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Original Article

Reproductive endocrinology

Sexual dysfunction in women with PCOS: a case control study

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ABSTRACT

STUDY QUESTION: What is the relationship of sex steroid levels with sexual function in women with and without polycystic ovary syndrome (PCOS)?

SUMMARY ANSWER: Women with PCOS reported more sexual dysfunction and more sexual distress compared to those without PCOS, but only few and weak associations between androgen levels and sexual function were observed.

WHAT IS KNOWN ALREADY: The literature shows that women with PCOS report lower levels of sexual function and sexual satisfaction and more sexual distress. Contributing factors seem to be obesity, alopecia, hirsutism, acne, infertility, anxiety, depression, and low self-esteem. In women with PCOS clinical and/or biochemical hyperandrogenism is common; its relationship with sexual function is, however, inconclusive.

STUDY DESIGN, SIZE, DURATION: This observational prospective case control study with 135 women (68 PCOS, 67 control) was conducted from March 2017 until March 2020.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Heterosexual women with and without PCOS, aged 18–40 years, in a steady relationship and without any comorbidities, underwent an extensive medical and endocrine screening using liquid chromatography-tandem mass spectrometry and validated sexual function questionnaires.

MAIN RESULTS AND THE ROLE OF CHANCE: Women with PCOS reported significantly lower sexual function (Female Sexual Function Index (FSFI) $P < 0.001$, partial $\eta^2 = 0.104$), higher levels of sexual distress (Female Sexual Distress Scale-Revised $P < 0.001$, partial $\eta^2 = 0.090$), and they more often complied with the definition of sexual dysfunction (41.2% vs 11.9%, $P < 0.001$, Phi $V = 0.331$) and clinical sexual distress (51.5% vs 19.4%, $P < 0.001$, Phi $V = 0.335$). Regression analysis adjusted for confounders showed only few and weak associations between androgen levels and sexual function, with each model explaining a maximum of 15% sexual function. Following significant Group × Hormone interactions, analyses for both groups separately showed no significant associations in the PCOS group. The control group showed only weak negative associations between testosterone and FSFI pain ($\beta = -6.022$, $P = 0.044$, Adj $R^2 = 0.050$), between FAI and FSFI orgasm ($\beta = -3.360$, $P = 0.023$, Adj $R^2 = 0.049$) and between androstenedione and clinical sexual distress ($\beta = -7.293$, $P = 0.036$, exp(β) = 0.001).

LIMITATIONS, REASONS FOR CAUTION: The focus of the study on sexual functioning potentially creates selection bias. Possibly women with more severe sexual disturbances did or did not choose to participate. Differences between women with PCOS and controls in relationship duration and hormonal contraceptive use might have skewed the sexual function outcomes.

WIDER IMPLICATIONS OF THE FINDINGS: Sexual function is impaired in women with PCOS. However, endocrine perturbations seem to have minimal direct impact on sexual function. Addressing sexuality and offering psychosexual counseling is important in the clinical care for women with PCOS.

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. Its prevalence is estimated to be 5–20% (Azziz *et al.*, 2016; Teede *et al.*, 2018). Two out of three of the following criteria need to be present to diagnose PCOS: (i) either clinical (hirsutism) or biochemical hyperandrogenism (elevated androgen serum levels), (ii) oligomenorrhea or amenorrhea, and (iii) polycystic ovaries on ultrasound (Rotterdam, 2004). PCOS is a distressing disease associated with lower quality of life (QoL), subfertility, depression, anxiety, eating disorders, diabetes, and cardiovascular disease (Teede *et al.*, 2018; Louwers and Laven, 2020). Both PCOS characteristics and the associated somatic and psychological comorbidities potentially influence sexual function and sexual satisfaction. Also, treatment of PCOS (e.g. prescribing the combined oral contraceptive pill (COCP) or metformin) can, as a result of lowering androgen levels, influence sexual function (Caruso *et al.*, 2009; Gateva and Kamenov, 2012; Steinberg Weiss *et al.*, 2021).

Sex-steroid hormones, in particular estrogens and androgens, play an important role in sexual function (Traish, 2010; Davis *et al.*, 2016), although the exact mechanisms by which these steroids exert their influence are still unclear (Davis *et al.*, 2019). Also, the relationship between androgen levels and sexual function in women is not fully elucidated (Davis *et al.*, 2019; Islam *et al.*, 2019) since some studies have not found a relationship between androgen levels and female sexual function (Davis *et al.*, 2005; Basson *et al.*, 2010; Zheng *et al.*, 2020) while others have (Heiman *et al.*, 2011; Islam *et al.*, 2019; Maseroli and Vignozzi, 2022). Only in the case of low androgen levels, e.g. as a result of oophorectomy, the relationship with impaired sexual function is more clear (Johansen *et al.*, 2016).

Little is known about sexual function in women who have androgen levels at the high end of the normal range or who have elevated androgen levels (Wierman *et al.*, 2010), except for the findings of studies in women with classical congenital adrenal hyperplasia (CAH), which suggest that hyperandrogenism is related to decreased sexual function (Krysiak *et al.*, 2016; Schernthaner-Reiter *et al.*, 2019; Dwiggins *et al.*, 2020; Kępczyńska-Nyk *et al.*, 2021). PCOS offers the opportunity to study female sexual function in relation to normal as well as elevated androgen levels. A meta-analysis has shown lower sexual functioning in women with PCOS, mainly affecting arousal, lubrication, and orgasm (Pastoor *et al.*, 2018). However, reports on sexual function in women with PCOS are contradictory with some studies reporting no differences in sexual function in women with PCOS (Murgel *et al.*, 2019; Zhao *et al.*, 2019) and other studies reporting more sexual problems in women with PCOS (Castelo-Branco and Naumova, 2020; Loh *et al.*, 2020).

The aim of this study was to compare sexual function and sexual distress in women with PCOS and a control group and to examine the relationship with sex steroid levels.

Materials and methods

Participants

Women with PCOS were mainly recruited through Dutch PCOS patient support groups. PCOS was diagnosed according to the Rotterdam criteria. Age matched healthy control women were recruited through advertisements on websites recruiting participants for medical research.

Inclusion criteria were an age between 18 and 40 years old and a stable heterosexual relationship for at least 6 months. The control group had regular menstrual cycles without any signs of PCOS. To be included, participants were allowed to either not using hormonal contraceptives (for at least 3 months prior to the start of their participation in this research project) or using COCPs for at least 3 months.

Exclusion criteria were a psychiatric disorder, pregnancy or breastfeeding, having undergone a radical hysterectomy or prolapse surgery, and current or recent medical disorders (other than PCOS) or use of medication (apart from hormonal contraceptives) that are known to influence sexual function, e.g. selective serotonin reuptake inhibitors spironolactone and metformin (Pastoor *et al.*, 2020).

A power calculation for the full study protocol was performed which resulted in needing 67 participants per group (Pastoor *et al.*, 2020).

Data were collected from March 2017 to March 2020.

Ethical approval

The study was approved by the METC Erasmus Medisch Centrum Rotterdam (nr. NL55484.078.16, d.d. 12 April 2016), METC Leiden Den Haag Delft (nr. P16.299, d.d. 23 June 2016), and METC Amsterdam UMC (nr. 2016_182, d.d. 14 July 2016). Written informed consent was obtained from every participant. Participants received financial compensation for participating in the full study protocol that included an extensive medical and endocrine screening, completion of questionnaires, and an assessment of sexual response in the psychophysiological laboratory. More details can be found in the protocol article (Pastoor *et al.*, 2020).

Blood samples and medical screening

The medical and endocrine assessment was performed on Day 3–5 of the menstrual cycle in women reporting regular menstrual cycles. Those on COCPs were assessed on Day 8 after a 7 day pause. Women with PCOS and ovulatory dysfunction were assessed on a random day. Peripheral venous blood samples were collected before 10.00 a.m. after an overnight fast to assess androgen levels, gonadotrophin concentrations, sex hormone-binding globulin (SHBG), estradiol, progesterone, and 17-OH progesterone (Dietz de Loos *et al.*, 2021).

Biochemical analysis

Plasma was stored at −80°C. Androgens (testosterone, dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione) and 17-OH progesterone were measured in the fasting blood samples with liquid chromatography-tandem mass spectrometry (LC–MS/MS) (intra-assay coefficient variations <3%, inter-assay coefficient variations <5%, accredited under ISO 15189). Qualification limits for steroids are testosterone 0.06 nmol/l, DHEAS 0.004 nmol/l, DHEA 3.6 nmol/l, androstenedione 0.1 nmol/l, progesterone 0.3 nmol/l, and 17-OH-progesterone 0.4 nmol/l.

SHBG was determined with the Siemens Immulite 2000XPi (analytic sensitivity 0.02 nmol/l) and from 2020 with IDS-ISYS (analytic sensitivity ≤0.15 nmol/l). Data were not corrected for platform change as there was no proportional or constant bias ($Y = -0.58 + 1.02\times$).

The free androgen index (FAI) was calculated as: (testosterone (nmol/l)/sex hormone-binding globulin (SHBG) (nmol/l) × 100). Biochemical hyperandrogenism was defined as FAI > 2.9 (Bui *et al.*, 2015) and/or testosterone >2.0 nmol (Dietz de Loos *et al.*, 2021).

Estradiol was measured by Roche Elecsys according to manufacturer specifications with detection limit 18 pmol and intermediate precision <10.6%.

Questionnaires

All women completed questionnaires on demographic characteristics and sexual function. Sexual function was assessed with the 19-item Female Sexual Function Index (FSFI) with six subscales (desire, arousal, lubrication, orgasm, satisfaction, pain). Higher scores indicate better sexual function, and a total score <26.55 is indicative of sexual dysfunction (ter Kuile *et al.*, 2006).

Sexual distress was assessed with the 13-item Female Sexual Distress Scale-Revised (FSDS-R). Higher scores indicate more sexual distress, and a total score ≥15 is indicative for clinically significant sexual distress (ter Kuile *et al.*, 2006). An FSFI total score <26.55 combined with an FSDS-R total score ≥15 is considered as indicating clinically significant sexual dysfunction (ter Kuile *et al.*, 2006).

Questionnaires were available in a software program that was used through a secure hosting platform with ISO 27001 and NEN 7510 certification. Two-step authentication was installed.

Statistical analyses

Statistical analyses were performed with IBM SPSS Statistics (v.25 and v.28.01, SPSS, Inc., IL, USA). Before analysis, the dependent variables were examined for fit between distributions and the assumptions of the analyses.

Means or percentages for all outcome measures were calculated and compared between the two groups using ANOVA or Chi square tests or, in case of variables with non-normal distribution, with nonparametric Mann–Whitney *U* tests. Quartiles for testosterone and FAI were calculated and differences between groups were compared with Chi square tests.

Effect sizes are reported as partial η^2 (0.01: small effect size, 0.06: medium effect size, 0.14 or higher: large effect size) for ANOVAs and Phi (0.01: small effect size, 0.30: medium effect size, 0.50: large effect size) for Chi square tests. For the Mann–Whitney *U* tests, effect sizes were calculated as z/square root of N and reported as an approximate value of *r*.

Log transformed endocrine values were used to perform linear regression analyses and logistic regression analyses to examine associations between endocrine values and sexual function outcomes, progressively including as independent variables: group (PCOS vs control), the interaction of hormone and group, and variables known to affect sexual function, age, duration of relationship, and COCP use (Bel *et al.*, 2015; Zheng *et al.*, 2020). When the interaction of hormone with group was significant in the regression analysis, indicating that associations of hormone and sexual function were different for women with and without PCOS, we also calculated associations for the two groups separately. P-values of 0.05 were considered significant.

To correct for multiple testing, a Bonferroni correction was performed for 55 comparisons (5 exposures and 11 outcomes) resulting in an alpha of 0.0009. All regression results were compared to this new *P*-value. Original regression results are presented.

Results

Participants

Data from 68 women with PCOS and 67 control women were used. Table 1 shows their general characteristics, PCOS characteristics and endocrine values. The groups differed in age, relationship duration and COCP use. Mean BMI was not significantly different between the groups. Both the PCOS group and the control group consisted mainly of lean participants. In the control group, pre-obesity was more prevalent and in the PCOS group obesity Class I, II and III were more prevalent (Table 1). However, the groups are small and the significance cannot be determined reliably.

PCOS characteristics and endocrine results were as expected. Significantly more control women fell in the lowest quartile of testosterone (<0.74 nmol/l) and FAI (<1.11 nmol/l) levels (respectively 38.8% controls vs 11.8% PCOS, $P < 0.01$, Phi = −0.311; 32.8% controls vs 16.2% PCOS, $P < 0.05$, Phi = −0.194), while more women with PCOS fell in the highest quartile of testosterone (>1.29 nmol/l) and FAI (>2.65 nmol/l) levels (respectively 7.5% controls vs 39.7% PCOS, $P < 0.01$, Phi = 0.379; 4.5% controls vs 44.1% PCOS, $P < 0.01$, Phi = 0.461).

Sexual function and sexual distress

Women with PCOS reported a significantly lower total FSFI score compared to control women ($M = 25.09 \pm 6.69$ vs $M = 28.78 \pm 3.83$, $P < 0.001$, partial $\eta^2 = 0.104$), scored significantly lower on all FSFI scales except pain (Fig. 1A), and showed a significantly higher FSDS-R score ($M = 17.57 \pm 13.20$ vs $M = 9.90 \pm 11.24$, $P < 0.001$, partial $\eta^2 = 0.090$). These test results showed the same pattern when age, relationship duration and COCP use were included as covariates in the analyses. Also, women with PCOS significantly more often complied with the definition of sexual dysfunction compared to women without PCOS (Fig. 1B).

Associations between androgens and SHBG and sexual function and sexual distress

The simple regression model without adjustment for other variables showed only a significant positive association of DHEA with FSFI satisfaction, indicating higher sexual satisfaction with higher DHEA levels. No significant associations between sexual function outcomes and testosterone or FAI (Fig. 2A and B; Supplementary Tables S1 and S2) or androstenedione or DHEA levels were observed (Supplementary Tables S1 and S2).

With adjustment for age, relationship duration and COCP use and including the interaction of hormone and group in the model (Supplementary Table S3), the association between DHEA and sexual satisfaction disappeared. This analysis also revealed significant interactions between hormone and group for testosterone and FSFI pain, DHEA and FSFI orgasm, FAI and FSFI orgasm, testosterone and FSDS-R ≥15, androstenedione and FSDS-R ≥ 15, and DHEA and FSFI < 26.55, indicating that the associations between hormone levels and sexual function were different for women with and without PCOS. For these associations, we also ran regression analyses for both groups separately, showing no significant associations between hormone levels and sexual function outcomes in the PCOS group. In the control group, there were significant negative associations of testosterone and FSFI pain, FAI and FSFI orgasm, and androstenedione and FSDS-R ≥ 15, indicating more pain and worse orgasmic functioning but less clinical sexual distress with higher androgen levels (Supplementary Table S4). However, androgen levels explained at maximum 15% of the variance in sexual outcome (Supplementary Table S3) and only 8% in the final model (Supplementary Table S4). After correction for multiple testing with Bonferroni, none of the results remained significant.

Discussion

Women with PCOS reported significantly lower sexual function and higher sexual distress. Significantly more women in the PCOS group than in the control group complied with the definition of sexual dysfunction, and sexual function was impaired in all FSFI domains except pain. We found only few and weak

Table 1. General characteristics, ethnicity, PCOS characteristics, endocrine values, and androgen levels, in quartiles, for the control group and the PCOS group.

	Controls N = 67	PCOS N = 68	P-value	Effect size
General characteristics	Mean ± SD	Mean ± SD		
Age, y	25.89 ± 5.69	27.64 ± 5.74	*	0.167
Relationship duration, months	39.75 ± 44.14	62.98 ± 57.51	**	0.262
Educational level				
Low, primary level, n (%)	2 (3.0)	0 (0.0)	NS	0.198
Medium, high school level, n (%)	27 (40.3)	26 (38.2)		
High, applied sciences or academic level, n (%)	38 (56.8)	42 (61.8)		
Ethnicity				
Caucasian, n (%)	53 (79.0)	57 (83.8)	NA	NA
Hindu, n (%)	2 (3.0)	1 (1.4)		
Black, n (%)	4 (6.0)	0 (0.0)		
Asian, n (%)	2 (3.0)	2 (3.0)		
Mediterranean, n (%)	2 (3.0)	3 (4.4)		
Mixed, n (%)	3 (4.5)	5 (7.4)		
Not reported, n (%)	1 (1.5)	0 (0.0)		
BMI, mean (range)	23.55 (18–35)	24.79 (17–42)	NS	0.006
BMI underweight <18.5, n (%)	2 (3.0)	5 (7.5)	NA	NA
BMI normal ≤18.5 to ≥24.9, n (%)	43 (64.2)	42 (62.7)		
BMI pre-obesity ≤25.0 to ≥29.9, n (%)	18 (26.9)	6 (9.0)		
BMI obesity class I ≥30.0 to ≤34.9, n (%)	3 (4.5)	6 (9.0)		
BMI obesity class II ≤35.0 to ≤39.9, n (%)	1 (1.5)	6 (9.0)		
BMI obesity class III ≥ 40.0, n (%)	0 (0)	2 (3.0)		
COCP use, n (%)	36 (53.7)	14 (20.6)	**	–0.343
PCOS characteristics				
Oligomenorrhea or amenorrhea, n (%)	0 (0)	59 (86.8)	**	0.876
PCOM, based on AFC right and/or left ovary, n (%)	30 (44.8)	64 (95.5)	**	0.554
Hirsutism, n (%)	2 (3.0)	26 (38.2)	**	0.447
Acne, n (%)	6 (9.0)	15 (22.1)	*	0.181
Hyperandrogenism biochemical, n (%)	2 (3.0)	32 (47.1)	**	0.508
Endocrine values				
Testosterone, nmol/l	0.85 ± 0.28	1.34 ± 0.63	**	0.490
FAI	1.39 ± 0.67	2.70 ± 1.65	**	0.467
DHEA, nmol/l	17.14 ± 7.44	23.42 ± 12.07	**	0.261
DHEA-S, nmol/l	4.76 ± 2.41	5.35 ± 2.83	NS	0.104
Androstenedione, nmol/l	3.44 ± 1.18	5.48 ± 2.70	**	0.474
SHBG, nmol/l	73.63 ± 42.28	66.39 ± 50.45	*	–0.199
FSH, U/l	6.29 ± 2.00	5.81 ± 2.37	NS	–0.139
LH, U/l	4.12 ± 1.65	9.19 ± 14.14	**	0.334
E2, pmol/l	167.87 ± 108.75	251.37 ± 242.03	*	0.199
Progesterone, nmol/l	1.58 ± 3.79	3.39 ± 7.41	NS	0.023
17-OHP, nmol/l	1.05 ± 0.79	2.06 ± 1.95	**	0.343
Androgen levels, quartiles				
Testosterone quartile 1, n (%)	26 (38.8)	8 (11.8)	**	–0.311
Testosterone quartile 4, n (%)	5 (7.5)	27 (39.7)	**	0.379
Free androgen index quartile 1, n (%)	22 (32.8)	11 (16.2)	*	–0.194
Free androgen index quartile 4, n (%)	3 (4.5)	30 (44.1)	**	0.461

* <0.05, ** <0.01, NS, not significant.
Test results were obtained with Chi square tests for percentages and Mann–Whitney *U* tests for the other variables.
Effect sizes are reported as Phi for percentages and as an approximate value of *r* for the Mann–Whitney *U* tests (z/square root of N).
SD, standard deviation; y, given in years; n, absolute number; %, percentage of total group; BMI, body mass index; COCP, combined oral contraceptive pill; PCOM, polycystic ovarian morphology; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; FAI, free androgen index; SHBG, sex hormone-binding globulin; LH, luteinizing hormone; FSH, follicle stimulating hormone; 17-OHP, 17-hydroxyprogesterone; E2, estradiol.

associations between androgen levels and sexual function, with the proportion of explained variance in sexual function in the models never exceeding 15%.

As expected, androgen levels in women with PCOS were significantly higher than in control women. Higher androgen levels were not associated with better sexual function. In fact, we did not find any relationship between androgen levels and sexual function in the PCOS group. Several studies have attempted to shed light on the relationship between androgens and sexual function in women with PCOS. Studies that found higher androgen levels to be related to lower sexual function in women with PCOS reported: a negative association between testosterone levels and sexual desire (Elkhiat *et al.*, 2015); a negative relationship between free and total testosterone and total FSFI score (Ercan *et al.*, 2013); and that lowering androgen levels by administering oral contraceptives improved sexual pleasure, orgasm, satisfaction and pain (Caruso *et al.*, 2009). Other studies found that higher levels of androgens were related to better sexual function by reporting: higher FAI with better total sexual function and higher testosterone with better total sexual function, satisfaction and orgasm (Mansson *et al.*, 2011); higher testosterone with better desire, arousal, orgasm, and total sexual function (Stovall *et al.*, 2012); and a negative association between testosterone levels and sexual pain, indicating less sexual pain with higher testosterone (Mantzou *et al.*, 2021). One study found a positive relationship between free testosterone and DHEAS with frequency of erotic dreams (Glowinska *et al.*, 2020). Some studies did not find a significant relationship between endocrine levels and sexual function

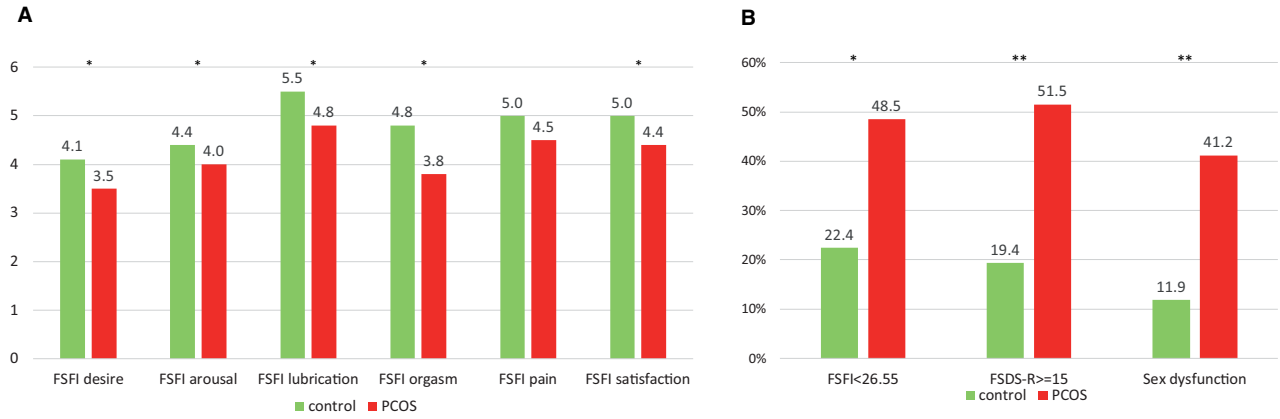

Figure 1. Questionnaire scores for FSFI and FSDS-R for both the control and the PCOS group. (**A**) FSFI mean domain scores for the control group and the PCOS group. FSFI, Female Sexual Function Index; *$P < 0.05$. Effect sizes: FSFI desire (partial $\eta^2 = 0.072$), FSFI arousal (partial $\eta^2 = 0.070$), FSFI lubrication (partial $\eta^2 = 0.072$), FSFI orgasm (partial $\eta^2 = 0.084$), FSFI pain (partial $\eta^2 = 0.021$), FSFI satisfaction (partial $\eta^2 = 0.048$). (**B**) Percentage women scoring in the dysfunctional range of the FSFI (<26.55), FSDS-R (≥15), and both the FSFI and FSDS, for the control group and the PCOS group. FSFI, Female Sexual Function Index; FSDS-R, Female Sexual Distress Scale-Revised, Sexual Dysfunction = FSFI < 26.55 and FSDS-R ≥ 15, **$P < 0.001$, *$P < 0.05$. Effect sizes: FSFI < 26.55 (Phi = 0.273), FSDS-R ≥ 15 (Phi = 0.335), Sexual dysfunction (Phi = 0.331).

(Ferraresi *et al.*, 2013; Zueff *et al.*, 2015; Kałużna *et al.*, 2021; Naumova *et al.*, 2021) or an inconclusive one (Gateva and Kamenov, 2012). More indirect associations were reported through hirsutism and acne, all showing higher levels of hirsutism or acne associated with lower sexual function, lower sexual satisfaction or a stronger negative impact on sexual function (Elsenbruch *et al.*, 2003; Hahn *et al.*, 2005; Drosdzol *et al.*, 2007; Tan *et al.*, 2008; Akbari Sene *et al.*, 2021; Taghavi *et al.*, 2021). Summarizing, more studies seem to report a negative relationship between androgen levels and sexual function directly or indirectly in women with PCOS. However, the reports are not consistent and none of these studies used LC–MS/MS to assess androgen levels, which might make results less reliable.

In addition, research in another group with hyperandrogenism, women with classical CAH, has shown lower sexual function and less sexual satisfaction suggesting that biochemical hyperandrogenism is related to lower sexual function (Krysiak *et al.*, 2016; Schernthaner-Reiter *et al.*, 2019; Dwiggins *et al.*, 2020; Kępczyńska-Nyk *et al.*, 2021). As in women with PCOS, clinical signs of hyperandrogenism, body image, mood, and QoL are mentioned as explanations for lower sexual function in women with CAH (Krysiak *et al.*, 2016; Schernthaner-Reiter *et al.*, 2019; Kępczyńska-Nyk *et al.*, 2021).

In our control group, we found only very few and weak associations between androgen levels and sexual function with low explained variance. This group showed androgen levels in the normal range, and showed better sexual function and less sexual distress compared to the PCOS group. Based on the literature (Traish, 2010; Wahlin-Jacobsen *et al.*, 2015; Davis *et al.*, 2016, 2019; Wahlin-Jacobsen *et al.*, 2017), it was expected to find a relationship between sex steroid levels and sexual function with lower androgen levels to be associated with lower sexual function. However, as mentioned, our results showed the opposite. Taken together, the literature shows inconsistent findings concerning the relationship between androgens and female sexual function. Some studies have not found a relationship between androgen levels and female sexual function (Davis *et al.*, 2005; Basson *et al.*, 2010), while others have (Heiman *et al.*, 2011; Islam *et al.*, 2019; Maseroli and Vignozzi, 2022). It has been proposed that these inconsistencies in the literature might be due to several factors. First, some have used assays that are not reliable to assess low levels of androgens in women (Nappi, 2015). In large studies using LC–MS/MS, the current golden standard for assessing sex steroids in women (Taylor *et al.*, 2015), no strong associations between androgen levels and sexual function were found (Wahlin-Jacobsen *et al.*, 2017; Zheng *et al.*, 2020), similar to the present study. Secondly, androgens seem to exert their influence on sexual function within a tight physiological range. In case of hyperandrogenism, women are most likely above this range, which could explain the absence of associations between androgen levels and sexual function in women with PCOS in the present and other studies (Noroozzadeh *et al.*, 2017; Nasiri Amiri *et al.*, 2018; Steinberg Weiss *et al.*, 2021). In case of low androgen levels, for example as a result of using COCPs (Zimmerman *et al.*, 2014) or oophorectomy (Braunstein *et al.*, 2005; Davis *et al.*, 2019), sexual function is negatively influenced. Concluding, our results show that androgens only play a minor role in female sexual function, which is in line with other studies using LC–MS/MS to assess sex steroids and investigate associations with female sexual function (Wierman *et al.*, 2010; Davis *et al.*, 2019; Zheng *et al.*, 2020).

The strengths of this study lie in the use of well validated questionnaires including a measure for distress about sexual function, the extensive endocrine and medical screening of all participants with the use of LC–MS/MS, and the availability of data on sexual function in women within a range of normal to hyper-physiological androgen levels. To the best of our knowledge, this is the first study to assess sexual distress in women with PCOS compared to women without PCOS (Pastoor, in preparation). Assessing distress is important as it is a requirement for diagnosing sexual dysfunction. It is also an indicator for the clinical relevance to address sexual function and for offering counseling or treatment. A weakness of this study might be selection bias, possibly selecting more women with sexual problems then without. Also, differences between the two groups in BMI (not significant), age, relationship duration and COCP use, factors that are known to be potential influences on sexual function (Zimmerman *et al.*, 2014; Wahlin-Jacobsen *et al.*, 2015; Roumen *et al.*, 2017; Wahlin-Jacobsen *et al.*, 2017; Sarwer *et al.*, 2018) might have skewed the results on sexual functioning. However, including these variables as covariates resulted in similar statistical outcomes. Additionally, we selected a relatively healthy

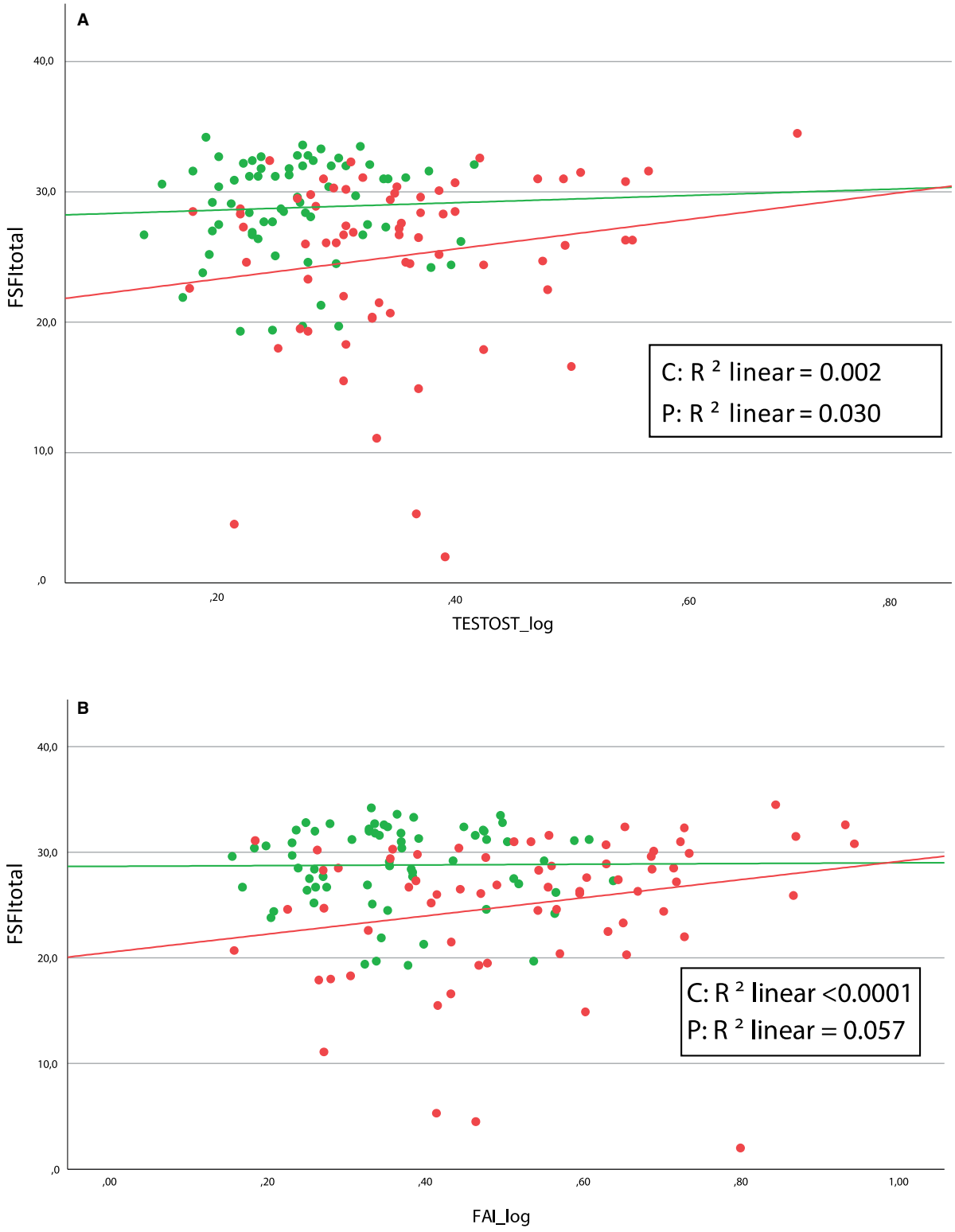

Figure 2. Scatterplots for associations between FSFI total and testosterone and FAI. Control: green; PCOS: red. (**A**) Associations between Testosterone and FSFI total score for the PCOS group and the control group. FSFI, Female Sexual Function Index; Testost, Testosterone. Data are log transformed. (**B**) Associations between FAI and FSFI total score for the PCOS group and the control group. FAI, Free Androgen Index. Data are log transformed.

population by excluding comorbidities. In a group with more comorbidities, for example those with metabolic disease or diabetes, we would expect to find lower sexual function, as is reported in the literature (Di Francesco *et al.*, 2019; Winkley *et al.*, 2021). Also, participants in our group were relatively lean. This healthier and more lean population possibly resulted in less severe sexual function which could make the results less generalizable to the complete PCOS population. Fourth, for diagnostic reliability and consistency reasons, we assessed all control women in the early follicular phase of the menstrual cycle. Since endocrine levels vary during the menstrual cycle, the results of this study might not be generalizable to other phases in contrast

to the study of Zheng et al. (2020) which corrected for the different menstrual cycle phases. Fifth, we acknowledge that the number of participants was small for regression analyses with multiple variables, and that our analysis included a large number of comparisons which increases the risk of Type I error. Applying a post hoc Bonferroni correction, none of our results could be considered significant. Therefore, we should be conservative in our interpretation of the individual associations we identified. Finally, one has to keep in mind that the case control design of our study does not permit interpretation of causal relationships, and by doing a large number of comparisons, the risk of erroneous inferences increases.

In women with PCOS other medical and psychological risk factors such as diabetes, hypertension, depression, anxiety (Brotto et al., 2016; McCabe et al., 2016), and negative body image (Woertman and van den Brink, 2012; Wallwiener et al., 2016) might explain sexual function more than androgen levels do. Future research should focus on these other factors. Also, research using methods assessing subjective and genital sexual arousal responses may shed additional light on the association between androgen levels and sexual responsivity in women with PCOS (Pastoor et al., 2020).

Clinical implications of our results are that sexual function is an important topic to assess in women with PCOS since they not only report low sexual functioning but also high levels of distress about their sexual function problems. Also, endocrine levels are not clinically useful diagnostic indicators of sexual function and will most likely not be first line treatment for improving sexual function. A thorough biopsychosocial assessment is necessary in order to be able to determine factors that influence sexual function in a specific case. Tailor-made treatment including psychosexual treatment is needed and seems to be effective (Golbabaei et al., 2019; Mashhadi, 2022; Tuncer and Oskay, 2022).

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Authors' roles

H.P.: study design, study execution, statistical analyses, manuscript drafting, and critical discussion. S.B. and J.S.E.L.: study design, interpreting statistical analyses, manuscript drafting, and critical discussion. E.T.M.L.: study design.

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Conflict of interest

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