Android fat distribution affects some hemostatic parameters in women with polycystic ovary syndrome compared with healthy control subjects matched for age and body mass index

Maria Raquel Marques Furtado de Mendonça-Louzeiro, M.D.,[a]
Joyce Maria Annichino-Bizzacchi, M.D., Ph.D.,[b] and Cristina Laguna Benetti-Pinto, M.D., Ph.D.[a]

[a] Department of Gynecology and Obstetrics, School of Medical Sciences, and [b] Department of Internal Medicine, Hemostasis Laboratory, Blood Center, University of Campinas, São Paulo, Brazil

Objective: To correlate hemostatic parameters with clinical markers of fat distribution and laboratory variables in women with polycystic ovary syndrome (PCOS) compared with healthy control subjects.
Design: Cross-sectional study.
Setting: Tertiary teaching hospital.
Patient(s): Forty-five women with PCOS and 45 control women matched for age and body mass index (BMI).
Intervention(s): Clinical evaluation and venipuncture.
Main Outcome Measure(s): Age, BMI, waist circumference (WC), hip circumference (HC), waist-hip ratio (WHR), Ferriman-Gallwey index, fasting glucose, fasting insulin, total testosterone, free testosterone (FT), thrombin-activatable fibrinolysis inhibitor (TAFI), D-dimer, plasminogen activator inhibitor (PAI) 1, and the parameters of thrombin generation test (TGT), including the lag time (Tlag), time to peak thrombin generation (Tmax), peak concentration (Cmax), and the area under the thrombin generation curve (TAUC).
Result(s): In the PCOS group, BMI and WC correlated positively with TAFI, D-dimer, PAI-1, Cmax, and TAUC; HC with D-dimer and PAI-1; WHR with TAFI, D-dimer, and PAI-1; glucose with TAFI; insulin and homeostasis-model assessment of insulin resistance with PAI-1; and FT with Cmax and TAUC. Age correlated positively with D-dimer and PAI-1, and negatively with Tlag and Tmax. In the control group, there were no correlations between clinical markers of fat distribution and hemostatic parameters, but age and fasting glucose correlated positively with PAI-1, and FT with Tmax and TAUC.
Conclusion(s): In PCOS, android body fat distribution may directly affect hemostatic parameters, particularly in young and overweight women. Further studies are needed to establish a correlation between these results and an increase in thromboembolic risk. (Fertil Steril® 2015;104:467–73. ©2015 by American Society for Reproductive Medicine.)
Key Words: Polycystic ovary syndrome, hemostatic parameters, body fat distribution, fibrinolysis, venous thrombosis

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Reprint requests: Cristina Laguna Benetti-Pinto, M.D., Ph.D., Departamento de Ginecologia e Obstetrícia, Faculdade de Ciências Médicas, Universidade Estadual de Campinas (UNICAMP), Av. Alexander Fleming, 101, Cidade Universitária, 13083-881 Campinas, São Paulo, Brazil (E-mail: laguna.unicamp@gmail.com).

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Polycystic ovary syndrome (PCOS) is a highly prevalent condition, affecting 5%–10% of women of reproductive age (1–3). In addition to the reproductive disorders and the symptoms of excess androgen production, patients with PCOS often present with metabolic abnormalities that include obesity, dyslipidemia, and

insulin resistance (IR). Consequently, they may be at a greater risk of glucose intolerance, type 2 diabetes mellitus (4), metabolic syndrome, subclinical atherosclerosis, and vascular dysfunction, with an increased risk for cardiovascular disease (CVD) (5–10).

Obesity plays a crucial role in the development of both IR and the proinflammatory state that is part of the metabolic syndrome. Although the metabolic abnormalities may be present regardless of body mass index (BMI), obesity, particularly abdominal obesity, is considered to be a clinical predictor of metabolic abnormalities. Abdominal circumference is increased in women with PCOS. This is indicated by a greater waist-to-hip ratio (WHR), which reflects an increase in visceral fat (11). Visceral fat contains the proinflammatory cytokines that are known to promote IR: tumor necrosis factor a and interleukin-6 (12). Some authors also report that the excess androgen production characteristic of PCOS probably favors early abdominal obesity, facilitating IR as well as stimulating the hypertrophy of adipocytes (13).

Thus, the typical features of PCOS are well known risk factors for CVD (14). However, although it is assumed that the disorders of the hemostatic system present in PCOS may contribute to increased risk of cardiovascular events, evidence in the literature is conflicting and based on only a few studies (14–18), with many questions remaining to be answered, particularly regarding pathogenesis and risk factors (19, 20). A recent study showed that thrombin generation is faster in young and overweight women with PCOS, suggesting a greater risk of hypercoagulability (21); however, although hypotheses have been put forward on the relationship between different hemostatic parameters and fat distribution, androgens, and IR, this question remains to be fully clarified. Therefore, the present study was developed based on the hypothesis that differences may be present in the association between some clinical and laboratory parameters and the hemostatic parameters of women with PCOS compared with women without PCOS, paired for age and BMI.

The objective of the present study was to correlate hemostatic parameters with clinical markers of fat distribution and laboratory variables in women with PCOS compared with healthy control women matched for age and BMI.

SUBJECTS AND METHODS

Subject Selection

A cross-sectional study was conducted with 45 women with PCOS (Rotterdam Consensus definition, 2003) (22) and 45 women with normal ovarian function (control group). The women with PCOS were each paired, one to one, with control women according to age (±2 years) and BMI (±2 kg/m^2). The study participants were 18–35 years old, had not been using any hormonal methods of contraception for ≥3 months before enrollment, and were receiving care at the gynecologic endocrinology (case) and family planning (control) outpatient clinics at the Department of Gynecology and Obstetrics, School of Medical Sciences, University of Campinas, Brazil.

The study group consisted of women with PCOS attending the gynecologic endocrinology outpatient clinic who fulfilled the inclusion criteria and had not been using any hormonal contraceptive method in the preceding 3 months. If these criteria were met, the women were invited to participate in the study and were included sequentially until the required number of participants was reached. The participants in the control group were selected at the family planning clinic from a group of women scheduled to have an intrauterine device inserted. All had regular menstrual cycles (24–35 days) and had not been using any hormonal contraceptive method or any other type of medication that could alter the menstrual cycle for ≥3 months. None of these women had hirsutism, and at clinical examination all were evaluated according to the Ferriman-Gallwey index (23). They were also submitted to ultrasonography to verify the position of the intrauterine device, and polycystic ovaries were not found in any of them. Therefore, it is reasonable to assume that none of the women in the control group had PCOS. Women were selected one by one for this control group, i.e., for each woman in the study group, a woman was selected to be her pair in the control group.

The following clinical variables were evaluated in the two groups: age, BMI, waist and hip measurements, WHR, and Ferriman-Gallwey index. Laboratory variables included fasting glucose, fasting insulin, insulin resistance according to the homeostasis model of assessment (HOMA-IR) (24), total testosterone, free testosterone (FT), and hemostatic parameters thrombin-activatable fibrinolysis inhibitor (TAFI), D-dimer, plasminogen activator inhibitor (PAI) 1, and thrombin generation test (TGT).

Exclusion criteria consisted of pregnancy, chronic diseases, such as hypothyroidism, hyperprolactinemia, late-onset congenital adrenal hyperplasia, kidney failure, and liver failure, BMI ≥40 kg/m^2 (morbid obesity), history of cancer or thromboembolic disease, and the use of any medication that could interfere with coagulation or fibrinolysis, such as aspirin, heparin, or any other anticoagulant, antiplatelet drug, or hormone.

The study was approved by the institution's Internal Review Board, and every participant signed an informed consent form.

Laboratory Tests

Blood sampling. All samples were collected between 7:30 and 10:00 a.m. (to avoid the effect of the daily variation in the hemostatic system), after ≥12 hours fasting, from the antecubital vein in the left arm, with minimal or no venous occlusion (protracted venous occlusion may stimulate PAI-1 production by the endothelial cells and alter the results of other markers of hemostasis). Blood sampling was performed between the 3rd and the 9th days of the menstrual cycle, or >60 days after the last menstrual period for the women with PCOS.

To measure hemostasis parameters (TAFI, D-dimer, PAI-1, and TGT), 14 mL peripheral blood was collected in 3.8% sodium citrate in a proportion of 9:1 and immediately centrifuged at 3,500 rpm for 15 minutes. The plasma was divided into aliquots of 400 μL and stored in a freezer at −80°C until analysis. For the biochemical and hormone