Endocrine (2019) 63:632–638
https://doi.org/10.1007/s12020-018-1781-3

ORIGINAL ARTICLE

Effects of dehydroepiandrosterone (DHEA) supplementation on sexual function in premenopausal infertile women

Vitaly A. Kushnir[1,2] · Sarah K. Darmon[1] · David H. Barad[1,3] · Andrea Weghofer[1,4] · Norbert Gleicher[1,3,4,5]

Received: 19 July 2018 / Accepted: 1 October 2018 / Published online: 11 October 2018

Abstract

Purpose To investigate the effects of dehydroepiandrosterone (DHEA) supplementation on female sexual function in premenopausal infertile women of advanced ages.

Methods This observational study was conducted in an academically affiliated private fertility center. Patients included 87 premenopausal infertile women, 50 of whom completed the study including the Female Sexual Function Index (FSFI) questionnaires and comprehensive endocrine evaluation before and 4–8 weeks after initiating 25 mg of oral micronized DHEA TID.

Results Age of patients was 41.1 ± 4.2 years, BMI 24.4 ± 6.1 kg/m^2, 86% were married, and 42% were parous. Following supplementation with DHEA, all serum androgen levels increased (each $P < 0.0001$), while FSH levels decreased by 2.6 ± 4.4 from a baseline of 10.3 ± 5.4 mIU/mL ($P = 0.009$). The FSFI score for the whole study group increased by 7% (from 27.2 ± 6.9 to 29.2 ± 5.6; $P = 0.0166$). Domain scores for desire increased by 17% ($P = 0.0004$) and by 12% for arousal ($P = 0.0122$); lubrication demonstrated an 8% trend towards improvement ($P = 0.0551$), while no changes in domain scores for orgasm, satisfaction, or pain were observed. Women in the lowest starting FSFI score quartile (<25.7), experienced a 6.1 ± 8.0 (34%) increase in total FSFI score following DHEA supplementation. Among these women, improvements in domain categories were noted for desire (40%), arousal (46%), lubrication (33%), orgasm (54%), satisfaction (24%), and pain (25%).

Conclusions This uncontrolled observational study implies that supplementation with DHEA improves sexual function in older premenopausal women with low baseline FSFI scores.

Keywords Female sexual function · Infertility · Hormone status · Androgens · Dehydroepiandrosterone (DHEA)

Introduction

Female sexual dysfunction (FSD) represents a significant worldwide problem [1]; in contrast to male sexual dysfunction, it is only unsatisfactorily addressed by currently available treatments [2]. Only one drug, flibanserin, has been approved by the Food and Drug Administration (FDA), despite "small treatment effects and substantial safety concerns" [3].

Causes of FSD include anatomic, psychogenic, organic etiologies which cause personal distress due to abnormal desire, arousal, orgasm, or sexual pain [4]. FSD is often age-related and associated with low serum androgen levels in both pre- and post-menopausal women [5–7]. Low androgen levels are associated with female sexual function index domains [6]. Among those, low sexual desire is the most common in women at midlife [8].

In healthy women, androgen levels peak during late teens and early twenties, coinciding with peak fertility, and then gradually decline with advancing age [9, 10]. Abnormally low androgen levels are often found in women with premature ovarian aging/occult primary ovarian insufficiency (POA/oPOI), in association with aging-related physiologic diminished ovarian reserve (DOR) and in relatively rare cases of adrenal insufficiency [11, 12]. Low androgen levels

✉ Vitaly A. Kushnir
vkushnir@thechr.com

1 The Center for Human Reproduction, New York, NY, USA

2 Department of Obstetrics and Gynecology, Wake Forest School of Medicine, Winston-Salem, NC, USA

3 Foundation for Reproductive Medicine, New York, NY, USA

4 Department of Obstetrics and Gynecology, Medical University of Vienna, Vienna, Austria

5 Stem Cell Biology and Molecular Embryology Laboratory, The Rockefeller University, New York, NY, USA

can also be iatrogenic, as in patients treated with aromatase inhibitors. Such women, indeed, have also been reported to suffer from low sexual desire [13].

Low androgen levels are a common finding among older premenopausal women [5–7]. Since the literature supports an important role for androgens in female sexual function, it is not surprising that transdermal testosterone (T) supplementation has been used with some success to treat FSD and in particular hypoactive sexual desire disorder (HSDD) [14, 15]. However, the use of systemic dehydroepiandrosterone (DHEA) therapy has been more controversial [14, 16, 17] and appears to demonstrate a degree of effectiveness in improving sexual function only in peri- and postmenopausal women [18] and, possibly, those suffering from adrenal insufficiency [19]. In menopausal women, vaginal administration of DHEA has been found effective and safe in alleviating genitourinary symptoms [20], and, therefore, recently received FDA approval for this indication.

For over a decade, our group has pioneered the use of DHEA supplementation in infertile women with POA/oPOI and DOR who have low androgen levels [21–24]. In these women, restoration of adequate androgen levels within the ovarian microenvironment may improve ovarian function and possibly fertility treatment outcomes, a process thought to be the consequence of androgen effects on small growing follicles, mediated via testosterone effects on the androgen-receptors in granulosa cells [25–28].

In the process of treating thousands of so-affected infertile women, we noticed that many spontaneously reported improvements in libido, sexual desire and, sometimes, even pain status, leading to the paradoxical situation of women refusing to discontinue DHEA supplementation once they conceived. When we in a review of the literature were unable to find a study that investigated the effectiveness of DHEA on female sexuality in older premenopausal women, this study was developed. It is important to note that this study was *not* performed in women who presented for medical care because of sexual dysfunction. To the contrary, here investigated patients uniformly presented because of longstanding infertility, over 90% had failed prior infertility treatments elsewhere. Indeed, until they completed a first baseline questionnaire after consenting to participate in this study, the issue of sexual dysfunction was not raised, unless patients themselves brought up the subject during the initial consultation, which was almost never the case. Our study, therefore, involves older premenopausal women with infertility but not women previously diagnosed with FSD. Though it has been suggested that sexual dysfunction may be somewhat more frequent in infertility patients than in the general population [29, 30], our study population approximates much more an older general, premenopausal female patient population than one with diagnosis of FSD. The objective of this study was to investigate the effects of DHEA supplementation on female sexual function in pre-menopausal infertile women of advanced ages prior to initiation of fertility treatment.

Materials and methods

A group of 87 consecutively presenting new infertility patients agreed to participate in this observational study conducted in an academically affiliated private fertility center. All patients were asked to complete the self-reported Female Sexual Function Index (FSFI) questionnaire [31] prior to initiation to DHEA supplements and again 4–8 weeks later. The patients' fertility treatments were not affected by their participation in this study, in laboratory investigations, and/or timing of procedures. Patients underwent the same standard endocrine evaluations all patients undergo at our center, including measurement of serum androgen levels: DHEA, DHEAS, total (TT), and free testosterone (FT) before, and 4–8 weeks after, initiating 25 mg of oral micronized DHEA supplementation (Fertility Nutraceuticals, LLC, New York, NY) three times daily. All blood samples were collected between 8 a.m. and 10 a.m. All hormone levels were obtained by commercial assays (LabCorp, Burlington, NC). All androgen levels were measured using high-pressure liquid chromatography/tandem mass spectrometry.

Our fertility center serves a population of infertile women with a high prevalence of DOR, mostly due to advanced female age and/or POA/oPOI among younger women. Since we demonstrated that relative hypoandrogenism is a common finding in most infertile patients with DOR [11, 22, 32, 33], such patients are at our center routinely pre-supplemented with DHEA based on their androgen levels for a minimum of 6 weeks prior to initiating infertility treatments. In this study, effects of DHEA supplementation on sexual function were examined before patients were started on any other hormones to enhance fertility (estrogens, progestins, growth hormone, gonadotropins, clomiphene, gonadotropin-releasing hormone analogues, and glucocorticoids). The investigated patient population consisted of older premenopausal infertile women without the evidence of FSD which causes distress.

Fifty out of initial 87 patients (57.5%) who had completed the first evaluation, also submitted within 4–8 weeks the follow-up FSFI questionnaire and had a repeat endocrine evaluation. The 37 patients who did not return for follow-up were considered to have withdrawn from the study if at least two attempts by staff to have them complete the second questionnaire had failed. Most of these patients choose not to pursue treatment at our center while several conceived spontaneously while on DHEA supplementation.

Statistics

Power analysis indicated that to detect a change in FSFI score of 2.0 with 0.8 power, a total of 50 patients would need to complete a questionnaire following DHEA supplementation. Pearson correlation was used to investigate relationships between FSFI scores and patient demographics, as well as, hormone levels. Comparisons of FSFI scores and endocrine parameters before—and after—DHEA supplementation were made using paired *T*-tests. Based on starting FSFI scores patients were further subdivided into quartiles. Patient responses before and after DHEA supplementation from those in the lowest and highest quartiles were then compared. Groups were compared using a two-sampled *T*-test or Chi-square test. A P-value < 0.05 was considered significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc. Cary, NC).

Results

Table 1 shows demographics and baseline endocrine parameters for 50 patients who completed the study. Table 1 also confirms that women who withdrew from the study prior to completing the second FSFI questionnaire had similar clinical characteristics as those who completed the study. Baseline FSFI scores for patients that completed the study were (27.2 ± 6.9; range 2.8–34.8). Pearson correlation showed no relationship between baseline FSFI scores and patient age, body mass index (BMI), ovarian reserve parameters, anti-Müllerian hormone (AMH) and follicle stimulating hormone (FSH), androgen (DHEA, DHEAS, TT, FT), cortisol or sex hormone binding globulin (SHBG) levels.

Table 2 shows that following supplementation with DHEA all serum androgen levels (DHEA, DHEAS, TT, FT) increased from baseline ($P < 0.0001$ for all); while FSH levels decreased from a baseline of 10.3 ± 5.4 mIU/mL by 2.6 ± 4.4 mIU/mL ($P = 0.009$). SHBG decreased from a baseline of 92.7 ± 43.2 nmol/L by 24.0 ± 39.4 nmol/L ($P = 0.0002$). There was no change noted in cortisol and AMH levels.

Data presented in Table 2 also demonstrate that, following supplementation with DHEA, the FSFI score for the study group increased by 7% (from 27.2 ± 6.9 to 29.2 ± 5.6; $P = 0.0166$). Domain scores for desire significantly increased by 17% and by 12% for arousal. Domain score for lubrication demonstrated an 8% trend towards improvement ($P = 0.0551$), while no significant changes in domain scores for orgasm, satisfaction, or pain were observed.

Women in the lowest starting FSFI score quartile (<25.7) revealed a 6.1 ± 8.0 (34%) increase in the total FSFI score (Table 3). The improvement for these women was noted in all domain categories, including desire 1.0 ± 0.8 (40%), arousal 1.3 ± 1.7 (46%), lubrication 0.8 ± 2.3 (33%), orgasm 1.0 ± 2.3 (54%), satisfaction 0.9 ± 1.3 (24%), and pain 0.9 ± 2.3 (25%). Moreover, Table 3 shows that FT increased more in patients with the lowest starting FSFI score quartile (1.8 ± 1.3 pg/mL) than among patients in the highest quartile (≥31.9) (0.5 ± 1.4 pg/mL, $P = 0.04$).

Figure 1 shows the distribution of FSFI scores pre- and post-DHEA supplementation. The data presented in this figure supports that in Table 3. Together they show that while the average FSFI scores improved for the whole study group, the increase was most pronounced among women with the lowest baseline FSFI scores, while women with relatively high baseline FSFI scores did not show further increase following DHEA supplementation.

Table 1 Patient demographics, baseline hormone levels, and baseline FSFI scores for 50 premenopausal infertile women who completed the study and for 37 women who withdrew following initial evaluation

Patient demographics	Completed study $N = 50$	Withdrew from study $N = 37$	
Age (years)	41.1 ± 4.2	40.3 ± 4.1	0.4675
BMI (kg/m^2)	24.4 ± 6.1	24.9 ± 4.7	0.7232
Married	43 (86%)	26 (74.3%)	0.1120
Parous	21 (42%)	13 (36.1%)	0.4803
Race			0.7718
White	25 (50%)	19 (54.3%)	
Black	8 (16.0%)	7 (20.0%)	
Hispanic	7 (14.0%)	4 (11.4%)	
Asian	7 (14.0%)	4 (11.4%)	
FSFI mean score (range)	27.2 (2.8–34.8)	27.0 (2–36)	0.8798
Desire	3.5 (1.2–6)	3.6 (1.2–6)	0.7046
Arousal	4.3 (0–6)	4.3 (0–6)	0.9449
Lubrication	4.8 (0–6)	4.9 (0–6)	0.6385
Orgasm	4.7 (0–6)	4.5 (0–6)	0.5845
Satisfaction	4.9 (1.2–6)	4.6 (0.8–6)	0.2974
Pain	5.1 (0–6)	5.2 (0–6)	0.6384
Baseline hormone levels			
AMH (ng/mL)	1.0 ± 1.3	0.9 ± 1.4	0.9120
FSH (mIU/mL)	10.3 ± 5.4	14.3 ± 9.9	0.0419
Total testosterone (ng/dL)	23.3 ± 14.0	21.8 ± 13.9	0.6351
Free testosterone (pg/mL)	1.7 ± 1.2	1.7 ± 1.2	0.9737
DHEA (ng/dL)	247.7 ± 150.5	237.8 ± 118.5	0.7510
DHEAS (μg/dL)	141.1 ± 94.6	158.6 ± 93.0	0.4085
SHBG (nmol/L)	92.7 ± 43.2	90.2 ± 51.7	0.8146
Cortisol (μg/dL)	9.1 ± 5.0	9.2 ± 6.3	0.9405

Discussion

Because older infertile women are usually relatively hypoandrogenic [11, 22, 32, 33], and because, at our center such patients are routinely supplemented with DHEA while their androgen levels are monitored, our patient population is ideal for assessing DHEA effects on female sexual

Table 2 Effect of DHEA supplementation on sexual function and hormone levels in a group of 50 premenopausal infertile women

	Mean	Std. dev.	*P*-value
Δ FSFI score	2.0	5.6	0.0166
Δ Desire	0.6	1.1	0.0004
Frequency	0.5	1.1	0.0015
Level	0.5	1.0	0.0016
Δ Arousal	0.5	1.3	0.0122
Frequency	0.3	1.2	0.0917
Level	0.4	1.3	0.0232
Confidence	0.4	1.1	0.0124
Satisfaction	0.4	1.4	0.0443
Δ Lubrication	0.4	1.3	0.0551
Frequency	0.3	1.2	0.0517
Difficulty	0.3	1.4	0.1372
Maintaining	0.3	1.3	0.0844
Difficulty	0.2	1.5	0.3141
Δ Orgasm	0.1	1.5	0.6749
Frequency	0.0	1.4	0.9178
Difficulty	0.1	1.5	0.5581
Satisfaction	0.1	1.7	0.7298
Δ Satisfaction	0.3	1.2	0.1065
Closeness	0.3	1.1	0.1289
Relationship	0.2	1.2	0.1534
Overall	0.3	1.2	0.0790
Δ Pain	0.2	1.3	0.2017
During	0.3	1.1	0.0428
Following	0.2	1.2	0.1847
Level	0.0	1.3	0.8235
Δ Hormone			
AMH (ng/mL)	0.0	0.6	0.7384
FSH (mIU/mL)	−2.6	4.4	0.0092
Total testosterone (ng/dL)	15.1	20.1	<0.0001
Free testosterone (pg/mL)	1.4	2.2	<0.0001
DHEA (ng/dL)	235.1	189.2	<0.0001
DHEAS (μg/dL)	276.3	179.5	<0.0001
SHBG (nmol/L)	−24.0	39.4	0.0002
Cortisol (μg/dL)	1.3	8.0	0.4527

Table 3 Effect of DHEA supplementation on sexual function and hormone levels of premenopausal infertile women in the lowest starting FSFI score quartile compared to those in the highest FSFI score quartile

Baseline characteristics	Baseline FSFI score < 25.7 $N = 12$	Baseline FSFI score ≥ 31.9 $N = 13$	*P* value
Age (years)	41.8 ± 4.0	41.6 ± 3.4	0.8828
BMI (kg/m^2)	23.2 ± 2.6	23.5 ± 8.8	0.8977
AMH (ng/mL)	0.9 ± 1.2	1.0 ± 1.3	0.8656
FSH (mIU/mL)	9.7 ± 4.8	9.8 ± 5.3	0.9845
Total testosterone (ng/dL)	27.4 ± 24.0	21.2 ± 9.5	0.3991
Free testosterone (pg/mL)	1.3 ± 0.8	1.8 ± 1.6	0.4193
DHEA (ng/dL)	296.5 ± 184.5	221.8 ± 142.2	0.2842
DHEAS (μg/dL)	169.9 ± 151.1	140.1 ± 90.9	0.5686
SHBG (nmol/L)	69.8 ± 18.8	101.9 ± 50.4	0.0593
Cortisol (μg/dL)	8.4 ± 3.1	8.0 ± 3.8	0.7937
Δ FSFI score	6.1 ± 8.0	−1.0 ± 2.7	0.0059
Δ Desire	1.0 ± 0.8	−0.1 ± 0.6	0.0003
Δ Arousal	1.3 ± 1.7	−0.2 ± 0.5	0.0068
Δ Lubrication	0.8 ± 2.3	−0.1 ± 0.6	0.1742
Δ Orgasm	1.0 ± 2.3	−0.5 ± 1.1	0.0525
Δ Satisfaction	0.9 ± 1.3	0.0 ± 0.7	0.0422
Δ Pain	0.9 ± 2.3	−0.1 ± 0.4	0.1292
Δ Hormone			
AMH (ng/mL)	0.0 ± 0.6	0.1 ± 0.6	0.9018
FSH (mIU/mL)	−3.6 ± 2.6	−1.6 ± 3.5	0.3866
Total testosterone (ng/dL)	16.4 ± 18.5	11.8 ± 18.6	0.5504
Free testosterone (pg/mL)	1.8 ± 1.3	0.5 ± 1.4	0.0359
DHEA (ng/dL)	291.0 ± 227.7	275.7 ± 186.6	0.8610
DHEAS (μg/dL)	305.6 ± 202.5	274.8 ± 131.0	0.6674
SHBG (nmol/L)	–15.8 ± 41.1	−21.0 ± 51.6	0.7912
Cortisol (μg/dL)	2.5 ± 1.6	−0.4 ± 5.5	0.3461

function. This study was, indeed, conceived after many patients on DHEA supplementation reported improvements in libido and other sexual function parameters.

Because sexual dysfunction has been reported to be increased in infertile women [29, 30], we were not surprised that baseline FSFI scores (27.2 ± 6.9, range 2.8–34.8) were marginally lower than those previously described among healthy controls (30.5 ± 5.3) of similar age, but remarkably higher than among patients with female sexual arousal disorder (19.2 ± 6.6) [31]. We did not find any correlation between FSFI scores and patient demographics, ovarian reserve parameters, or baseline androgen levels for the whole study group.

Also unsurprising were observed changes in endocrine parameters following DHEA supplementation. The observed increases in all androgens, decrease in SHBG and FSH levels, and no change in AMH and cortisol levels are consistent with prior studies in menopausal women [34].

Interestingly, the whole patient cohort showed mild improvement in FSFI scores. Considering that here investigated patients were primarily *not* FSD patients, this seems like a remarkable result, suggesting beneficial effects of DHEA supplementation at this age on female sexual well-being. On the other hand, the magnitude in improvement in FSFI scores by 7% for the whole study cohort is like that seen with placebo treatment in various randomized trials conducted in FSD patients [35], which diminishes the clinical significance of this finding. More importantly, it was patients in the lowest starting FSFI quartile who experienced the most profound increase in scores by 34%.

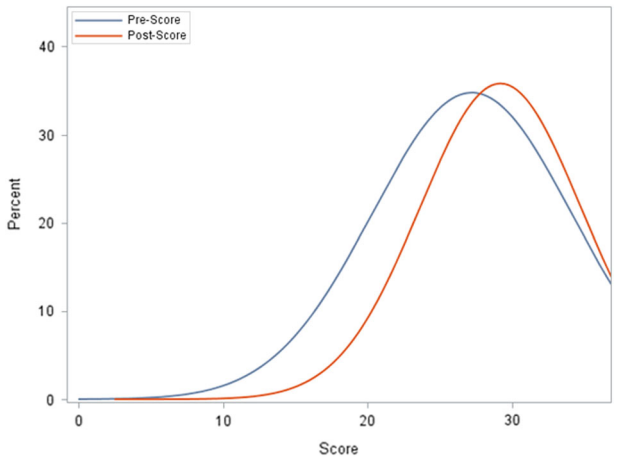

Fig. 1 Distribution of FSFI scores pre- and post-DHEA supplementation in a group of 50 premenopausal infertile women. While FSFI scores improved for the whole study group, the increase was most pronounced among women with the lowest baseline FSFI scores

In other words, those study subjects who had evidence of sexual dysfunction benefitted most from DHEA supplementation.

Interestingly, these patients also demonstrated a significantly larger increase in FT levels than patients in the highest FSFI quartile who did not experience improvements in FSFI scores. Combined, these data suggest a dose–response relationship in patients with relative sexual dysfunction and absence of such a relationship in women with normal sexual function. Though it is important to note that we did not investigate whether women with low FSFI scores suffered distress, which is integral to the diagnosis of FSD [4, 36].

While this makes biological sense, androgen metabolism is complex: steroidogenic capacity declines with age and multiple genetic and enzymatic factors affect the conversion of DHEA to bioactive testosterone [32]. This may also be one reason why some prior studies of DHEA supplementation in women with sexual dysfunction have been unsuccessful [14]; although some improvements in peri- and post-menopausal women [18] and those suffering from adrenal insufficiency [19] have been described. Moreover, the biochemical complexity involved in the conversion of DHEA to bioactive testosterone may also explain conflicting results of prior studies of DHEA supplementation, while studies utilizing testosterone supplementation have been more consistent in improving female sexual function. One hypothesis is that DHEA may be converted not only to androgens but also to progestins which could counter androgenic benefits on sexual function.

Another obvious reason is that, like in female infertility, not every woman with sexual dysfunction is hypoandrogenic. One cannot expect DHEA to be effective in normoandrogenic patients. Primarily hypoandrogenic premenopausal women with sexual dysfunction will, therefore, likely respond well to DHEA supplementation. This raises the question how a female patient in this age group can be defined as hypoandrogenic since there are no agreed to testosterone levels below which a woman can be currently classified as being hypoandrogenic [14]. In infertility practice, we consider women as androgen-deficient if their testosterone levels are in the lower third of normal range and if they demonstrate sex hormone binding globulin levels above 100 nmol/L [11, 22, 32]. Whether this also represents an appropriate definition for hypoandrogenic women with sexual dysfunction in a general population remains to be confirmed.

Limitations and cautions

Several limitations in the design of this study warrant caution: First, we reemphasize that this is not a study of women diagnosed with FSD but of older premenopausal women with infertility. They, therefore, are more representative of a general older population, with possibly mildly higher prevalence of sexual dysfunction [29, 30].

Patients in this observational study acted as their own controls in that FSFI scores in each patient were compared before and after DHEA supplementation. This study format is inferior to that of a prospectively randomized placebo-controlled trial but, still, offers an acceptable level of evidence, especially considering that involved patients did not have primary personal interests in the issue here investigated, as none had entered treatment because of sexual dysfunction or with the intent of improving sexual function. We also did not use questionnaires beyond the FSFI, to enquire about the frequency of intercourse.

Finally, 42.5% of women did not complete the second questionnaire. Such a large dropout rate, raises the possibility of selection bias. Not able to refute such a possibility, we would argue that the most likely dropouts would be those women least affected by DHEA, while those most beneficially affected would want to stay in the study. It, therefore, is possible that our data somewhat exaggerate the beneficial effects of DHEA, even though, as Table 1 demonstrates, dropouts and study patients were very similar in their respective clinical phenotypes. This would also explain the remarkably clear and statistically robust outcome improvements observed in a relatively small patient population.

Conclusions

This observational study offers evidence that DHEA supplementation may benefit selected premenopausal women

with low baseline sexual function. DHEA supplementation offers little or no benefit in premenopausal women with normal sexual function. Therefore, a prospective randomized controlled study should be designed to address the effects of DHEA in a population of premenopausal women with low baseline sexual function.

Funding This work was supported by the Foundation for Reproductive Medicine and intramural funds of the Center for Human Reproduction.

Author contributions V.A.K., D.H.B., and N.G. developed the concept of the study; all authors contributed to data accumulation. S.K.D., A.W., and V.A.K. contributed to data analysis; all authors contributed to data interpretation. V.A.K. wrote the manuscript. All authors contributed to revisions of the manuscript and approved the final submission. V.A.K. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Availability of data and material Anonymized patient level data are accessible by contacting Mrs. Jolanta Tapper at jtapper@thechr.com.

Compliance with ethical standards

Conflict of interest N.G. and D.H.B. are co-inventors on several pending and already awarded U.S. patents claiming fertility benefits from androgen supplementation in women with low functional ovarian reserve (LFOR). Both receive royalties from Fertility Nutraceuticals, LLC, in which N.G. also holds shares. Other authors declare that they have no conflict of interest.

Ethics approval This study received Institutional Review Board (IRB) approval (ER11052015-01) on 11/11/2015 from the IRB of the Center for Human Reproduction. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

References

1. M.E. McCool, A. Zuelke, M.A. Theurich, H. Knuettel, C. Ricci, C. Apfelbacher, Prevalence of female sexual dysfunction among premenopausal women: a systematic review and meta-analysis of observational studies. Sex. Med. Rev. **4**, 197–212 (2016)
2. J.M. Weinberger, J. Houman, A.T. Caron, J. Anger, Female sexual dysfunction: a systematic review of outcomes across various treatment modalities. Sex Med Rev. 2018 Feb 3. pii: S2050-0521(18)30001-5. https://doi.org/10.1016/j.sxmr.2017.12.004
3. H.V. Joffe, C. Chang, C. Sewell, O. Easley, C. Nguyen, S. Dunn, K. Lehrfeld, L. Lee, M.J. Kim, A.F. Slagle, J. Beitz, FDA approval of flibanserin—treating hypoactive sexual desire disorder. N. Engl. J. Med. **374**, 101–104 (2016)
4. R. Basson, J. Berman, A. Burnett, L. Derogatis, D. Ferguson, J. Fourcroy, I. Goldstein, A. Graziottin, J. Heiman, E. Laan, S. Leiblum, H. Padma-Nathan, R. Rosen, K. Segraves, R.T. Segraves, R. Shabsigh, M. Sipski, G. Wagner, B. Whipple, Report of the international consensus development conference on female sexual dysfunction: definitions and classifications. J. Urol. **163**, 888–893 (2000)
5. A.T. Guay, J. Jacobson, Decreased free testosterone and dehydroepiandrosterone-sulfate (DHEA-S) levels in women with decreased libido. J. Sex Marital Ther. **28**(Suppl 1), 129–142 (2002)
6. B. Turna, E. Apaydin, B. Semerci, B. Altay, N. Cikili, O. Nazli, Women with low libido: correlation of decreased androgen levels with female sexual function index. Int. J. Impot. Res. **17**, 148–153 (2005)
7. R.E. Nappi, To be or not to be in sexual desire: the androgen dilemma. Climacteric **18**, 672–674 (2015)
8. R. Worsley, R.J. Bell, P. Gartoulla, S.R. Davis, Prevalence and predictors of low sexual desire, sexually related personal distress, and hypoactive sexual desire dysfunction in a community-based sample of midlife women. J. Sex. Med. **14**, 675–686 (2017)
9. M.M. Kushnir, T. Blamires, A.L. Rockwood, W.L. Roberts, B. Yue, E. Erdogan, A.M. Bunker, A.W. Meikle, Liquid chromatography-tandem mass spectrometry assay for androstenedione, dehydroepiandrosterone, and testosterone with pediatric and adult reference intervals. Clin. Chem. **56**, 1138–1147 (2010)
10. N. Orentreich, J.L. Brind, R.L. Rizer, J.H. Vogelman, Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. J. Clin. Endocrinol. Metab. **59**, 551–555 (1984)
11. N. Gleicher, A. Kim, A. Weghofer, V.A. Kushnir, A. Shohat-Tal, E. Lazzaroni, H.J. Lee, D.H. Barad, Hypoandrogenism in association with diminished functional ovarian reserve. Hum. Reprod. **28**, 1084–1091 (2013)
12. N. Gleicher, V.A. Kushnir, A. Weghofer, D.H. Barad, The importance of adrenal hypoandrogenism in infertile women with low functional ovarian reserve: a case study of associated adrenal insufficiency. Reprod. Biol. Endocrinol. **14**, 23 (2016)
13. P.J. Robinson, R.J. Bell, M.K. Christakis, S.R. Ivezic, S.R. Davis, Aromatase inhibitors are associated with low sexual desire causing distress and fecal incontinence in women: an observational study. J. Sex. Med. **14**, 1566–1574 (2017)
14. S.R. Davis, R. Worsley, K.K. Miller, S.J. Parish, N. Santoro, Androgens and female sexual function and dysfunction—findings from the Fourth International Consultation of Sexual Medicine. J. Sex. Med. **13**, 168–178 (2016)
15. M. Khera, Testosterone therapy for female sexual dysfunction. Sex. Med. Rev. **3**, 137–144 (2015)
16. M. Panjari, S.R. Davis, DHEA therapy for women: effect on sexual function and wellbeing. Hum. Reprod. Update **13**, 239–248 (2007)
17. R.F. Spark, Dehydroepiandrosterone: a springboard hormone for female sexuality. Fertil. Steril. **77**(Suppl 4), S19–S25 (2002)
18. C.S. Scheffers, S. Armstrong, A.E. Cantineau, C. Farquhar, V. Jordan, Dehydroepiandrosterone for women in the peri- or postmenopausal phase. Cochrane Database Syst. Rev. **1**, CD011066 (2015)
19. W. Arlt, F. Callies, J.C. van Vlijmen, I. Koehler, M. Reincke, M. Bidlingmaier, D. Huebler, M. Oettel, M. Ernst, H.M. Schulte, B. Allolio, Dehydroepiandrosterone replacement in women with adrenal insufficiency. N. Engl. J. Med. **341**, 1013–1020 (1999)
20. F. Labrie, D.F. Archer, W. Koltun, A. Vachon, D. Young, L. Frenette, D. Portman, M. Montesino, I. Côté, J. Parent, L. Lavoie, A. Beauregard, C. Martel, M. Vaillancourt, J. Balser, É. Moyneur; VVA Prasterone Research Group, Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. Menopause **23**, 243–256 (2016)

21. N. Gleicher, D.H. Barad, Dehydroepiandrosterone (DHEA) supplementation in diminished ovarian reserve (DOR). Reprod. Biol. Endocrinol. **9**, 67 (2011)
22. N. Gleicher, A. Kim, A. Weghofer, A. Shohat-Tal, E. Lazzaroni, H.J. Lee, D.H. Barad, Starting and resulting testosterone levels after androgen supplementation determine at all ages in vitro fertilization (IVF) pregnancy rates in women with diminished ovarian reserve (DOR). J. Assist. Reprod. Genet. **30**, 49–62 (2013)
23. N. Gleicher, A. Weghofer, D.H. Barad, Improvement in diminished ovarian reserve after dehydroepiandrosterone supplementation. Reprod. Biomed. Online **21**, 360–365 (2010)
24. D. Barad, H. Brill, N. Gleicher, Update on the use of dehydroepiandrosterone supplementation among women with diminished ovarian function. J. Assist. Reprod. Genet. **24**, 629–634 (2007)
25. A. Sen, S.R. Hammes, Granulosa cell-specific androgen receptors are critical regulators of ovarian development and function. Mol. Endocrinol. **24**, 1393–1403 (2010)
26. A. Sen, H. Prizant, A. Light, A. Biswas, E. Hayes, H.J. Lee, D. Barad, N. Gleicher, S.R. Hammes, Androgens regulate ovarian follicular development by increasing follicle stimulating hormone receptor and microRNA-125b expression. Proc. Natl. Acad. Sci. U.S.A. **111**, 3008–3013 (2014)
27. L.T. Lin, P.H. Wang, S.N. Chen, C.J. Li, Z.H. Wen, J.T. Cheng, K.H. Tsui, Protection of cumulus cells following dehydroepiandrosterone supplementation. Gynecol. Endocrinol. **33**, 100–104 (2017)
28. H. Prizant, N. Gleicher, A. Sen, Androgen actions in the ovary: balance is key. J. Endocrinol. **222**, R141–R151 (2014)
29. C.R. Mendonça, J.T. Arruda, M. Noll, P.M.O. Campoli, W.N.D. Amaral, Sexual dysfunction in infertile women: a systematic review and meta-analysis. Eur. J. Obstet. Gynecol. Reprod. Biol. **215**, 153–163 (2017)
30. L.S. Millheiser, A.E. Helmer, R.B. Quintero, L.M. Westphal, A. A. Milki, R.B. Lathi, Is infertility a risk factor for female sexual dysfunction? A case-control study. Fertil. Steril. **94**, 2022–2025 (2010)
31. R. Rosen, C. Brown, J. Heiman, S. Leiblum, C. Meston, R. Shabsigh, D. Ferguson, R. D'Agostino, The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J. Sex Marital Ther. **26**, 191–208 (2000)
32. A. Shohat-Tal, A. Sen, D.H. Barad, V. Kushnir, N. Gleicher, Genetics of androgen metabolism in women with infertility and hypoandrogenism. Nat. Rev. Endocrinol. **11**, 429–441 (2015)
33. N. Gleicher, K. Seier, V.A. Kushnir, A. Weghofer, Y.G. Wu, Q. Wang, D.F. Albertini, D.H. Barad, Associations between peripheral androgens and cortisol in infertile women. J Steroid Biochem Mol Biol. 2016 Apr;158, 82-89
34. M. Stomati, P. Monteleone, E. Casarosa, B. Quirici, S. Puccetti, F. Bernardi, A.D. Genazzani, L. Rovati, M. Luisi, A.R. Genazzani, Six-month oral dehydroepiandrosterone supplementation in early and late postmenopause. Gynecol. Endocrinol. **14**, 342–363 (2000)
35. J.M. Weinberger, J. Houman, A.T. Caron, D.N. Patel, A.S. Baskin, A.L. Ackerman, K.S. Eilber, J.T. Anger, Female sexual dysfunction and the placebo effect: a meta-analysis. Obstet. Gynecol. **132**(2), 453–458 (2018)
36. J.L. Shifren, B.U. Monz, P.A. Russo, A. Segreti, C.B. Johannes, Sexual problems and distress in United States women: prevalence and correlates. Obstet. Gynecol. **112**, 970–978 (2008)