a study from Denmark showed that the baseline FG and 2-hPG were risks of developing T2DM[15]. In fact, pre-diabetes is an important predictor of T2DM development in the general population[34,35].

Unlike the current report that there was no difference in BMI between PCOS women with and without T2DM, many studies demonstrated that baseline BMI was higher in T2DM than non-DM groups (33.6 versus 28.0 kg/m², $p<0.001$[14]; and 32.3 versus 26.3 kg/m², $p<0.001$[15]). Rubin et al[15] found that BMI was a predictor of development of T2DM compared PCOS women with and without developed T2DM. Morgan et al[36] showed that a 1% increase in BMI was associated with a 2% increase in risk of T2DM. Although there were differences in BMI between ethnics, it seemed that there was a higher risk of developed T2DM in PCOS women in each ethnic. The mean BMI were varied from 26.1 for Iran PCOS women to 28.6-31 kg/m² for European PCOS women[14,15,37], while 24.8 kg/m² was used in the current study. Although Asian women had a lesser BMI, there was a higher IR and higher risk of T2DM[25]. It is better to use obesity defined by BMI. Obesity was an important risk factor of developing T2DM in the current study with OR of 4.2. that supported other studies in which only PCOS women were followed without controls[14]. A long-term prospective study reported obesity was the important predictor of developing T2DM, with the fact that incidence rates were steadily increased with BMI. The incidence rates were 0.25, 0.63, and 2.02 per 100 person-years at BMI of less than 25, 25 to 29.9 and more than 30 kg/m², respectively[14]. Another National population-based follow-up study showed that BMI was significantly higher in PCOS than control women[37]. In new cases of AGT including T2DM, IFG and IGT at the end of the study were more prevalent in PCOS women than the controls. This significant difference was found in the overweight and obese women, but not in the lean women[37].

Age may be a risk factor for T2DM with contradicting data. Gambineri et al(14) demonstrated that age was higher in Italian women with PCOS who developed T2DM than who did not (45.9±8.3 versus 38.9±6.9, p<0.001). This finding was supported by another study showing that a median age at T2DM diagnosis was 31 (26 to 36) versus 28 (22 to 34) years for PCOS women with and without developed T2DM[15]. However, age was not shown to be a risk factor of development of T2DM when using Cox regression models, in spite of a long-term follow-up of 11.1 to 16.9 years[14,15]. Age also was higher in PCOS women with T2DM than without, but did not reach statistical significance in the current study. This might be due to a small sample size, especially in the PCOS with T2DM group. When compared to non-PCOS controls, the median age at diagnosis was lower in PCOS women than in the controls (31 versus 35 years, p<0.001)[15]. Eighty-two percent of PCOS women versus 66% of controls (p<0.001) were younger than 40 years at T2DM diagnosis[15]. Kazemi Jaliseh et al[16] also demonstrated multiple adjusted hazard ratio of incidence of T2DM of PCOS women younger than 40 years, which was 4.9 (2.5 to 9.3) compared to those older than 40 years.

Interestingly, the authors found that non-DM AGT could be converted to NGT at 2- and 4-year follow-ups. Four out of 32 (12.5%) and two out of 23 (8.7%) at 2-and 4-year follow-ups, respectively, converted from non-DM to NGT in the current study. This could be found in the survey of the general population[38]. A systemic review had shown that the regression from pre-diabetes to NGT ranged from 33% to 59% after one to five years follow-up and the regression rate decreased overtime to a range of 17% to 42% after 6 to 11 years follow-up[38]. This conversion was found in the PCOS women as well[21]. One out of three PCOS women with IGT regressed to NGT after 2.6 years follow-up[21]. However, non-DM AGT is an important risk factor for various vascular diseases[39], and for developing T2DM[40]. A close follow-up of this group of women is mandatory, since it has a possibility to reverse to IGT and even develop to T2DM in the future.

The strength of the current study is that, firstly, the Rotterdam criteria was used for the diagnosis of PCOS women studied. A few reports on incidence of T2DM in PCOS women diagnosed by the Rotterdam criteria has been published[15,21]. Secondly, only one report involved Asian women with PCOS has been published[16]. The current study is the first report on incidence of T2DM in Thai women with PCOS, and may be the first publication among East and Southeast Asian women with PCOS. However, there is a limitation that some women did not attend follow-up as the protocol. Of these, 27 (18%) out of 150 PCOS women got pregnant and 24 (16%) were lost follow-up. Although the part of women did not include in the study, it should not significantly influence the results in the current study. The women excluded could have a similar risk for developing to T2DM. For example, PCOS women who got pregnant had a higher chance of gestational diabetes with OR of 2 to 3 compared to those without PCOS[41,42]. After GDM, these PCOS women are at high risk for persistent AGT. Palomba et al[43] reported a relative risk of AGT of 3.45 (95% CI 1.82 to 6.58) in PCOS women with GDM at 18-month follow-up. Furthermore, the incidence of T2DM in the current study was similar to the others[12,13,21].

In conclusion, the incidence rate of non-DM AGT from the baseline NGT was 18.3% after a 4-year follow-up. The overall incidence of T2DM was 12.3% (14 out of 114) assessed over four years. The incidence rates were 34.4% and 3.7% in the non-DM AGT and NGT groups, respectively. Obesity and non-DM AGT at baseline were the important risk factors for conversion to T2DM. Evidence has shown that regular follow-ups should be performed for all women with PCOS, especially in women with obesity and/or having non-DM AGT.

What is already known on this topic?

The incidence rates of T2DM have been reported for more than a decade. These were mostly determined in Western PCOS women. In addition, almost all studies included PCOS women diagnosed by the NIH criteria.

What this study adds?

This study reported the incidence of T2DM in Thai women with PCOS diagnosed using the Rotterdam criteria. The current study may be the first report for detecting the incidence of T2DM among East and Southeast Asian women with PCOS.

Conflicts of interest

The authors declare no conflict of interest.

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