Assessment of insulin resistance in lean women with polycystic ovary syndrome

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Objective: To develop and validate a specific simple measure of insulin sensitivity using oral glucose tolerance test (OGTT) values for lean polycystic ovary syndrome (PCOS) women.
Design: Retrospective study.
Setting: Gynecologic Outpatient Clinic of University Hospital, affiliated with Unit of Gynecologic Endocrinology.
Patient(s): Totals of 201 lean and 198 overweight/obese (ov-ob) nondiabetic PCOS patients were retrospectively selected.
Intervention(s): None.
Main Outcome Measure(s): All patients underwent OGTT, euglycemic-hyperinsulinemic clamp, and androgenic and biochemical assays. The predictive performance of each insulin resistance (IR) index was analyzed with the use of receiver operating characteristic (ROC) curves.
Result(s): Higher correlation coefficients with clamp studies were obtained with the Belfiore Area ($R_S = 0.579$) and the homeostasis-model assessment (HOMA)-M_{120} ($R_S = -0.576$) in lean PCOS patients and with the Sib ($R_S = 0.697$) in ov-ob PCOS patients. The best predictive index of IR in lean PCOS was a HOMA-M_{120} value of ≥ 12.8 or more (area under the ROC curve [AUC] 92.4%). In the ov-ob PCOS population, the best predictive performance was obtained by a Sib of ≤ 10.2 or less (AUC 85.7%).
Conclusion(s): IR should be assessed in all PCOS women, both lean and ov-ob subjects. The HOMA-M_{120} resulted as a very simple tool, validated specifically for the lean PCOS woman whose cardiometabolic impairment is more frequently misunderstood. (Fertil Steril® 2014;102:250–6. ©2014 by American Society for Reproductive Medicine.)
Key Words: Polycystic ovary syndrome, insulin resistance, HOMA-M_{120}, clamp

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The polycystic ovary syndrome (PCOS) is among the most common endocrine disorders encountered in the reproductive-age female population, affecting ~2.2%–26% of these women (1), and represents one of the most frequent causes of secondary amenorrhea and infertility, due to chronic anovulation and hyperandrogenism.

PCOS is currently diagnosed with the use of the 2003 Rotterdam Criteria based on the presence of at least two of the following conditions: 1) oligoamenorrhea and/or anovulation; 2) hyperandrogenism (clinical and/or biochemical); and 3) polycystic ovary on ultrasound examination (2).

In addition to these gynecologic symptoms, PCOS is characterized by several metabolic disorders recently subjected to extensive investigations. Nowadays, particular emphasis is placed on the presence of insulin resistance (IR) with compensatory hyperinsulinemia (HI) being that obesity and alterations in glucose metabolism are observed more frequently in women with PCOS compared with the general population (3).

Interestingly, when associated with central obesity, IR is recognized as part of a complex syndrome associated with several cardiovascular risk factors, such as dyslipidemia, hypertension, dysfibrinolysis, and glucose intolerance (4).

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The criterion standard methods to assess insulin sensitivity (euglycemic-hyperinsulinemic clamps and minimal model analysis) are expensive, time consuming, and difficult to apply in large-scale clinical or epidemiologic studies, so easier methods are required. These difficulties have raised interest in obtaining new glucose and insulin measurements in the fasting state or during an oral glucose tolerance test (OGTT) (5). Several indices have been described and validated as reference methods for PCOS women (6–8). Unfortunately, several of these indices—especially glycemic or insulinemic basal evaluation—were found to be not reliable or predictive measures of IR in lean PCOS women, this subpopulation showing neither fasting HI nor increased basal hepatic glucose production (HGP) (6, 9–11). Indeed, the IR evaluation in lean PCOS patients could be underestimated in clinical practice, owing to the absence of obesity, a well known important cardiometabolic risk factor.

Based on these observations, the aim of the present study was to develop and validate a specific simple measure of insulin sensitivity with the use of OGTT values in lean PCOS women.

In our clinical practice, the most used IR indices are homeostasis-model assessment (HOMA) (12, 13) and insulinemic 2-hour area under the curve (AUCi 2h), both derived from OGTT and their use being manageable in daily practice. In the present study, we retrospectively analyzed the results of glycemic and insulinemic OGTT (30, 60, 90, 120, and 180 minutes) in lean PCOS patients. Afterward, a modified HOMA-IR formula was applied to each time-course value of glycemia and insulinemia (Table 1). Furthermore, the best resulting IR predictive index, the HOMA-M_{120}, was compared with other indices of insulin sensitivity (Supplemental Table 1, available online at www.fertstert.org) to assess its validity as IR measure in lean PCOS women.

In a second part of this study, we applied the HOMA-M_{120} in overweight-obese (ov-ob) PCOS women and compared it with other indices of insulin sensitivity in order to verify the validity of our new index in this subpopulation as well.

MATERIALS AND METHODS

Study Population

The Institutional Review Board of our institute at the Policlinico Gemelli, Rome, approved this protocol study.

Totals of 201 lean (body mass index [BMI] ≤ 25 kg/m^2) and 198 ov-ob (BMI >25 kg/m^2) PCOS women, aged 18–35 years, were selected from our database among patients who attended the Unit of Gynecologic Endocrinology of our University Hospital from January 2010 to September 2012. All women had spontaneous onset of puberty and normal sexual development, all had oligoamenorrhea with chronic anovulation since puberty, and none of them had taken any medication known to affect plasma sex steroids, lipid, or glucose metabolism for ≥ 3 months before attending our outpatients clinic.

PCOS was diagnosed according to the Rotterdam criteria (2). All selected women had no diabetes mellitus (DM), impaired glucose tolerance, or other hormonal dysfunctions (hypothalamic, pituitary, thyroidal, or adrenal causes). Indeed, to validate a screening method for primary prevention, all PCOS patients with impaired glucose tolerance or type 2 DM were excluded from the present study.

No patients smoked more than ten cigarettes per day or drank more than 300 g alcohol per week. Breast cancer, altered liver or kidney parameters, history of major thromboembolism, and hypertension also were considered to be exclusion criteria.

Anthropometric, Clinical, and Biochemical Variables

BMI, waist-hip ratio (WHR), hirsutism, acne, blood pressure, and family history of early coronary artery disease were analyzed in all patients.

Obesity was defined as BMI >27 kg/m^2 (7, 14, 15) (normal range 19–25 kg/m^2). Overweight was defined as BMI 25–27 kg/m^2.

For the determination of WHR, waist circumference was determined as the minimum value between the iliac crest and the lateral costal margin, and hip circumference was calculated as the maximum value over the buttocks.

Hirsutism was evaluated with the use of the Ferriman-Gallwey (FG) map scoring system (hirsutism was diagnosed if FG >8) (16), and clinical acne was defined by a history of persistence of acne (presence of acne on most days for ≥ 3 years) and presence of more than ten inflammatory acne lesions (17). Family history of early coronary artery disease was defined as first-degree relative with history of myocardial infarction at age <60 years.

TABLE 1

Insulin resistance predictivity of HOMA-IR and our modifications in lean PCOS patients.

				95% CI						
Index	**Cutoff**	**AUC (%)**	**SE**	**Lower boundary**	**Upper boundary**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	***P* value**
HOMA-IR	≥1.7	60.7	0.06	0.504	0.703	46	78	43	80	NS
HOMA-M_{30}	≥24	66.6	0.06	0.565	0.757	61.5	74.3	45.7	84.6	.007
HOMA-M_{60}	≥19.8	73.1	0.06	0.633	0.815	80.7	64.8	44.7	90.6	<.001
HOMA-M_{90}	≥20.6	85	0.05	0.764	0.914	69.2	93.1	78.3	89.5	<.001
HOMA-M_{120}	≥12.8	92.4	0.02	0.841	0.955	89	87	72	96	<.001
HOMA-M_{180}	≥2.6	75	0.06	0.640	0.840	86.9	52.6	42.6	90.9	<.001

Note: Cutoff: criterion value corresponding with highest Youden index. AUC = area under the receiver operating characteristic curve; HOMA = homeostasis-model assessment; IR = insulin resistance; PPV = positive predictive value; NPV = negative predictive value; NS = not statistically significant ($P>.05$).

Morciano. PCOS and insulin resistance. Fertil Steril 2014.