EXTENDED REPORT

Mental wellbeing and quality of sexual life in women with primary Sjögren's syndrome are related to circulating dehydroepiandrosterone sulphate

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Objectives: To evaluate the possible effect of androgen status on sexuality and mental wellbeing in patients with primary Sjögren's syndrome (pSS).
Methods: Serum levels of dehydroepiandrosterone sulphate (DHEA-S), testosterone (T), androstenedione, sex hormone binding globulin (SHBG), and the SHBG/T ratio were measured in 21 women with pSS. Sexual life was assessed by a Swedish version of the McCoy scale, which covers sexual experience and responsiveness during the past 30 days. A standardised questionnaire, the Psychological General Well-Being Index (PGWB), was used to examine quality of life and psychological symptoms in patients with pSS.
Results: Positive correlations were found between DHEA-S serum levels and the total McCoy score (r_s=0.62; p<0.01), as well as the subscales of this score reflecting arousal (0.59; p<0.05), desire (r_s=0.52; p<0.05), and satisfaction (r_s=0.66; p<0.01). Serum DHEA-S concentrations were also related to the total PGWB score (r_s=0.60; p<0.01) and subscales of this score: depression (r_s=0.62; p<0.01), wellbeing (r_s=0.64; p<0.01), general health (r_s=0.67; p<0.01), and self control (r_s=0.67; p<0.01). Total McCoy and PGWB scores and their subscales were not related to the serum levels of testosterone and androstenedione or the T/SHBG ratio.
Conclusions: Circulating levels of the weak androgen DHEA-S are positively related to the quality of sexual life and mental wellbeing in women with pSS.

Primary Sjögren's syndrome (pSS) is a slowly progressive autoimmune disease primarily affecting the exocrine glands and resulting in mucosal dryness.[1] In addition, a wide spectrum of non-exocrine manifestations from various organs—the lungs, kidneys, blood vessels, and muscles—may be seen.[2 3] The involvement of the central nervous system (CNS) has been increasingly recognised in patients with pSS during the past decade. The CNS manifestations may sometimes become severe, with symptoms such as hemiparesis, encephalopathy, and dementia.[4–7] Some investigators have also reported frequent psychiatric symptoms in pSS, including a high incidence of sleep disturbance.[4 8] We recently reported that depression and anxiety were the dominant neuropsychiatric manifestations in patients with pSS and that their mental wellbeing was significantly reduced compared with controls.[9 10] The decrease in wellbeing was particularly experienced by those women with pSS who were receiving oestrogen therapy. Primary Sjögren's syndrome mainly affects women during the fourth and fifth decades of life with a female:male ratio of 9:1,[11] further suggesting that sex hormones play a part in the development and/or pathophysiology of the disease.

In recent years, attention has been drawn to the influence of androgens and in particular dehydroepiandrosterone (DHEA) and its sulphated metabolite DHEA-S on autoimmune diseases.[12–15] DHEA and DHEA-S are weak androgens which are secreted by the adrenal glands in response to adrenocorticotrophic hormone.[16] The possible influence of androgens in pSS has been studied in animal models.[17–19] The results indicate that androgen administration strongly suppresses the inflammatory reaction in the female mouse model of Sjögren's syndrome. We have recently also found reduced serum concentrations of these hormones in women with pSS, both at rest and after adrenal stimulation.[20] In the present study we raised the question of whether or not reduced circulating levels of androgens are linked to the increased incidence of neuropsychiatric manifestations and the impaired quality of life seen in women with pSS.

PATIENTS AND METHODS

Patients

Twenty one female patients (mean age 56, range 39–73 years) with pSS according to the preliminary European Community guidelines[21] were included in the study. The patients included also fulfilled the Copenhagen criteria.[22] The patients were recruited from a database of the hospital. All the patients who fulfilled the diagnostic criteria agreed to take part in the study. Each patient therefore had keratoconjunctivitis sicca demonstrated by the pathological Schirmer-I test (<5 mm/5 min) and/or a short break-up time (<10 sec) and/or positive rose bengal staining (at least two of three tests abnormal); xerostomia was demonstrated by a total stimulated salivary gland secretion rate of <0.1 ml/min and/or abnormal lower lip glandular biopsy and/or pathological salivary gland scintigraphy (at least two of three tests abnormal). The patients were investigated at the outpatient clinic at the Department of Rheumatology, University Hospital of Uppsala.

The onset of the disease occurred 1–15 years (mean four years) before the study. Eight patients had non-exocrine manifestations: Raynaud's phenomenon (n=5), non-erosive arthritis (n=2), and sun sensitivity (n=3). No patient was treated with disease modifying drugs, apart from one who was treated with hydroxychloroquine. Seven patients were receiving oestrogen treatment and 14 were postmenopausal.

Abbreviations: CNS, central nervous system; DHEA-S, dehydroepiandrosterone sulphate; PGWB, Psychological General Well-Being Index; pSS, primary Sjögren's syndrome; SHBG, sex hormone binding globulin

Table 1 Androgen hormone levels and sex hormone binding globulin in 21 patients with primary Sjögren's syndrome. The data are presented as the mean (range)

DHEA-S (μmol/l)	Testosterone (nmol/l)	Androstenedione (nmol/l)	SHBG (nmol/l)	T/SHBG ratio
2.3 (0.6–5.8)	0.7 (0.3–1.8)	4.0 (0.7–8.4)	63 (28–125)	0.02 (0.004–0.5)

SHBG, sex hormone binding globulin; T, testosterone.

Fourteen of the patients had positive serology; 10 had antinuclear antibodies and eight were anti-SSA and SSB positive. All the patients were cohabiting or married, except one who was divorced. No patient had any signs of diabetes mellitus or thyroid dysfunction or any other endocrine disorders.

The inflammatory activity was estimated by measuring the erythrocyte sedimentation rate according to Westergren (normal value 2–15 mm/1st h) and C reactive protein (normal value ≤10 mg/l).

Controls

Fifteen healthy women who were not receiving any drugs served as controls for a comparison of the DHEA-S levels. Their mean age was 57 years (range 40–73), and nine were postmenopausal.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee at the Medical Faculty at Uppsala University.

Hormone measurements

Androstenedione was measured by radioimmunoassay (Androstenedione Radioimmunoassay Kit; Ortho-Clinical Diagnostics, Texas, USA). Total testosterone and DHEA-S were measured by solid phase radioimmunoassay (Diagnostic Products Corporation, Los Angeles, USA). Sex hormone binding globulin (SHBG) was measured by a time resolved sandwich fluoroimmunoassay (Wallac OY, Turku, Finland).

Questionnaires

The women were asked to complete two questionnaires, the McCoy Sexual Rating Scale[23] and the Psychological General Well-Being Index (PGWB).[24] The questionnaires were sent to the patients at home and returned by mail.

McCoy Sexual Rating Scale

Sexual life was assessed using a Swedish version of the McCoy scale which covers sexual experience and responsiveness during the past 30 days.[23] This instrument contains 10 items on a seven point scale relating to different aspects of sexual life, such as frequency of intercourse, orgasm frequency, sexual pleasure and satisfaction, lubrication, dyspareunia, arousal, sexual fantasies, and satisfaction with partner.

Psychological General Well-Being Index (PGWB)

The schedule is a self assessed inventory related to general wellbeing[24] and has been shown to be reliable and valid. It has been used in various clinical settings such as postmenopausal distress[25] and in adults with growth hormone deficiency.[26] The PGWB comprises 22 items with a six point response scale. The factors of anxiety, depressed mood, positive wellbeing, self control, general health, and vitality are related to the total score. The subscales of these measured factors have three to five items. For each item, there are six response options that are rated on a scale of 1 to 6, according to the intensity or frequency of the affective experience. A value of 1 is given for the most negative options and 6 for the most positive options. The score range for the PGWB is 22–132; a higher score represents better wellbeing.

Specific questions

We used isolated questions to assess tiredness and pain in the patients. To assess tiredness, we asked how the patients had felt for the past week on a scale of 1 to 6 with extreme points as "none of the time" and "the whole time". Pain was assessed on a scale of 1 to 6 with extreme points of "no pain" and "very bad pain".

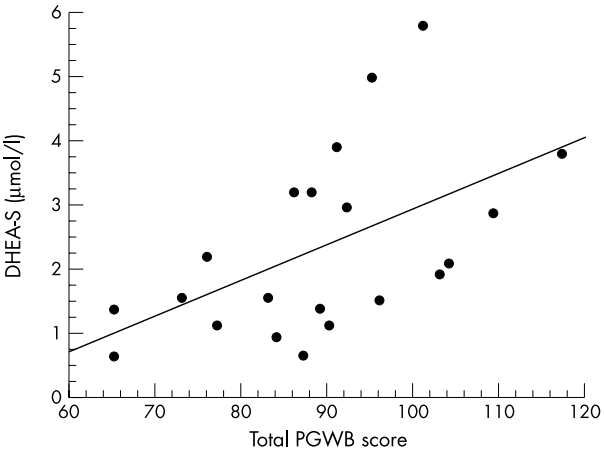

Figure 1 Correlation between DHEA-S levels and total PGWB score in 21 patients with primary Sjögren's syndrome (r_s=0.60, p<0.01).

Statistical analysis

Values are given as the mean (SEM) (range). Non-parametric tests (Mann-Whitney U and Spearman's rank correlation test) were used to analyse data; a p value <0.05 was considered significant.

RESULTS

Table 1 presents the measured serum levels of DHEA-S, testosterone, androstenedione, SHBG, and the testosterone/SHBG ratio in the women with pSS. The mean DHEA-S level was significantly lower in the patients with pSS than in controls (2.3 *v* 3.5 μmol/l, respectively; p<0.05). The mean (SEM) erythrocyte sedimentation rate value was 18 (3) mm/1st h (range 5–42) and the mean serum C reactive protein value ≤10 (0.4) mg/l (range 10–16).

The total mean (SD) score for the PGWB scale was 88.9 (13) in the patients with pSS. The total PGWB score correlated with the serum DHEA-S level (fig 1) but not with the serum levels of testosterone and androstenedione or the testosterone/SHBG ratio. Table 2 shows the PGWB subscale data in relation to hormone levels. The variables of depression, mental wellbeing, general health, and self control were all related to the DHEA-S values. General health and self control were also correlated to the serum levels of testosterone and androstenedione (table 2). No correlation was seen between the PGWB score and T/SHBG ratio.

Four of our patients had no active sex life and were therefore excluded from the calculations relating to the possible relationship between the McCoy rating scale and hormone serum levels. Significant positive correlations were seen between serum DHEA-S and total McCoy score (fig 2), the item assessing arousal, and the subscores for desire and satisfaction (table 3). No such correlation was seen between the

Table 2 Correlation coefficients between the mean scores on the Psychological General Well-Being Scale Index and androgen hormone levels in 21 patients with primary Sjögren's syndrome

	Total score	Anxiety	Depression	Wellbeing	General health	Vitality	Self control
Age	0.11	–0.33	–0.14	–0.50	0.02	0.57*	0.02
DHEA-S	0.60**	0.17	0.62**	0.64**	0.67**	0.23	0.67**
T	0.37	0.05	0.03	0.10	0.51*	0.05	0.51*
A-4	0.39	0.16	0.28	0.34	0.49*	–0.06	0.50*
T/SHBG	0.05	0.11	–0.08	–0.08	0.12	–0.22	0.12

Spearman's rank correlation coefficients. Significant correlations *p<0.05, **p<0.01.
T, testosterone; A-4, androstenedione; SHBG, sex hormone binding globulin.

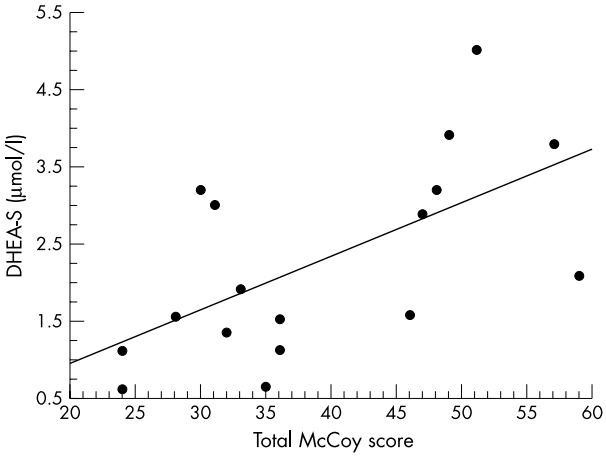

Figure 2 Correlation between DHEA-S levels and total McCoy score in 17 patients with primary Sjögren's syndrome (r_s=0.62, p<0.01).

total McCoy score or its subscores and the testosterone and androstenedione levels or the T/SHBG ratio, except between testosterone and dyspareunia (table 3). Ten (59%) and nine (53%) patients complained of vaginitis sicca and dyspareunia, respectively.

No differences in hormone levels were found in postmenopausal or premenopausal patients or between those receiving hormone replacement treatments or not. No association was found between vaginitis sicca and the hormone variables. There was no correlation between age and the DHEA-S levels or the total McCoy score. The hormone serum levels and the sexual or psychological wellbeing variables were not related to tiredness, pain, or laboratory inflammatory activity.

DISCUSSION

In this study the influence of endogenous androgens on psychological wellbeing and sexuality in women with pSS was investigated. Our findings show that there is a correlation between low serum DHEA-S concentrations and poorer mental wellbeing and decreased sexual quality of life in these patients.

Dehydroepiandrosterone and its sulphated metabolite DHEA-S are important intermediary products in the sex hormone pathway and can be converted to the potent androgens of testosterone, dihydrotestosterone, and androstenedione.[27] Furthermore, DHEA and DHEA-S are present in the brain in rodents and primates, including humans.[28] DHEA and DHEA-S have been classified as neurosteroids, referring to the fact that their accumulation in the brain is at least partly dependent on their synthesis de novo in the CNS.[28–30] Much has been published about the potential effects of DHEA and DHEA-S on various systems and their changes in endogenous concentrations associated with different diseases.[31] We have previously studied major androgens participating in the hypothalamic-pituitary-adrenal axis after the intravenous administration of corticotrophin releasing hormone. The results of that study showed that women with pSS have decreased serum concentrations of DHEA-S both at baseline and after stimulation compared with healthy controls.[20] The reason for this abnormality in androgen metabolism in patients with pSS is unknown, but it may reflect a selective defect in the production of DHEA-S in the adrenal glands as the cortisol synthesis was intact. The observed dissociation between adrenal androgen synthesis and cortisol production may be constitutional but may also be secondary to the inflammatory disease process. It has been shown that immune adrenal interactions may play a part in the dysregulation of adrenal androgen production in pSS, as proposed for other autoimmune diseases like systemic lupus erythematosus.[32 33]

We have previously reported that women with pSS often have psychiatric symptoms and poorer wellbeing, which may affect their quality of life.[9 10] We have also observed that oestrogen treatment has a negative effect on their wellbeing in contrast with the expected positive effect in healthy women receiving hormone replacement therapy.[34] This observation made us suspect that a change in the oestrogen/androgen balance may contribute to the poorer quality of life in women with pSS.

Studies of depression in relation to serum DHEA-S concentrations have produced conflicting results.[31] Barrett-Connor *et al* found that decreased levels of DHEA-S were significantly associated with depressed mood in a cohort of community dwelling postmenopausal women,[35] whereas Cawood and Bancroft found no such connection.[36] In an open labelled

Table 3 Correlation coefficients between psychosexual and androgen hormone variables in 17 women with primary Sjögren's syndrome

	Total McCoy	Arousal	Desire	Satisfaction	Dyspareunia
Age	–0.13	–0.21	–0.23	–0.07	–0.36
DHEA-S	0.62**	0.59*	0.52*	0.66**	0.65**
T	–0.31	–0.16	–0.07	–0.26	0.47*
A-4	–0.20	0.10	0.08	0.44	0.33
T/SHBG	–0.39	–0.18	–0.29	–0.42	0.13

Spearman's rank correlation coefficients. Significant correlations *p<0.05, **p<0.01.
T, testosterone; A-4, androstenedione.

study, DHEA administration had beneficial effects on symptoms of depression.[37] The studies of sense of wellbeing and DHEA-S have also produced a diffuse picture,[31 38 39] but a large French epidemiological study demonstrated a correlation between circulating concentrations of DHEA-S and the feeling of wellbeing.[27] By restoring DHEA-S to young adult levels in both men and women of advancing age, an improvement in physical and psychological wellbeing was obtained in both sexes.[38] In our study, we found an association between low DHEA-S levels and lower total score on the PGWB in women with pSS. Furthermore, there were strong correlations between serum DHEA-S and the subscales for depression, sense of wellbeing, general health, and self control. The link observed previously between serum DHEA-S and neuropsychiatric symptoms and the present observations in women with pSS may reflect the neuroactive role which DHEA-S has for some important functions in the CNS, including the modulation of neurotransmission, brain excitability, and behaviour.[30 40] Experimental studies have also shown that DHEA-S provides neuroprotection. However, the role of DHEA-S in the human CNS function still remains unclear.

Knowledge of the influence of endogenous androgens on sexual life in women is limited.[23 41] Although there is consensus that sexual interest and activity decline in women as they get older, consistent evidence that this is due to hormonal changes is lacking.[36] For a variety of reasons, it can be assumed that rheumatic diseases affect sexual function. Firstly, patients have physical limitations due to pain and immobility and, secondly, drugs can cause fatigue, impotence, and lack of desire. Moreover, patients may have problems with self esteem and body image. Women with Sjögren's syndrome have diminished vaginal lubrication, which may cause painful intercourse.[42] About 60% of our patients had difficulty with intercourse because of vaginal dryness and dyspareunia, but we found no association between the total McCoy score and decreased vaginal lubrication, suggesting that psychosocial factors may have a more important role in sexual function than physical limitations attributable to pSS. A longitudinal study of the effects of menopause on sexuality showed that testosterone was associated with the frequency of sexual behaviour.[23] In our study we found a correlation between DHEA-S and decreased psychosexual function and not with testosterone or androstenedione. This may support the notion that DHEA-S is important for the androgen status and sexual function of women with pSS.

The wide spectrum of symptoms in pSS includes neuropsychiatric manifestations.[4 9] Our observations that women with pSS have lower serum DHEA-S levels than age matched women and that low serum DHEA-S is linked to poorer wellbeing raises the question of whether androgen status has a pathophysiological role in the development and symptomatology of pSS. Glucocorticoid treatment depresses the adrenal synthesis of androgens.[43] So, the previously reported low levels of DHEA-S in systemic lupus erythematosus and rheumatoid arthritis may be due, at least in part, to current or previous glucocorticoid treatment.[12–14] A drug mediated influence of this kind can definitely be excluded in our patients with pSS who had never received glucocorticoids. It is not possible to say from this study whether or not an impaired DHEA synthesis in pSS precedes the disease or is a secondary manifestation of the disease process. However, the possibility remains that the androgen status is of importance for manifestations other than poorer wellbeing in patients with pSS, because androgen administration to female mice with Sjögren's syndrome has a successful effect on the inflammatory disease attack on exocrine glands.[17–19]

The current means of ameliorating various symptoms in patients with pSS using pharmacological principles are limited. We suggest that the restoration of DHEA-S to normal circulating levels in women with pSS should be considered as a possible future strategy to improve their mental wellbeing and the quality of their sexual life.

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REFERENCES

1 **Moutsopoulus H**, Talal N. Immunological abnormalities in Sjögren's syndrome. In: Talal N, Moutsopoulus HM, Kassan SS, eds. *Sjögren's syndrome. Clinical and immunological aspects*. Berlin: Springer, 1987:258–65.
2 **Fox R**, Howell F, Bone R, Michelson P. Primary Sjögren's syndrome: clinical and immunopathological features. Semin Arthritis Rheum 1984;14:77–103.
3 **Moutsopoulos H**, Chused T, Mann D, Klippel J, Fauci A, Frank M, *et al*. Sjögren's syndrome (sicca syndrome): current issues. Ann Intern Med 1980;92:212–26.
4 **Hietaharju A**, Yli-Kerttula U, Hakkinen V, Frey H. Nervous system manifestations in Sjogren's syndrome. Acta Neurol Scand 1990;81:144–52.
5 **Caselli RJ**, Scheithauer BW, Bowles CA, Trenerry M, Meyer FB, Smigeslky JS, *et al*. The treatable dementia of Sjögren's syndrome. Ann Neurol 1991;30:98–101.
6 **Andonopoulos A**, Lagos G, Drosos A, Moutsopoulos H. The spectrum of neurological involvement in Sjögren's syndrome. Br J Rheumatol 1990;29:21–3.
7 **Mauch E**, Völk C, Kratzch G, Krapf H, Kornhuber H, Laufen H, *et al*. Neurological and neuropsychiatric dysfunction in primary Sjögren's syndrome. Acta Neurol Scand 1994;89:31–5.
8 **Gudbjörnsson B**, Broman J, Hetta J, Hällgren R. Sleep disturbance in patients with primary Sjögren's syndrome. Br J Rheumatol 1993;32:1072–6.
9 **Valtysdottir S**, Gudbjörnsson B, Lindqvist U, Hallgren R, Hetta J. Anxiety and depression in patients with primary Sjögren's syndrome. J Rheumatol 2000;27:165–9.
10 **Valtysdottir S**, Gudbjörnsson B, Hallgren R, Hetta J. Psychological well-being in patients with primary Sjögren's syndrome. Clin Exp Rheumatol 2000;18:597–600.
11 **Ahmed A**, Penhale W, Talal N. Sex hormones, immune responses, and autoimmune diseases. Mechanisms of sex hormone action. Am J Pathol 1985;121:531–51.
12 **Derksen R**. Dehydroepiandrosterone (DHEA) and systemic lupus erythematosus. Semin Arthritis Rheum 1998;27:335–47.
13 **Lahita R**, Bradlow H, Ginzler E, Pang S, New M. Low plasma androgens in women with systemic lupus erythematosus. Arthritis Rheum 1987;30:241–8.
14 **Masi A**. Sex hormones and rheumatoid arthritis: cause or effect relationships in a complex pathophysiology? Clin Exp Rheumatol 1995;13:227–40.
15 **Van Vollenhoven R**, Engleman E, McGuire J. Dehydroepiandrosterone in systemic lupus erythematosus. Arthritis Rheum 1995;38:1826–37.
16 **Nieschlag E**, Loriaux D, Ruder H, Zucker I, Kirschner M, Lipsett M. The secretion of dehydroepiandrosterone and dehydroepiandrosterone sulphate in man. J Clin Endocrinol 1973;57:123–34.
17 **Sato E**, Ariga H, Sullivan D. Impact of androgen therapy in Sjögren's syndrome: hormonal influence on lymphocyte populations and Ia expression in lacrimal glands of MRL/Mp-lpr/lpr mice. Invest Ophthalmol Vis Sci 1992;33:2537–45.
18 **Sato E**, Sullivan D. Comparative influence of steroid hormones and immunosuppressive agents on autoimmune expression in lacrimal glands of a female mouse model of Sjögren's syndrome. Invest Ophthalmol Vis Sci 1994;35:2632–42.
19 **Sullivan D**, Edwards J. Androgen stimulation of lacrimal gland function in mouse models of Sjögren's syndrome. J Steroid Biochem Mol Biol 1997;60:237–45.
20 **Valtysdottir ST**, Wide L, Hällgren R. Low serum dehydroepiandrosterone sulphate (DHEA-S) in women with primary Sjögren's syndrome as an isolated sign of impaired HPA-axis function. J Rheumatol 2001;28:1259–65.
21 **Vitali C**, Bombardieri S, Moutsopoulos H, Balestrieri G, Bencivelli W, Bernstein *RM, et al*. Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. Arthritis Rheum 1993;36:340–7.
22 **Manthorpe R**, Oxholm P, Prause JU, Schiodt M. The Copenhagen criteria for the classification of Sjögren's syndrome. Scand J Rheumatol 1986;61(suppl):19–21.
23 **McCoy N**, Davidson J. A longitudinal study of the effects of menopause on sexuality. Maturitas 1985;7:203–10.

24 **Dupuy HJ**. The Psychological General Well-Being (PGWB) Index. In: Wenger NK, Mattson ME, Furberg CF, Elinson J, eds. *Assessment of quality of life in clinical trials of cardiovascular therapies*. Le Jacq Publishing, 1984:170–83.
25 **Wiklund I**, Karlberg J, Mattson L-Å. Quality of life of postmenopausal women on a regimne of transdermal estradiol therapy: A double-blind placebo-controlled study. Am J Obstet Gynecol 1993;168:824–30.
26 **Burman P**, Broman JE, Hetta J, Wiklund I, Erfurth EM, Hagg E, *et al*. Quality of life in adults with growth hormone (GH) deficiency: response to treatment with recombinant human GH in a placebo-controlled 21-month trial. J Clin Endocrinol Metab 1995;80:3585–90.
27 **Baulieu E**. Dehydroepiandrosterone (DHEA): a fountain of youth? J Clin Endocrinol Metab 1996;81:3147–51.
28 **Sternberg E**. Neural-immune interactions in health and disease. J Clin Invest 1997;100:2641–7.
29 **Basedovsky H**, del Rey A. Immune-neuro-endocrine interactions: facts and hypotheses. Endocr Rev 1996;17:64–102.
30 **Akwa Y**, Baulieu E-E. Dehydroepiandrosterone sulfate and dehydroepiandrosterone: neuroactive neurosteroids. Curr Opinol Endocrinol Diab 2000;7:160–7.
31 **Kroboth P**, Salek F, Pittenger A, Fabian T, Frye R. DHEA and DHEA-S: a review. J Clin Pharmacol 1999;39:327–48.
32 **Wolkersdorfer G**, Lohmann T, Marx C, Schroder S, Pfeiffer R, Stahl H, *et al*. Lymphocytes stimulate dehydroepiandrosterone production through direct cellular contact with adrenal zona reticularis cells: a novel mechanism of immune endocrine interactions. J Clin Endocrinol Metab 1999;4:550–9.
33 **Chrousos G**. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 1995;332:1351–62.
34 **Nathorst-Böös J**, Wiklund I, Mattson L-Å, Sandin K, von Schoultz B. Is sexual life influenced by transdermal estrogen therapy? A double blind placebo controlled study in postmenopausal women. Acta Obstet Gynecol Scand 1993;72:656–60.
35 **Barrett-Connor E**, von Muhlen D, Laughlin G, Kripke A. Endogenous levels of dehydroepiandrosterone sulfate, but not other sex hormones, are associated with depressed mood in older women: the Rancho Bernardo Study. J Am Geriatr Soc 1999;47:685–91.
36 **Cawood E**, Bancroft J. Steroid hormones, the menopause, sexuality and well-being of women. Psychol Med 1996;26:925–36.
37 **Wolkowitz OM**, Reus VI, Roberts E, Manfredi F, Chan T, Raum WJ, *et al*. Dehydroepiandrosterone (DHEA) treatment of depression. Biol Psychiatry 1997;41:311–18.
38 **Morales A**, Nolan J, Nelson J, Yen S. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. J Clin Endocrinol Metab 1994;78:1360–7.
39 **Barnhart K**, Freeman E, Grisso J, Rader D, Sammel M, Kapoor S, *et al*. The effect of dehydroepiandrosterone supplementation to symptomatic perimenopausal women on serum endocrine profiles, lipid parameters, and health-related quality of life. J Clin Endocrinol Metab 1999;84:3896–902.
40 **Baulieu E-E**. Neurosteroids: of the nervous system, by the nervous system, for the nervous system. Recent Prog Horm Res 1997;52:1–32.
41 **McCoy N**, Winnifred C, Davidson J. Relationships among sexual behavior, hot flashes and hormone levels in perimenopausal women. Arch Sex Behav 1985;14:385–94.
42 **Skopouli F**, Papanikolaou S, Malamou-Mitsi V, Papanikolaou N, Moutsopoulos H. Obstetric and gynaecological profile in patients with primary Sjögren's syndrome. Ann Rheum Dis 1994;53:569–73.
43 **Masi A**, Da Silva J, Cutolo M. Perturbation of hypothalamic-pituitary-gonadal (HPG) axis and adrenal androgen (AA) function in rheumatoid arthritis. Baillieres Clin Rheumatol 1996;10:295–331.