Clinically useful predictors of conversion to abnormal glucose tolerance in women with polycystic ovary syndrome

Marie-Hélène Pesant, M.D., and Jean-Patrice Baillargeon, M.D., M.Sc.

Division of Endocrinology, Department of Medicine, University of Sherbrooke, Sherbrooke, Quebec, Canada

Objective: To determine clinically useful predictors of conversion from normal to abnormal glucose tolerance (AGT) in women with polycystic ovary syndrome (PCOS) during regular follow-up, considering that optimal timing for retesting with an oral glucose tolerance test (OGTT) is unknown.
Design: Retrospective cohort study.
Setting: Reproductive endocrinology clinic of an academic center.
Patient(s): Glucose-tolerant PCOS women having a follow-up OGTT $\geq$1 year later.
Intervention(s): Regular clinical follow-up.
Main Outcome Measure(s): Sets of criteria associated with the lowest false negative rate and an optimal specificity.
Result(s): Out of 83 women with PCOS, 24.1% converted to AGT during a median follow-up of 3.0 years, including 3.6% who converted to diabetes. Conversion to AGT was significantly associated with glucose excursion and 2-hour glucose during the normal OGTT, increase in fasting glucose (FG) and body mass index during follow-up, and homeostasis model–assessment insulin resistance and FG at follow-up. The best predictive set of criteria was a baseline glucose excursion of >25 mg/dL or an increase in FG of $\geq$5%. Using these criteria would have saved 45% of the OGTTs, without missing any conversion to AGT.
Conclusion(s): Although our results need to be validated, we determined that using glucose excursion during the previously normal OGTT in combination with another predictor (e.g., increase in FG or glycosylated hemoglobin), could greatly reduce the number of OGTTs performed in PCOS women during their regular follow-ups, with a minimal rate of missed cases. (Fertil Steril® 2011;95:210–5. ©2011 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome, diabetes, impaired glucose tolerance, conversion to abnormal glucose tolerance, oral glucose tolerance test, fasting glucose

Polycystic ovary syndrome (PCOS) stands as the most common endocrinopathy among young women, affecting 6%–10% of women of childbearing age (1). Beyond representing the most frequent cause of hyperandrogenism and female infertility, PCOS puts young women at increased risks for diabetes and cardiovascular diseases. Moreover, conversion from normal (NGT) to impaired (IGT) glucose tolerance (2) and from IGT to type 2 diabetes mellitus (T2DM) is increased two- to fivefold in the PCOS population (2–4).

Because of these increased metabolic risks, many organizations recommend screening for T2DM in PCOS women. Moreover, the Androgen Excess Society recommends screening these women with an OGTT instead of fasting glucose (FG), as supported by the results of our previously published study (5). It is important to determine the glucose tolerance status of women with PCOS, because it will influence the choice of treatment, e.g., the use or addition of an insulin sensitizer (1) and cardiovascular preventive strategies. Because conversion from normal to abnormal glucose tolerance (AGT) is increased in PCOS, it seems to be reasonable to retest regularly in this population. However, the optimal timing for retesting is unknown. Furthermore, OGTT testing is time consuming (2 hours), often poorly tolerated (6), and costly due to the supervision by personnel.

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Reprint requests: Jean-Patrice Baillargeon, M.D., M.Sc., University of Sherbrooke, Sherbrooke, QC J1H 5N4, Canada (FAX: 819-564-5292; E-mail: jp.baillargeon@usherbrooke.ca).

Accordingly, we undertook a retrospective review of our PCOS population to find clinically useful predictors of conversion from NGT to AGT after $\geq$1 year of regular follow-up, while women were taking their medications for PCOS management, to target women who could avoid retesting with an OGTT at this time.

SUBJECTS AND METHODS

Study Group

We retrospectively reviewed the medical records of all PCOS women followed at the Reproductive Endocrine Clinic of the Centre hospitalier universitaire de Sherbrooke (CHUS), in Sherbrooke, Canada, from July 2003 to December 2009. The Institutional Review Board of CHUS and University of Sherbrooke approved the study protocol.

As recommended by the 1990 National Institutes of Health (NIH) Consensus Conference (7), the diagnosis of PCOS was defined by: 1) oligo- or anovulation; 2) hyperandrogenism (clinical and/or biochemical); and 3) exclusion of other hyperandrogenic or anovulatory disorders, including congenital adrenal hyperplasia (17OH-P $\leq$330 ng/dL), androgen-secreting tumors (total T <260 ng/dL and DHEAS <700 μg/dL), Cushing syndrome (low-dose dexamethasone test when suspected clinically), hyperprolactinemia, and hypothyroidism. Although ovarian ultrasounds were not performed in most women, these more stringent criteria are in accordance with both the 2003 Rotterdam (8) and the revised 1990 NIH (9) diagnostic criteria. Women also needed to have: 1) an OGTT with NGT; and 2) a second OGTT performed $\geq$1 year later. This OGTT had to be the next eligible OGTT or the next one that was abnormal, to capture all PCOS women who eventually converted to AGT. OGTTs performed during pregnancy were not considered. IGT was defined according to the American Diabetes Association (ADA) as 2-hour glucose $\geq$140 mg/dL during the OGTT, with diabetes diagnosed when the

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2-hour glucose was ≥200 mg/dL (10). We did not exclude women taking oral contraceptives or antidiabetic agents, even if they can modify the results of the OGTT, because those drugs are part of the routine clinical practice and therefore PCOS women are usually using these drugs when tested for AGT.

Data Collection

Variables noted in Table 1 were recorded from the closest visit occurring within 6 months of an OGTT. Metabolic syndrome (MetS) was defined according to the 2001 NIH NCEP-ATPIII by ≥3 of the following criteria: waist circumference ≥88 cm or body mass index (BMI) ≥30 kg/m^2, triglyceride level ≥150 mg/dL, high-density lipoprotein (HDL) <50 mg/dL, blood pressure ≥130/85 mm Hg, and FG ≥110 mg/dL (11).

Assays

Blood samples were assayed at the clinical laboratory of the CHUS. Total T and 17OH-P levels were assayed by RIA and SHBG by immunoradiometric assay. Serum free T was calculated by the method of Sodergard et al. (12) using a serum albumin concentration of 4.0 g/dL. TSH, PRL, glucose, total cholesterol, triglycerides, and HDL-cholesterol (HDL-C) were measured by chemiluminescence. LDL-cholesterol (LDL-C) was calculated using the Friedewald equation (13). Glycosylated hemoglobin (Hb_{A1c}) was measured by high-pressure liquid chromatography (G7 HPLC Analyser; Tosoh Bioscience, Tokyo, Japan). Inter- and intraassay coefficients of variation were 2.5% for glucose, <10% for total T and <8.5% for all other steroid hormones.

Statistical Analyses

Statistical analyses were performed using JMP 7.0 software (SAS Institute, Cary, NC). Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR). Variables that were not normally distributed based on the normal quantile plot test were log-transformed for all statistical analyses and reported as geometric means with interquartile range. Mean values are reported ± SD. Paired Student *t* and McNemar tests were used to compare results between the initial and follow-up visits. Statistical significance was considered when the *P* value was ≤.05 for all analyses.

Chi-square tests and univariate logistic regressions were performed to determine factors associated with conversion toward AGT. Each identified variable was then analyzed using a receiver operating characteristic (ROC) curve to define the best cut-off values, based on the lowest likelihood ratio for a negative test [LR(−)] when the specificity is ≥50%. A low LR(−) minimizes the false negative rate for an optimal specificity (14).

These predictive criteria were used to determine the set of criteria that were independent predictors of the conversion to AGT, following a stepwise forward-backward multivariate logistic regression (based on next highest relative risk). All defined criteria were tested alone or in combination for their ability to identify women who converted to AGT by using chi-square. Combination of more than two criteria did not add significantly to reported predictive models. Subgroup-stratified analyses were performed to determine the effect of potential confounders, namely obesity status, medication use, and duration of follow-up.

RESULTS

Characteristics of the Subjects at Baseline and During Follow-Up

Between July 2003 and December 2009, 302 women with PCOS were seen, of which 57 did not have an OGTT performed. Of the remaining 245 PCOS women, 30 had their initial OGTT <1

TABLE 1

Characteristics of the subjects (n = 83) at baseline and during the follow-up oral glucose tolerance test (OGTT).

Characteristic	Result at initial OGTT	Result at second OGTT	*P* value[a]
Age (y)	27.3 ± 7.2	30.7 ± 7.2	<.0001
First-degree family history of T2DM	26.5%		
BMI (kg/m^2)	33.8 ± 7.9	33.9 ± 8.0	.81
% overweight or obese	83.1%	84.3%	.56
AGT	0%	24.1% (3.6% with T2DM)	
Fasting glucose (mg/dL)	83 ± 9	84 ± 12	.10
2-h glucose (mg/dL)	103 ± 19	117 ± 38	.0002
Glucose excursion during OGTT (mg/dL)[b]	21 ± 19	33 ± 35	.0009
Hb_{A1c} (%)	5.1 ± 0.4	5.3 ± 0.4	<.0001
Fasting insulin level (μU/mL)[c]	14.2 (8.0–21.7) (n = 34)	10.4 (6.2–15.1) (n = 45)	.03 (n = 19)
Maximal insulin level during OGTT (μU/mL)[c]	123.0 (78.1–184.8) (n = 26)	94.8 (64.3–134.9) (n = 41)	.13 (n = 14)
HOMA-IR[c]	19.7 (11.0–27.7) (n = 33)	14.2 (8.6–22.1) (n = 45)	.01 (n = 18)
Triglycerides (mg/dL)[c]	117 (89–158)	119 (86–163)	.78
HDL-cholesterol (mg/dL)	49 ± 11	52 ± 14	.02
Total T (ng/dL)	89 ± 35	52 ± 26	<.0001
SHBG (μg/dL)[c]	1.00 (0.59–1.59)	1.00 (0.55–1.71)	.98
Free T (ng/dL)	1.73 ± 1.16	1.04 ± 0.83	<.0001
% with metabolic syndrome	38.6%	27.7%	.050
% with insulin sensitizer	23.2%	59.0%	<.0001
% with oral contraceptive	15.7%	30.1%	.007
% with antiandrogens	4.8%	16.9%	.004

Note: Results are reported as mean ± SD or proportions. To convert values for glucose to mmol/L, multiply by 0.0556; for insulin to pmol/L, multiply by 6.9; for triglycerides to mmol/L, multiply by 0.0113; for cholesterol to mmol/L, multiply by 0.0259; for SHBG to nmol/L, multiply by 34.7; for total T to nmol/L, multiply by 0.0347; and for free T to pmol/L, multiply by 34.7. The normal ranges for ovulatory women are as follows: total T <70 ng/dL; calculated free T <1.30 ng/dL. AGT = abnormal glucose tolerance; BMI = body mass index; Hb_{A1c} = glycosylated hemoglobin; HOMA-IR = homeostatic model assessment of insulin resistance; T2DM = type 2 diabetes mellitus.

[a] Paired *t* test for continuous variables and McNemar test for proportions.

[b] Glucose excursion is 2-hour glucose level minus baseline glucose level.

[c] Log-transformed and reported as geometric means with interquartile range.

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