

Increased risk markers in women with polycystic ovary syndrome and gestational diabetes mellitus during mid-pregnancy

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Abstract

Objective: This study aimed to investigate application of the urine albumin-to-creatinine ratio (ACR), serum beta 2-microglobulin (β 2-MG), and cystatin C as risk markers in a cohort of women with polycystic ovary syndrome (PCOS) for the incidence of gestational diabetes mellitus (GDM).

Methods: In this cross-sectional study, we analyzed 312 pregnant women with PCOS and classified them as those with and without GDM. For all participants, elbow venous blood and clean middle urine were collected in the morning after 8 hours of an empty stomach.

Results: Logistic regression analysis showed that the ACR, urine β 2-MG levels, and serum cystatin C levels were important markers for women with PCOS concomitant with GDM. Receiver operating characteristic curve analysis showed that the area under the curve of CysC was 0.81 with the threshold based on >0.93 and that of β 2-MG was 0.72 with the threshold based on >1.25 .

Conclusions: Increased levels of β 2-MG and cystatin C and a high ACR might be risk factors for Chinese women with PCOS and GDM during mid-pregnancy.

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Keywords

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age with the basis of the diagnosis of hyperandrogenemia, hyperinsulinemia, chronic anovulation, and other endocrine abnormalities.¹ Most women with PCOS are at risk for developing gestational diabetes mellitus (GDM) during pregnancy.^{2,3} Women with PCOS and GDM may share risk factors and show abnormalities in glucose homeostasis, hypertension, systemic inflammation, and dyslipidemia. Additionally, PCOS and GDM are closely related to the onset and development of kidney abnormalities. A previous study showed that there was a rising trend for tubular proteinuria markers in patients with PCOS.⁴ In a long-term follow-up study, GDM was found to be an independent risk factor for maternal renal dysfunction.⁵ Because kidney abnormalities impose a high economic burden on daily life, examining clinical markers for kidney insufficiency under PCOS and GDM is important.

The albumin-to-creatinine ratio (ACR) is increasingly being accepted as an easy and acceptable marker for reflecting the state of pathophysiological vascular dysfunction and appears to be related to enhanced metabolic risk.^{6,7} Patel et al.⁸ reported that a high ACR in women with PCOS may be a useful marker of cardiovascular dysfunction. A high ACR is also closely associated with women who have GDM and develop overt diabetes after

pregnancy, which indicates evident renal dysfunction clinically.⁹ Interestingly, despite elevated ACR values for diabetes, kidney failure, and cardiovascular events, Friedman et al.¹⁰ did not show a relationship between the ACR and incident diabetes in subjects in the pre-diabetic state.

In addition to the ACR, beta 2-microglobulin (β 2-MG) and cystatin C are low molecular weight proteins that are important markers of renal tubular damage. β 2-MG is a component of the human leukocyte antigen class I molecule and is present in all nucleated cells and most biological fluids, including serum, urine, and synovial fluid.¹¹ β 2-MG and cystatin C are reliable and important markers of renal damage in patients with diabetes, and they are significantly elevated compared with control subjects.^{12,13} In women with PCOS, cystatin C may be a new strategy in clinical practice for early detection of individuals who are at high risk for long-term metabolic and cardiovascular events.¹⁴

Although similar metabolic effects are associated with PCOS and GDM, few studies have examined the underlying indicators for changes in renal function under PCOS and GDM.¹⁵ The urine ACR, β 2-MG levels, and cystatin C levels are not routinely used to diagnose and evaluate renal function in Chinese pregnant women with PCOS. Therefore, in this study, we aimed to evaluate the ACR in women with PCOS and GDM to determine whether it is increased above the normal range, and to clarify the effects of the ACR, β 2-MG

levels, and cystatin C levels on the status of GDM and PCOS.

Materials and methods

Participants

We identified pregnant women with PCOS (pregnancy was achieved after standard treatment) who delivered between January 2014 and January 2018, and underwent screening for GDM during pregnancy in the study. The primigravid women with PCOS had adequate data for classification of GDM. The cohort of women was divided into the following two groups: pregnant women with PCOS and GDM (GDM group) and pregnant women with PCOS without GDM (control group). Women in both of the groups were recruited for the study after 24 weeks of pregnancy. All women were evaluated at Nantong Maternity and Child Health Hospital. The study was approved by the Ethics Committee of Nantong Maternity and Child Health Hospital and each patient provided informed consent in accordance with the Declaration of Helsinki (Y2017016).

The diagnosis of PCOS was based on the 2003 European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine Rotterdam criteria as the presence of at least two of the following three features¹⁶: (1) oligo- or anovulation; (2) hyperandrogenism and/or biochemical signs of hyperandrogenism; and (3) polycystic ovary morphology by ultrasound.

The diagnosis of GDM was based on a 75-g oral glucose tolerance test at 24 to 28 weeks' gestation.¹⁷ GDM was confirmed if two or more oral glucose tolerance test values exceeded the following: for venous plasma, 5.6 mmol/L at 0 minutes; 10.1 mmol/L at 1 hour, and 8.5 mmol/L at 2 hours. Patients with suspected GDM at

>28 weeks' gestation returned to the clinical unit for an oral glucose tolerance test.

During the study period, the criteria for the diagnosis of PCOS and GDM remained unchanged. Exclusion criteria were as follows: age of <18 or >45 years; a history of alcohol and/or smoking; diagnosed with GDM before 24 weeks' gestation or with overt diabetes; hyperprolactinemia; adrenal dysfunction and thyroid dysfunction; dyslipidemia; hypertension; coronary artery disease; and congestive heart failure.

Baseline characteristics and blood and urine analysis

All of the subjects were screened before initiation of the study. Data of baseline characteristics were collected for the following variables: age, weight, height, body mass index, and a family history of diabetes. Blood and urine collection was performed for lipid analysis (high-density lipoprotein, low-density lipoprotein, and triglycerides), and measurement of fasting glucose, fasting insulin, total testosterone, urine albumin, urine creatinine, serum cystatin C, and urine β 2-MG levels. These data were collected by consent and approval from each patient. The ACR was estimated as the amount of urine albumin divided by creatinine levels in urine. We defined an elevated ACR as >20 mg/g and microalbuminuria of 30 to 300 mg/g on the basis of the common standard.^{18,19}

Statistical methods

Statistical analyses were performed using SPSS for Windows statistical software (ver. 17.0; SPSS Inc., Chicago, IL, USA). Data are presented as mean \pm standard deviation or the geometric mean (95% confidence interval [CI]), median with interquartile range, or percentage for categorical variables. Normality of distribution was evaluated by the D'Agostino–Pearson omnibus normality test. Continuous variables were compared

by using the Student's t test between the two groups. Categorical data were analyzed by the chi-square test. Logistic regression analysis was performed to analyze the association between variables with changes in GDM. Receiver operating characteristic (ROC) curve analysis was used to analyze the optimal cutoff value of variables, with the maximum sensitivity and specificity. The area under the curve (AUC) quantified the accuracy of the predicted outcome. A P value of <0.05 was considered statistically significant.

Results

We identified 312 pregnant women with PCOS, and there were 82 in the GDM

group and 230 in the control group. The general and biochemical characteristics of the studied population are shown in Table 1. Parameters such as age, weight, height, body mass index, a family history of diabetes, high-density lipoprotein cholesterol levels, low-density lipoprotein cholesterol levels, triglyceride levels, total testosterone levels, systolic blood pressure, and diastolic blood pressure were not significantly different between the groups. Mean fasting glucose and insulin levels in the GDM group were significantly higher than those in the control group (both $P < 0.001$). The median urine albumin level and the mean ACR in the GDM group were significantly higher than those

Table 1. Comparison of general and biochemical characteristics between the two groups.

Characteristics	GDM (n = 82)	Non-GDM (n = 230)	P value
Age (years)	28.79 ± 3.34	29.61 ± 3.02	0.18
Weight (kg)	63.5 ± 3.95	62.46 ± 4.28	0.2
Height (cm)	161.8 ± 4.14	162.3 ± 3.86	0.58
BMI (kg/m ²)	24.31 ± 2.12	23.75 ± 1.76	0.13
Family history of diabetes	13 (29)	10 (60)	0.05
HDL cholesterol (mmol/L)	1.40 ± 0.21	1.39 ± 0.19	0.79
LDL cholesterol (mmol/L)	2.48 ± 0.32	2.40 ± 0.30	0.2
Triglycerides (mmol/L)	1.10 ± 0.21	1.15 ± 0.17	0.2
Fasting glucose (mmol/L)	7.86 ± 0.86	4.93 ± 0.51	<0.001
Fasting insulin (μIU/mL)	16.83 ± 3.15	9.72 ± 2.41	<0.001
Total testosterone (nmol/L)	1.74 ± 0.54	1.63 ± 0.58	0.33
Urine albumin (mg/L)	8.66 (7.58, 10.23)	7.46 (5.78, 9.20)	0.005
Urine creatinine (μmol/L)	6.35 (4.58, 7.93)	5.59 (3.78, 7.03)	0.056
ACR (<20 mg/g, n = 57)	13.89 ± 3.68	10.03 ± 3.23	<0.001
ACR (>20 mg/g, n = 25)	28.16 ± 4.68	10.03 ± 3.23	<0.001
Systolic BP(mm Hg)	113.1 ± 8.43	114.3 ± 7.36	0.81
Diastolic BP (mm Hg)	71.62 ± 5.31	71.27 ± 4.7	0.72
CysC (mg/L)	1.08 ± 0.19	0.89 ± 0.17	<0.001
β2-MG (mg/L)	1.59 ± 0.49	1.26 ± 0.25	<0.001

GDM, gestational diabetes mellitus; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACR, albumin-to-creatinine ratio; β2-MG, beta 2-microglobulin; CysC, cystatin C; BP, blood pressure.

in the control group (all $P < 0.01$). However, there was no significant difference in urine creatinine levels between the two groups ($P = 0.056$). We also found that mean $\beta 2$ -MG and cystatin C levels were significantly higher in the GDM group than in the control group (both $P < 0.001$).

Because the distribution of urine albumin and urine creatinine levels was not normal, subsequent regression analysis was carried out on logarithmically transformed data. Univariate and multivariate logistic regression models were constructed out to analyze several factors for the effect of GDM in patients with PCOS (Table 2). In multivariate analysis, we found that the ACR (odds ratio [OR] 1.681, 95% CI 1.387–1.972), $\beta 2$ -MG (OR 3.511, 95% CI 1.663–5.958), and CysC (OR 4.108, 95% CI 1.665–8.508) were associated with increased renal damage of GDM in patients with PCOS.

According to ROC analysis, three risk factors showed a predictive effect of renal damage. The optimal cutoff value of the ACR was >10.5 , with an AUC value of 0.77 (95% CI 0.69–0.84), sensitivity of 82.86%, and specificity of 54.35%. The optimal cutoff value of $\beta 2$ -MG was >1.25 ,

with an AUC value of 0.72 (95% CI 0.61–0.78), sensitivity of 76.3634%, and specificity of 55.84%. The optimal cutoff value of CysC was >0.93 , with an AUC value of 0.81 (95% CI 0.68–0.84), sensitivity of 78.18%, and specificity of 64.94% (Figure 1).

Discussion

Because of changes in traditional Chinese dietary habits shifting to a high-sugar and

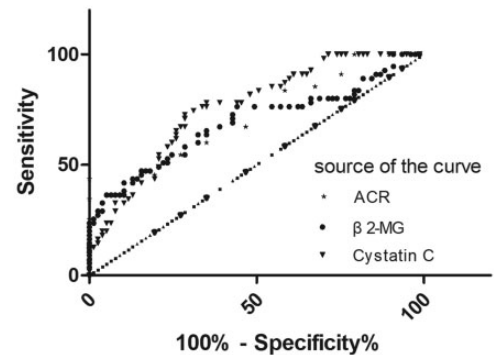


Figure 1. Receiver operating characteristic curve analysis of the predictive probabilities of ACR/ $\beta 2$ -MG/CysC for gestational diabetes mellitus in women with polycystic ovary syndrome. ACR, albumin-to-creatinine ratio; $\beta 2$ -MG, beta 2-microglobulin; CysC, cystatin C.

Table 2. Logistic regression analysis for evaluating variables involved in gestational diabetes mellitus in women with polycystic ovary syndrome.

Variables	Univariate regression			Multivariate regression		
	OR	95% CI	P value	OR	95% CI	P value
BMI	1.141	0.898–1.451	0.28	–	–	–
HDL	1.007	0.958–1.059	0.78	–	–	–
LDL	1.021	0.989–1.055	0.20	–	–	–
Triglycerides	1.004	0.978–1.031	0.61	–	–	–
Total	1.010	0.982–1.039	0.49	–	–	–
ACR	1.771	1.476–2.102	<0.001	1.681	1.387–1.972	<0.001
CysC	3.648	1.865–6.568	<0.001	4.108	1.665–8.508	<0.001
$\beta 2$ -MG	3.271	1.754–5.808	<0.001	3.511	1.663–5.958	<0.001

OR, odds ratio; CI, confidence interval; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACR, albumin-to-creatinine ratio; $\beta 2$ -MG, beta 2-microglobulin; CysC, cystatin C.

high-fat diet and a delayed childbearing age, PCOS has become the most common endocrine and gynecological disorder in women of childbearing age in China.²⁰ An increasing amount of studies have indicated that PCOS might be a promising risk factor for GDM.²¹ Therefore, examination of the relationship between PCOS and GDM has received an increasing amount of attention. GDM, which is defined as a common obstetric complication, has a temporary effect, but long-term risk, in women with PCOS. According to previous evidence on the relation between GDM and PCOS, both of these pathological states lead to renal damage.⁴ However, few studies have investigated changes in parameters for signs of renal function in women with PCOS concomitant with GDM.¹⁵ In our study, we report new findings on urine ACR, urine β 2-MG, and serum cystatin C levels in women with PCOS. We found that the values of those parameters were significantly higher in the GDM group than in the control group. Logistic regression analysis also showed that the ACR, β 2-MG, and cystatin C were independent risk factors. Additionally, β 2-MG and cystatin C levels may be significantly higher with higher AUC values, as tested in the ROC curve.

GDM shows insulin resistance and abnormal levels of blood glucose, which might be the facilitating factors for pathological damage in patients with PCOS.^{22,23} Therefore, a useful clinical index to assess the difference associated with GDM compared with those without GDM in women with PCOS subjects is important.

β 2-MG is used as a biomarker for detecting incipient diabetic nephropathy and has a threshold at 1.86 mg/L for clinical diagnosis.²⁴ β 2-MG in patients on dialysis causes local formation of β 2-MG amyloid, which can be modified by advanced glycation end-products.²⁵ This might partially explain variable generation of β 2-MG in response to serum high glucose levels.

Interestingly, a previous cross-sectional study suggested that β 2-MG had no association with levels of glucose and glycated hemoglobin (in an adjusted model).²⁶ ROC curve analysis in our study showed that β 2-MG had high sensitivity and specificity for predicting pathological changes. The mechanisms to explain such differences may relate to recruited patients with an older age, different races, and other basic clinical characteristics. To the best of our knowledge, investigation of the role of β 2-MG in previous studies was mostly performed in patients on dialysis, which represented the end stage of kidney disease.²⁷ Hyperglycemia might be harmful in renal function by releasing inflammatory cytokines and developing microangiopathy.²⁸ However, whether there are elevated β 2-MG levels in patients with PCOS and GDM remains unclear. In our study, β 2-MG levels were significantly higher in the GDM group than in the control group. Our finding is in line with a previous study, which showed that glucose disorder was correlated with an increase in serum β 2-MG levels.¹²

Cystatin C levels are a risk predictor for advanced metabolic syndrome in women with PCOS.¹⁴ Additionally, pathological changes in cystatin C levels can predict various diseases because this protein is excreted by glomerular filtration. Therefore, increased levels of this protein are associated with renal dysfunction directly. We found that serum cystatin C levels were elevated in the GDM group compared with the control group. This was a cross-sectional study and follow-up data were missing. Therefore, the effect of PCOS on serum cystatin C level should be investigated further.

We consider that the ACR is a promising parameter in relation to the effect of GDM on PCOS. In young PCOS cases, urinary albumin excretion (defined as an ACR >6.93 μ g/mg) appears to be an important

sign of metabolic problems, and it might help in discriminating PCOS at risk of future cardiovascular disease.²⁹ A prospective study investigated the associations between a history of GDM and the glomerular filtration rate and ACR with 9- to 16-year follow-up assessment after pregnancy.⁹ This previous study showed that only women who had GDM and developed overt diabetes after pregnancy showed an elevated ACR, but GDM without subsequent diabetes was not significantly related to the ACR. Our results are not completely consistent with this previous study. We found that a high ACR was an important risk factor for renal damage in women with GDM and PCOS. Possible explanations for our finding could be pre-pregnancy confounders, such as maternal age, educational attainment, different racial/ethnic groups, different glucose load severity in the captured cohort, and the use of assisted reproductive techniques. Additionally, we screened all women with PCOS at 24 to 28 weeks of gestation. However, ROC analysis showed that the AUC value of the ACR was 0.77 with moderate sensitivity and low specificity.

The main strength of our study was the results of clinical parameters in women with PCOS and GDM, which are meaningful for assessing the effect of GDM during mid-pregnancy. Those parameters could add to the existing literature in identification of renal derangement in women with PCOS who are at high risk of developing GDM.

Some potential limitations of this study should be mentioned. First, this was a single-center, cross-sectional study with a limited number of samples. Longitudinal assessment over time is required to determine the natural history of women with PCOS. Second, the ACR was assessed by single-spot urine collection instead of 24-hour urinary albumin excretion, which may have obscured measurement of albuminuria in certain participants. Third,

other renal function parameters, such as the glomerular filtration rate, should also be considered in the future.

In conclusion, the present study provides epidemiological evidence that higher cystatin C and β 2-MG levels and a higher ACR may be easy and non-invasive parameters for examining changes caused by GDM among pregnant patients with PCOS. Additionally, cystatin C and β 2-MG show a high AUC in distinguishing between those who develop GDM and those who do not. Further research in larger populations is required to identify the effect of these indicators on the risk of GDM in women with PCOS.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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