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 ($P>.05$).

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TABLE 2

Clinical, biochemical, and endocrine characteristics of studied PCOS populations.

Parameters	Lean (n = 201)	Overweight/obese (n = 198)	*P* value
Age (y), mean ± SD	29 ± 4	28 ± 4	NS
BMI (kg/m^2), median (range)	22.81 (19–24.53)	28.42 (26–31)	.022
WHR, median (range)	0.65 (0.48–0.83)	0.82 (0.69–0.89)	.034
Family history, n (%)	54 (26.86)	61 (30.80)	NS
Hypertension, n (%)	12 (5.97)	32 (16.16)	.028
Total cholesterol (mg/dL), mean ± SD	193.21 ± 32.13	184.31 ± 26.24	NS
LDL Cholesterol (mg/dL), mean ± SD	109.72 ± 23	112 ± 29.36	NS
HDL cholesterol (mg/dL), mean ± SD	44.51 ± 14.63	39.58 ± 13.47	.029
Triglycerides (mg/dL), mean ± SD	79 ± 24.34	116 ± 28.42	.021
T (ng/mL), median (range)	0.62 (0.27–0.81)	0.66 (0.31–0.85)	NS
FAI, mean ± SD	6.41 (3.43–7.54)	8.72 (5.3–9.97)	.031
SHBG (nmol/L), median (range)	42.3 (35.3–64)	29.5 (18.6–34.3)	.022
A (ng/mL), median (range)	3.51 (1.57–4.23)	3.42 (1.83–3.93)	NS
DHEAS (ng/mL), median (range)	3,295 (1,646–2,790)	3,095 (2,013–3,763)	NS
17OH-P (ng/mL), median (range)	0.73 (0.48–0.79)	0.82 (0.46–0.94)	NS
Ovarian volume (cm^3), median (range)	11.52 (9.14–13.87)	11.96 (8.17–15.86)	NS

Note: A = androstenedione; BMI = body mass index; FAI = free androgen index; HDL = high-density lipoportein; LDL = low-density lipoportein; NS = not statistically significant (*P*>.05); WHR = waist-hip ratio.

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At day 3 of a spontaneous menstrual cycle or after amenorrhea >60 days (with plasma progesterone <1.5 ng/mL), blood samples were obtained at 7 a.m., after an overnight fast, to measure the levels of total T (coefficients of variation 0.2–0.7 ng/mL), SHBG (coefficients of variation 25–100 nmol/L/L), androstenedione (A; coefficients of variation 0.40–3.0 ng/mL), 17-hydroxyprogesterone (17OH-P; coefficients of variation 0.2–1.2/1.0–3.0 ng/mL), DHEAS (coefficients of variation 800–3,500 ng/mL), triglycerides (coefficients of variation 20–170 mg/dL), total cholesterol (coefficients of variation 130–200 mg/dL), and high- and low-density lipoprotein (HDL and LDL) cholesterol (coefficients of variation HDL >45 mg/dL, LDL <130 mg/dL).

The free androgen index (FAI; coefficients of variation <5) was calculated by the following formula: T × 100/SHBG.

All patients underwent transvaginal ultrasonography. Ovarian volume was calculated by the following formula: $V = (\pi/6) \times D_{length} \times D_{width} \times D_{thickness}$, where D denotes the dimension. PCO morphology was defined by the presence of ≥12 follicles measuring 2–9 mm in diameter in each ovary and/or increased ovarian volume (>10 cm^3) (2). On the same day, patients underwent an OGTT, and 2 days later the euglycemic-hyperinsulinemic clamp was performed after another overnight fast.

A normal glycemic response to OGTT was defined according to criteria of the American Diabetes Association (18). The euglycemic-hyperinsulinemic clamps and the OGTTs (75 g) were performed as previously described (19, 20). In particular, the plasma glucose concentration was held constant (clamped) at basal levels by a variable glucose infusion with the use of the negative feedback principle (19). During the steady-state phase, the rate of glucose infusion is equal to the rate of total glucose uptake, and is therefore a measure of tissue insulin sensitivity, labeled "M." M was expressed as mg/kg of body weight per minute. We preferred this index as measure of insulin sensitivity, because the M/I ratio fails to narrow the range of individual sensitivity values (20).

The presence of IR was defined as an M value <4.45 mg/kg/min calculated by the mean ± 2 SD of the M values obtained by euglycemic-hyperinsulinemic clamps performed in a group of 50 control normo-ovulatory lean women evaluated in the early follicular phase of their cycles (7).

Assays

All hormones were measured in our laboratory. Levels of A, T, SHBG, DHEAS, and 17OH-P were measured in duplicate by RIA methods with the use of a commercial kit (Radim).

Insulin was determined with the use of an immunoradiometric assay (Diasorin) and glucose plasma concentration with the glucose oxidase technique with a glucose analyzer (Beckam). Total cholesterol and triglyceride concentrations were determined with the use of an enzymatic assay (Bristol). HDL concentrations were determined after precipitation of chylomicrons, VLDL, and LDL (Boehringer). A magnesium chloride/phosphotungstic acid technique was used to precipitate LDL from the bottom fraction after ultracentrifugation.

Computation of HOMA-M_{120} and Comparison of Various IR Indices

The HOMA-M_{120} was adapted from the HOMA-IR index developed and published by Matthews et al. (12). He used a simplified algorithm based on the HOMA-model computerized results, which express the product of fasting glucose

and insulin divided by 22.5 (or by 405 if glucose was expressed in mg/dL).

We modified this index with the use of a different time evaluation of the glucose and insulin plasma levels after OGTT, and we tested each of the resulting indices in the lean PCOS women (Table 1). In particular, the modified HOMA-M_y indices were calculated as follows:

$$\text{HOMA-M}_y = G_y(\text{mg/dL}) \times I_y(\mu\text{IU/mL})/405$$
$$\text{or}$$
$$G_y(\text{mmol/L}) \times I_y(\mu\text{IU/mL})/22.5$$

Where y indicates 30-, 60-, 90-, 120-, or 180-minute glucose and insulin values from the OGTT.

The 120-minute glucose and insulin evaluation (HOMA-M_{120}) was the resulting best IR index in lean PCOS women (Table 1) and subsequently was compared to several other indices of insulin sensitivity obtained from the OGTT (Supplemental Table 1) to assess its relative validity as a measure of IR in lean PCOS women.

Afterward, we wanted to investigate if our index could be considered to be a valid IR marker in ov-ob PCOS women as well. To this aim, we applied the HOMA-M_{120} in this subpopulation and compared the obtained results to several other indices of insulin sensitivity.

Statistical Analyses

All results are expressed as mean ± SD or as median and range as appropriate. All variables for evaluation of insulin sensitivity were examined for normality of distribution with the Kolmogorov-Smirnov goodness-of-fit test. Because of the nonparametric distribution of the analyzed variables, Spearman rank correlation coefficient (R_S) was used to study the strength of association between measurements of insulin sensitivity.

The performance of each index for insulin sensitivity was described and compared as follows. Receiver operating characteristic (ROC) curves were built and analyzed with the use of the SPSS release 15.0 package. A statistical comparison of the areas under the ROC curves (AUCs) was made according to methods previously described by Hanley and McNeil (21). For each studied group, comparisons were made between the best predictive indices and all other parameters considered. Starting from arbitrarily set up cutoff values, ROCs were computed assuming a nonparametric distribution. SE, asymptotic significance, and asymptotic 95% confidence intervals were also reported.

The positive predictive value (PPV) and the negative predictive value (NPV) were calculated as well. $P<.05$ was considered to be statistically significant.

RESULTS

Clinical, Biochemical, and Endocrine Characteristics

As expected, BMI and WHR were significantly higher in the ov-ob PCOS group than in the lean PCOS group (Table 2).

No significant differences were observed in terms of total cholesterol or LDL cholesterol. At univariate analysis, the ov-ob PCOS patients showed significant higher levels of triglycerides ($P=.021$) and FAI ($P=.031$) and lower HDL cholesterol ($P=.029$) and SHBG ($P=.022$) levels than the lean PCOS group (Table 2). No statistical differences were found between ov-ob and lean PCOS patients regarding family history of early coronary artery disease. However, hypertension was statistically more frequent in ov-ob than in lean PCOS women ($P=.028$; Table 2).

All the other characteristics and the endocrine parameters were found to be similar between the studied groups, and, as expected, both ov-ob and lean PCOS populations had a median ovarian volume >10 cm^3 (Table 2).

Insulin Resistance Indices in Lean PCOS Women

According to the cutoff of 4.45 mg/kg/min (M value) for the diagnosis of IR evaluated by euglycemic-hyperinsulinemic clamp studies, 53 lean PCOS women (26.3%) were classified as insulin resistant.

The IR predictivity of HOMA-IR and our time-related modifications in lean PCOS patients are presented in Table 1. The best IR-predictive performance in this subpopulation was obtained with HOMA-M_{120}, with an AUC of 92.4%.

A comparison between the AUCs of HOMA-M_{120} and the other HOMA-M_y indices showed a statistically significant difference ($P<.05$ for all comparisons; data not shown).

Furthermore, we tested our index in association with the other fasting or OGTT-derived indices in the lean PCOS women. Supplemental Table 2 (available online at www.fertstert.org) presents several correlation coefficients (R_S) between M values obtained by euglycemic-hyperinsulinemic clamp and the other IR indices in lean PCOS women. The R_S values are presented in decreasing order within the lean PCOS group, with HOMA-M_{120}, Belfiore area, and Stumvoll index showing the highest R_S values.

Moreover, we examined the sensitivity and specificity of various cutoff values for these indices. Supplemental Figure 1 (available online at www.fertstert.org) shows the ROC curve graphs with sensitivity plotted against 1 − specificity. The predictive performance of the best cutoff values of IR for the lean PCOS patients is presented in Table 3. The AUCs (%) are presented in decreasing order within the table. Our index, the HOMA-M_{120}, showed the best predictive performance in the IR diagnosis with a cutoff of ≥ 12.8 or more (AUC 92.4%). According to this cutoff, 25 cases out of 201 lean PCOS women would be misclassified (6 insulin-resistant patients coded as insulin-sensitive and 19 insulin-sensitive patients coded as resistant, representing a specificity of 87% and a sensitivity of 89%). A comparison between the AUCs of HOMA-M_{120} and the other best predictive indices of IR for lean PCOS women showed a statistically significant difference ($P<.05$ for all comparisons; data not shown).

Insulin Resistance Indices in ov-ob PCOS Women

The 198 ov-ob PCOS patients were evaluated with the euglycemic-hyperinsulinemic clamp, and 143 of them (72%)

TABLE 3

Predictivity of parameters of insulin resistance in lean PCOS patients.

				95% CI						
Index	**Cutoff**	**AUC (%)**	**SE**	**Lower boundary**	**Upper boundary**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	***P* value**
HOMA-M_{120}	≥12.8	92.4	0.02	0.841	0.955	89	87	72	96	<.001
Belfiore area	≤0.90	88.6	0.04	0.815	0.943	80	89	72	93	<.001
$ISI_{0,120}$	≤85	88.5	0.04	0.813	0.941	88	79	60	95	<.001
Si_{120}	≤3.1	88.4	0.03	0.810	0.943	96	68	52	96	<.001
Stumvoll	≤10.3	83.5	0.04	0.748	0.902	65	91	74	88	<.001
Matsuda and DeFronzo	≤7.5	80.9	0.05	0.718	0.881	69	86	64	89	<.001
SiM	≤2.8	79.7	0.05	0.705	0.871	77	76	53	90	<.001
AUCi 2h	≥8658	78.4	0.05	0.690	0.860	54	95	77	85	<.001
Drivsholm	≤1.5	72.9	0.06	0.630	0.813	58	89	65	85	<.001
AUCg 2h	≥13650	70.2	0.06	0.602	0.790	77	63	43	89	.001
Quicki	≤0.3	60.7	0.06	0.504	0.703	46	78	43	80	NS
HOMA-IR	≥1.7	60.7	0.06	0.504	0.703	46	78	43	80	NS
Belfiore basal	≤1.1	60.7	0.06	0.504	0.703	46	78	43	80	NS
Bennet	≤0.09	59.6	0.06	0.494	0.693	27	95	70	79	NS
Sib	≤16.9	57.2	0.06	0.469	0.671	50	70	37	80	NS
IGI	≥1.4	55.9	0.06	0.456	0.658	46	71	36	79	NS

Note: Cutoff: criterion value corresponding with highest Youden index. Abbreviations as in Table 2.

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were classified as insulin resistant (compared with 26.3% of lean; $P<.001$).

The R_S between M values and the other fasting or OGTT-derived indices of IR for the ov-ob PCOS women are also presented in Supplemental Table 2. The higher R_S values within ov-ob PCOS women were found for Sib, Belfiore basal, HOMA-IR, and Quicki.

Supplemental Figure 1 shows the ROC curve graphs of the IR indices analyzed in this population. As presented in Table 4, Sib, Belfiore basal and HOMA-IR seemed to be the best predictive performance indices in diagnosing IR with cut-offs of, respectively ≤10.2 (85.7%), ≤0.87 (84.1%), and ≥2.62 (84.1%), respectively.

When we compared the AUC of Sib with the AUCs of the other best predictive indices of IR, we found no statistical significant differences (Sib vs. HOMA, Belfiore basal, Bennet, Quicki, Matsuda index, and SiM: $P>.05$ for all comparisons; data not shown).

DISCUSSION

Recognition of the relationship between PCOS and IR dates to 1980 (3, 22). At present, IR and hyperinsulinemia are well known to be important features of PCOS, stimulating ovarian androgen secretion, and suppressing SHBG production (23, 24).

TABLE 4

Predictivity of parameters of insulin resistance in ov-ob PCOS patients.

				95% CI						
Index	**Cutoff**	**AUC (%)**	**SE**	**Lower boundary**	**Upper boundary**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	***P* value**
Sib	≤10.2	85.7	0.04	0.780	0.934	80	77	90	60	<.001
HOMA-IR	≥2.62	84.1	0.04	0.752	0.898	62	93	96	49	<.001
Belfiore basal	≤0.87	84.1	0.04	0.749	0.897	62	93	96	49	<.001
Bennet	≤0.09	82.3	0.04	0.739	0.889	61	93	96	48	<.001
Quicki	≤0.32	82.2	0.04	0.738	0.888	61	93	96	48	<.001
Matsuda and DeFronzo	≤9.7	82.1	0.04	0.737	0.888	92	58	85	75	<.001
SiM	≤2.22	80.8	0.04	0.723	0.877	89	61	85	68	<.001
AUCi 2h	≥6907	80.8	0.04	0.722	0.876	80	77	90	60	<.001
Drivsholm	≤1.76	79.8	0.04	0.711	0.869	68	87	93	52	<.001
Belfiore area	≤0.92	77.4	0.04	0.684	0.848	71	71	86	49	<.001
Stumvoll	≤7.04	77.3	0.04	0.684	0.847	64	87	93	48	<.001
Si_{120}	≤0.8	75.9	0.04	0.669	0.835	50	97	97	43	<.001
HOMA-M_{120}	≥14.07	74.3	0.04	0.651	0.821	70	74	87	49	<.001
$ISI_{0,120}$	≤73.9	71.8	0.05	0.624	0.799	67	74	87	47	<.001
IGI	≥1.78	66.2	0.05	0.566	0.749	49	90	93	40	.003
AUCg 2h	≥14085	64.5	0.06	0.548	0.733	71	64	84	46	.027

Note: Cutoff: criterion value corresponding with highest Youden index. Abbreviations as in Table 2.

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Approximately 70% of women affected by this syndrome in the United States are overweight or obese (whereas in Italy this percentage is lower) (25), which is frequently associated with high insulin levels and reduced insulin sensitivity. Interestingly, a similar picture of IR was observed in a considerable number of normal-weight PCOS subjects as well. Actually several earlier studies in the literature yielded conflicting results on the link among PCOS, obesity, and IR. In particular, Chang et al. (10) and Dunaif et al. (9, 26), using different methods, suggested that reduced insulin sensitivity is present in both obese and nonobese women. Research conducted in 2004 in a large group of European lean PCOS patients showed that this subpopulation had significantly less IR compared with ov-ob PCOS women (27). Surprisingly, there is evidence in American and Asian PCOS women that the IR in these patients is independent from their BMI (28, 29). These conflicting results seem to suggest that ethnic background and dietary composition associated with a more sedentary lifestyle in the United States might play a role in the metabolic status of these women. Overall, IR in PCOS appears to be strongly correlated with obesity, because it is often present when PCOS and obesity are combined (9, 26, 30).

Interestingly, it is well known that only ov-ob PCOS women have decreased insulin-mediated suppression of HGP, and obesity has a synergistic deleterious effect on this metabolic process (9, 31). Actually, it has been hypothesized that normal-weight women with PCOS could be affected by an "intrinsic" form of IR whereas obese patients have a combined form of IR due in part to the syndrome itself and in part to the weight excess. In fact, lean PCOS patients could be considered to be a "unique model" to study the natural history of IR per se, because the IR occurs in the presence of normal glucose tolerance.

Based on these observations, the aim of the present study was to validate a specific IR index for lean PCOS patients. Because these patients have neither fasting HI nor increased basal HGP (6, 9–11), our study raised the following question: In lean PCOS patients, could a temporally delayed assessment of glucose and insulin concentrations during OGTT be more predictive of IR than a standard fasting evaluation, such as with HOMA-IR?

In this study we demonstrated that for lean PCOS population, the best predictive value was obtained with HOMA-M_{120} (Table 3), whereas for ov-ob PCOS women the best predictive value was obtained by Sib, as described by Avignon et al. (32). In contrast, HOMA-M_{120} could not be considered to be a reliable index of IR in ov-ob PCOS patients. Actually, in the ov-ob PCOS population no significant differences were observed between the AUC of Sib and those of the other best predictive IR indices. Nevertheless, based on the PPV and NPV as well as on its highest AUC, in our opinion Sib is the most accurate index for IR evaluation in ov-ob PCOS patients.

Moreover, we can hypothesize a physiopathologic reason for the strength of predictive performance of our HOMA-M_{120} in lean PCOS women. Owing to the above-mentioned absence of fasting HI and high HGP in this subpopulation, we could obtain an IR-predictive index similar to the criterion standard clamp only after a glucose load and 120 minutes of evaluation of the glucose and insulin concentrations. Interestingly, our hypothesis is further supported by the other best predictive indices of IR in lean PCOS women, which, similarly to HOMA-M_{120}, are all OGTT derived and characterized by a 120-minute assessment (Table 4). In contrast, in the ov-ob PCOS women, fasting evaluation of glucose and insulin concentrations is sufficient to obtain the best IR-predictive performance. These observations are consistent with the hypothesis of a different metabolic asset in lean and ov-ob PCOS populations, the latter being characterized by fasting HI as well as increased basal HGP due to decreased insulin-mediated suppression of HGP.

Interestingly, we excluded from our study any subjects with impaired glucose tolerance or type 2 DM to validate a screening method for primary prevention of glycometabolic sequelae. The absence of the important cardiometabolic risk factor represented by obesity often misguides clinicians when lean PCOS patients are evaluated. Actually, IR even in lean women represents an important risk factor for glycometabolic and cardiovascular sequelae (33–35).

The strength of the present paper is the introduction of a very simple tool, specifically elaborated and validated for lean PCOS women, whose cardiometabolic impairment could be more frequently misunderstood. A multicenter study will be needed to test the HOMA-M_{120} in a larger simple size and in a non-white lean PCOS population.

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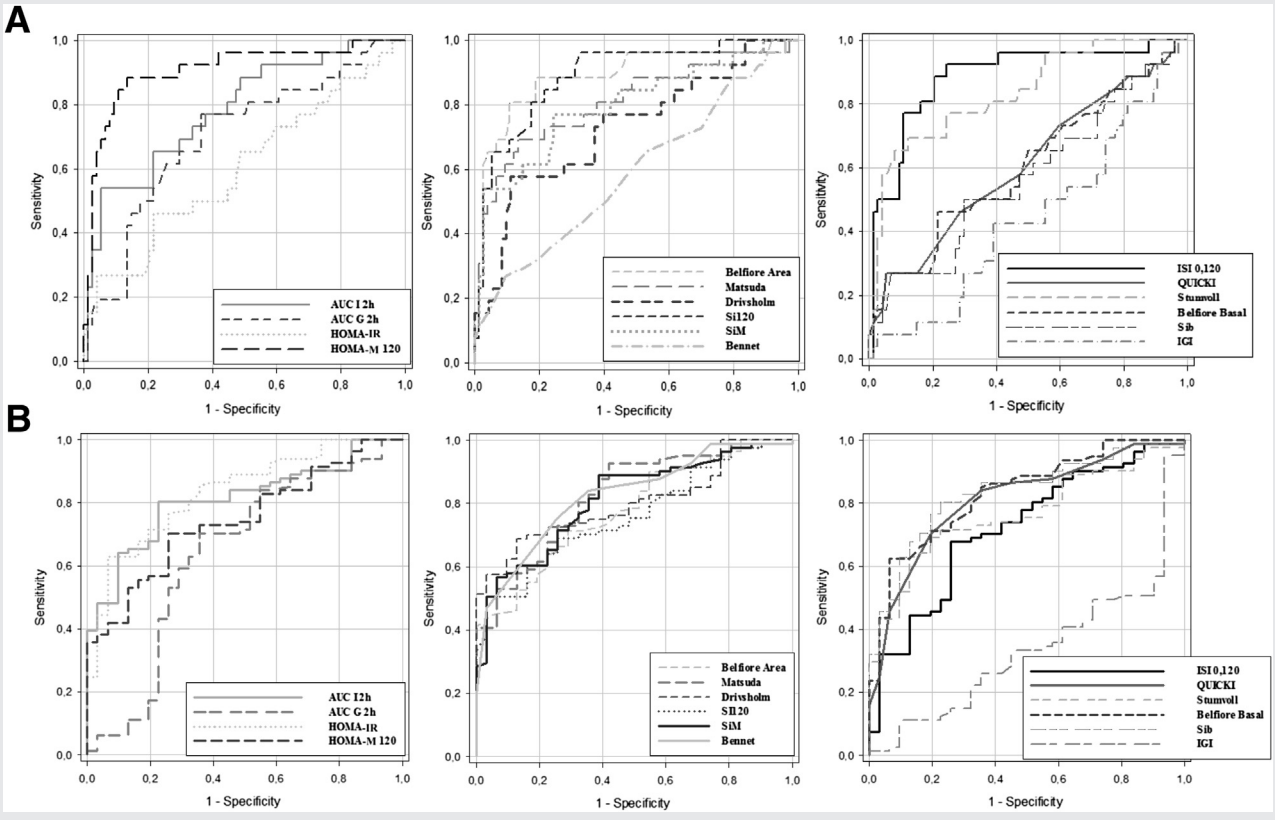
SUPPLEMENTAL FIGURE 1



Receiver operating characteristic curve analysis of different fasting or OGTT-derived parameters in (A) lean and (B) ov-ob PCOS patients. Sensitivity plotted against 1 − specificity.

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SUPPLEMENTAL TABLE 1

Indexes of insulin sensitivity derived from fasting and OGTT.

Index	Formula	Reference
HOMA-M_{120}	$\frac{G_{120}(mg/dL)*I_{120}(\mu IU/mL)}{405}$	
Belfiore area	$\frac{2}{AUC\ I\ (\mu IU/mL))*AUC\ G(mg/dL)+1}$	Belfiore F, et al., 1998 (36)
Belfiore basal	$\frac{2}{I(\mu IU/mL)*G(mg/dL)+1}$	Belfiore F, et al., 1998 (36)
Matsuda and DeFronzo	$\frac{10000}{\sqrt{(G*I)*(G\ mean\ OGTT*I\ mean\ OGTT)}}$	Matsuda M, DeFronzo RA, 1999 (37)
Bennet	$\frac{1}{ln\ G(mg/dL)*ln\ I(\mu IU/mL)}$	Anderson RL, et al., 1995 (38)
Quicki	$\frac{1}{\log(I(\mu IU/mL))+\log(G(mg/dL))}$	Katz A, et al., 2000 (39)
HOMA-IR	$\frac{G(mmol/L)*I(\mu IU/mL)}{22.5}$	Matthews DR, et al., 1985
Sib	$\frac{100.000.000}{I(\mu IU/mL)*G(mg/dL)*(150(mL)*BW(Kg))}$	Avignon A, et al., 1999
Si_{120}	$\frac{100.000.000}{I120(\mu IU/mL)*G120(mg/dL)*(150(mL)*BW(Kg))}$	Avignon A, et al., 1999
SiM	$\frac{(0.137*Sib)+Si120}{2}$	Avignon A, et al., 1999
Drivsholm	$\frac{AUC\ 120(G(mg/dL))}{AUC\ 120(I(\mu IU/mL))}$	Drivsholm T, et al., 1999 (40)
IGI	$\frac{I_0-I_{30}(\mu IU/mL)}{G_0-G_{30}(mg/dL)}$	Gauglitz GG, et al., 2009 (41)
$ISI_{0,120}$	$\frac{MCR}{\log MSI}$	Gutt M, et al., 2000 (42)
Stumvoll	$[0.226-(0.0032*BMI)-(0.0000645*I_{120}(pmol/L)]$ $-[0.00375*G_{90}(mmol/L)]*100$	Stumvoll M, et al., 2000 (43)

Note: Where is not specified, common or System International units can be used. Conversion factors to System International Units: glucose, 0.05551; insulin, 7.175. G = glucose; I = insulin; G mean OGTT = mean glucose value during OGTT; I mean OGTT = mean insulin value during OGTT; G_{120} = glucose value during OGTT at 120 min; I_{120} = insulin value during OGTT at 120 min; BW = body weight; Ref.n. = number of reference.

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SUPPLEMENTAL TABLE 2

Spearman correlation coefficients (R_S) between several indices of insulin sensitivity and the M value obtained by the euglycemic-hyperinsulinemic clamp in lean and overweight/obese PCOS patients.

Index	Lean		Overweight/obese	
Belfiore area	$R_S = 0.579$	$P<.001$	$R_S = 0.538$	$P<.001$
HOMA-M_{120}	$R_S = -0.576$	$P<.001$	$R_S = -0.468$	$P<.001$
Stumvoll	$R_S = 0.576$	$P<.001$	$R_S = 0.613$	$P<.001$
Si_{120}	$R_S = 0.556$	$P<.001$	$R_S = 0.533$	$P<.001$
AUCi 2h	$R_S = -0.543$	$P<.001$	$R_S = -0.525$	$P<.001$
$ISI_{0,120}$	$R_S = 0.517$	$P<.001$	$R_S = 0.476$	$P<.001$
SiM	$R_S = 0.493$	$P<.001$	$R_S = 0.629$	$P<.001$
Matsuda and DeFronzo	$R_S = 0.491$	$P<.001$	$R_S = 0.648$	$P<.001$
Drivsholm	$R_S = 0.457$	$P<.001$	$R_S = 0.481$	$P<.001$
AUCg 2h	$R_S = -0.267$	$P=.007$	$R_S = -0.270$	$P=.004$
Quicki	$R_S = 0.253$	$P=.011$	$R_S = 0.658$	$P<.001$
HOMA-IR	$R_S = -0.253$	$P=.011$	$R_S = -0.658$	$P<.001$
Belfiore basal	$R_S = 0.253$	$P=.011$	$R_S = 0.658$	$P<.001$
Bennet	$R_S = 0.241$	$P=.016$	$R_S = 0.650$	$P<.001$
Sib	$R_S = 0.222$	$P=.026$	$R_S = 0.697$	$P<.001$
IGI	$R_S = -0.202$	$P<.044$	$R_S = -0.245$	$P=.010$

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