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Diagnosis of disorders of glucose tolerance in women with polycystic ovary syndrome (PCOS) at a tertiary care center: fasting plasma glucose or oral glucose tolerance test?

Andrés E. Ortiz-Flores, Manuel Luque-Ramírez, Elena Fernández-Durán, Francisco Alvarez-Blasco, Héctor F. Escobar-Morreale *

Diabetes, Obesity and Human Reproduction Research Group, Department of Endocrinology & Nutrition, Hospital Universitario Ramón y Cajal & Universidad de Alcalá & Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS) & Centro de Investigación Biomédica en Red Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Madrid, 28034, Spain

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ABSTRACT

Background: The risk of developing prediabetes and type 2 diabetes (dysglycemia) may be increased in women with PCOS. Whether an oral glucose tolerance test (OGTT) should be performed routinely in all PCOS women at presentation or should be recommended only to a selected subset of patients is still controversial.
Basic Procedures: At a tertiary care center, we conducted a retrospective, observational study including 400 women with PCOS submitted to an OGTT. Our primary objective was to assess the diagnostic agreement between two algorithms commonly used for the screening of dysglycemia in these women: i) relying only on fasting plasma glucose (FPG) or ii) considering both fasting and/or 120-min plasma glucose concentrations during an OGTT. We conducted the analysis considering all patients as a whole, and also after stratifying them by body weight, androgen concentrations and age.
Main Findings: The OGTT detected dysglycemia in 24.5% of patients, whereas only 14.3% women would have been diagnosed using FPG levels alone. The latter missed as many as 40% of women with dysglycemia in our series, including all cases of diabetes. Diagnostic agreement between both algorithms was only 0.55 ($\kappa = 0.103$; 95% CI: 0.05–0.16). Areas under the receiver operating characteristic curve for dysglycemia were 0.86 (95%CI: 0.81–0.91) for FPG and 0.91 (95%CI = 0.87–0.95) for 120-min plasma glucose during the OGTT. FPG was not accurate in predicting dysglycemia in women with PCOS regardless of the presence of insulin resistance, weight excess, hyperandrogenemia and age.
Principal Conclusions: Relying on FPG alone is not adequate for the screening of disorders of glucose tolerance in women with PCOS; such diagnosis should rely on the results of an OGTT regardless of age, weight and/or androgen concentrations.

1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects 5 to 20% of premenopausal women in the general population [1,2]. The prevalence of PCOS is increased in women with weight excess [3,4] and, conversely, patients with PCOS are at increased risk of developing metabolic disturbances, such as abdominal adiposity, dyslipidemia, hypertension, insulin resistance and/or glucose intolerance [5–8].

The prevalence of disturbances of glucose metabolism in women with PCOS is increased compared with the general population, reaching figures as high as 20% to 35% for impaired glucose tolerance (IGT) [9], 5% to 10% for type 2 diabetes [10], and over 10% for gestational diabetes [11]. Hence, screening for abnormalities of glucose metabolism is recommended for patients with PCOS [12].

The most accurate test for such a screening is the oral glucose tolerance test (OGTT) [7,12]. Whether or not this test must be offered to all patients with PCOS, or only to the subset of women at higher risk – such as those with weight excess, hyperandrogenemia or age over 40 year-old – is still a matter of debate [13–15]. In fact, the most recent guidelines for the management of PCOS recommend using either fasting plasma glucose (FPG), glycated hemoglobin (HbA_{1c}) or an OGTT for such diagnosis

Abbreviations: AE-PCOS, Androgen Excess and Polycystic Ovary Syndrome Society; AUC, area under the curve; BMI, body mass index; CV, coefficient of variation; DHEAS, dehydroepiandrosterone-sulfate; HbA_{1c}, glycated hemoglobin; HOMA-β, homeostatic model assessment of β-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; FPG, fasting plasma glucose; LC-MS/MS, liquid chromatography-tandem mass spectrometry; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; RIA, radioimmunoassay; ROC, receiver operating characteristic; SHBG, sex hormone-binding globulin.

* Corresponding author at: Department of Endocrinology and Nutrition, Hospital Universitario Ramón y Cajal, Carretera de Colmenar km 9'1, E-28034 Madrid, Spain.
E-mail address: hectorfrancisco.escobar@salud.madrid.org (H.F. Escobar-Morreale).

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[15], despite the fact that primary prevention of type 2 diabetes has been proved only in patients with IGT regardless of their FPG or HbA_{1c} [16]. An expert panel appointed by the Androgen Excess and Polycystic Ovary Syndrome Society (AE-PCOS) suggested in 2007 that an OGTT should be performed in all women with PCOS, yet some members of the panel considered that screening should be restricted to obese women and/or lean women showing additional risk factors for disorders of glucose tolerance such as family history of diabetes, personal history of gestational diabetes or/and women over age 40 [12]. This more restrictive approach was also adopted later in statements endorsed by the AE-PCOS [13], the European Society of Endocrinology [14] and the European Society of Human Reproduction and Embryology [15]. In conceptual agreement, the 2012 consensus of the European Society of Human Reproduction and Embryology and the American Society of Reproductive Medicine considered that all PCOS women were not at the same risk for disordered glucose tolerance, indicating that an OGTT should be restricted to patients presenting with hyperandrogenism and anovulation, *acanthosis nigricans*, obesity, family history of diabetes or a history of gestational diabetes [17]. However, because most of the studies supporting these recommendations did not analyze with detail the impact of age, obesity and presence or absence of androgen excess on the development of disorders of glucose tolerance in these patients, the scientific evidence supporting these recommendations is far from being convincing.

Even though universal OGTT screening is now recommended for all pregnant women without known diabetes mellitus after 24 weeks of gestation [18,19], such a screening should be conducted earlier in the pregnancies of women with PCOS because of their increased risk of gestational diabetes [11]. Early screening in PCOS should rely on FPG, OGTT or HbA_{1c} at the first prenatal visit [16] according to the American Diabetes Association yet very a recent guideline states that, if not performed before conception, an OGTT should be offered to all pregnant women with PCOS at 20 weeks of gestation [15]. After 24 weeks of gestation screening must be repeated obtaining an OGTT as recommended for all pregnant women [18,19].

In order to provide new insights in which to base future recommendations, our primary objective was to establish the diagnostic agreement between the two most commonly used diagnostic algorithms for disordered glucose tolerance in non-pregnant women with PCOS: i) using FPG alone, or ii) relying on plasma glucose concentrations at fasting and after 120-min of a 75-g OGTT. As secondary objectives, we aimed to: i) analyze the influence of weight excess, androgen excess and age on these results, and ii) to determine the diagnostic performance of FPG levels compared to 120-min glucose after OGTT for predicting dysglycemia in these patients.

2. Subject and Methods

2.1. Study Population

We conducted a retrospective observational study including 588 premenopausal women aged 14 to 49 yr-old attending, from January 1998 to May 2018, the outpatient Reproductive Endocrinology clinic of our tertiary care center because of symptoms of androgen excess or menstrual dysfunction. None of these women had a previous diagnosis of prediabetes or diabetes mellitus before being submitted to an OGTT. For the present study, we excluded: i) all patients who did not fully meet the criteria for the diagnosis of PCOS [20] (including 55 women with World Health Organization class 2 ovulatory dysfunction, 125 women presenting with idiopathic hirsutism and/or isolated biochemical hyperandrogenism, one women presenting with isolated polycystic ovarian morphology); and ii) women with secondary etiologies ($n = 7$). Hence, 400 women were included in the final analysis. All these women had not received treatment with oral contraceptives, antiandrogens or insulin sensitizers for at least three months before the OGTT was performed.

2.2. Ethical Approval

The study followed the principles of the Declaration of Helsinki. Before conducting the study, all women from our Reproductive Endocrinology clinic had signed an informed consent form for the inclusion of a selection of coded clinical variables in an electronic database for clinical research purposes.

2.3. Analysis Variables, Sampling and Assays

We collected a minimum dataset in an electronic case form that included age, weight, height, BMI, waist and hip circumference, glucose and insulin after a 12-h overnight fasting and after 30, 60, 90 and 120 min of a 75-g oral glucose load, and a sex hormone profile that included serum total testosterone, sex hormone-binding globulin (SHBG), calculated free testosterone, androstendione, and dehydroepiandrosterone-sulfate (DHEAS) concentrations. Blood samples were obtained between days 5 and 10 of a spontaneous or progestin-induced menstrual bleeding, or at random in amenorrheic women after excluding pregnancy using appropriate tests.

Total testosterone concentrations were measured by a direct commercial radioimmunoassay (Spectria Testosterone RIA, Orion Diagnostica Oy, Espoo, Finland). The Spectria® testosterone RIA has been distributed by Cisbio Bioassays, Codolet, France with the trade name TESTO-CT2 since 2014. This radioimmunoassay had analytical and functional detection limits below 0.1 nmol/l and 0.3 nmol/l, respectively, an intra-assay coefficient of variation (CV) below 9% for concentrations over 1.3 nmol/l, and interassay CVs of 11.6% at 3.3 nmol/l, and below 10% for concentrations above 4.9 nmol/l. The Spectria® testosterone RIA has been recently validated against liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays in samples of healthy prepubertal and pubertal girls and boys characterized by very low testosterone concentrations [21]. SHBG, androstendione, and DHEAS concentrations were measured using automated immunochemiluminescence (Immulite 2000, Siemens Healthcare S.L., United Kingdom) with a mean intra-assay CV of 2.5%, 8.8% and 4.9%, respectively. Free testosterone levels were calculated from total testosterone concentrations and SHBG levels [22].

Glucose was determined by the hexokinase/glucose-6-phosphate dehydrogenase method (Architect c16000, Abbott Diagnostics, Lake Forest, Illinois, United States) and insulin was measured by automated immunochemiluminescence (Architect i2000©, Abbott Diagnostics). The glucose and insulin assays had an intra-assay CV of 2%, and their inter-assay CVs were 0.84% and 3.1%, respectively.

Homeostasis models assessment of insulin resistance (HOMA-IR), and β-cell function (HOMA-β) were calculated using the equations proposed by Matthews et al. [23]. The composite insulin sensitivity index, calculated from the circulating glucose and insulin concentrations during the OGTT, served as an estimation of whole body insulin sensitivity [24].

2.4. Definitions

PCOS was diagnosed when two of the following conditions were met: i) clinical hyperandrogenism and/or biochemical hyperandrogenism; ii) chronic oligo- or anovulation; and iii) polycystic ovarian morphology assessed on ultrasound, provided that secondary etiologies were excluded by appropriate testing, including Cushing disease, thyroid dysfunction, hyperprolactinemia and non-classic congenital adrenal hyperplasia [20,25]. Clinical hyperandrogenism included hirsutism (defined by a modified Ferriman-Galwey score ≥ 8) regardless of circulating androgen concentrations, whereas the presence of acne in adult women and alopecia were only considered as signs of hyperandrogenism if accompanied by hyperandrogenemia. The specific methods used to evaluate these criteria have been described in detail elsewhere [26]. Hyperandrogenemia was defined as calculated

free testosterone and/or dehydroepiandrosterone-sulfate (DHEAS) concentrations above the 95th percentile of our in-house reference range, i.e. free testosterone levels >34.7 pmol/l and/or DHEAS concentrations >9.2 μmol/l for women aged 18 to 24 yr-old, >8.1 μmol/l for women aged 25 to 34 yr-old, and >7 μmol/l for women aged 35 to 49 yr-old. These data were obtained from a cohort of 147 premenopausal women comprised of healthy female volunteers consecutively recruited from the hospital staff, and overweight or obese women seeking medical attention in our department [27]. None of these control women had any signs or symptoms of hyperandrogenism or menstrual dysfunction, or had a history of infertility, ovariectomy, or hysterectomy. Before recruitment, none of the control women had a diagnosis of hypertension, diabetes, or cardiovascular events, or had received treatment with oral contraceptives or antiandrogenic, antidiabetic, or antihypertensive drugs during the 6 preceding months.

Ovulatory dysfunction was defined as menstrual cycles <21 days, or >35 days, or <8 cycles per year. Amenorrhea was considered when menstrual cycle length was >90 days. In addition, in women with normal menstrual cycles, ovulatory dysfunction was assessed by measuring serum progesterone concentrations during the luteal phase of the menstrual cycle [15].

Dysglycemia [28] was diagnosed when patients showed impaired fasting glucose [(IFG), FPG ≥ 5.6 mmol/l), impaired glucose tolerance (IGT, 120-min glucose ≥7.8 mmol/l) or diabetes (FPG ≥ 7 mmol/l and/or 120 min glucose ≥11.1 mmol/l) [16].

Patients were classified as lean (BMI < 25 kg/m^2), overweight (25.0–29.9 kg/m^2) or obese (BMI ≥ 30.0 kg/m^2). Finally, we stratified patients depending of being younger or older than age 40 [12,13,29].

2.5. Sample Size

We estimated sample size for the primary objective of analyzing differences in the proportions of paired measurements within a single group of patients (https://www.imim.cat/ofertadeserveis/software-public/granmo/). For these calculations, we used the prevalences of dysglycemia already reported in patients with PCOS using FPG (5.4%) or OGTT (11.7%) in a similar study [30]. Setting alpha at 0.05 and power at 0.95 for a two-sided test, recognizing as statistically significant such a difference in proportions would need the inclusion of at least 385 women with PCOS.

2.6. Statistical Analysis

Data are shown as medians (25th–75th percentiles) or counts (percentage) as appropriate. The normal distribution of continuous variables was assessed by the Kolmogorov-Smirnov test. A two-step approach for transforming skewed variables was applied as necessary [31]. Comparisons among categorical variables were performed by χ^2 test. We quantified the degree of agreement between diagnostic algorithms by the Cohen's kappa (κ) coefficient and its 95%CI, which measures inter-rater reliability of both algorithms for the diagnosis of dysglycemia. A κ value >0.8 was considered as a strong level of agreement [32]. Diagnostic agreement was also calculated as the sum of patients showing normal or abnormal results according to both algorithms, divided by the total of patients. Results were also stratified according to BMI, age and circulating androgen values. Receiver operating characteristic (ROC) curve analysis and area under the ROC curve (AUC) were used for the assessment of diagnostic performance. ROC curve analyses for combined variables were also performed after conducting a logistic binary regression to obtain their predicted probabilities. Comparisons among ROC curves were performed by the method of DeLong et al. [33] using Medcalc® statistical software. A P value < 0.05 was considered statistically significant.

Table 1
Clinical and biochemical characteristics of the population.

	Women with PCOS (n = 400)	
Age (yr-old)	26	(20−30)
Family history of diabetes	192	(48)
Body mass index (kg/m^2)	28.6	(22.9–34.2)
Waist circumference (cm)	82	(69–94)
Hip circumference (cm)	104	(94–113)
Total testosterone (nmol/l)	2.1	(1.7–2.6)
Free testosterone (pmol/l)	40	(29–54)
Dehydroepiandrosterone-sulfate (μmol/l)	5.9	(4.2–7.7)
Androstendione (nmol/l)	11.5	(9.4–15.0)
Fasting glucose (mmol/l)	4.9	(4.6–5.3)
Glucose at 120 min of the OGTT (mmol/l)	6.2	(5.4–7.4)
HOMA-IR	2.1	(1.3–3.6)
HOMA-β	147	(95–215)
Insulin sensitivity index	4.1	(2.4–6.5)

Abbreviations: HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; OGTT, 75 g oral glucose tolerance test. Data are medians (25th–75th percentiles) or counts (percentage). To convert to metric units, multiply total testosterone by 28.8 and free testosterone by 0.0288 (results in ng/dl), androstendione by 0.287 (results in ng/ml), dehydroepiandrosterone-sulfate by 368 (results in ng/ml) and glucose by 18 (result in mg/dl).

3. Results

3.1. Primary Outcome: Agreement Between Diagnostic Algorithms for Dysglycemia

The clinical and biochemical characteristics of the patients are summarized in Table 1. The diagnostic algorithm using FPG alone for screening glucose tolerance detected IFG in 57 (14.3%) of the 400 women with PCOS, whereas none of them showed the FPG ≥ 7 nmol/l cut-off value required for the diagnosis of diabetes. On the contrary, the OGTT-based diagnostic algorithm that considered both fasting and 120-min glucose concentrations detected dysglycemia in 98 (24.5%) of the same 400 patients, including 10 patients who actually had diabetes because their 120-min glucose concentrations were ≥ 11.1 mmol/l. The diagnostic agreement between the two diagnostic algorithms used here for diagnosing dysglycemia was 0.55 (κ = 0.103; 95% CI: 0.05–0.16).

In fact, of the 343 patients presenting with normal FPG, the OGTT revealed IGT in 38 (11.1%) and diabetes in 3 (0.9%). On the other contrary, of the 57 women presenting with IFG, 120-min plasma glucose concentrations were normal in 30 (52.6%), indicated IGT in 20 (35.1%) and diabetes in 7 (12.3%).

3.2. Secondary Outcomes

3.2.1. Influence of Weight Excess, Hyperandrogenemia and Age

The prevalence of dysglycemia increased in women with weight excess (Fig. 1, left panels) and with hyperandrogenemia (Fig. 1, right panels) regardless of the diagnostic algorithm applied. A similar pattern was observed for age, yet the very limited sample size of women over age 40 in our population precluded a definite conclusion (data not shown). Of note, diabetes was only diagnosed in obese women presenting with hyperandrogenemia (Fig. 1). Conversely, dysglycemia was found in only 3% of lean, non-hyperandrogenemic patients with PCOS under age 40 when FPG was not altered.

The diagnostic agreement for dysglycemia between the two diagnostic algorithms used here was 0.51 in lean (κ = 0.029; 95% CI: −0.023–0.082); 0.56 in overweight (κ = 0.128; 95%CI: 0.017–0.239); and 0.57 in obese (κ = 0.049; 95%CI: 0.051–0.242) patients. Similarly, these figures were 0.53 in non-hyperandrogenemic women (κ = 0.060; 95%CI: −0.022–0.142) and 0.56 in those with increased serum androgen concentrations (κ = 0.124; 95%CI: 0.054–0.194). Finally, diagnostic agreement was 0.57 in women under age 40 (κ = 0.095; 95%CI: 0.041–0.149) but 0.70 in women over this age (κ = 0.400; 95%CI:

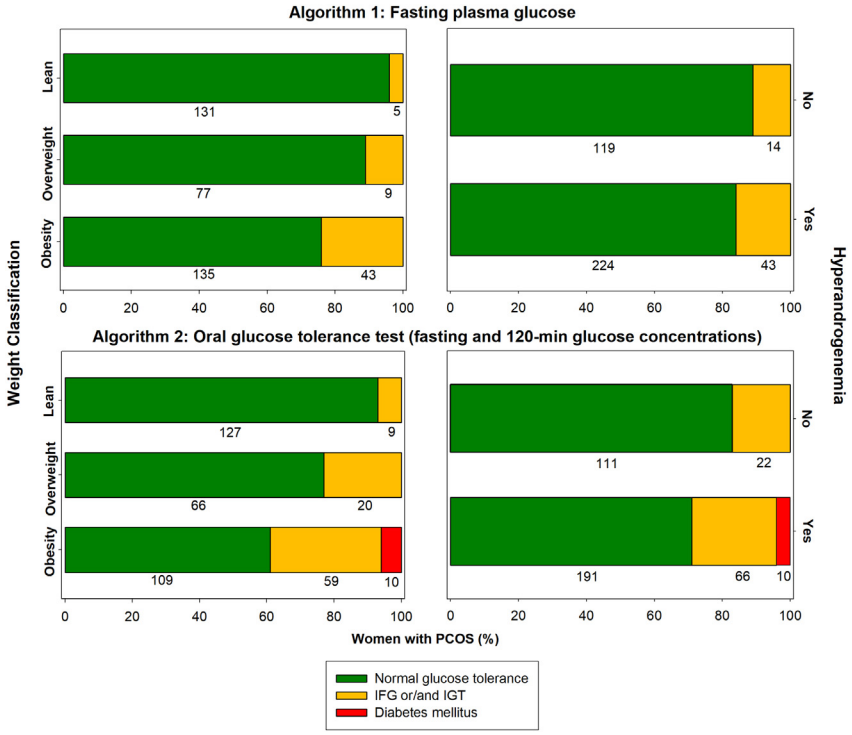

Fig. 1. Comparison between diagnostic algorithms for dysglycemia in PCOS according to weight categories (left panels) and the presence or absence of hyperandrogenemia (right panels). The X axis represents the percentages of women with PCOS showing normal glucose values (green bars), prediabetes (IFG and/or IGT, yellow bars) or diabetes (red bars). Figures under the bars show the number of patients included in each category. Abbreviations: IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PCOS, polycystic ovary syndrome.

0.006–0.794), even though the number of the latter was possibly too small to support this estimation.

Interestingly, the disagreement between FPG and postload glucose concentrations was present even in the subgroup of lean, normoandrogenemic women under age 40: of the 65 of such younger women who presented with normal FPG, 2 actually had IGT on the OGTT and, conversely, the 4 patients showing IFG had normal 120-min glucose concentrations during the OGTT. Of note, the youngest patient with documented dysglycemia was 14 years old and had both obesity and hyperandrogenemia. Nonetheless, IGT was also diagnosed in a 15-year-old woman with a BMI of 20 kg/m^2 and normal circulating androgens.

3.2.2. ROC Curve Analysis

To analyze the separate performances of FPG and of OGTT 120-min glucose for the diagnosis of dysglycemia we performed ROC curve analyses (Fig. 2). The AUC for FPG was 0.86 whereas the AUC for 120-min glucose levels during the OGTT was 0.91, yet this difference did not reach statistical significance ($P = 0.146$, Fig. 2). In addition, the AUC of FPG for predicting an abnormal OGTT 120-min glucose concentration was only 0.74 (95%CI: 0.674–0.807, $P < 0.001$).

After adding age, BMI, hyperandrogenemia, and/or HOMA-IR to FPG, the AUC for predicting dysglycemia did not improve, showing values below 0.90 in all analyses (Table 2).

4. Discussion

Our present results highlight that only the OGTT-based diagnostic algorithm, by measuring both FPG and 120-min plasma glucose, is accurate for the diagnosis of disorders of glucose tolerance in women with PCOS regardless of risk factors for such disorders such as weight excess, obesity and age.

This finding agrees with most [34–38], but not all [39], previous reports addressing populations with diverse ethnic background. Albeit FPG may serve for the screening of dysglycemia in the general population [16], in women with PCOS the diagnostic agreement between diagnostic algorithms based on FPG alone or on the results of the OGTT was only slight according to the κ coefficient [32]. Importantly,

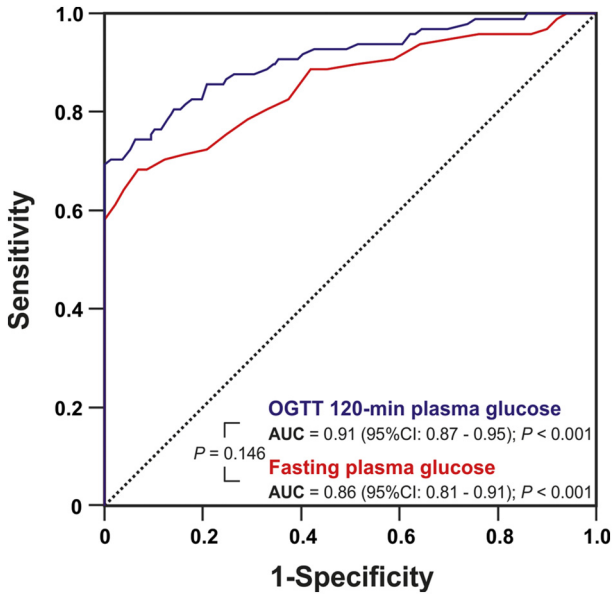

Fig. 2. ROC curves and AUCs for fasting plasma glucose concentrations (red curve) and for 120-min glucose levels during the OGTT (blue curve) in predicting dysglycemia. These curves result from plotting the sensitivity against 1-specificity for each of all the glucose values in the study. A hypothetical ROC curve lying on the diagonal dotted line would reflect the performance of a diagnostic test that is no better than chance level, i.e. a test which yields the positive or negative results unrelated to the true disease status. Abbreviations: AUC: area under the curve; OGTT: oral glucose tolerance test; ROC: receiver operating characteristic.

Table 2
Receiver operating characteristic (ROC) curve analyses for predicting dysglycemia after stratifying by age, body mass index, hyperandrogenemia and insulin resistance, alone or combined with fasting plasma glucose.

Variable	AUC	95% CI	*P* value
Age (years-old)	0.69	0.63–0.75	<0.001
Body mass index (kg/m^2)	0.74	0.68–0.79	<0.001
Free testosterone (pmol/l)	0.61	0.55–0.68	0.001
HOMA-IR	0.78	0.72–0.83	<0.001
FPG + age			
≥25 years-old	0.87	0.82–0.92	<0.001
≥30 years-old	0.86	0.81–0.91	<0.001
≥35 years-old	0.86	0.81–0.91	<0.001
≥40 years-old	0.86	0.81–0.91	<0.001
FPG + body mass index			
≥25 kg/m^2	0.88	0.83–0.92	<0.001
≥30 kg/m^2	0.86	0.82–0.92	<0.001
FPG + hyperandrogenemia	0.86	0.81–0.91	<0.001
FPG + HOMA-IR	0.86	0.81–0.91	<0.001
FPG + age + body mass index	0.88	0.84–0.93	<0.001
FPG + age + body mass index + hyperandrogenemia	0.88	0.84–0.93	<0.001
FPG + age + body mass index + hyperandrogenemia + HOMA-IR	0.88	0.84–0.93	<0.001

Abbreviations: FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance.
In ROC curve analyses of combined variables for predicting dysglycemia, FPG was introduced as a continuous variable in binary logistic regression models, and hyperandrogenemia (no = 0/yes = 1), HOMA-IR (≤3.2 = 0/>3.2 = 1), age (<25 yr-old = 0/≥25 yr-old = 1), and BMI (<25 kg/m^2 = 0/≥25 kg/m^2 = 1) were introduced as independent dichotomous variables.

using FPG alone missed >40% of the women with dysglycemia in our series of women with PCOS, including 10 patients who were finally diagnosed with diabetes according to the results of plasma glucose at 120-min of the OGTT. Not surprisingly, ROC curve analysis casted serious doubts upon the performance of IFG in predicting the OGTT 120-min glucose values at the clinical setting.

Even though in our series the frequency of dysglycemia clearly increased in women presenting with IFG, weight excess, hyperandrogenemia and/or age above 40, the diagnostic agreement of FPG-based and OGTT-based algorithms for dysglycemia was poor or slight when categorizing our population according to these risk factors.

Hence, our present results strongly suggest that the correct approach for the screening of glucose tolerance in women with PCOS should not rely on FGP values alone and requires obtaining an OGTT regardless of any other risk factors such as weight, circulating androgen concentrations or age. This finding may be related to the well-known fact that the abnormalities in carbohydrate metabolism in women with PCOS are characteristically postprandial [12]. Differences with respect to the general population in the mechanism involved in the development of these abnormalities may contribute to this particularity of PCOS: in patients with PCOS androgen excess and insulin resistance have been described as the major determinants of glucose intolerance, whereas in women without androgen excess such determinants were familial aggregation of defective insulin secretion and adiposity [40]. Postprandial dysglycemia reflects peripheral insulin resistance rather than increased endogenous glucose production. Even though obesity has a significant impact on insulin sensitivity in PCOS, many studies have demonstrated a significant decrease in insulin-mediated glucose disposal in women with PCOS regardless of their BMI [41]. Such peripheral defect in insulin action may be related to intrinsic abnormalities of insulin signaling in muscle and adipose tissue or be caused by the in vivo hyperandrogenic and proinflammatory milieu present in these women [42]. In skeletal muscle, mitochondrial dysfunction by increasing oxidative stress may foster insulin resistance as well [43]. Finally, a subset of women with PCOS and weight excess have increased iron tissue depots with respect to age- and BMI-matched non-hyperandrogenic women that can impair insulin secretion, decrease insulin clearance, and specifically, muscle glucose uptake [44].

Even though FPG may miss abnormalities of glucose tolerance in as many as 58% of overweight and obese women with PCOS [34,45], our present results – obtained from a mostly Caucasian population of Spain – indicated that the poor performance of IFG as a marker of glucose intolerance in PCOS was not restricted to women with weight excess but also applied to lean patients, as has been previously reported in other populations [30,35].

For the reasons outlined above, our present results agree with clinical guidelines that rely only on the OGTT for the screening of disorders of glucose metabolism [12,25,46] and do not support others that recommended using FPG for such a purpose, restricting the use of OGTT to women with PCOS and additional risk factors for diabetes [13–15,17,20,47–49].

An entirely different issue is whether or not testing for disorders of glucose tolerance is actually needed in lean women with PCOS since IGT was found in only 3% of them in our series, and no lean patient presented with diabetes in ours and others' series [50]. According to Wilson and Jungner criteria [51], the use of an OGTT for the screening of dysglycemia in women with PCOS would be justified. IGT and diabetes are important health problems that may be present for years before the onset of symptoms, and there are accepted treatments for patients with these conditions such as lifestyle modification and/or metformin that can performed at virtually any clinical setting following evidence-based guidelines. Furthermore, the OGTT is easy to conduct, does not require complicated equipment, and is acceptable even in vulnerable populations. Finally, the cost of case finding is economically balanced in relation to possible expenditure on medical care as a whole.

Hence, the screening for dysglycemia using a standard 75 g 2-h OGTT in women with PCOS matches these criteria, including the subgroup of lean patients in whom such dysglycemia is less frequent. Furthermore, screening women with PCOS for disorders such as non-classic congenital adrenal hyperplasia – a disease with a similar 3% prevalence in women presenting with symptoms of androgen excess [52] – is recommended nowadays for the correct diagnosis of PCOS [20,53,54], even though the cost of such a screening is much higher – serum 17-hydroxyprogesterone measurements are expensive – and this diagnosis usually has no immediate therapeutic consequences for most adult patients not seeking pregnancy [52].

4.1. Strengths and Limitations

Among the strengths of our study, we would highlight the large series of subjects recruited that were evaluated at the clinical setting with a standardized method, and the systematic review of subjects' clinical recordings that followed such evaluations. The use of a local range for the determination of androgens using a particularly sensitive testosterone assay provides strength to our study.

However, we are aware of the weaknesses derived from the observational and retrospective design of the study that precluded us from ruling out information bias despite of our best efforts. Hence, future prospective studies need to be suggested to confirm the present findings. Also, we reported only on glucose tolerance at a single time point whereas, in clinical practice, confirmatory results are required for a definitive diagnosis in asymptomatic subjects. We did not systematically assess HbA_{1c} levels in our series yet its determination did not appear to improve diagnostic performance of glucose intolerance in women with PCOS in older studies [55,56]. Ovarian ultrasound was not performed routinely in hyperandrogenic women with ovulatory dysfunction. Thus, we cannot analyze the impact of polycystic ovarian morphology on glucose tolerance, even though this finding does not appear to confer any extra cardiometabolic risk to women with androgen excess [57]. Also, we did not assess additional risk factors for dysglycemia such as prior history of gestational diabetes. Moreover, most of the patients in our study were Mediterranean Caucasians and, therefore, we cannot extrapolate our findings to populations of different race and ethnicity, even though our results agree with those already

reported in other populations as abovementioned. Additionally, since the patients with PCOS were recruited at the clinical setting, referral bias was possible and the results might not apply to patients in the general population. Moreover, the small sample size of women over age 40 in our series, who also had weight excess and/or hyperandrogenemia in most cases, makes difficult drawing any definitive conclusions in older women. However, a prospective population-based study showed that incidence of prediabetes and diabetes was higher in women with PCOS younger than 40 years compared with women from the general population, difference that was not observed in older women [58]. Lastly, we cannot make any recommendation about re-screening for dysglycemia during follow-up of patients with PCOS presenting with normal glucose tolerance at baseline, since we did not address prospectively this issue.

4.2. Further Clinical Implications

The lack of accuracy of FPG for the diagnosis of dysglycemia in our series of women with PCOS supports the need of an OGTT at diagnosis in all cases, in order to ascertain their cardiometabolic risk, implement therapeutic strategies, and schedule their follow-up. Nowadays, there is no consensus among available clinical guidelines on this important issue, with some guidelines validating the use of FPG and/or HbA_{1c} for the screening of dysglycemia in women with PCOS. Our present results argue strongly against these recommendations because a significant percentage of patients with PCOS not showing any risk factor actually have abnormalities in glucose tolerance, and their screening using FPG would miss many of these cases. Therefore, if availability is not a concern, an OGTT should be recommended to all patients with PCOS at presentation. However, these clinical implications pertain only to women with PCOS at the clinical setting, and must not be extrapolated to other population.

5. Conclusions

An OGTT is the most accurate method for the diagnosis of disorders of glucose tolerance in women with PCOS at the clinical setting. FPG, on the contrary, is less accurate in predicting IGT and diabetes in these women, even in the subgroup of lean non-hyperandrogenemic patients under age 40. Whether screening the subset of patients with PCOS at the lesser risk for dysglycemia should take into account the relatively small prevalence on the one hand, and the easiness, availability and small cost of the procedure together with the clinical consequences of such diagnosis, on the other hand.

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Conflicts of Interest

The Authors have no conflicts of interest to declare.

Author's Roles

A.O.F., and H.F.E.-M. performed the statistical analysis. F.A.B, H.F.E.-M., M.L.-R., and E.F-D recollected all the data in an electronic database for research purposes. A.O.F. reviewed the clinical data using the electronic or written records if necessary. A.O.F. and M.L.-R. wrote the first draft of the article. H.F.E.-M. wrote the final version of the manuscript. All the authors contributed to intellectual content. All the authors share responsibility for the entire content of the manuscript and approved the final submission.

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