

The Polycystic Ovary Syndrome Associated with Morbid Obesity May Resolve after Weight Loss Induced by Bariatric Surgery

Héctor F. Escobar-Morreale, José I. Botella-Carretero, Francisco Álvarez-Blasco, José Sancho, and José L. San Millán

Departments of Endocrinology (H.F.E.-M., J.I.B.-C., F.A.-B., J.S.) and Molecular Genetics (J.L.S.M.), Hospital Ramón y Cajal, Madrid E-28034, Spain

Context: The polycystic ovary syndrome (PCOS) is frequently associated with obesity. However, there are very few data about PCOS in morbid obesity, especially with regard to its evolution after bariatric surgery.

Objective: The objective of this study was to evaluate the response of PCOS to the sustained and marked weight loss achieved by bariatric surgery in morbidly obese women.

Design: This was a longitudinal prospective nonrandomized evaluation.

Settings: The study was performed at an academic hospital.

Patients: Thirty-six consecutive premenopausal women submitted to bariatric surgery were screened for PCOS, which was present in 17.

Interventions: Bariatric surgery was performed.

Main Outcome Measures: Hyperandrogenism, menstrual function, and insulin resistance were estimated before and at least 6 months after bariatric surgery in 12 patients with PCOS.

Results: Weight loss (41 ± 9 kg after 12 ± 5 months) was paralleled by decreases in the hirsutism score (from 9.5 ± 6.8 to 4.9 ± 4.2 ; $P = 0.001$), total (from 69 ± 32 to 42 ± 19 ng/dl; $P < 0.02$) and free testosterone (from 1.6 ± 0.7 to 0.6 ± 0.3 ng/dl; $P < 0.005$), androstenedione (from 4.1 ± 1.5 to 3.0 ± 0.9 ng/ml; $P < 0.02$), and dehydroepiandrosterone sulfate (from 2000 ± 1125 to 1353 ± 759 ng/ml; $P < 0.005$); amelioration of insulin resistance estimated by homeostasis model assessment (from 6.0 ± 3.0 to 1.6 ± 1.0 ; $P < 0.001$); and restoration of regular menstrual cycles and/or ovulation in all patients.

Conclusions: The PCOS is a frequent finding in women with morbid obesity and may resolve after weight loss induced by bariatric surgery. (*J Clin Endocrinol Metab* 90: 6364–6369, 2005)

THE POLYCYSTIC OVARY syndrome (PCOS) is possibly the most common endocrine disorder in premenopausal women, presenting with a 6.5% prevalence in Spain (1). Although the etiology of PCOS remains largely unknown, the primary defect consists of increased androgen synthesis and secretion by ovarian thecal cells (2, 3), which is favored in many patients by the hyperinsulinism resulting from insulin resistance (4).

Obesity, particularly an abdominal deposition of fat, is common in PCOS patients (5). Together with the presence of insulin resistance, obesity contributes to the 43% prevalence of the metabolic syndrome in PCOS patients (6).

Diet-induced weight loss ameliorates the clinical signs and symptoms of PCOS, including hyperandrogenism and insulin resistance (7), menstrual dysfunction (8), and oligoovulation (9). However, the magnitude of the weight loss usually attained after caloric restriction combined with increased physical activity is usually moderate, in the range of 5–10% of the initial body weight, and is frequently not maintained for long periods of time (10, 11). Therefore, PCOS patients

usually require treatment with insulin sensitizers or oral contraceptives to control their symptoms (12) even after successful nonpharmacological treatment.

Given the disappointing results of diet-based approaches to the treatment of obesity, during the past years the interest in bariatric surgery has increased dramatically (13, 14). A recent meta-analysis of the effects of bariatric surgery in more than 22,000 procedures found an average weight loss of 61%, associated with the complete resolution or improvement of diabetes, hyperlipidemia, hypertension, and obstructive sleep apnea in more than 60% of the patients (15). Although the follow-up period in most of the studies reviewed in this meta-analysis was shorter than 2 yr, a recently published, large prospective study conducted in Sweden (16) confirmed that, although much less important, the weight loss and metabolic benefits of bariatric surgery were maintained 10 yr after the surgical procedure, a result that is especially important considering the worsening of obesity and associated metabolic disorders of obese subjects treated conventionally during a similar follow-up (16).

Despite PCOS being a very prevalent disorder that is frequently associated with obesity and the metabolic syndrome, very little is known about this disorder in women presenting with morbid obesity. In the present study we have obtained a prospective estimate of the prevalence of PCOS in morbidly obese women submitted to bariatric surgery and have evaluated the changes in the PCOS phenotype induced by the

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Abbreviations: BMI, Body mass index; PCOS, polycystic ovary syndrome.

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marked and sustained weight loss attained by these women after the surgical procedure.

Subjects and Methods

Subjects

All premenopausal women reporting to the Department of Surgery of Hospital Ramón y Cajal for bariatric surgery from June 2000 to January 2004 were prospectively recruited. All subjects were Caucasian, from European ancestry. The ethics committee of the Hospital Ramón y Cajal approved the protocol, and informed consent was obtained from each patient.

Surgical procedure

The indication for bariatric surgery was morbid obesity in all patients, defined by a body mass index (BMI) of 40 kg/m² or more or a BMI of 35 kg/m² or more in the presence of significant comorbidity (17). In all these women, weight loss strategies based on caloric restriction combined with increased physical activity had failed repeatedly. Patients were treated by Scopinaro's biliopancreatic diversion (18) or by laparoscopic gastric bypass (19), according to the evaluation and choice of the surgeon.

Criteria for health and disease

The diagnosis of PCOS was established according to the criteria derived from the 1990 National Institute of Child Health and Human Development (NICHD) conference (20). Specifically, PCOS was defined by oligoovulation, clinical and/or biochemical hyperandrogenism and exclusion of hyperprolactinemia (serum prolactin, <24 ng/ml), non-classic congenital adrenal hyperplasia (basal 17-hydroxyprogesterone, <2 ng/ml), and androgen-secreting tumors (20, 21). Evidence for oligoovulation was provided by chronic oligomenorrhea or, in regularly menstruating women, by luteal phase progesterone levels less than 4 ng/ml or basal body temperature charts.

Hormone profiles

Hirsutism was quantified by the modified Ferriman-Gallwey score (22). Between 0800 and 0900 h and after a 12-h overnight fast, an indwelling iv line was placed in a forearm vein; after 15–30 min, basal blood samples were obtained for the measurement of serum glucose, insulin, prolactin, total testosterone, SHBG, calculated free testosterone, 17-hydroxyprogesterone, androstenedione, and dehydroepiandrosterone sulfate. All samples were immediately centrifuged, and serum and plasma were separated and frozen at –20 °C until assayed.

The technical characteristics of the assays employed for hormone measurements have been reported previously (23, 24). The free testosterone concentration was calculated from total testosterone and SHBG concentrations, assuming a serum albumin concentration of 4.3 g/liter and taking a value of 1×10^9 liter/mol for the association constant of SHBG for total testosterone and a value of 3.6×10^4 liters/mol for that of albumin for total testosterone (25). In nondiabetic women, insulin resistance in the fasting state was determined using homeostasis model assessment (26).

The reference ranges (5th and 95th percentiles) for serum androgen and SHBG levels were determined from those of a control group of 81 nonhyperandrogenic women (age, 31 ± 8 yr; BMI, 29.0 ± 7.6 kg/m²). For fasting insulin levels and insulin resistance, the reference values were obtained from the subgroup of lean women ($n = 32$; age, 28 ± 5 yr; BMI, 20.9 ± 2.4 kg/m²) of this control population.

Statistical analysis

Results are expressed as the mean $\pm$ SD unless otherwise stated. The Kolmogorov-Smirnov statistic was applied to continuous variables. Logarithmic or square root transformations were applied as needed to ensure a normal distribution of the variables. Comparisons between the different groups of women at baseline were performed by one-way ANOVA, followed by the Games-Howell *post hoc* test. Paired *t* tests were used to compare the variables at the beginning of the study with those

observed at reevaluation. Analyses were performed using SPSS10 for Macintosh (SPSS, Inc., Chicago, IL). $P < 0.05$ was considered statistically significant.

Results

Cross-sectional study

Seventeen of thirty-six (47%) premenopausal morbidly obese women who underwent bariatric surgery from June 2000 to January 2004 had PCOS. After removing from the calculations seven women previously diagnosed with PCOS in our outpatient clinic to obtain an unbiased estimate of the prevalence of this disorder in morbid obesity, PCOS was present, yet previously undiagnosed, in 10 of 29 women (35%). One of these seven women was being treated with oral contraceptives at the time of surgery (we used the data obtained at the diagnosis of PCOS as the baseline evaluation for the cross-sectional study). Another patient had been treated with oral contraceptives for oligomenorrhea in the past, but had not been diagnosed with PCOS before recruitment. She had not taken oral contraceptives for more than 6 months at the time of the initial evaluation, when the diagnosis of PCOS was established. She underwent bariatric surgery and preferred to be treated again with oral contraceptives to assure contraception. Therefore, these two women were not reevaluated after surgery for the persistence of PCOS, because of the interference of oral contraceptives on menstrual function and hormone profiles.

Another five patients had increased total and/or free testosterone levels, associated with mild hirsutism in one of them, but their menstrual cycles were regular, precluding the diagnosis of PCOS according to NICHD criteria. The remaining 14 women did not have hyperandrogenic disorders.

The comparison of clinical and biochemical variables in the three groups of women are summarized in Table 1. These groups were comparable in terms of BMI, waist circumference, waist to hip ratio, blood pressure, and pulse rate. The hirsutism score was increased in PCOS patients compared with nonhyperandrogenic women, with regularly menstruating hyperandrogenic women presenting with intermediate values. Serum androgen concentrations were increased in PCOS and hyperandrogenic women, but insulin resistance, as estimated by increased fasting insulin levels and homeostasis model assessment values, was higher than that in nonhyperandrogenic women only in PCOS patients.

Regarding other insulin resistance-associated disorders, one PCOS patient presented with diabetes and hypertension, another had diabetes and dyslipidemia, and two were hypertensive, but their glucose tolerance and lipid levels were normal. Only one of the regularly menstruating hyperandrogenic women had hypertension, whereas three of the nonhyperandrogenic women had hypertension, one had diabetes, and one had dyslipidemia.

Follow-up of PCOS patients

After initial evaluation and surgery, all the patients were offered reevaluation of PCOS at the endocrinology outpatient clinic, whereas nutritional and surgical follow-up were

TABLE 1. Clinical and biochemical characteristics of the premenopausal women with morbid obesity submitted to bariatric surgery

Characteristic	PCOS patients (n = 17)	Hyperandrogenic women with regular menstrual cycles (n = 5)	Nonhyperandrogenic women (n = 14)
Age (yr)	29.8 ± 5.3	31.4 ± 3.6	33.9 ± 8.1
Body mass index (kg/m ²)	50.7 ± 7.1	48.4 ± 6.0	48.4 ± 6.9
Systolic blood pressure (mm Hg)	126 ± 13	124 ± 11	127 ± 16
Diastolic blood pressure (mm Hg)	74 ± 10	77 ± 4	73 ± 9
Waist circumference (cm)	119 ± 13	119 ± 9	116 ± 9
Waist-to-hip ratio	0.83 ± 0.08	0.85 ± 0.06	0.83 ± 0.08
Hirsutism score	8.1 ± 6.3 ^a	5.2 ± 2.5	1.5 ± 2.0
Total testosterone (ng/dl)	73 ± 33 ^a	120 ± 69 ^a	48 ± 18
Free testosterone (ng/dl)	1.6 ± 0.7 ^a	2.1 ± 0.8 ^a	0.9 ± 0.4
SHBG (μg/dl)	211 ± 124 ^a	303 ± 152	334 ± 119
Androstenedione (ng/ml)	3.8 ± 1.4	3.7 ± 0.7	2.8 ± 0.9
Dehydroepiandrosterone sulfate (ng/ml)	2001 ± 964	2067 ± 262	1325 ± 607
Fasting glucose (mg/dl)	110 ± 63	107 ± 43	94 ± 21
Fasting insulin (μU/ml)	23.0 ± 11.2 ^{a,b}	13.9 ± 4.0	13.8 ± 7.2
Homeostasis model assessment insulin resistance	5.79 ± 2.78 ^a	3.77 ± 2.09	3.50 ± 2.80

Data are means ± SD. To convert to SI units, multiply androstenedione by 3.19 (results in nmol/liter), dehydroepiandrosterone sulfate by 0.002714 (results in μmol/liter), glucose by 0.0555 (results in mmol/liter), insulin by 6.945 (results in pmol/liter), SHBG by 0.111 (results in nmol/liter), free testosterone by 34.67 (results in pmol/liter), and total testosterone by 0.03467 (results in nmol/liter).

^a $P < 0.05$ compared with nonhyperandrogenic women.

^b $P < 0.05$ compared with hyperandrogenic women presenting with regular menstrual cycles.

conducted independently at the nutrition and surgical units of Hospital Ramón y Cajal. Of the 17 morbidly obese women presenting with PCOS, reevaluation was possible in 12 of them (Fig. 1). As stated above, two patients chose oral contraceptives as treatment for PCOS and to assure contraception, and were not evaluated later because this treatment would interfere with clinical and hormonal evaluation. One patient chose follow-up at her referral hospital, located in a different city, and therefore was not available for reevaluation. Finally, reevaluation was not possible in two patients because of surgical complications: one died during the immediate postoperative period because of surgical complications followed by sepsis of abdominal origin and multiorgan failure, and another patient could not be reevaluated because

of severe malnutrition associated with an eating-pattern disorder that developed after initial surgery, given that long-term amenorrhea was present, thereby precluding an accurate estimation of ovulatory function.

The mean weight loss in the 12 women available for follow-up was 41 ± 9 kg (95% confidence interval, 36–47 kg; $P < 0.001$) after 12 ± 5 months. Weight loss was paralleled by a marked improvement in clinical and biochemical hyperandrogenism, including amelioration of hirsutism and normalization of total and free testosterone, androstenedione, and dehydroepiandrosterone sulfate concentrations in all but one patient, associated with an increase in circulating SHBG and restoration of insulin sensitivity, as reflected by the decrease in fasting insulin levels and homeostasis model assessment insulin resistance (Fig. 2).

Regular menstrual cycles were restored in the 12 PCOS patients after weight loss. Furthermore, in 10 of these patients who were available for determination of luteal phase serum progesterone concentrations, values above 4 ng/ml (10 ± 4 ng/ml; range, 5–16 ng/ml) confirmed ovulation in all of them, suggesting that the restoration of menstrual cycle regularity was also accompanied by restoration of ovulation in these hyperandrogenic patients. Therefore, in none of the 12 PCOS patients could this diagnosis be sustained after the marked weight loss achieved after bariatric surgery.

Finally, diabetes and dyslipidemia resolved in the PCOS patient presenting with both disorders; in another patient, diabetes returned to glucose intolerance, whereas hypertension persisted, and in one of the two PCOS patients presenting with hypertension but no other metabolic complication, blood pressure returned to normal after weight loss.

Discussion

Our present results show that hyperandrogenism is very common among morbidly obese premenopausal women;

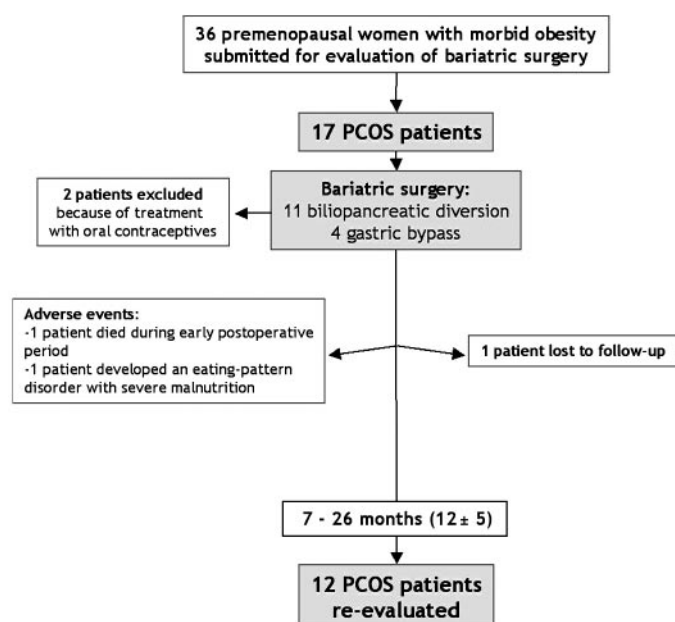


FIG. 1. Flow of the follow-up study.

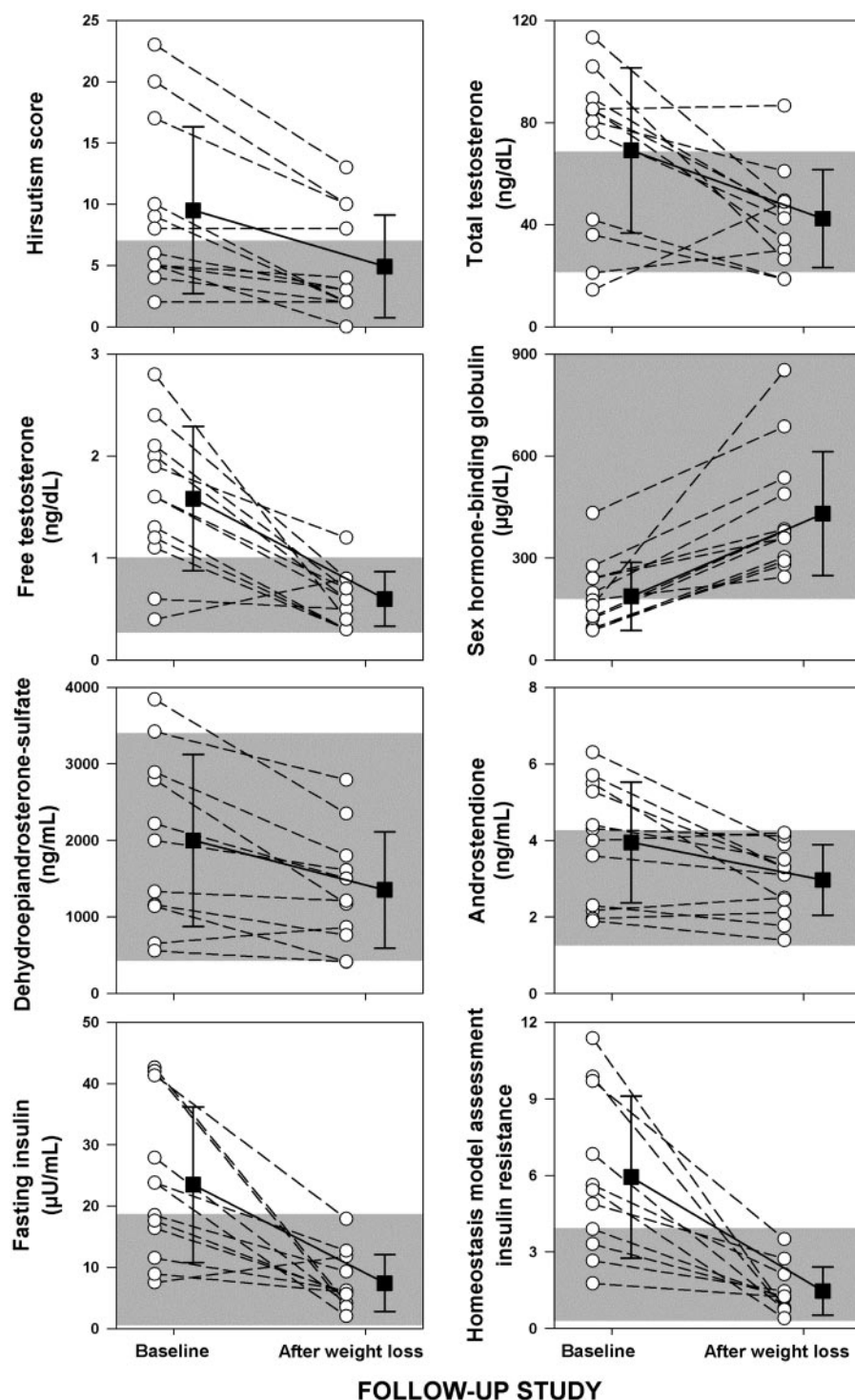


FIG. 2. Clinical and biochemical characteristics of the morbidly obese PCOS patients submitted to bariatric surgery, before and after weight loss. $\circ$, Individual values; $\blacksquare$, mean $\pm$ SD. The shaded areas represent the reference range for each variable. All paired comparisons are statistically significant ($P \leq 0.02$). To convert to Systeme International units, multiply androstenedione by 3.19 (results in nmol/liter), dehydroepiandrosterone sulfate by 0.002714 (results in μ mol/liter), insulin by 6.945 (results in pmol/liter), SHBG by 0.111 (results in nmol/liter), free testosterone by 34.67 (results in pmol/liter), and total testosterone by 0.03467 (results in nmol/liter).

we observed a 6- to 7-fold increase in the prevalence of PCOS (defined by NICHD criteria) in women with morbid obesity compared with the 6.5% figure found by us in unselected female blood donors from Madrid, Spain (1). Of note, this increased prevalence could have been more impressive had we used ultrasound examination of the ovaries, considering that some of the hyperandrogenic women presenting with regular menstrual cycles possibly had

polycystic ovaries, thereby fulfilling Rotterdam criteria for the diagnosis of PCOS (27).

Compared with nonhyperandrogenic women with morbid obesity, PCOS and hyperandrogenic patients with regular menstrual cycles presented with similarly increased total and free testosterone levels, but insulin resistance, as estimated from fasting insulin levels and homeostasis model assessment values, was present only in the PCOS

group. Therefore, a higher degree of insulin resistance appears to be related to the chronic menstrual dysfunction of these obese premenopausal women.

Aside from providing for the first time evidence for a very frequent association of morbid obesity with PCOS, our present data strongly suggest that the sustained and marked weight loss achieved after bariatric surgery leads to the almost complete resolution of PCOS in these women, such as occurs with other components of the metabolic syndrome (15). First, all PCOS patients recovered regular and/or ovulatory menstrual cycles after weight loss. Second, this was paralleled by a marked improvement in the indexes of insulin resistance evaluated, which returned to the reference range for the lean premenopausal population. Finally, hirsutism improved, and serum androgen concentrations returned to the reference range in all but one patient. Therefore, the diagnosis of PCOS could not be sustained in any of these patients after bariatric surgery.

The frequent occurrence of PCOS in women with morbid obesity predisposes these women not only to the metabolic and cardiovascular complications of the metabolic syndrome (6, 28, 29), but also to the significant reproductive morbidity (30), increased prevalence of sleep apnea (31), and substantial impairment in the quality of life (32, 33) associated with PCOS. Therefore, the presence of PCOS should be screened in women with morbid obesity. Moreover, the excellent response of hyperandrogenism and ovulatory dysfunction to bariatric surgery together with the improvement of insulin resistance and associated metabolic disorders might be considered another indication for this type of treatment in morbidly obese PCOS patients.

This is especially important considering that even initially successful diet-based strategies for weight loss are seldom effective in the long run (10, 11). Successful weight loss maintenance, defined as intentional weight loss of at least 10% of the initial body weight that is maintained at least 1 yr after (34), may occur in approximately 20% of overweight individuals who undergo a standard behavioral weight loss program (35). On the contrary, the results of bariatric surgery are sustained for years in most patients (14), with a reported 10-yr maintenance of a 20% loss of initial body weight in as many as 73.5% of obese subjects treated by gastric bypass (16). However, the possibility of severe adverse events of obesity surgery (or even fatal events, such as occurred in one of our patients) must be carefully considered, and therefore, this surgical procedure should be only performed when standard weight loss strategies have failed.

In summary, PCOS is a very frequent disorder in premenopausal women with morbid obesity and may undergo complete resolution after bariatric surgery. Therefore, the possibility of having PCOS should be considered in every premenopausal woman with morbid obesity, and its presence may favor bariatric surgery as an extremely efficient treatment for the metabolic, hyperandrogenic, and reproductive manifestations of this prevalent disorder.

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Address all correspondence and requests for reprints to: Dr. Héctor F. Escobar-Morreale, Department of Endocrinology, Hospital Ramón y Cajal, Carretera de Colmenar km 9'1, Madrid E-28034, Spain. E-mail: hescobarm.hrc@salud.madrid.org.

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