

Prevalence of functional disorders of androgen excess in unselected premenopausal women: a study in blood donors

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Submitted on November 23, 2011; resubmitted on January 2, 2012; accepted on January 18, 2012

BACKGROUND: The polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women. On the contrary, the prevalences of other disorders of androgen excess such as idiopathic hyperandrogenism and idiopathic hirsutism remain unknown. We aimed to obtain an unbiased estimate of the prevalence in premenopausal women of (i) signs of androgen excess and (ii) PCOS, idiopathic hyperandrogenism and idiopathic hirsutism.

METHODS: A multicenter prevalence survey included 592 consecutive premenopausal women (393 from Madrid, Spain and 199 from Bologna, Italy) reporting spontaneously for blood donation. Immediately before donation, we conducted clinical and biochemical phenotyping for androgen excess disorders. We determined the prevalence of (i) hirsutism, acne and alopecia as clinical signs of androgen excess and (ii) functional disorders of androgen excess, including PCOS, defined by the National Institute of Child Health and Human Development/National Institute of Health criteria, idiopathic hyperandrogenism and idiopathic hirsutism.

RESULTS: Regarding clinical signs of hyperandrogenism, hirsutism and acne were equally frequent [12.2% prevalence; 95% confidence interval (CI): 9.5–14.8%], whereas alopecia was uncommon (1.7% prevalence, 95% CI: 0.7–2.7%). Regarding functional disorders of androgen excess, PCOS and idiopathic hirsutism were equally frequent (5.4% prevalence, 95% CI: 3.6–7.2) followed by idiopathic hyperandrogenism (3.9% prevalence, 95% CI: 2.3–5.4).

CONCLUSIONS: Clinical signs of hyperandrogenism and functional disorders of androgen excess show a high prevalence in premenopausal women. The prevalences of idiopathic hyperandrogenism and idiopathic hirsutism are similar to that of PCOS, highlighting the need for further research on the pathophysiology, consequences for health and clinical implications of these functional forms of androgen excess.

Key words: epidemiology / hirsutism / acne / alopecia / hyperandrogenism

Introduction

Functional disorders account for most cases of androgen excess in premenopausal women. In clinical series, polycystic ovary syndrome (PCOS) affects ~70–72% of the patients, followed by idiopathic hyperandrogenism in 15%, idiopathic hirsutism in 10% and non-classic congenital hyperplasia in 3%, with androgen secreting tumors and

other rare disorders accounting for <1% of cases (Azziz *et al.*, 2004a; Glintborg *et al.*, 2004; Unluhizarci *et al.*, 2004b; Carmina *et al.*, 2006; Escobar-Morreale *et al.*, 2008).

Estimates of the prevalence of functional androgen disorders in the general population are only available for PCOS: these prevalences range from 4 to 14% (Knochenhauer *et al.*, 1998; Diamanti-Kandarakis *et al.*, 1999; Asuncion *et al.*, 2000; Azziz *et al.*, 2004b; Goodarzi *et al.*,

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2005; Chen et al., 2008; Kumarapeli et al., 2008; March et al., 2010; Moran et al., 2010; Tehrani et al., 2011). In contrast, the population prevalences of other androgen excess disorders such as idiopathic hyperandrogenism or idiopathic hirsutism remain unknown. The extrapolation of the distribution of hyperandrogenic disorders found in clinical series to the data obtained in studies addressing the prevalence of PCOS yielded a rough estimate of the prevalence of non-PCOS functional androgenic disorders of ~2% (Carmina, 2006a,b).

With the aim of providing estimates of the prevalences of (i) clinical signs of hyperandrogenism such as hirsutism, acne and alopecia and (ii) functional disorders of androgen excess, we have studied a large series of premenopausal women from Spain and Italy reporting spontaneously for blood donation. As will be seen, not only PCOS but other functional disorders of androgen excess are quite prevalent in premenopausal women.

Materials and Methods

Study design

Investigators attended the blood bank facilities of the participating hospitals on every afternoon of the work week and invited all premenopausal women reporting spontaneously for blood donation to participate in the study. Almost all women invited agreed to participate in the study, with no differences in race, ethnicity or socioeconomic status between women who agreed and the very few who refused participation. We recruited women who were found suitable for blood donation. Recruitment continued until the total number of women indicated by sample size analysis was reached.

We scored hirsutism using a modification of the Ferriman-Gallwey method (Hatch et al., 1981). The presence or absence of acne and androgenic alopecia was recorded, and weight, height, waist and hip circumferences were measured.

A history form was completed, including menstrual dating and irregularity, past history of hirsutism and acne, reproductive and gynecological history and use of medication including oral contraceptive pills among other data. In women who were receiving hormonal drugs, their menstrual history before treatment and the reason for treatment were recorded. None of the subjects were younger than 18 year olds, which is the minimum legal age for blood donation in Spain and Italy.

Serum samples were stored at -20°C until assayed. The study was approved by the institutional review board of the participating hospitals, and written informed consent was obtained from all the subjects.

Assays

We measured total testosterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), androstenedione, thyrotropin and prolactin. Total testosterone, SHBG, DHEAS, androstenedione, prolactin and thyrotropin were measured, each hormone in a single assay. The same automated immunochemiluminescence method was used in Spain and Italy for these measurements (Immulite, 2000, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). 17-hydroxyprogesterone was measured by direct RIA only in women potentially diagnosed with PCOS (ImmuChem, ICN Biomedicals, Inc., Costa Mesa, CA, USA). As reported by the manufacturer, the lower detection limits of the assays were 0.5 nmol/l for total testosterone, 0.02 nmol/l for SHBG, 0.4 $\mu\text{mol/l}$ for DHEAS, 1.0 nmol/l for androstenedione, 3.4 mIU/l for prolactin and 0.004 $\mu\text{IU/ml}$ for thyrotropin. The mean intra-assay coefficients of variation were as follows: 7.4% for total testosterone, 6.5% for

SHBG, 6.9% for DHEAS, 6.2% for prolactin, 7.1% for thyrotropin and 9.5% for 17-hydroxyprogesterone. Of note, the total testosterone immunochemiluminescence assay used here is based on a direct radioimmunoassay (Coat-A-Count Total Testosterone, Siemens Medical Solutions Diagnostics) that showed similar performance compared with in-house and commercial liquid chromatography/mass spectrometry (LC/MS) testosterone assays in large clinical studies (Legro et al., 2010). The free androgen index and free testosterone concentrations were calculated from total testosterone and SHBG concentrations (Vermeulen et al., 1999).

Criteria for the definition of PCOS and other functional disorders of androgen excess

Because ultrasound examination of the ovaries was not possible in all women, the National Institute of Child Health and Human Development/National Institute of Health (NICHD/NIH) criteria (Zawadzki and Dunaif, 1992) were used for the diagnosis of PCOS and other functional disorders of androgen excess.

PCOS was defined by the presence of menstrual dysfunction, clinical hyperandrogenism and/or hyperandrogenemia and exclusion of specific etiologies (Zawadzki and Dunaif, 1992). Menstrual dysfunction was considered when the women had oligomenorrhea, defined by more than six cycles with a length of >35 days per year, and/or when the patient had no menstrual bleeding for 3 consecutive months (Goodman, 2007). Clinical hyperandrogenism was defined by the presence of hirsutism, represented by a modified Ferriman-Galway score of 8 or more, persistence of acne during the third decade of life or later or the presence of androgenic alopecia (Zawadzki and Dunaif, 1992). Following the recommendations of the manufacturer of the immunoassays used here, we proceeded to establish the reference ranges for circulating androgens in our laboratory. Hyperandrogenemia was defined by a circulating total or free testosterone, androstenedione, DHEAS and/or free androgen index above the 95th percentile of all the women studied here who were not taking hormonal medication nor had previous ovariectomy or hysterectomy: total testosterone >2.2 nmol/l, free testosterone >42 pmol/l, DHEAS >7 $\mu\text{mol/l}$, androstenedione >12 nmol/l and/or free androgen index >15 . These in-house reference limits were lower than those reported by the manufacturer for premenopausal women for total testosterone (>2.8 ng/dl) and DHEAS (>10 $\mu\text{mol/l}$) but coincided for androstenedione (12 nmol/l).

Specific etiologies were excluded in all women who presented with both criteria for the diagnosis of PCOS. Hyperprolactinemia and thyroid dysfunction were excluded by the finding of serum prolactin and thyrotropin levels within the normal range. Basal or cosyntropin-stimulated 17-hydroxyprogesterone levels served to rule out non-classic 21-hydroxylase deficiency (Azziz et al., 1999). Clinical assessment served to rule out androgen-secreting tumors, Cushing's syndrome and anabolic drug use or abuse.

We defined idiopathic hyperandrogenism by increased androgen levels and signs of androgen excess in women presenting with regular menstrual cycles of normal length. Idiopathic hirsutism required the presence of both normal androgen levels and regular menstrual cycles of normal length.

The isolated finding of acne was not considered as an androgen excess disorder if not accompanied by menstrual dysfunction or by other clinical or biochemical evidence of androgen excess. Finally, women presenting with oligomenorrhea but no clinical or biochemical hyperandrogenism were diagnosed with non-androgenic oligomenorrhea.

Women under hormonal contraception were classified in a separate group, unless there was a previous diagnosis of any of the disorders described above, or their clinical history and physical examination were enough to sustain such diagnoses with certainty.

Statistical analysis

Sample size analysis used the Ene 3.0 software (<http://www.e-biometria.com>, last accessed 19 August 2011). Considering our previous report of a 6.5% prevalence of PCOS in blood donors (Asuncion *et al.*, 2000), a total of 584 women would be needed to provide a new estimation with 95% normal asymptotic confidence interval (CI) and 2% precision.

We calculated prevalences and 95% confidence intervals (95% CI) considering women from Spain and Italy as a whole, and also separately for each country. Continuous variables were expressed as medians and interquartile ranges. Logarithmic and square root transformation were applied to ensure normality of skewed variables as needed. One-way ANOVA followed by the least significant difference *posthoc* test served to compare the different groups of women. When variables remained skewed after transformation, we applied the Kruskal–Wallis test. In case of a statistically significant result, we used Mann–Whitney tests, applying a Bonferroni correction to the level of significance, to analyze the comparisons among groups. Categorical variables were compared by χ^2 or Fisher's exact tests as appropriate. $P < 0.05$ was considered statistically significant for all tests with the exception mentioned above.

Results

Prevalence of clinical signs of androgen excess

Hirsutism was present in 72 of the 592 premenopausal women (12.2% prevalence, 95% CI: 9.5–14.8%), including 46 women from Spain (11.7% prevalence, 95% CI: 8.5–14.9%) and 26 women from Italy (13.1% prevalence, 95% CI: 8.4–17.7%). The prevalence was not different among countries ($\chi^2 = 0.208$, $P = 0.648$). The 95th percentile of the modified Ferriman–Gallwey score was 10 when considering women from Spain and Italy as a whole or when considering women from these countries separately.

The overall prevalence of acne was the same as that of hirsutism, yet not all the women presenting with acne had hirsutism and vice versa: acne was present in 72 of the 592 premenopausal women (12.2% prevalence, 95% CI: 9.5–14.8%), including 48 women from Spain (12.2% prevalence, 95% CI: 9.0–15.5%) and 24 women from Italy (12.1% prevalence, 95% CI: 7.5–16.6%). The prevalence was not different among countries ($\chi^2 = 0.003$, $P = 0.957$).

Alopecia was found only in 10 of the 592 women (1.7% prevalence, 95% CI: 0.7–2.7%), including 8 women from Spain (2.0% prevalence, 95% CI: 0.6–3.4%) and 2 women from Italy (1.0% prevalence, 95% CI: –0.4–2.4%). The prevalence was not different among countries ($P = 0.508$ by Fisher's exact test).

Prevalence of functional disorders of androgen excess

The prevalences of the different disorders of androgen excess as defined above are summarized in Table I. Functional disorders of androgen excess affected 87 of the 592 premenopausal women studied here (14.7% prevalence, 95% CI: 11.8–17.5). Among these disorders, PCOS and idiopathic hirsutism were equally frequent (32 of 592 women, 5.4% prevalence, 95% CI: 3.6–7.2), followed by idiopathic hyperandrogenism (23 of 592 women, 3.9% prevalence, 95% CI: 2.3–5.4).

Isolated acne, acne without any other sign or symptom of androgen excess, was found in 31 women (5.2% prevalence, 95% CI: 3.4–7.0) and non-androgenic oligomenorrhea was diagnosed in 25 women (4.2% prevalence, 95% CI: 2.6–5.8), whereas 148 women were under hormonal treatment solely for the purpose of contraception (25.0% prevalence, 95% CI: 21.5–28.5). The remaining 301 female blood donors were healthy and did not match any of the diagnostic categories described above.

All these prevalences were similar when analyzing women from Spain and Italy separately (Table I).

Reproductive history and clinical and hormonal variables

Women from Spain and Italy were comparable in terms of age [median and interquartile range 31 (12) versus 33 (13) years], body mass index [25 (5) versus 24 (5) kg/m²] and age at menarche [12 (3) versus 12 (3) year]. The phenotypic variables of the women studied here depending on the diagnosis received are summarized in Tables II and III. Women with functional disorders of androgen excess, PCOS, idiopathic hyperandrogenism and idiopathic hirsutism, and women receiving hormonal drugs for contraception were younger compared with healthy women and with those diagnosed with non-androgenic oligomenorrhea (Table II).

Regarding reproductive history, menarche occurred at a younger age in women with idiopathic hirsutism compared with healthy women and with women diagnosed with non-androgenic oligomenorrhea (Table II). The percentage of women who had had at least one pregnancy (Table III) was higher in healthy women (42%), in women diagnosed with non-androgenic oligomenorrhea (44%) and in women with isolated acne (39%) compared with women under hormonal contraception (28%) or women diagnosed with idiopathic hirsutism (25%), idiopathic hyperandrogenism (30%) and, especially, women with PCOS (19%).

Furthermore, when considering the number of women who have had more than one pregnancy, the differences between healthy women and women with functional forms of androgen excess were even larger, particularly for women with PCOS and idiopathic hirsutism (Table III). On the contrary, the abortion rate (number of abortions divided by number of pregnancies of each woman) was not different among the study groups (data not shown, Kruskal–Wallis $\chi^2 = 5.12$, $P = 0.529$).

The hirsutism score was higher in women with functional forms of androgen excess compared with healthy women, women on hormonal contraception, non-androgenic oligomenorrhea and women presenting with isolated acne (Table II). Among the disorders of androgen excess, women with idiopathic hirsutism showed slightly higher hirsutism scores compared with women with PCOS (Table II).

Women with PCOS had higher body mass index (their median value was in the overweight range) compared with healthy women and women on hormonal contraception, with other groups showing intermediate values (Table II). No statistically significant differences were observed in clinical indexes of abdominal adiposity such as waist circumference and waist hip ratio, or in blood pressure and heart rate (Table II).

As expected from the criteria used to define the diagnostic categories, serum androgen levels were higher in women with idiopathic

Table I Prevalence of functional disorders of androgen excess and other diagnoses.

	Whole population (n = 592)		Women from Spain (n = 393)		Women from Italy (n = 199)	
	Prevalence (%)	95% CI (%)	Prevalence (%)	95% CI (%)	Prevalence (%)	95% CI (%)
Functional hyperandrogenism	14.7	11.8–17.5	14.5	11.8–18.0	15.1	10.1–20.0
Polycystic ovary syndrome	5.4	3.6–7.2	5.1	2.9–7.3	6.0	2.7–9.3
Idiopathic hyperandrogenism	3.9	2.3–5.4	3.6	1.7–5.4	4.5	1.6–7.4
Idiopathic hirsutism	5.4	3.6–7.2	5.9	3.5–8.2	4.5	1.6–7.4
Acne without menstrual dysfunction or hyperandrogenism	5.2	3.4–7.0	4.8	2.7–7.0	6.0	2.7–9.3
Non-androgenic oligomenorrhea	4.2	2.6–5.8	5.3	3.1–7.6	2.0	0.1–4.0
Hormonal contraception	25.0	21.5–28.5	24.9	20.7–29.2	25.1	19.1–31.2

No differences were observed between Spain and Italy in the prevalence of these disorders ($\chi^2 = 4.850$, $P = 0.563$).

hyperandrogenism and women with PCOS compared with healthy women (Table II). The serum androgen concentrations of women with idiopathic hirsutism, isolated acne and non-androgenic oligomenorrhea were similar to those of healthy women (Table II). We did not observe differences in SHBG levels of women with disorders of androgen excess and women with isolated acne, non-androgenic oligomenorrhea and healthy women (Table II). On the contrary, women receiving hormonal contraception showed increased serum SHBG concentrations and reduced free testosterone levels and FAI values, compared with all the other groups (Table II). Furthermore, their androstenedione and DHEAS levels were also decreased compared with healthy women, and only their total testosterone concentrations were similar to those of healthy women (Table II).

Discussion

Our present results indicate that clinical signs of hyperandrogenism, and functional forms of androgen excess, are very prevalent in premenopausal women.

Our data provide for the first time an assessment of the prevalences of functional forms of androgen excess other than PCOS such as idiopathic hyperandrogenism and idiopathic hirsutism in the general population. These disorders are actually much more frequent than previously expected (Carmina, 2006a,b) as the prevalence of idiopathic hirsutism in premenopausal women equals that of PCOS, and the prevalence of idiopathic hyperandrogenism is only slightly lower.

The importance of this finding is that most research efforts and clinical recommendations in the area of androgen excess are focused nowadays on PCOS, whereas much less interest is devoted to idiopathic hyperandrogenism and idiopathic hirsutism. Hopefully, the recognition of the large proportion of premenopausal women affected by these non-PCOS androgen excess phenotypes will change this situation, facilitating knowledge about their pathogenesis and providing recommendations for their clinical management.

Our study demonstrates that PCOS has a prevalence of 5.4% with a 95% CI of 3.6–7.2% in women from the Mediterranean area when diagnosed according to strict NICHHD criteria; our earlier study demonstrated a 6.5% prevalence in Madrid (Asuncion et al., 2000).

The use of blood donors as a minimally biased sample of the population has considerable advantages, but also imposed some limitations to our study. Among the advantages (Asuncion et al., 2000) are that: (i) blood donors are usually healthy people, not seeking medical care for any reason at the time of donation; (ii) in Spain and Italy blood donation is not rewarded in any way, so there is no bias derived from the socio-economic background; (iii) blood donors have mixed ethnic origins, representing the population where they live; (iv) there is no pre-selection of blood donors, as they come to the hospital without scheduling and (v) it is easy to obtain blood samples from them.

Among the limitations, we were not able to control sampling for fasting, time of the day or phase of the menstrual cycle, and as these women were only studied on the day reporting for blood donation, we were not able to obtain accurate estimations of ovulatory function having to rely on menstrual history instead. But more importantly, we had no access to ultrasonography at the blood banks of our institutions precluding the use of ovarian morphology as a diagnostic criterion. Therefore, we had to rely on older NICHHD/NIH criteria instead of applying more recent definitions of PCOS (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004; Azziz et al., 2006; Azziz et al., 2009).

These limitations possibly caused an underestimation of the prevalence of PCOS in our series of blood donors at the expense of an overestimation of the prevalence of other androgenic phenotypes; an accurate estimation of ovulatory function in hirsute and hyperandrogenic women presenting with regular menstrual cycles of normal length would have probably revealed anovulatory cycles in some of them (Azziz et al., 1998). Moreover, ultrasonography would have probably revealed polycystic ovarian morphology in some women, from our idiopathic hyperandrogenism and idiopathic hirsutism groups, who would have been diagnosed with ovulatory PCOS according to Androgen Excess and PCOS Society criteria and Rotterdam consensus (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004; Azziz et al., 2006; Azziz et al., 2009), and from our non-androgenic oligomenorrhea group, who also would have been diagnosed with PCOS according to Rotterdam consensus (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Of note, a recent study (March et al., 2010) that used ultrasound evaluation of ovarian

Table II Clinical and biochemical variables of female blood donors from Spain and Italy according to diagnostic categories.

	Polycystic ovary syndrome ^a (n = 32)	Idiopathic hyperandrogenism (n = 23)	Idiopathic hirsutism (n = 32)	Isolated acne (n = 31)	Hormonal contraceptives (n = 148)s	Non-androgenic oligomenorrhea (n = 25)	Healthy women (n = 301)
Age (years)	27 (10) ^b	27 (12) ^b	28 (9) ^b	32 (11)	29 (10) ^b	32 (10)	33 (13) ^{d,f-h}
Age at menarche (years)	12 (2)	12 (2)	11 (1) ^{b,d}	12 (3)	13 (1) ^f	13 (3)	12 (1) ^f
Body mass index (kg/m ²)	26.2 (6.5) ^{b,d}	23.8 (7.1)	24.0 (5.5)	23.7 (4.1)	22.7 (4.3) ^h	24.0 (6.3)	23.3 (4.5) ^h
Waist circumference (cm)	81 (16)	80 (11)	75 (13)	78 (18)	75 (12)	77 (21)	75 (12)
Waist hip ratio	0.774 (0.070)	0.753 (0.076)	0.779 (0.079)	0.765 (0.093)	0.754 (0.080)	0.767 (0.087)	0.753 (0.076)
Hirsutism score	8 (4) ^{b-f}	8 (5) ^{b-e}	10 (4) ^{b-e,h}	4 (3) ^{f-h}	3 (3) ^{f-h}	3 (3) ^{f-h}	3 (3) ^{f-h}
Systolic blood pressure (mmHg)	125 (13)	120 (16)	120 (15)	120 (12)	120 (15)	119 (17)	120 (12)
Diastolic blood pressure (mmHg)	80 (6)	79 (9)	75 (11)	70 (10)	76 (10)	78 (12)	77 (10)
Heart rate (bpm)	74 (17)	75 (11)	73 (14)	76 (16)	76 (14)	76 (10)	74 (15)
Total testosterone (nmol/l)	2.1 (1.9) ^{b-f}	1.7 (0.7) ^{b-f}	0.9 (0.7) ^{g,h}	0.8 (0.7) ^{g,h}	0.7 (0.5) ^{g,h}	1.0 (0.6) ^{g,h}	0.9 (0.7) ^{g,h}
Free testosterone (pmol/l)	31 (31) ^{b,d}	35 (21) ^{b-f}	17 (14) ^{d,g}	17 (14) ^{d,g}	7 (7) ^{b,c,e-h}	14 (14) ^{d,g}	14 (10) ^{d,g,h}
Free androgen index	4.8 (6.4) ^{b,d}	5.4 (5.3) ^{b,d-f}	2.6 (2.3) ^{d,g}	2.7 (3.1) ^{d,g}	0.7 (0.9) ^{b,c,e-h}	2.4 (3.9) ^d	2.2 (2.8) ^{d,g,h}
SHBG (nmol/l)	41 (19) ^d	33 (29) ^d	41 (49) ^d	40 (30) ^d	129 (51) ^{b,c,e-h}	47 (38) ^d	46 (34) ^d
DHEAS (μmol/l)	4.9 (3.2) ^d	6.0 (3.5) ^{b-d,f}	3.3 (1.8) ^g	3.7 (2.8)	2.5 (2.4) ^{b,g,h}	3.3 (2.5) ^g	3.4 (2.8) ^{d,g}
Androstenedione (nmol/l)	10.1 (3.1) ^{b-f}	9.4 (4.9) ^{b-f}	5.2 (4.9) ^{g,h}	5.2 (3.1) ^{d,g,h}	4.5 (3.1) ^{b,e,g,h}	4.9 (2.4) ^{g,h}	5.6 (4.5) ^{d,g,h}

Data are medians (interquartile range).

DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone-binding globulin.

^aThe hormone concentrations of 13 women with PCOS who were under hormonal contraception at the time of sampling were not included in the calculations.

^bP < 0.05 compared with healthy controls.

^cP < 0.05 compared with non-androgenic oligomenorrhea.

^dP < 0.05 compared with hormonal contraceptives.

^eP < 0.05 compared with isolated acne.

^fP < 0.05 compared with idiopathic hirsutism.

^gP < 0.05 compared with idiopathic hyperandrogenism.

^hP < 0.05 compared with polycystic ovary syndrome.

Table III Number of pregnancies of female blood donors from Spain and Italy according to diagnostic categories.

	Polycystic ovary syndrome (n = 32)	Idiopathic hyperandrogenism (n = 23)	Idiopathic hirsutism (n = 32)	Isolated acne (n = 31)	Hormonal contraceptives (n = 148)	Non-androgenic oligomenorrhea (n = 25)	Healthy women (n = 301)
Number of pregnancies							
0	26 (81.3)	16 (69.6)	24 (75.0)	19 (61.3)	106 (71.6)	14 (56.0)	174 (57.8)
1	3 (9.4)	3 (13.0)	5 (15.6)	3 (9.7)	25 (16.9)	6 (24.0)	43 (14.3)
2	1 (3.1)	3 (13.0)	1 (3.1)	8 (25.8)	12 (8.1)	3 (12.0)	49 (16.3)
3	2 (6.3)	0 (0)	2 (6.3)	1 (3.2)	4 (2.7)	1 (4.0)	26 (8.6)
4	0 (0.0)	1 (4.4)	0 (0.0)	0 (0.0)	1 (0.7)	1 (4.0)	9 (3.0)

Data are counts (percentages). In order to fulfill the χ^2 assumption that <20% of the expected counts were <5 and all individual expected counts were 1 or greater, we compared the 0 pregnancy category with the category that resulted from merging the 1, 2, 3 and 4 pregnancy category. After merging, no cells had expected count <5 and the minimum expected count was 8.28. The difference was significant with $\chi^2 = 15.7$ and $P = 0.016$.

morphology reported prevalences of PCOS in the range of 10–12% as defined by these recent definitions (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004; Azziz et al., 2006; Azziz et al., 2009).

The reproductive history of the women studied here revealed that functional androgen excess disorders compromised fecundity similarly and irrespective of serum androgen concentrations. This finding suggests that women with PCOS, idiopathic hyperandrogenism and idiopathic hirsutism may share pathophysiological mechanisms and that they may represent a continuous spectrum of the severity of the phenotype expressed as a result of these mechanisms of disease.

In conceptual agreement, women with idiopathic hirsutism may show subtle abnormalities in adrenal and ovarian androgen secretion if studied extensively by functional testing (Escobar-Morreale et al., 1997) and, as a group, may present with serum androgen levels that are slightly higher than those of healthy women (Unluhizarci et al., 2004a). Also, these women may present with circulating androgen levels within the normal range because of the insufficient functional sensitivity of most of the assays currently used for their measurement (Rosner et al., 2007; Rosner and Vesper, 2010). In this regard, our study is limited by the relatively insensitivity of the immunoassays used for androgen measurements, as we have not been able to measure such levels using more sensitive LC/MS assays. However, recent studies in a large cohort of PCOS patients indicated that the poor performance of current androgen assays is not limited to immunoassays but is also common to LC/MS methods, and that a direct radioimmunoassay method, from the same manufacturer of the immunochemiluminescence kits, that we have used in our laboratories performs similarly when compared with in-house and commercial LC/MS testosterone assays in a clinical setting (Legro et al., 2010). Also, because we have only excluded non-classic congenital adrenal hyperplasia in women who fulfilled the criteria for the diagnosis PCOS, some of the women finally diagnosed with idiopathic hyperandrogenism or idiopathic hirsutism might have actually suffered from this inherited disorder. However, this possibility is small, as non-classic congenital adrenal hyperplasia is a rare finding (<4%) even in Italian and Spanish women presenting with hyperandrogenic symptoms (Carmina et al., 2006; Escobar-Morreale et al., 2008).

The fact that only PCOS patients among women with functional hyperandrogenism showed increased BMI compared with healthy women suggests that weight excess plays a major modifying role in the expression of the hyperandrogenic phenotype (Escobar-Morreale and San Millan, 2007) particularly with regard to ovulatory function (Legro et al., 1998), and in fact PCOS women were those presenting with the worst pregnancy rates.

Our present results suggest that the isolated finding of acne in premenopausal women may be a normal variant: when presenting in the absence of menstrual irregularity and any other evidence of androgen excess, women with acne show pregnancy rates, BMI, indexes of abdominal adiposity, hirsutism scores and serum androgen levels comparable to that of healthy women. Similarly, the phenotype of the non-androgenic oligomenorrhea group was not different from that of healthy women. The fact that the pregnancy rate of these women was not reduced further suggests that these women were actually healthy. Finally, the group of women receiving hormonal contraception showed the expected impact of these drugs on pregnancy rate and on serum androgen and SHBG concentrations, but no influence on weight or indexes of abdominal adiposity.

Regarding the prevalence of clinical signs of hyperandrogenism, hirsutism and acne were quite frequent showing 12% prevalences, but alopecia was a much rarer event affecting <2% of premenopausal women. Moreover, our study suggests that the cut-off value of the hirsutism score should be increased in our countries from 8 or above to 10 or above as the latter is the figure that corresponds to the 95th percentile of premenopausal women. Furthermore, our study raised doubts about the accuracy of isolated acne as an indicator of an underlying androgen excess disorder, in agreement with the latest recommendations from the Androgen Excess and PCOS Society (Azziz et al., 2006, 2009).

In summary, functional disorders of androgen excess show a high prevalence in premenopausal women. The fact that idiopathic hyperandrogenism and idiopathic hirsutism, and not only PCOS, are among the most common endocrine disorders in women during their reproductive years should stimulate further research on the pathophysiology, consequences for health and clinical implications of these non-PCOS functional forms of androgen excess.

Acknowledgements

We thank all the medical and technical staff of the participating hospitals for their collaboration in recruitment and sampling of the population studied.

Authors' roles

R.S., A.G. and M.A recruited the subjects and phenotyped the subjects. R.S., A.G., M.A., M.A.M.-G. and H.F.E.-M. contributed to data mining, statistical analysis and drafting of the manuscript. R.P. and H.F.E.-M. designed the study and provided administrative support and funding. H.F.E.-M. wrote the final version of the manuscript. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding

This study was supported by grants PI080944 and PII10357 from Instituto de Investigación Carlos III, Spanish Ministry of Economy and Competitiveness. CIBERDEM is also an initiative of Instituto de Investigación Carlos III.

Conflict of interest

None declared.

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