Prevalence of Polycystic Ovary Syndrome and Hyperandrogenemia in Female-to-Male Transsexuals

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Introduction: It has been postulated that the prevalence of polycystic ovary syndrome (PCOS) in female-to-male transsexuals (FMTs) is higher than normal.

Aim: The aim of the study was to investigate the prevalence of PCOS and hyperandrogenemia in FMTs, compared with controls.

Methods: Sixty-one FMTs were evaluated using the Rotterdam 2003 criteria and National Institutes of Health 1990 criteria for the diagnosis of PCOS, compared with 94 controls.

Main Outcome Measure(s): Oligoovulation, anovulation, clinical and biochemical signs of hyperandrogenism and polycystic ovaries, and prevalence of PCOS were measured.

Results: The prevalence of PCOS was 11.5% in FMTs and 9.6% in controls (not significant) with National Institutes of Health 1990 criteria and 14.8% in FMTs and 12.8% in controls (not significant) with the Rotterdam 2003 criteria. Without adjustments and using multivariate analysis in a logistic regression model with adjustments for age, body mass index, and calculated free testosterone, the odds ratio for the prevalence of PCOS was not found to be significantly increased. However, there was a significantly higher prevalence of biochemical hyperandrogenism in FMTs. Hyperandrogenemia was associated with a moderate increase in the odds ratio for the prevalence of PCOS, at 1.08 and 1.07 ($P < 0.001$ and $P = 0.001$), for the two definitions used in this study, respectively.

Conclusions: PCOS was not significantly increased in FMTs in comparison with controls. However, FMTs more frequently had biochemical hyperandrogenism. **(*J Clin Endocrinol Metab* 93: 1408–1411, 2008)**

Several studies have reported a higher-than-normal prevalence of polycystic ovary syndrome (PCOS) in female-to-male transsexuals (FMTs) (1–4), but the numbers of patients were small, 16 each in two of the studies (2, 3), and ultrasound was not used for diagnosis (1) or not always (4, 5). A higher prevalence of PCOS was not confirmed in one study including 96 FMTs, but it assessed only the patients' menstrual history and LH and testosterone levels, without ultrasound examinations of the ovaries (6).

The aim of the present study was to use clinical, biochemical, and ultrasound criteria to diagnose PCOS in a group of FMTs, using the complete diagnostic procedures described in the National Institutes of Health (NIH) 1990 and Rotterdam 2003 criteria. Using the NIH 1990 definition in unselected women of reproductive age, the prevalence of PCOS is 6.5–8.0% (7). The 2003 Rotterdam criteria incorporated ultrasound of polycystic ovaries into the diagnostic procedure (8). Using these criteria to diagnose PCOS, the prevalence may be 1.5 times higher, at 9.5–12.0% of women (9, 10).

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Abbreviations: ASN, Androgen-secreting neoplasm; BMI, body mass index; cFT, circulating free testosterone; CI, confidence interval; CV, coefficient of variation; DHEAS, dehydroepiandrosterone sulfate; FMT, female-to-male transsexual; HAIRAN, hyperandrogenic insulin-resistant acanthosis nigricans; mFG, modified Ferriman-Gallwey; NCAH, nonclassical adrenal hyperplasia; OR, odds ratio; PCOS, polycystic ovary syndrome; TT, total testosterone.

Subjects and Methods

Subjects

The prevalence of PCOS in healthy FMTs (n = 61) was compared prospectively with that in healthy unselected controls (n = 94). The study was approved by the Ethics Committee at Erlangen University Hospital, and the participants provided informed consent. Their medical history was recorded, and serum chemistry profiles, hormonal analyses, and ultrasound examinations were performed. Polycystic ovaries were diagnosed using vaginal ultrasound. FMTs were examined prospectively before receiving any androgen therapy. Only patients who confirmed that they had not taken any hormone preparation were included in our analysis.

Criteria defining PCOS

NIH criteria

Theses included hyperandrogenism and/or hyperandrogenemia and oligoovulation after exclusion of other androgen excess disorders (11).

Rotterdam 2003 criteria

These criteria included at least two of the following three features: 1) oligoovulation and/or anovulation; 2) clinical and/or biochemical signs of hyperandrogenism; and 3) polycystic ovaries after exclusion of other androgen excess disorders (8).

Defining biochemical hyperandrogenemia

Measuring serum testosterone in women is challenging (12–14). Circulating free testosterone (cFT) was calculated using the formula provided by the International Society for the Study of the Aging Male (http://www.issam.ch/freetesto.htm), from total testosterone (TT) and SHBG in the same sample, without taking the albumin concentration into account (15, 16). Hyperandrogenemia was defined as cFT 0.028 nmol/liter or greater.

Defining clinical hyperandrogenism

Alopecia and acne are unreliable clinical signs of hyperandrogenism (7), but hirsutism is an important clinical indicator of androgen excess, present in about 60% of women with PCOS (7, 14). The presence of terminal hair in primarily masculine areas was assessed by a single investigator during the first consultation in every patient (16). The modified Ferriman-Gallwey (mFG) score was used to score the hirsutism pattern. Patients with an mFG score of 6 or greater were considered hirsute (14, 17).

Assessment of ovulation status

The major clinical signs, oligomenorrhea or amenorrhea, vary in duration but are generally unambiguous (7). The interval between bleeding episodes was assessed. In patients with amenorrhea during the previous year and women with cycles longer than 35 d, serum was obtained randomly and patients were regarded as anovulatory. In women with regular menstrual cycles of 26–35 d, serum was obtained between d 3 and 5 of the cycle and serum progesterone was measured between d 22 and 24 during the same cycle. Progesterone levels greater than 4 ng/ml indicated ovulation, less than 4 ng/ml, anovulation (14, 17).

Exclusion of other androgen excess disorders

To diagnose PCOS, other hyperandrogenic conditions were excluded: 21-hydroxylase-deficient nonclassical adrenal hyperplasia (NCAH); hyperandrogenic insulin-resistant acanthosis nigricans (HAIRAN) syndrome; and an androgen-secreting neoplasm (ASN). To exclude NCAH in patients with repeated 17-hydroxyprogesterone levels of 6 nmol/liter or greater, an ACTH stimulation test was performed. 17-Hydroxyprogesterone levels rising to 30 nmol/liter or greater 30–60 min after ACTH administration were considered diagnostic of NCAH. If TT was greater than 8 nmol/liter, computed tomography of the adrenal gland was carried out to exclude an ASN (16). Women of the control group who had received hormonal therapy, including oral contraceptives or steroid medications, 3 months or less before the study were excluded.

Biochemical measurements

Measurements were performed in a routine diagnostic endocrinology laboratory using established commercial assays (Diagnostic Products Corp., Los Angeles, CA), routinely monitored by participation in external quality-control programs. All samples of FMTs and controls were measured within one assay run.

TT was measured quantitatively using a solid-phase competitive chemiluminescent enzyme immunoassay. The intraassay coefficients of variation (CV) were 16.3, 11.7, and 10.0% at the levels of 0.93, 2.98, and 5.26 nmol/liter. The corresponding interassay CVs were 24.3, 13.0, and 10.3%.

Prolactin was measured using an immunometric assay. The intraassay CVs were 2.8, 3.6, and 2.3% at the levels of 186.6, 402.6, and 466.6 mIU/liter. The corresponding interassay CVs were 8.2, 7.4, and 5.9%. No cross-reactivity with other compounds is known.

Dehydroepiandrosterone sulfate (DHEAS) was measured using a solid-phase competitive chemiluminescent enzyme immunoassay. The intraassay CVs were 8, 6.5, and 6.3% at the levels of 4.42, 5.81, and 14.14 μmol/liter. The corresponding interassay CVs were 9.8, 9.3, and 8.8%.

LH, FSH, and SHBG were measured with immunometric assays.

Statistics

Numerical variables are presented as means ± SD, unless otherwise noted. For bivariate analysis, Wilcoxon rank-sum tests were used to compare parameters between FMTs and the control group. Multivariate logistic regression analysis was performed to assess the odds ratios for diagnosing PCOS in FMTs in comparison with the control group after adjustment for cFT, age, and body mass index (BMI). It was assessed whether the diagnostic criteria for PCOS (anovulation, hirsutism, hyperandrogenemia, and ultrasound evidence of polycystic ovaries), and the diagnosis of PCOS itself based on the Rotterdam and NIH criteria were more frequent in the control group or in FMTs, using the χ^2 test of independence with Yates correction. Calculations were all performed using the SPSS program (version 13.0 for Windows; SPSS, Inc., Chicago, IL). All hypothesis tests were two sided. $P < 0.05$ was considered statistically significant.

Results

No evidence of NCAH, HAIRAN, or ASN was found in either the control group or FMT group. Sixty-five women in the control group had not received oral contraceptives for more than 6 months, whereas 29 women stopped oral contraceptives between 3 and 6 month before they were included in our study. Using bivariate analysis, TT and also cFT and calculated bioavailable testosterone were significantly higher in FMTs, whereas SHBG was significantly lower in FMTs in comparison with controls.

Using the Rotterdam 2003 criteria, the prevalence of PCOS was 14.8% in FMTs in comparison with 12.8% in controls (Table 1). Using the NIH criteria, the prevalence of PCOS was 11.5% in FMTs in comparison with 9.6% in controls. Neither of these differences was statistically significant. Nor were there any significant differences between the two groups with regard to the prevalence of the clinically diagnostic criteria for PCOS (anovulation, hirsutism, and polycystic ovaries). How-

TABLE 1. Clinical and hormonal parameters for FMTs and control women

	Control group (n = 94)	FMTs (n = 61)	*P* value
Age (yr)	29.57 ± 7.72	29.98 ± 7.33	0.816[a]
BMI (kg/m^2)	25.57 ± 6.19	25.02 ± 6.35	0.482[a]
LH (IU/liter)	8.36 ± 13.38	7.96 ± 5.94	0.826[a]
FSH (IU/liter)	6.74 ± 5.22	8.64 ± 5.94	0.361[a]
PRL (ng/ml)	11.93 ± 8.27	12.38 ± 6.25	0.713[a]
DHEAS (pmol/liter)	6.02 ± 3.46	6.44 ± 3.13	0.430[a]
TT (nmol/liter)	1.48 ± 0.62	1.86 ± 0.82	0.001[a]
cFT (nmol/liter)	0.019 ± 0.012	0.031 ± 0.019	<0.001[a]
SHBG (nmol/liter)	60.65 ± 41.65	44.48 ± 22.44	0.006[a]
Anovulation	20 (21.3%)	13 (21.3%)	0.845[b]
Hirsutism (mFG score ≥ 6)	19 (20.2%)	16 (26.3%)	0.797[b]
Hyperandrogenemia	19 (20.2%)	27 (44.3%)	0.002[b]
PCO	14 (14.9%)	6 (9.8%)	0.501[b]
PCOS (Rotterdam)	12 (12.8%)	9 (14.8%)	0.909[b]
PCOS (NIH)	9 (9.6%)	7 (11.5%)	0.912[b]

The data are shown as means ± SD. The prevalence rates for the diagnostic criteria for PCOS and the prevalence of PCOS itself are in accordance with the different definitions. PCO, Polycystic ovaries; PRL, prolactin.

[a] Two-sample Wilcoxon comparisons.

[b] χ^2 test of independence incorporating the Yates correction for continuity.

ever, hyperandrogenemia was significantly more frequent in FMTs in comparison with controls.

Without adjustments, the odds ratio (OR) for the diagnosis of PCOS based on the Rotterdam 2003 criteria was 1.18 [95% confidence interval (CI) 0.46–3.01; $P = 0.725$], and the OR for the diagnosis of PCOS based on the NIH criteria was 1.22 (95% CI 0.43–3.5; $P = 0.705$). The probability of diagnosing PCOS was not significantly increased in FMTs. Multivariate analysis using a logistic regression model with adjustments for age, BMI, and cFT did not reveal a significantly increased OR for the prevalence of PCOS using either the Rotterdam or NIH criteria. However, an increase in cFT was associated with a moderate increase in PCOS, with ORs of 1.08 and 1.07 ($P < 0.001$ and $P = 0.001$) for the different definitions used in this study. The results are shown in Table 2.

Discussion

To our knowledge, this is the first prospective investigation of the prevalence of PCOS in FMTs in comparison with healthy controls using the complete diagnostic procedures specified in the NIH 1990 and Rotterdam 2003 criteria for PCOS. The prevalence of PCOS in the general population ranges from 3 to 12.4%, depending on the diagnostic criteria used, population studied, and recruitment process used (9, 18, 19).

Prevalence rates between 9.6% using the NIH 1990 definition and 12.8% using the Rotterdam 2003 definition were noted in the control group, in agreement with the published data. In this study, the prevalence rates were not significantly higher in the FMT group, at 11.5 and 14.8% using the NIH 1990 and Rotterdam 2003 definitions, respectively. Independently of the definition used, the most important factor associated with an increase in the risk of PCOS was hyperandrogenemia, diagnosed using the cFT criterion. Hyperandrogenemia was diagnosed significantly more often in FMTs in the study. FMTs are sometimes self-medicating with androgen preparations, and even small amounts of hormonal preparations may affect the assay results. Sometimes they may not even be cognizant of the fact that they are taking hormones. However, only patients who confirmed that they had not taken any hormone preparation were included

TABLE 2. Risk for the prevalence of PCOS in accordance with the Rotterdam and NIH criteria after multivariate analysis using a logistic regression model with adjustment for age, BMI, and cFT

	OR	*P* value	95% CI	
Rotterdam criteria				
FMTs[a]	0.28	0.062	0.08	1.07
Age (yr)	0.84	0.163	0.87	1.02
BMI (kg/m^2)	1.00	0.994	0.91	1.10
cFT (nmol/liter)	1.08[b]	<0.001	1.04	1.13
NIH criteria				
FMTs[a]	0.33	0.142	0.08	1.45
Age (yr)	0.93	0.110	0.84	1.02
BMI (kg/m^2)	1.04	0.371	0.95	1.15
cFT (nmol/liter)	1.07[b]	0.001	1.03	1.12

[a] Reference control group.

[b] The OR was calculated for a change in cFT of 0.001.

in our analysis. A screening for potential self-medication was not done, and this is a possible limitation of our study, which might explain the higher prevalence of hyperandrogenemia in FMTs.

These results differ from those of many earlier studies describing a higher prevalence of PCOS among FMTs (1–4). The strength of the present study lies in its rigorous testing for the presence of PCOS using state-of-the-art criteria (8, 11), incorporating transvaginal ultrasonography. The number of patients included was also larger than in earlier studies (2–4), with the exception of Baba *et al.* (1), which included 69 FMTs. The levels of TT and cFT in the FMT group were significantly higher than in the controls, although there was considerable overlap with the nontranssexual controls. Specific identifiable disorders associated with adrenal androgen excess were not present either in 94 of the control individuals or in 61 of the FMTs. This may be due to the small number of patients studied. However, approximately 20% of PCOS women show evidence of adrenal androgen excess, mostly with elevated levels of DHEAS (9). In the present study, there were no differences between DHEAS levels in control women and FMTs; DHEAS levels were in a moderately high range in both groups. It must therefore be assumed that the source of the higher levels of androgens in FMTs is predominantly ovarian, although serum LH levels were not higher in FMTs than in controls.

In conclusion, using rigorous state-of-the-art criteria for diagnosing PCOS, this study did not confirm a significantly higher prevalence of PCOS in a group of 61 FMTs. The FMTs had significantly higher androgen levels, probably of ovarian origin. Alternatively, this may be due to undetected self medication with androgens before inclusion in the study, although there was considerable overlap with nontranssexual controls.

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