Coagulation and Fibrinolytic Indices During the First Trimester of Pregnancy in Women With Polycystic Ovary Syndrome: A Preliminary Study

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Abstract

Objective: To evaluate the levels of coagulation and fibrinolytic markers during the first trimester of pregnancy in women with polycystic ovary syndrome (PCOS) and determine the effects of PCOS and obesity on the levels of these hemostatic markers. **Methods:** A cross-sectional study was conducted in Beijing, China, on women with PCOS ($n = 50$), healthy women ($n = 50$), pregnant women with PCOS ($n = 50$), and healthy pregnant women ($n = 50$) at 12 weeks of pregnancy. Coagulation and fibrinolytic parameters were measured. **Results:** The interaction between PCOS and pregnancy appears to exert effects on the activities of coagulation factors VIII and X. The interaction between PCOS and obesity also seems to affect the level of von Willebrand factor. **Conclusions:** Pregnant women with PCOS, especially women who are obese, are observed to be in a more prohemostatic state during the first trimester.

Keywords

polycystic ovary syndrome, pregnancy, obesity, coagulation, fibrinolysis

Introduction

Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism, ovulatory dysfunction, insulin resistance (IR), and PCO morphology. Polycystic ovary syndrome is one of the most common endocrine abnormalities in women of reproductive age, with a reported prevalence of 4% to 8%.¹ Women with PCOS exhibit short-term complications, such as hyperinsulinemia, dyslipidemia, hypertension, and obesity, which are components of the metabolic syndrome that increases the risk of cardiovascular events.²

In addition, coagulation and fibrinolysis dysregulation may contribute to cardiovascular disease (CVD). Several studies have observed disturbances in the hemostatic system of women with PCOS, including the prothrombotic state, as characterized by hypercoagulability and hypofibrinolysis.^{3,4} Moreover, the body mass index (BMI) of women may influence the coagulation and fibrinolysis systems.^{5,6}

A normal pregnancy is associated with major changes in hemostasis, including increased concentrations of clotting factors and decreased fibrinolytic activity, especially during the second and third trimesters.^{7,8}

When women with PCOS become pregnant, the effects of coagulation and fibrinolytic disturbances on the mother and the

fetus must be considered. Studies have demonstrated that PCOS during pregnancy is associated with higher rates of gestational diabetes mellitus (5%-40%), pregnancy-induced hypertension (10%-30%), preeclampsia (8%-15%), preterm delivery (6%-15%), and small-for-gestational-age infants (no precise number reported) than pregnancies without PCOS.⁹

Additionally, some studies reported that during the first trimester, pregnant women with PCOS may have higher rate of miscarriage than healthy pregnant women. The higher rate of miscarriage is probably due to elevated concentrations of plasminogen activator inhibitor 1 (PAI-1).¹⁰

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Therefore, the coagulation and fibrinolytic systems of pregnant women with PCOS appears not to be in equilibrium—with the balance seemingly tipped to the prothrombotic state. However, it remains unclear how PCOS and pregnancy affect hemostatic indices in pregnant women with PCOS and whether obesity has any influence on this imbalanced hemostatic state in pregnant women with PCOS. Henceforth, the primary objective of this study is to assess the changes in hemostatic indices when healthy and PCOS women become pregnant. Another aim of this study is to evaluate whether having PCOS and/or obesity exert any influence on these markers.

Materials and Methods

Patients

This was a cross-sectional study conducted at the Department of Obstetrics and Gynecology at the PLA General Navy Hospital from April 18, 2011, to May 4, 2012. A total of 50 women with PCOS (25 obese women and 25 nonobese women) at 12 weeks of pregnancy (singleton pregnancy), who were diagnosed with PCOS before pregnancy, and 50 nonpregnant women with PCOS (22 obese women and 28 nonobese women) who were diagnosed with PCOS for the first time were recruited for the study. The ages of the women with PCOS ranged from 26 to 33 years, and this age range represented women in the reproductive age group. It was important to assess this particular group of pregnant women and determine whether there were any potential adverse effects of PCOS and obesity on pregnancy outcomes, as the risk for pregnancy complications can also increase with age alone.^{11,12}

The PCOS was defined according to the Rotterdam criteria.¹ Of the following 3 features, 2 are required for a diagnosis of PCOS: (1) the presence of 12 or more follicles in each ovary that are 2 to 9 mm in diameter and/or an increased ovarian volume (>10 mL) according to an ovarian ultrasound; (2) oligomenorrhea (an intermenstrual interval of more than 35 days and fewer than 8 menstrual cycles in the past year) and/or amenorrhea (the absence of menstrual bleeding in the past 90 days); and (3) clinical and/or biochemical evidence of excessive androgen levels. The information regarding these patients was obtained from their medical records.

For the control group, we selected 50 healthy pregnant women (25 obese women and 25 lean women) and 50 healthy nonpregnant women (25 obese women and 25 lean women) of similar ages, socioeconomic levels, and BMIs with singleton pregnancies, from the Department of Obstetrics and Gynecology during the same period. Women in the control group, including healthy pregnant women and healthy nonpregnant women, reported a history of regular 28- to 32-day menstrual cycles and an absence of hirsutism or other manifestations of hyperandrogenism, no signs of polycystic ovaries based on a transvaginal ultrasound before pregnancy, and no history of drug therapy—including contraceptive pills, anti-inflammatory drugs, or hormonal drugs—3 months prior to the study. Both healthy

pregnant women and pregnant women with PCOS were concurrently recruited at 12 weeks of pregnancy.

Women were excluded from this study based on pertinent information obtained from their medical records or via hormone testing prior to pregnancy. The exclusion criteria included chronic medical conditions (eg, hypertension, diabetes mellitus, autoimmune, or inflammatory disorders), hyperprolactinemia, an androgen-secreting neoplasm, congenital adrenal hyperplasia, Cushing syndrome, thyroid disease, or infectious diseases. In addition, smokers and women who self-reported that they had a history of alcohol or drug abuse were excluded from this study.

All participants signed an informed consent form, and the study protocol was approved by the ethics committee of the PLA General Navy Hospital.

Anthropometry

Body height to the nearest 0.5 cm and weight to the nearest 0.1 kg were measured in standing patients who wore light clothing and no shoes. BMI was calculated as the weight in kilogram (kg) divided by the square of height in meters. Women with a BMI > 24.9 are defined as obese, and those with a BMI ≤ 24.9 are defined as nonobese.

Study Procedure

Peripheral blood of 8 mL were obtained between 08:00 AM and 08:30 AM after an overnight fast because of the diurnal variation in the fibrinolytic variables. A total of 50 nonpregnant women with PCOS experienced oligo/amenorrhea; therefore, their blood was sampled independent of the cycle day. Blood samples were collected from 100 pregnant women at 12 weeks of gestation. The 150 blood samples were centrifuged within 30 minutes of collection for 10 minutes at 3000 rpm, and the supernatants were stored at −40°C until analysis (within 2 weeks) of the activities of coagulation factors VIII (FVIII) and X (FX) as well as the concentrations of von Willebrand factor (vWF), PAI-1, tissue plasminogen activator (t-PA), and D-dimer. These hemostatic variables were selected as FVIII, FX, and vWF were essential components of the coagulation cascade. D-dimer, PAI-1, and t-PA performed major roles in the fibrinolytic system.

Hemostatic Variables

The activities of FVIII and FX were measured using the coagulation factor FVIII and FX deficient plasma reagent (Siemens Healthcare Diagnostics Inc, Newark, Delaware), respectively, in a CA-7000 coagulation autoanalyzer (Sysmex Corporation, Hyogo, Japan) using coagulometric methods. The plasma mass concentrations of t-PA and PAI-1 were measured using a t-PA kit and PAI-1 kit (Sunbio, Shanghai, China), respectively, using the ACL TOP 700 coagulation autoanalyzer (Beckman Instrument, Lexington, Kentucky) via an enzyme-linked immunosorbent assay. The plasma mass concentrations of D-dimer and vWF:Ag were measured using a D-dimer kit and von

Table 1. Hemostatic Variables in Participants.^a

Characteristics	Healthy (n = 50)	PCOS (n = 50)	PCOS Pregnancy (n = 50)	Healthy Pregnancy (n = 50)
Age, years	28.5 ± 1.9	28.5 ± 1.8	28.9 ± 2.0	28.4 ± 1.7
BMI, kg/m ²	23.7 ± 3.2	23.9 ± 4.0	24.1 ± 3.2	23.2 ± 2.3
Activity of FVIII ^b , %	67.0 ± 15.5	69.0 ± 13.7	90.8 ± 16.4	77.6 ± 15.0
vWF:Ag ^{c,d,e} , %	88.1 ± 26.4	95.9 ± 24.7	173.2 ± 30.4	155.4 ± 32.8
Activity of FX ^b , %	90.6 ± 15.3	129.4 ± 30.9	172.3 ± 24.6	157.8 ± 24.3
D-dimer, ng/mL ^{c,e}	84.5 ± 13.9	85.1 ± 21.4	152.9 ± 21.2	146.3 ± 28.1
PAI-1, ng/mL ^{c,d,e}	37.6 ± 11.9	50.5 ± 18.6	55.3 ± 17.9	47.8 ± 8.7
t-PA, ng/mL ^{c,e}	7.2 ± 2.2	7.3 ± 2.2	6.9 ± 2.0	5.9 ± 1.4

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; FVIII, coagulation factor VIII; FX, coagulation factor X; PAI-1, plasminogen activator inhibitor 1; PCOS, polycystic ovary syndrome; SD, standard deviation; t-PA, tissue plasminogen activator; vWF, von Willebrand factor;

^a Values are expressed as means ± SD utilizing the 2-way ANOVA models used for statistical analysis.

^b There was significant interaction effect between PCOS status and pregnancy.

^c There was no significant interaction effect between PCOS status and pregnancy.

^d Main effect of PCOS status (PCOS vs healthy) controlling for the effect of pregnancy, $P < .05$.

^e Main effect of pregnancy (nonpregnancy vs pregnancy) controlling for the effect of PCOS status, $P < .05$.

Willebrand factor antigen kit (Instrumentation Laboratory, Bedford, Massachusetts), respectively, in the ACL TOP 700 coagulation autoanalyzer using the latex-enhanced immunoassay method.

Statistical Analyses

Statistical analyses were performed using SPSS for Windows (version 16.0, Chicago, Illinois). The data were presented as the mean ± standard deviation (SD). When a particular variable exhibited heterogeneity, transformation was performed before analysis. First, a 2-way analysis of variance (ANOVA) model was fitted to evaluate the effects of PCOS status (PCOS vs healthy) and pregnancy (pregnancy vs nonpregnancy) on healthy women and women with PCOS, for each hemostatic index after adjusting for age and BMI. Second, the differences were determined using an analysis of covariance (ANCOVA) to adjust for age between obese and nonobese healthy pregnant women and between obese and nonobese pregnant women with PCOS. Third, we used 2-way ANOVA to evaluate the effects of PCOS status (PCOS vs healthy) and BMI (obese vs nonobese) on pregnant women for each hemostatic index. The results of the main effect tests are reported based on the 2-way ANOVA. The interaction effect was considered not to be significant when $P > .05$. A P value of .05 or less was considered significant.

Results

Effect of PCOS and Pregnancy on Nonpregnant and Pregnant Women

We utilized 2-way ANOVA with PCOS and pregnancy as independent variables to perform comparisons on the following 4 groups of women, that is, nonpregnant healthy women, nonpregnant women with PCOS, healthy pregnant women, and pregnant women with PCOS.

Effects attributable to PCOS. The PCOS appeared to affect the levels of vWF:Ag and PAI-1 that were more elevated in

nonpregnant women with PCOS and pregnant women with PCOS than that in healthy nonpregnant women and healthy pregnant women, respectively (Table 1).

Effects attributable to pregnancy. Pregnancy also seemed to exert effects on the levels of vWF:Ag, PAI-1, D-dimer, and t-PA when using the 2-way ANOVA and controlling for the effect of PCOS (Table 1).

Interaction between PCOS and pregnancy. The interaction between PCOS and pregnancy had significant effects on FVIII and FX ($P < .05$) but exerts no significant effects on the levels of vWF:Ag, D-dimer, PAI-1, and t-PA ($P > .05$; Table 1). The mean FVIII activity was $90.8\% \pm 16.4\%$ in pregnant women with PCOS, which was higher than that in healthy pregnant women, nonpregnant women with PCOS, and healthy nonpregnant women ($77.6\% \pm 15.0\%$, $69.0\% \pm 13.7\%$, and $67.0\% \pm 15.5\%$, respectively). The mean FX activity was $172.3\% \pm 24.6\%$ in pregnant women with PCOS, which was higher than that in healthy pregnant women, nonpregnant women with PCOS, and healthy nonpregnant women ($157.8\% \pm 24.3\%$, $129.4\% \pm 30.9\%$, and $90.6\% \pm 15.3\%$, respectively).

Impact of Obesity on Healthy Nonpregnant Women or Nonpregnant Women With PCOS

We analyzed the differences in hemostatic variables between nonobese and obese healthy nonpregnant women and between nonobese and obese nonpregnant women with PCOS. The levels of coagulation and fibrinolytic indices examined in healthy nonpregnant women and in nonpregnant women with PCOS are presented in Tables 2 and 3. The circulating activity levels of FVIII and FX and the concentrations of vWF:Ag, PAI-1, and t-PA were significantly higher in the obese women than that in the nonobese women (in both healthy nonpregnant women and nonpregnant women with PCOS). However, there were no significant differences in the D-dimer levels (84.2 ± 9.0 vs

Table 2. Hemostatic Variables in Healthy Nonpregnant Women.^a

Characteristics	Nonobese Women (n = 25)	Obese Women (n = 25)
Age, years	28.7 ± 1.7	28.3 ± 2.0
Activity of FVIII, %	54.3 ± 8.1	79.6 ± 9.5 ^b
vWF:Ag, %	80.3 ± 19.6	95.9 ± 30.2 ^b
Activity of FX, %	86.7 ± 15.2	94.6 ± 14.6 ^b
D-dimer, ng/mL	84.2 ± 9.0	88.9 ± 8.9
PAI-I, ng/mL	35.0 ± 7.5	41.5 ± 11.9 ^b
t-PA, ng/mL	6.3 ± 1.6	8.1 ± 2.5 ^b

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index; PAI-I, plasminogen activator inhibitor I; t-PA, tissue plasminogen activator; vWF, von Willebrand factor; FVIII, coagulation factor VIII; FX, coagulation factor X; SD, standard deviation.

^a Values are expressed as means ± SD. BMI > 24.9, obese women; BMI ≤ 24.9, nonobese women.

^b Significant difference between nonobese and obese healthy nonpregnant women in ANCOVA with adjustment for age.

Table 3. Hemostatic Variables in Nonpregnant Women With PCOS.^a

Characteristic	Nonobese Women (n = 28)	Obese Women (n = 22)
Age, years	28.1 ± 1.5	29.0 ± 2.0
Activity of FVIII, %	60.5 ± 4.3	78.9 ± 14.4 ^b
vWF:Ag, %	88.7 ± 21.2	104.4 ± 26.2 ^b
Activity of FX, %	119.0 ± 22.8	141.6 ± 34.9 ^b
D-dimer, ng/mL	81.3 ± 17.8	89.7 ± 24.6
PAI-I, ng/mL	45.3 ± 9.5	56.7 ± 24.2 ^b
t-PA, ng/mL	6.2 ± 1.6	8.5 ± 2.1 ^b

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index; PCOS, polycystic ovary syndrome; PAI-I, plasminogen activator inhibitor I; t-PA, tissue plasminogen activator; vWF, von Willebrand factor; FVIII, coagulation factor VIII; FX, coagulation factor X; SD, standard deviation.

^a Values are expressed as means ± SD. BMI > 24.9, obese women; BMI ≤ 24.9, nonobese women.

^b Significant difference between nonobese and obese nonpregnant women with PCOS in ANCOVA with adjustment for age.

Table 4. Hemostatic Variables in Participants.^a

Characteristic	PCOS Pregnancy		Healthy Pregnancy	
	Obese	Nonobese	Obese	Nonobese
Age, years	29.4 ± 2.2	28.5 ± 1.8	28.4 ± 1.8	28.5 ± 1.7
Activity of FVIII, % ^{b,c,d}	95.4 ± 16.1	86.1 ± 15.7	82.5 ± 16.9	72.6 ± 11.1
vWF:Ag, % ^e	181.3 ± 29.9	165.2 ± 29.3	175.7 ± 30.7	135.1 ± 19.8
Activity of FX, % ^{b,c,d}	180.2 ± 27.5	164.4 ± 18.7	165.5 ± 27.6	150.1 ± 17.9
D-dimer, ng/mL ^b	156.7 ± 21.8	149.0 ± 20.2	151.8 ± 31.7	140.9 ± 23.4
PAI-I, ng/mL ^{b,d}	59.1 ± 12.9	50.3 ± 7.4	54.6 ± 12.0	47.1 ± 9.7
t-PA, ng/mL ^{b,d}	7.5 ± 1.6	6.3 ± 1.8	7.0 ± 1.8	5.6 ± 0.9

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; PCOS, polycystic ovary syndrome; plasminogen activator inhibitor I; t-PA, tissue plasminogen activator; vWF, von Willebrand factor; FVIII, coagulation factor VIII; FX, coagulation factor X; SD, standard deviation.

^a Values are expressed as means ± SD. The 2-way ANOVA models are used for statistical analysis. BMI > 24.9, obese women; BMI ≤ 24.9, nonobese women.

^b There was no significant interaction effect between PCOS status and BMI.

^c Main effect of PCOS status (PCOS vs healthy) controlling for the effect of BMI, $P < .05$.

^d Main effect of BMI (nonobese vs obese) controlling for the effect of PCOS status, $P < .03$.

^e There was significant interaction effect between PCOS status and BMI.

88.9 ± 8.9 ng/mL, $P > .05$ in Table 2; 81.3 ± 17.8 vs 89.7 ± 24.6 ng/mL, $P > .05$ in Table 3).

nonobese pregnant women with PCOS, obese healthy pregnant women, and nonobese healthy pregnant women (165.2% ± 29.3%, 175.7% ± 30.7%, and 135.1% ± 19.8%, respectively).

Impact of Obesity and PCOS on Pregnant Women

The results of the 2-way ANOVA on the effects of obesity and PCOS on pregnant women are presented in Table 4. The levels of D-dimer were not affected by either PCOS or obesity. Both PCOS and obesity variables exerted effects on activities of FVIII and FX, which were significantly elevated in PCOS obese and nonobese pregnant women when compared to healthy obese and nonobese pregnant women (Table 4). The PCOS variable appeared to exert effects on PAI-I and t-PA concentrations in pregnant women (Table 4). Interaction effects between PCOS and obesity were observed in vWF:Ag concentrations ($P < .05$). The mean vWF:Ag concentration was 181.3% ± 29.9% in obese pregnant women with PCOS, which was higher than that in

Discussion

In this study, we determined that by the end of the first trimester of pregnancy, there were significant changes in hemostatic indices of women with PCOS compared to the nonpregnant state. Additionally, obesity may influence hemostatic indices in pregnant women with PCOS.

Hemostatic Variables in Healthy Pregnant Women and Pregnant Women With PCOS

In the comparisons made among the 4 groups of women, that is, nonpregnant healthy group, pregnant healthy group,

Figure 1. A simplified representation of coagulation cascade and fibrinolysis. PAI-1 indicates plasminogen activator inhibitor 1; t-PA, tissue plasminogen activator; FVIII, factor VIII; FX, factor X.

nonpregnant women with PCOS, and pregnant women with PCOS, we found that the interaction between PCOS and pregnancy had significant effects on the activities of FVIII and FX.

Coagulation variables. Elevated levels of FVIII and FX could lead to hypercoagulability. Factor VIII is a component of the intrinsic coagulation pathway and is associated with the risk of venous thrombosis¹³ and increases during a normal pregnancy.⁷ Factor X is a vitamin K-dependent plasma glycoprotein that plays a pivotal role in the coagulation cascade, because it is the first enzyme in the common pathway of thrombin formation. Physiologically, FX is activated by TF (tissue factor)/FVIIa (extrinsic pathway) and FIXa/FVIIIa (intrinsic pathway). In turn, FXa catalyzes thrombin formation (Figure 1). Our study demonstrated that the effects of PCOS and pregnancy had interactions on the activity levels of FVIII and FX. These findings may be attributable to the fact that FVIII is synthesized from the endothelium. It seems that FVIII is elevated when the endothelium is injured due to the rising low-density lipoprotein (LDL) and insulin levels in women with PCOS or IR.^{3,14,15} Cholesterol and triglycerides were significant positive correlates of FX.¹⁶ Furthermore, dyslipidemia (low high-density lipoprotein-cholesterol and high LDL cholesterol levels), induced by pregnancy, can lead to an increase in TF synthesis,^{17,18} and TF enables cells to initiate the coagulation cascade, resulting in the increase in the activity levels of FVIII and FX. The rising levels of FVIII and FX, which is observed in pregnant women in our study, are probably due to

the initiation of coagulation cascade secondary to the physiological changes in lipid metabolism and increased levels of TF in pregnancy.

The vWF is a clotting protein, which is associated with the risk of venous thrombosis.¹⁹ In previous studies, vWF concentration was observed to be significantly increased in women with PCOS compared with controls²⁰ and increased during a normal pregnancy.⁷ In this study, PCOS and pregnancy appeared to exert a significant rise in the levels of vWF concentration independently, which was consistent with certain published studies.^{7,20} However, there was no interaction found between PCOS and pregnancy in our study, suggesting that these 2 variables were probably acting independently on the rise in vWF concentrations.

Fibrinolytic variables. D-dimer, a specific marker of fibrinolysis arising from the breakdown of cross-linked fibrin polymer by plasmin, increases throughout pregnancy and acts as a marker of fibrinolysis and hypercoagulability. The fibrin concentration is elevated in response to coagulation activation. Elevated levels of D-dimer indicate increased fibrinolysis following fibrin formation. D-dimer levels are significantly higher during early pregnancy²¹ and are significantly different between women with PCOS and controls in an earlier study.²² In this study, only pregnancy had effect on the D-dimer levels, either the interaction between PCOS and pregnancy or PCOS alone had no effect on D-dimer levels, which was consistent with some previously published studies,²¹ although another study

did not report similar findings.²² The fact that there were no significant differences in D-dimer levels between pregnant women with PCOS and controls may be because a number of pregnant women with PCOS before pregnancy accepted drug treatments (eg, metformin) that may reduce D-dimer levels.²³

The PAI-1 is the principal inhibitor of fibrinolysis and the most extensively studied hemostatic factor in PCOS. The PAI-1 is produced in adipocytes, endothelial cells, and hepatocytes in response to hormonal, metabolic, and inflammatory stimuli. The t-PA, primarily synthesized in vascular endothelial cells and secreted into the blood, converts inactive plasminogen into plasmin that is responsible for fibrin degradation. In contrast, PAI-1 regulates fibrinolysis by inhibiting t-PA. Increased PAI-1 activity is associated with hypofibrinolysis and may contribute to thrombosis. During a normal pregnancy, the coagulation process predominates over fibrinolytic activity. The level of PAI-1 increases during the third trimester, and the rise in PAI-1 is not significant during the first trimester.⁸ Moreover, the t-PA concentration decreases during the first 10 weeks⁸ and then increases beginning in the second trimester. Additionally, PAI-1 activity is higher in nonpregnant women with PCOS than that in controls after adjusting for age and BMI.⁶ In our study, pregnancy and PCOS affected PAI-1 concentration independently and only pregnancy affected t-PA concentration. Hyperandrogenism and IR (the 2 major key features in PCOS women) were attributed to PAI-1 concentration⁶; and dyslipidemia that pregnancy may induce could increase PAI-1 concentration.^{18,24}

In summary, PCOS and pregnancy appeared to affect the hemostatic indices independently. Moreover, the significant interaction between PCOS and pregnancy only affects the activity levels of FVIII and FX. Therefore, when nonpregnant women with PCOS become pregnant, they are likely to be in a more prothrombotic state than healthy women who get pregnant as the activities of FVIII and FX and the levels of WF and PAI-1, which are all involved in the coagulation cascade, are significantly higher in pregnant women with PCOS, as demonstrated in our study.

Differences Between Obese and Nonobese Pregnant Women

In our study, obesity appeared to exert an effect on the FVIII, FX, vWF:Ag, PAI-1, and t-PA concentrations in the nonpregnant healthy women and nonpregnant women with PCOS, although the D-dimer levels were unaffected. Due to the general effects of obesity on the hemostatic indices examined in our study population, we introduced obesity as 1 of 2 independent variables in a 2-way ANOVA that included all pregnant women as well.

In the analysis of the following comparisons between nonobese and obese healthy pregnant groups and nonobese and obese pregnant women with PCOS, we found that the interaction between PCOS and obesity had significant effect on vWF levels.

Coagulation variables. In the previous studies, vWF concentration was observed to be significantly increased in women with PCOS

compared with controls,²² and vWF was associated with the formation of triglyceride. In our study, the interaction between PCOS and obesity exerts a significant effect on vWF levels. These findings may be attributable to the fact that vWF is mainly released from the vascular endothelium. Hyperinsulinaemia, IR, and dyslipidemia, which often accompany PCOS, predispose to endothelial injury. Additionally, free fatty acids, associated with visceral obesity, could increase the production of endothelial factors such as vWF.²⁵ Moreover, vWF is often associated with visceral adipose tissue, particularly in women with abdominal obesity.²⁶

In pregnant women, both BMI and PCOS appear to influence the activity levels of FVIII and FX independently, which are consistent with those of the previous studies. The FVIII has been associated with triglyceride development, and the reasons of PCOS effect on the activity levels of FVIII and FX have been mentioned previously. However, FX has not been previously investigated in the studies of pregnant women with PCOS, and this is a novel observation in our study.

Fibrinolytic variables. The elevation of PAI-1 and t-PA levels in obese and nonobese pregnant women may be a function of obesity rather than a complication of PCOS. The effect of obesity on PAI-1 and t-PA levels was consistent with the results of the previous studies. The concentration of PAI-1 was positively correlated with BMI,⁶ and this substance was secreted by adipose tissue.²⁷ In the comparisons of obese and nonobese pregnant women, PAI-1 and t-PA concentrations were elevated in obese participants compared with those who were lean, regardless of their PCOS status. However, in the comparisons of healthy women (pregnant and nonpregnant) and women with PCOS (pregnant and nonpregnant), our results revealed that PCOS exerts significant effects on PAI-1 and t-PA concentrations. The differences that PCOS had effect on PAI-1 and t-PA may be influenced by the study patients. In our study population, some of the pregnant women with PCOS may have accepted drug treatments (eg, metformin) before pregnancy, which may have reduced PAI-1 and t-PA concentrations.²³

Additionally, our results suggested that neither PCOS nor obesity affected D-dimer levels. We have discussed earlier on the plausible reasons why PCOS does not seem to have any effect on D-dimer level. The D-dimer levels do not differ before or after adjusting for age and BMI,⁶ and the result of our study is consistent with some of the previous studies.⁶

In general, only vWF level was affected by the interaction between PCOS and obesity. This significant interaction is likely to affect the coagulation indices to promote a prothrombotic state in women who are obese and have PCOS.

The inability to measure and control for other factors (eg, diet, environmental factors, and physical activity) that could influence the levels of coagulation and fibrinolytic markers within the study population is a potential limitation of this study.^{28,29} Also, this study employs a cross-sectional study design; thus, we cannot infer that the changes of the coagulation and fibrinolytic indices in obese and nonobese pregnant women with PCOS will directly result in significant

complications later in pregnancy. Additionally, the small sample size used for comparison in this study may not detect any real difference between the various groups of women.

In conclusion, our results demonstrate that the hemostatic system in pregnant women with PCOS is likely to be in marked disequilibrium in the first trimester of pregnancy, which is demonstrated by the increasing concentrations of FVIII, FX, and vWF. The interaction between PCOS and pregnancy affects FVIII and FX concentrations, while the interaction between PCOS and obesity affects vWF concentrations. Therefore, obese pregnant women with PCOS are more prone to a prothrombotic state. Future prospective studies need to be conducted in the second and third trimesters in pregnant women with PCOS to provide further insights with regard to the possible changes in the later trimesters of pregnancy and any other complications observed in these women.^{9,30} These findings will have great potential in facilitating the development of interventions during pregnancy, which, hopefully, can reduce adverse obstetric outcomes in pregnant women with PCOS.

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Authors' Note

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