

Endocrine Aspects of Women's Sexual Function

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DOI: 10.1111/j.1743-6109.2009.01629.x

ABSTRACT

Introduction. Endocrine changes during aging as well as endocrine disorders may either directly or indirectly modulate female sexual function by altering sex hormones, or by impacting on vascular, neurogenic, or psychologic factors.

Aim. To review information on the impact of the hormonal changes associated with aging or those caused by endocrine disorders on female sexual function and current information on the risks and benefits of hormonal treatments.

Methods. Committee members outlined topics and reviewed the published literature on endocrine aspects of female sexual function over a 2-year period. Presentation of the recommendations were presented at the International Consultation on Sexual Medicine Paris, France 2009 and revised accordingly.

Main Outcome Measures. Quality of data published in the literature and recommendations were based on the GRADES system.

Results. Recommendations and guidelines concerning the role of sex hormones and endocrine disorders in female sexual function were derived.

Conclusions. Hormones are only one component of the many factors that contribute to normal sexual function in women. Further research is needed as to the impact of hormones and endocrine disorders on female sexual dysfunction and the benefits and risks of hormonal therapies. **Wierman ME, Nappi RE, Avis N, Davis SR, Labrie F, Rosner W, and Shifren JL. Endocrine aspects of women's sexual function. J Sex Med 2010;7:561–585.**

Key Words. Testosterone; Estrogen; Hypoactive Sexual Desire Disorder (HSDD); Menopause; Polycystic Ovarian Syndrome (PCOS); Premature Ovarian Failure (POF); Diabetes; Metabolic Syndrome

Introduction

Although our understanding of the physiology of sexual function in women is limited, there has been a renewed interest in the role of estrogens and testosterone (T) in normal sexual functioning in women. Endocrine changes during aging as well as endocrine disorders may either directly or indi-

rectly modulate sexual function by altering sex hormones, or by impacting on vascular, neurogenic and/or psychologic factors. This review will outline our current state of knowledge concerning the impact of the hormonal changes across the lifespan or those caused by endocrine disorders on female sexual function and information on the risks and benefits of hormonal treatment.

Review of the Limitations of Past and Current Sex Steroid Measurements and Reference Ranges for Women

Problems of Quality Control, Accuracy, and Sensitivity for T Assays (Level I Evidence)

Like those in the physical sciences, we should insist that there be a fixed traceable standard for all measurements. This definition forms the basis for accuracy-based proficiency testing. Although this is easier said than done, it can and has been done for a number of important analytes [1]. For T and estradiol (E2) proficiency testing in the United States, however, the principle of traceability is not followed. Rather, analytes embedded in a synthetic matrix are sent to client laboratories for assay; the laboratories' competences are not evaluated by the accuracy of their results but rather by a comparing their results with others using the same method. If a clinical laboratory changes instruments, new assays on the same patient cannot be compared with previous ones with confidence. Epidemiologic studies dealing with these hormones cannot be compared with another in which a different instrument/method was used. Nor can a new study by the same investigator be compared with a previous one if the original methods have become obsolete.

Total T

In 2005, The College of American Pathology (CAP) sent multiple unknown samples to over 1,000 participating laboratories to measure total T [2]. The mean levels of total T ranged from 33 to 772 ng/dL in the tested specimens and revealed a twofold difference in peer group means across all levels of total T. More strikingly, for samples in the mid-normal range for women, the spectrum of results obtained (mean 32.7 ng/dL), was 7–100 ng/dL! Alternatively, a single laboratory can compare the accuracy, sensitivity, and reproducibility of immunoassays for T with one another, and with a mass spectroscopy (MS)-based method. This approach has been the basis of a number of excellent studies [2–9]. The profound lack of accuracy, sensitivity, and reproducibility of most immunoassays for T is graphically illustrated by comparing 10 immunoassays [8] with a method based on MS. For the higher values of T, e.g., in the male range, there was at least a relationship between the MS-based method and the immunoassays. However, this was not true for values below about 8 nM, i.e., levels seen in the plasma of women and children. The disagreements are severe enough to render current immunoassay results, in women

and children, are virtually useless. As normal women, both pre- and postmenopausal, have a plasma T concentrations less than about 2.5 nM [10], it is clear that methods better than current automated immunoassays are needed to establish normal ranges. Together, these data suggest that prior studies attempting to correlate T levels with sexual function may not have been sensitive or specific enough to detect changes in women across the lifespan.

Free T (FT)

T binds sex hormone binding globulin (SHBG) and albumin. In men, albumin binds 50%, SHBG binds 48%, and 2% is free; in women the respective percentages are 66%, 33%, and 1%.[10]. The unbound portion, FT and/or that bound to albumin, is often considered the moiety that gets into the cell and results in androgenic effects. The situation is more complicated than that [11,12], but, as a practical matter, FT often correlates better with the hyperandrogenic state of the patient than does total T [13]. The optimal method to measure FT is disputed and the advantages and disadvantages of each method have been recently reviewed [2]. Importantly, all measurements of FT depend, among other things, on an accurate determination of total T (see discussion earlier). The measure of FT using a direct immunoassay has been soundly rejected in the literature [2,14–17] and ought not to be used.

In the United States, the Centers for Disease Control and The Endocrine Society have partnered to develop traceability in the measurement of T and to invite the clinical laboratory community to join in the effort [18].

A number of laboratories are focusing on the use of MS-based methods to assay T in biologic fluids [9,19]. The various methods differ somewhat, particularly in how the sample is treated before entering the mass spectrometer. Although the agreement among MS-based methods is much better than among immunoassays, compared either with each other or to MS-based methods, there is as yet no universally accepted method. However, compared with immunoassays, the agreement above 5 nM is excellent and below this concentration, is significantly better than any of the immunoassays.

Recommendations on T Assays

As the methods for the measurement of T gain the accuracy, sensitivity, and reproducibility that are necessary, normal ranges for women will have to

be ascertained across the life span, across the menstrual cycle and among various ethnicities. The study of T in women then will be able to proceed on a firm and rational basis. We therefore recommend the use of new assays to reassess changes in T levels across the lifespan and their relation to sexual function and dysfunction (Grade A).

We recommend the use of total T, in an assay of optimum sensitivity and specificity, and SHBG to calculate FT to assess plasma androgens (Grade A).

The Problems of Quality Control, Accuracy, and Sensitivity for E2 Assays (Level 1 evidence)

Total E2

The state of affairs with respect to E2 is similar to that for T. In postmenopausal women, where E2 levels are routinely <15 pg/mL, the risk of breast cancer and vertebral and/or hip fracture, may vary with E2 concentrations that are below the sensitivities of current commercial assays [20]. Other circumstances requiring more sensitive assays include: pubertal disorders; estrogens in men; monitoring of E2 in the context of anti-estrogen therapy (anti-ET; e.g., aromatase inhibition); and research in Alzheimer's disease and cardiovascular disorders [21]. Immunoassays for E2 lack the sensitivity, and hence the accuracy, to quantitate E2 in plasma at the concentrations present in the circumstances described earlier [22]. The CAP does "peer group" proficiency testing for E2 [23]. The lowest sample distributed, 70 pg/mL, is substantially greater than the values seen in men and postmenopausal women. Even so, the overall coefficient of variation of 66.4%, and the overall ratio of highest to lowest value of 70 on the same sample suggests the need to improve these assays at low concentrations.

Free E2

Like T, E2 is bound to SHBG and albumin in plasma. A major difference in binding constants results in a quite different distribution of the steroid in its major three physical states. In men, about 78% of E2 is bound to albumin, 20% to SHBG, and 2% is free whereas in women the respective percentages are 61%, 37%, and 2% [10]. There has been substantially less investigation of physiology/disease with free E2 as an end point. Like T, its estimate depends upon an accurate assay for total E2, leading to the same major difficulties seen with FT assays. Liquid chromatography mass spectrometry (LCMS)-based methods for E2 have been cumbersome [22,23], and until

recently were not optimized for routine clinical use or for large epidemiologic studies. Of late there has been a substantial effort to modify the methods to increase both their sensitivity and throughput [19,24–28]. Little data are available for estrone (E1) or other estrogens.

Recommendations for E2 Assays

We recommend that E2 levels across the lifespan be assessed with the newer assays to test whether levels correlate with female sexual function or dysfunction (Grade A).

The Potential Impact of Intracrinology and Female Sexual Dysfunction (FSD; Levels 1 and 2 Evidence)

Overview

Primates have adrenals that secrete large amounts of the inactive precursor steroid dehydroepiandrosterone (DHEA) that is converted into active androgens and/or estrogens in specific peripheral tissues [29,30]. As estrogen secretion by the ovaries stops at menopause, a major source of androgen and estrogenic precursors in women after menopause is DHEA of adrenal origin. There is also a significant decrease of androstenedione (a proximate precursor of both estrogens and T) secretion by postmenopausal ovaries. This change, coupled with a marked reduction in the formation of DHEA by the adrenals with age [31], results in a parallel fall in the formation of androgens and estrogens in peripheral target tissues for want of appropriate precursors and/or reduced activity of converting enzymes.

Classically, the effects of sex hormones were assumed to be secondary to the ovarian secretion into the plasma, followed by their uptake by an appropriate target tissue. Thus, one could assess their activity by measurement in peripheral plasma. Local biosynthesis and action of prohormones that can be converted into androgens and estrogens in target tissues termed "intracrinology" may bypass the exposure of other tissues to the hormones [29]. This process may be important in normal physiology, i.e., aromatization of prohormones to estrogens in the brain or androgenic precursors in the vagina. Alternatively, risks may be increased by local biosynthesis of sex hormones, e.g., increased aromatization of androgens to estrogens in breast tissue. Data on the conversion of DHEA to active sex hormones in target tissues have raised the possibility of its use as a prohormone replacement therapy [32].

Role of Estrogens in Female Sexual Function and Dysfunction: Evidence from Low Estrogen States and Effects of Estrogen Treatment

What is the Evidence that Estrogens Play an Important Role in FSD?

With the menopausal transition, women often experience cognitive changes, mood instability, night sweats and disrupted sleep [33]. Urogenital atrophy results in dyspareunia which may adversely impact on sexual function. Although vasomotor symptoms generally improve with time, in the absence of treatment urogenital atrophy may worsen with time since cessation of menses [34]. Vasomotor symptoms are more severe with surgical than with naturally occurring menopause, likely caused by the abrupt decline in estrogens at the time of bilateral oophorectomy [35–39]. One difficulty of using menopause as a model for studying the effects of estrogen deficiency and treatment on sexual function is that T levels also change, in some but not all studies [40–42]. Naturally menopausal women have gradual changes in their T levels with aging; surgically menopausal women experience an approximate 50% decrease in circulating concentrations at the time of bilateral salpingo-oophorectomy (BSO) [37,38,43–46]. Surgical menopause also is an imperfect model for studying the effects of estrogen on sexuality, as most women undergoing hysterectomy and BSO have underlying uterine pathology, e.g., fibroids, pelvic pain, or dysfunctional uterine bleeding; thus, sexual function may improve with treatment of the underlying gynecologic problem, independent of hormonal status [35,47]. Alternatively, BSO may be unwelcome, imposing premature infertility and negatively affecting sexual self-image and function.

Most evidence supports an important role for estrogens in healthy sexual functioning, principally by treating bothersome vasomotor symptoms and maintaining vaginal health. Estrogen deficiency results in sexual dysfunction if vaginal atrophy and dyspareunia occur, often leading secondarily to decreased sexual interest, arousal and response [34,48,49]. Sexual sensitivity of genital and non-genital skin is also linked to estrogen status. Vasomotor symptoms with associated sleep disruption, fatigue, and impaired quality of life also will have a negative effect on sexual function [34,50] ET may improve sexual function by treating vaginal atrophy and bothersome hot flashes and night sweats [51–53]. To summarize, a significant direct effect of estrogen on sexual interest, arousal and

orgasmic response, independent of its role in treating the foregoing menopausal symptoms, is not supported by current evidence.

Evidence from Observational Studies in Surgically Menopausal Women (Levels 2 and 3 Evidence)

Women who undergo BSO prior to natural menopause experience an abrupt decline in plasma estrogens [36–38,44,54,55]. The remaining estrogens present after BSO results from peripheral aromatization of adrenal prohormones. Optimally, oophorectomized women should be compared with hysterectomized women who retain their ovaries. Studies are imperfect, however, as the indications for surgery, the surgical procedures, and the accompanying T deficiency following oophorectomy may impact sexual function postoperatively.

In the Maryland Women's Health Study, over 1,000 women were interviewed before and after hysterectomy. Although 44% of the women had concurrent BSO, improvements in sexual functioning postoperatively were observed. The majority of women (88%), however, were taking hormone therapy (HT) postoperatively. Thus, the independent impact of estrogen deficiency on impaired sexual function could not be assessed. Predictors of post-hysterectomy low libido were pre-hysterectomy low libido and depression [36]. In a retrospective study that controlled for postoperative ET, approximately 100 women ages of 47–55 years were evaluated 2–6 years after hysterectomy. Comparisons were made between oophorectomized women not using ET, those using ET, and non-oophorectomized women. There were no differences in frequency of intercourse or orgasm, dyspareunia, arousal, or partner satisfaction between groups [44]. Non-estrogen-treated oophorectomized women had significantly worse scores for depression, anxiety, and psychological well-being compared with intact women, but these problems were not apparent in oophorectomized women receiving estrogen. As this study was not randomized, however, symptoms may have influenced the prescription of ET to the women and thus affected the outcomes. In summary, the ability to draw conclusions about the effects of estrogen on sexuality from studies of oophorectomized women is limited; women with higher sexual function preoperatively are less likely to elect BSO at the time of hysterectomy [54], and women with problems are more likely to elect postoperative ET.

Evidence from Clinical Trials of ET in Surgically Menopausal Women (Level 1 Evidence)

To assess the effects of estrogen and progestin therapy on sexual behavior, 49 women who had undergone hysterectomy with BSO were randomized in a double-blind, placebo (PL)-controlled crossover study to 3 months each of ethinyl E2 (EE), levonorgestrel (LNG), EE + LNG, or PL [56]. Comparing estrogen-containing regimens with PL, estrogen treatment was associated with significantly greater sexual desire, enjoyment, orgasmic frequency and lubrication. Of note, hot flashes occurred without HT use, and a significant effect of hot flashes on orgasmic frequency was observed. These data support a detrimental effect of menopausal symptoms on sexual function, which may be treated effectively with HT.

Evidence from Observational Cohort Studies in Naturally Menopausal Women (Level 2 Evidence)

There are conflicting results on the role of estrogens in sexual functioning as women undergo natural menopause. Most of the studies are cross-sectional, although several cohort studies examine the association between change in E2 levels and change in sexual functioning over the menopausal transition. The Penn Ovarian Aging Study was a longitudinal population-based cohort designed to examine the associations between variability and changes in reproductive hormones and symptoms associated with ovarian aging [57]. Women were aged 35–47 years at baseline, had normal menstrual cycles, with yearly hormonal measurements and various measures of sexual functioning assessed. At 4 years in 326 women, there were no significant differences in E2 levels between women with and without self-reported decreased libido [57]. However, depression, vaginal dryness and children living at home were associated with decreased libido. A major limitation of this study is that only 7.7% were classified as late menopausal and 4.3% as postmenopausal.

Follow-up analysis [58] using the Female Sexual Function Index (FSFI) assessed desire, arousal, lubrication, orgasm, satisfaction, and pain. Sexual dysfunction was defined as a total index score of 20 or below. Although sexual dysfunction increased over the transition, there was no association between sexual dysfunction and any of the domain scores and estrogen level or variability. Predictors of sexual dysfunction were absence of a sexual partner, high anxiety, and children under the age of 18 years living at home. A limitation of this study is the small number of women classified with

dysfunction (N = 102, 33% of sample). Freeman and coworkers [59] examined the association between hormones and reports of decreased libido or interest in sex over 9 years of follow-up of this cohort. A moderate association between lower mean levels of E2 and reports of decreased libido was found after adjusting for menopausal stage, age, race, history of depression, current smoking, body mass index (BMI), and perceived stress. In contrast to the prior studies, these analyses may have detected a significant association between E2 and libido because women were later in the transition; 22% were late transition and 35% were postmenopausal.

In the Melbourne Women's Health Project, a population-based longitudinal study of Australian-born white women aged 45–55 years at baseline, annual assessments included hormone levels, the Short Personal Experiences Questionnaire (SPEQ) and collection of a wide range of covariates. Among 336 women followed for 8 years, there was a significant association between decreasing E2 levels and sexual responsiveness (interest, arousal, enjoyment, orgasm) and dyspareunia, but not frequency of sexual activity [60]. Sexual responsiveness was adversely affected by aging and menopause transition [33]. Those women who had lower baseline scores on the SPEQ had lower E2 levels, and lower scores over time correlated with lower E2. Further studies examining relationship factors [61], showed that although E2 was related to libido, sexual responsiveness, and dyspareunia, prior function and relationship factors were more important than hormones.

More recently, Modelska et al. [62] examined the association between E2 and changes in sexual function over 3 years in postmenopausal women who participated in the raloxifene evaluation trial. All women were sexually active and at least 2 years postmenopause with a mean age of 65 years. E2 was assessed at baseline and dichotomized at 20 pmol/L. The sexual history questionnaire was administered at baseline and at 3 years. At baseline, women with E2 levels < 20 pmol/L reported significantly greater discomfort during sex and inability to relax, but there was no difference between groups in reported enjoyment, satisfaction, orgasm, interest, arousal, or difficulty during intercourse. After 3 years, women with E2 \geq 20 pmol/L had significantly less decline in sexual enjoyment, satisfaction and sexual feelings. There was no difference from women with low E2 in orgasm, lack of interest, inability to relax, arousal difficulty, or discomfort during intercourse,

whereas pain was more evident. Limitations of the study included that only 121 women showed a decline in sexual functioning and E2 was measured only at baseline.

Thus, some evidence supports the hypothesis that decreases in estrogens may be associated with changes in sexual functioning after menopause. Relationship factors and physical or mental health contributed to sexual functioning to a greater degree than either menopausal status or hormonal levels. Limitations of sex hormone assay sensitivity at lower levels used in all of these studies may have influenced the lack of clear correlation with hormonal levels (discussed in the section "Review of limitations of past and current sex steroid measurements and reference ranges for women").

Evidence from Observational Cross-Sectional Studies in Naturally Menopausal Women (Level 2 Evidence)

A cross-sectional study of 141 women aged 40–60 years with natural menopause with a current partner showed that no hormonal measure (including E2 and E1) correlated with various measures of sexuality [64]. Predictors of sexual functioning were the quality of the relationship and measures of well-being. Similarly, Gallicchio et al. [64] evaluated 265 perimenopausal sexually active women aged 45–54 years and found no association between overall sexual satisfaction and plasma E2, E1 or the free estrogen index. However, depressive symptoms and poor overall health were related to lower satisfaction.

More recently, Avis and coworkers [48] reported cross-sectional analyses from the Massachusetts Women's Health Study of the association between log E2 and various domains of sexual functioning among 200 women aged 51–61 years. Log E2 was negatively related to reporting pain during or after sexual intercourse in both univariate and multivariate analyses. Plasma E2 was not significantly related to a decline in sexual interest with age or satisfaction with current sexual relationship, desire, frequency of sex, arousal, or difficulty reaching orgasm. Factors predictive of better sexual functioning were physical and mental health, marital status (or new partner), and not smoking. Similarly, in the Study of Women's Health Across the Nation (SWAN), no association between sexual desire or arousal, and E2 levels was detected among 2,961 pre and perimenopausal women [40].

Thus, the literature in natural menopausal women provides conflicting data concerning the correlation of plasma E2 levels and sexual func-

tion. Issues related to sensitivity of sex hormone assays in postmenopausal woman must be considered (discussed in the section "Review of limitations of past and current sex steroid measurements and reference ranges for women"). Observational studies show that factors relating to mental and physical health and the partner relationship are more consistently related to sexual function than levels of estrogens.

Evidence from Clinical Trials of ET in Naturally Menopausal Women (Levels 1 and 2)

The effects of a transdermal patch containing 0.014 mg/day of transdermal E2 on sexual function in 417 postmenopausal women was studied in a randomized, double-blind, PL-controlled 2-year trial [65]. Participants were aged 60–80 years (mean age 66.8) with an intact uterus, and not recruited on a basis of sexual dysfunction. Outcome measures included frequency of sexual activity and the Medical Outcomes Study Sexual Problems Index, which includes items on loss of sexual interest, inability to relax and enjoy sex, difficulty becoming aroused, and difficulty in having an orgasm. Women assigned to E2 had significantly greater improvement in vaginal pain/dryness, but did not significantly differ in frequency of sexual activity or other sexual function domains. A study of 223 postmenopausal women aged 45–65 years "requiring hormone replacement therapy for climacteric symptoms" randomly assigned to 0.05 mg/day of transdermal estrogen reported greater sexual satisfaction and fewer sexual problems than those in the PL group [66]. Women in the E2 group reported greater satisfaction with frequency of sexual activity, greater sexual enjoyment, and decreased dyspareunia, but no difference in sexual arousal or orgasm [44]. A double-blind, randomized, PL-controlled study was performed in 285 sexually active postmenopausal women aged 45–65 (mean age 54 years) of daily oral low dose conjugated estrogens (0.45 mg) plus progesterone (1.5 mg) combined with 1 g conjugated estrogen vaginal cream (0.625 mg) [67]. Treated women showed a significant decrease in frequency of dyspareunia and an improvement in sexual interest, frequency and pleasure of orgasm compared both with the baseline and PL group, but no effect on frequency of sexual intercourse. Because this trial used a combination of oral estrogen/progestin therapy and vaginal estrogen cream, it is not possible to determine the relative impact of systemic vs. local estrogen treatment.

Thus, numerous studies of ET, whether oral, transdermal, or vaginal have demonstrated positive effects on vaginal pain and dryness. However, results on other aspects of sexual functioning are more mixed, with stronger results found for younger women. It is not surprising that results are less consistent for other aspects of sexual functioning, as observational studies show that sexuality in women is particularly complex and influenced by multiple hormonal and nonhormonal factors.

Summary of Data on Natural Menopause and Estrogen

E2 levels and Sexual Function (Level 2 Evidence)

Limitations of current research include: use of single hormone levels compared with fluctuations, variability in sexual functioning questionnaires with analysis of changes in individual items or a composite index, and also variability in the covariates included in analyses. Despite these differences, several patterns can be discerned. Studies of older women show consistent benefit. This would suggest that postmenopausal E2 levels may be more critical to sexual functioning than those during the transition. Studies including relationship factors and physical or mental health observe that these factors contribute more to sexual functioning than either menopausal status or hormonal levels.

Risks of systemic HT and ET (Levels 1 and 2 Evidence)

Daily estrogen/progestin therapy is associated with an increase in cardiovascular events in older postmenopausal women [68,69]. Recent guidelines support the limited use of Estrogen alone in hysterectomized women and estrogen-progestin in women with intact uterus for women reporting menopausal symptoms (mainly hot flashes) across menopausal transition and beyond. The benefit-risk ratio for menopausal HT is favorable during the years close to menopause (the so-called "window of opportunity") but decreases with aging and with time since menopause in previously untreated women [68,70,71]. Estrogen or estrogen/progestin therapy should be used at the lowest dose for the shortest duration that meets treatment goals. Any woman treated with ET or HT requires ongoing monitoring, which should include annual breast and pelvic examinations, mammography, and evaluation of abnormal bleeding.

Benefits and Risks of Low Dose Vaginal ET (Level 2 Evidence)

Vaginal estrogen preparations are effective and generally safe for treating urogenital atrophy and can improve vaginal lubrication and reduce dyspareunia [72,73]. Vaginal ET products include CE, estriol (not available in the U.S. market), and E2 at doses to avoid systemic absorption [74]. Vaginal E2 is contraindicated in women with a history of breast cancer because of the risk of increases in circulating estrogens [75,76]. All of the low-dose vaginal estrogen products are equally effective at the recommended doses. The choice of therapy should be guided by clinical experience and patient preference. Local ET should be continued for women as long as bothersome symptoms remain.

Evidence from Studies of Women with Premature Ovarian Failure (POF) (Levels 2 and 3 Evidence)

Evaluating the effects of estrogens on sexual function using models other than natural or surgical menopause is difficult. POF, menopause prior to the age of 40 years results in estrogen deficiency symptoms, but with the added psychological burden of unanticipated menopause and infertility. T levels also are lower, further complicating the assessment of the role of estrogens in sexuality in women with POF. In addition, POF may be associated with other autoimmune diseases, or be because of chemotherapy, pelvic surgery or radiation. The associated psychological burden and the underlying disease may independently alter sexual function.

Sexual well-being was compared in 81 women with POF and 68 age-matched control women with regular menstrual cycles [77]. Forty-eight of the women with POF (59%) were using HT. As expected, women with POF not using HT had significantly lower levels of E2 than HT users, whereas those using HT had lower bioavailable T levels than HT nonusers, likely caused by the effects of oral ET on SHBG. Overall, women with POF were less satisfied with their sexual life. They had fewer sexual fantasies, masturbated less frequently, and reported less arousal, lubrication, and increased genital pain during sexual activity. Sexual desire and frequency were similar to control women, although sexual satisfaction was lower [77]. Women with POF reported more anxiety, depression, somatization, sensitivity, hostility and psychological distress. HT users had higher scores for anxiety, depression and psychological distress than non-HT users, without differences for sexual activities, problems and satisfaction. A limitation

of the study is that women with problems may be more likely to elect HT use.

Evidence from Women with Hypothalamic Amenorrhea (Level 4 Evidence)

Women with hypothalamic amenorrhea experience estrogen deficiency because of the lack of hypothalamic–pituitary function and anovulation [78–81]. There may be urogenital atrophy, but vasomotor symptoms do not usually occur. Hypothalamic amenorrhea typically is caused by excess stress, intensive exercise, eating disorders, or other physiologic or psychologic conditions. Sexual function has been poorly investigated in these conditions. As HT typically is given to young women with hypothalamic amenorrhea to preserve bone mineral density, maintenance of vaginal health would be an expected benefit. No intervention studies, however, have been performed on the effects of HT on sexual function in women with hypothalamic amenorrhea.

Evidence from Women Using Hormone Antagonists or Agonists

Selective Estrogen Receptor Modulators (SERMs) and Sexual Dysfunction (Levels 2 and 3 Evidence)

Tamoxifen and raloxifene are SERM with estrogen agonistic activities on bone and antagonistic activities on breast [82]. Tamoxifen is used in the treatment of patients with breast cancer and for chemoprophylaxis in high risk women. Tamoxifen causes estrogenic changes in the vaginal epithelium [83,84], increased vaginal discharge [85], but can also cause pain, burning, or discomfort with intercourse [86]. Tamoxifen increases SHBG [87]. In breast cancer survivors older than age 50 years, tamoxifen did not worsen sexual function [88]. Major confounding influences related to sexual dysfunction in breast cancer survivors include concerns about relationships, depression, and increasing age [84].

Raloxifene is a newer SERM currently approved for the prevention and treatment of postmenopausal osteoporosis, and the prevention of breast cancer in high-risk women [82]. Raloxifene also increases SHBG levels. In healthy postmenopausal women, raloxifene lowered neither total nor free T, or DHEAS levels (Shifren et al., unpublished observations). Others, however, found modest changes in prohormones and adrenal steroids after 1 year of raloxifene [89]. The effects on sexual function was assessed in a sub-

study of a large, multicenter, randomized controlled trial (RCT) of the effects of 3 years of raloxifene on 600 postmenopausal women with osteoporosis compared with 300 receiving PL [90]. No differences between groups were observed in sexual desire, frequency, enjoyment, satisfaction, orgasm, or sexual problems. The effects of local vaginal ET with and without concurrent raloxifene were examined in two RCTs. In women treated with either conjugated estrogen cream [91], or an E2 vaginal ring [92], raloxifene vs. PL treatment resulted in similar improvements in signs and symptoms of vaginal atrophy, suggesting raloxifene did not block local E effects.

Aromatase Inhibitors (AIs) and Sexual Dysfunction (Level 4 Evidence)

Examining the effects of AIs is an interesting way to try to understand the impact of estrogen deficiency on female sexuality. Inhibiting the conversion of androgens to estrogens in postmenopausal women results in profound hypoestrogenemia by eliminating peripheral estrogen synthesis [93]. Limitations of this model are that these subjects are being treated for breast cancer. This diagnosis and the effects of chemotherapy, radiation, and mastectomy also have independent effects on sexual function. Women using AIs commonly experience urogenital atrophy, dyspareunia, and bothersome vasomotor symptoms and arthralgias. As ET is contraindicated, treatment of hot flashes with nonhormonal alternatives and regular use of nonhormonal vaginal moisturizers and lubricants is advised to improve sexual function in these women. Until such time as additional safety data are available on the effects of vaginal estrogen in women on AI therapy, routine use of local estrogen in women on AIs cannot be recommended.

Oral Contraceptive Use and Sexual Function (Level 2 Evidence)

Oral contraceptives used by premenopausal women comprise supraphysiologic levels of estrogens in combination with supraphysiologic progestins of variable androgenic activity to block ovulation [94]. The estrogenic components increase SHBG. Some have argued that the nonandrogenic progestins increase SHBG further and some suggest that these compounds may in turn decrease free T levels and impact on female sexual function [95]. Comparison studies across OCPs are limited with few prospective randomized controlled studies [96–98]. Over the years changes in dose and types of both estrogens and progestins confuse the issue. Clinically, practitio-

ners may choose to change the type of OCP administered in a premenopausal woman with sexual dysfunction.

Tibolone as Postmenopausal Therapy and Sexual Function (Levels 1 and 2 Evidence)

Tibolone is a synthetic steroid not available in the United States that is metabolized to two estrogenic metabolites, 3α and β , which then circulate predominantly in their sulfated inactive forms [99,100]. These metabolites become estrogenically active when desulfated by the sulfatase enzyme in target tissues. Tibolone itself and its 3β metabolite are also converted to a $\Delta 4$ -isomer that can activate both the progesterone and androgen receptor. Tibolone lowers SHBG and increases circulating FT, adding to its androgenicity [101]. Tibolone alleviated postmenopausal vasomotor symptoms and improves urogenital atrophy by increasing the vaginal maturation index [102,103], and was effective in postmenopausal women with symptoms of sexual dysfunction [99,104–106]. In a recent multicenter, double-blind, randomized, clinical trial, tibolone improved sexual well-being in postmenopausal women with low libido with improvements in desire arousal, satisfaction, and receptiveness compared with those receiving transdermal estrogen–progestin therapy [107]. Some concerns have been raised regarding the use of tibolone and risk of ischemic stroke in women over 60 years [100].

Recommendations

Based on a systematic review of the clinical trials evidence of estrogen therapies for treating sexual problems in women, we conclude the following:

- The decision to institute any hormonal therapy must be individualized and the patient adequately informed about risks and benefits (Grade A).
- ET may improve sexual function in those postmenopausal women with vaginal atrophy (Grade A).
- A significant effect of estrogens on sexual interest, arousal and orgasmic response, independent of its role in treating menopausal symptoms, is not supported by the majority of current evidence (Grade B).
- Tibolone is effective for the treatment of menopausal symptoms and vaginal atrophy, and in many women results in improved sexual function (Grade A). Potential risks of treatment,

including a possible increased risk of ischemic stroke, must be balanced against potential benefits.

- Women with premature menopause should use HT until the age of natural menopause, unless medically contraindicated (Grade C) [71,108].

Based on expert opinion, findings from various studies and understanding of hormone physiology and pathophysiology, we conclude the following:

- Because of the known potential risks, systemic ET may be recommended for the treatment of bothersome vasomotor symptoms in healthy menopausal women, whereas local vaginal ET may be preferred for the treatment of isolated vaginal symptoms (Grade A).
- As oral ET results in increased levels of SHBG and resulting low FT levels [109], transdermal ET may be considered when ET is elected and sexual function is a concern, although no RCTs to date have compared sexuality with oral vs. transdermal ET (Grade C).

Role of T in Female Sexual Function and Dysfunction: Evidence from Low T States and Effects of T Treatment

Evidence from Population-Based Epidemiologic Studies (Level 3 Evidence)

If androgens serve an important role in female sexual function, then clinical states associated with decreased androgens should be associated with sexual problems including low desire, arousal, and orgasmic response. Low androgen states include aging, surgical menopause, POF, hypopituitarism, and adrenal insufficiency. Although natural menopause is not associated with an abrupt decline in androgen concentrations, menopausal women have decreased T levels compared with younger women because of aging [42].

Observational studies assessed the effects of age and menopausal status on sexual function. A population-based study estimated the prevalence of self-reported sexual problems accompanied by personal distress in approximately 31,000 U.S. women aged 18 years and older. Although low desire, arousal and orgasm difficulties increased with age, distressing sexual problems peaked in women aged 45–64 years and actually were lowest in the elderly women [51]. A community-based, cross-sectional study of approximately 3,500 European and U.S. women showed that the prevalence of low desire increased with age, whereas the proportion of women distressed about their low

desire decreased with age [110]. A survey of 2207 U.S. women, using the same validated questionnaire, confirmed an increased prevalence of low sexual desire with increasing age, and among surgically and naturally menopausal women compared with premenopausal women. Distress about low desire in older and younger women with relatively recent BSO was similar to age matched women with intact ovaries. Women older than 45 years who underwent oophorectomy prior to menopause had fewer complaints of low desire as compared with women of similar age but with intact ovaries [111].

Several population based studies have assessed the direct relationship between T levels and sexual function. In a population-based, longitudinal study, 438 Australian women were studied for 8 years across the menopausal transition [61]. Sexual responsiveness was adversely affected by both aging and the menopausal transition, but all other aspects of sexual function, including frequency and libido, were adversely affected by becoming postmenopausal. In a cross-sectional analysis of data from 201 women aged 48–58 years in this same cohort, sexual responsiveness again declined with age, but T levels were not associated with any aspects of female sexual functioning [112]. A limitation of this study is that T was measured by a kit that lacked the sensitivity to measure T levels <20 ng/dL, commonly seen in women over the age of 45 years. A study of androgen concentrations and self-reported sexual function in a community-based, cross-sectional study of 1,423 Australian women ages of 18 to 75 years [46] found no clinically significant relationships between a low score on any domain of sexual function and a low total T, FT, or androstenedione level. There were associations between a plasma DHEAS level below the 10th percentile and low scores on several sexual function domains; however, the majority of women with low DHEAS levels did not have low sexual function [46].

Evidence from Observational Studies in Oophorectomized Women (Levels 2 and 3 Evidence)

To evaluate the isolated effects of T loss, oophorectomized/hysterectomized women should receive ET and be compared with hysterectomized women who retain their ovaries. However, the indications for surgery, the surgical procedures, the decision to keep or remove the ovaries and the accompanying estrogen deficiency or ET all may impact sexual function postoperatively. In the Maryland Women's Health Study, over 1,000

women were interviewed before and after hysterectomy [37]. Despite the fact that approximately 44% had concurrent BSO, significant improvements in sexual functioning postoperatively were noted. Oophorectomy, however, was associated with a 2.7-fold increase in the likelihood of not experiencing orgasms 12 months postoperatively [37]. Similar results were found in a retrospective Swedish study of approximately 700 women under age 55 years who underwent hysterectomy for benign disease. Although the majority of women reported an improved sexual life following hysterectomy, oophorectomized women receiving ET were significantly less likely to report improvement and more likely to report a worsening than non-oophorectomized women [38].

In a retrospective study that controlled for postoperative ET use, approximately 100 women between the ages of 47 and 55 years were evaluated 2–6 years following hysterectomy [45]. No differences in frequency of intercourse or orgasm, dyspareunia, arousal, or partner satisfaction was observed between groups. The only difference noted was decreased pleasure from intercourse in the oophorectomized women. No correlations were found between sexual function variables and androgens, including total T, free T, androstenedione (A), or DHEAS. A prospective, observational study of the effects of oophorectomy on sexual function in 362 perimenopausal women scheduled for elective hysterectomy for benign diseases also identified lower postoperative sexual function scores in women who underwent concurrent BSO compared with women with intact ovaries [55]. Interestingly, sexuality scores were unchanged by surgery in the hysterectomy plus BSO group, so these differences were all caused by lower preoperative sexuality scores in women electing BSO. In addition, there were no correlations between changes in androgen levels postoperatively and changes in sexuality measures. Two further prospective studies failed to show a worsening of sexual function after elective hysterectomy in women followed for 3 years [113,114].

In a national sample of approximately 952 U.S. women with sexual partners, the prevalence of HSDD was compared between premenopausal, naturally postmenopausal, and surgically postmenopausal women [115]. Although the prevalence of HSDD was significantly greater in young surgically postmenopausal women (aged 20–49 years) than in age-matched premenopausal women, there was no significant difference in HSDD prevalence between surgically and natu-

rally postmenopausal women, aged 50–70 years. Observational studies of oophorectomized women, therefore, are not generally consistent with the hypothesis that decreased T levels affect sexual function in women.

Evidence from Clinical Trials of T Therapy in Postmenopausal Women (Level I Evidence)

Two Cochrane reviews have examined the benefits and risks of T plus HT vs. HT alone for peri- and postmenopausal women. The most recent analysis included 35 studies with 4,768 participants [116,117]. Most trials included only postmenopausal women, both naturally and surgically menopausal. Many different T regimens were examined, both pharmacologic and physiologic dosing regimens. The median study duration was 6 months (range 1.5–24 months). The major methodological limitations described were differences in diagnostic criteria for study entry, a lack of a washout period in the crossover studies and attrition bias. The pooled estimate from the clinical trials suggested that the addition of T to HT regimens improved sexual function scores and number of total satisfying sexual episodes in postmenopausal women who were able to have some (two to three/month) satisfying sexual episodes at baseline [117]. Beneficial effects were seen for the composite sexual function score and domains of sexual activity, coital frequency, responsiveness, and libido. Adverse effects included decreases in high-density lipoprotein cholesterol levels with oral therapy that was not observed with transdermal treatment and increased incidence of excess hair growth and acne. Discontinuation from treatment was similar between groups. There was insufficient evidence of a treatment effect for perimenopausal/premenopausal women or for other outcomes examined, including well-being, fatigue, menopausal symptoms, cognition, body composition, and bone health. Another large review of safety data also concluded that except for hirsutism and acne, the therapeutic administration of T in physiologic doses was safe for up to several years [118].

Several recent clinical trials add clarification of the role for T therapy in improving female sexual function. A series of double-blind, randomized, PL-controlled studies examined the efficacy and safety of a transdermal T patch (300 mcg) in postmenopausal women with HSDD [119,120]. Two multicenter trials evaluated 24 weeks of T patch treatment in over 1,000 surgically menopausal women with HSDD receiving concomitant ET. At baseline, women reported approximately three sat-

isfying sexual episodes in 4 weeks, with a mean increase of approximately two events in T-treated women, compared with an increase of one satisfying event with PL. A 450-mcg patch, however, did not confer benefit beyond PL [121] suggesting the lack of a dose response effect of the T patch.

In addition to increased sexual activity, significant improvements were seen in all domains of sexual function in T-treated women compared with PL, including desire, arousal, orgasm, pleasure, concerns, responsiveness, sexual self-image, and distress. More women receiving T reported a “meaningful overall benefit” compared with PL-treated women. Despite the low absolute change in satisfying sexual events, the degree of benefit seen with T therapy in these studies was “clinically meaningful” to women [122].

Adverse event profiles were similar except for a higher incidence of unwanted hair growth in T-treated women. Other androgenic adverse events such as acne, alopecia or voice deepening were more common in T-treated women, though not statistically significant. The safety and efficacy of transdermal T (300 mcg) for 24 weeks was also studied in a double-blind, PL-controlled, randomized trial of 549 naturally menopausal women with HSDD on concomitant ET. Total satisfying sexual episodes increased significantly from baseline in T-treated women compared with PL (2.1 episodes vs. 0.5) [123]. Small but statistically significant improvements also were seen in all domains of sexual function assessed, including sexual desire and personal distress.

As almost all studies of T therapy were performed in the setting of concurrent ET, a double-blind, PL-controlled trial examined the safety and efficacy of T treatment for HSDD in 814 postmenopausal women not receiving ET [124]. Women were randomized to 150 or 300 mcg of transdermal T per day or PL; efficacy was measured to week 24 and safety to week 52. The increase in the 4-week frequency of satisfying sexual episodes was significantly greater in the women receiving 300 mcg T per day compared with PL (2.1 episodes vs. 0.7), although not in the group receiving the lower T dose (150 mcg per day) [124]. Both doses resulted in significant increases in desire and decreases in distress compared with PL. Androgenic adverse events, principally unwanted hair growth, was higher in the women receiving 300 mcg T compared with PL, although rates of acne, alopecia and voice deepening were similar among the three groups [124]. Vaginal bleeding was more common in the

300 mcg T group, though no cases of endometrial hyperplasia or carcinoma were diagnosed. There were no differences between groups in vital signs or weight, serum lipid, or lipoprotein profiles, measures of carbohydrate metabolism, liver function, or other laboratory tests. Breast cancer was diagnosed in four women who received T, as compared with none who received PL ($P = \text{NS}$).

Transdermal T has been studied in only limited populations of premenopausal women with HSDD [125]. Premenopausal women ages 30–45 years with HSDD were randomized to treatment with a T cream (10 mg/day) vs. PL in a double-blind crossover study for 12 weeks with a 4 week washout. Thirty-one women completed the study. T treatment resulted in statistically significant improvements in the composite scores and many subscale scores of both the Psychological General Well-Being Index and the Sabbatsberg Sexual Self-Rating Scale. Resulting T levels were in the high normal to high range. In a larger RCT, 261 women age 35 to 46 years were randomized to PL or three different doses of a transdermal T spray [126]. Over the 16 weeks treatment period, the two higher doses were associated with a significant increase in satisfactory sexual events compared with PL.

Variable recommendations by international medical societies concerning T therapy in women have been published. In 2005, The North American Menopause Society concluded that postmenopausal women with decreased sexual desire associated with distress and with no other identifiable cause may be candidates for T therapy [127]. Transdermal formulations were preferred over oral products because of the absence of first-pass hepatic effects. Treatment was contraindicated in women with breast or uterine cancer, or in those with cardiovascular or liver disease. Women should be informed of all potential risks and that data on long-term use were lacking, suggesting administration at the lowest dose for the shortest time. The “limited use” of T therapy is confusing as the presumed need for treatment is long term as women tend to remain sexually active as long as they have a functional partner. In 2006, The Endocrine Society concluded that although there was evidence for short-term efficacy of T patches in selected populations, generalized use of T by women was not recommended because of inadequate indications for treatment and the lack of evidence of safety in long-term studies [128].

International drug regulatory agencies have conflicting opinions regarding the approval of

androgen therapy for women. An advisory panel of the United States Food and Drug Administration did not recommend approval of the transdermal T patch for surgically menopausal women, principally because of concerns regarding the absence of information on long-term safety. The European Commission approved the Intrinsa T patch (300 mcg) in July 2006 for use in the United Kingdom and European Union for surgically menopausal women with HSDD on concurrent ET (<http://www.emea.europa.eu/humandocs/PDFs/EPAR/livensa/063006en1.pdf>).

More recently in 2009, the British Drug and Therapeutics Bulletin recommend against the routine use of the T patch.

Summary of Evidence on T Treatment for HSDD

Evidence from double-blind, randomized, PL-controlled trials support the efficacy and short-term safety of the T patch in surgically and naturally postmenopausal women with HSDD. The majority of data are from large multicenter trials of the transdermal T patch (300 mcg). Of note, women in these clinical trials were carefully selected with exclusion of women with other medical conditions, psychiatric disorders, dyspareunia, or using antidepressants; thus, findings may not extend to these populations. Use of T alone in estrogen deficient postmenopausal women has shown effectiveness in short-term studies, but long term this regimen would result in a nonphysiological E-to-T ratio. Long-term risks of an unopposed T patch are unknown. Regarding risks, androgenic adverse events appear to be increased with T use, but unwanted hair growth and acne are cosmetic problems, which are easily recognized, treated, and resolve with cessation of therapy. Of greatest concern are as yet unknown long-term risks of T treatment in women, including cardiovascular disease and breast cancer. Several thorough reviews of relevant basic science research and observational studies address the potential effects of T therapy on breast cancer risk with different conclusions [129–131].

Several epidemiologic studies have raised the concern of the associations of higher T levels in aging women with increased cardiovascular risk. In the Women’s Health Study, lower SHBG and higher free androgen index as a measure of free T correlated with hyperglycemia and risk of cardiovascular risk [132]. In the SWAN, a longitudinal 9-year study of 949 subjects, an increase in bioavailable T was associated with increased risk of the metabolic syndrome (MetS) [133]. Similarly in

a cohort of 390 postmenopausal women enrolled in the Women's Ischemia Syndrome Evaluation study of women evaluated for cardiac ischemia, history of prior irregular menses and current biochemical hyperandrogenemia was associated with more angiographic CAD and worsening cardiovascular event free survival [134]. Bell et al., however, showed a relationship with SHBG and cardiovascular risk variables, but not free T [135]. These epidemiologic data may reflect the detection of an aging cohort of women with prior premenopausal hyperandrogenism and its associated insulin resistance. However, further studies are needed to balance the potential benefits and risks of long-term T therapy in postmenopausal women.

Recommendations

Based on a systematic review of the clinical trials' evidence of androgen therapies for treating sexual problems in women, we conclude the following:

- The decision to institute any T therapy must be individualized and the patient adequately informed about known and potential risks and benefits (Grade A).
- T patch therapy increases satisfying sexual activity, libido, arousal, and orgasmic response in postmenopausal women with HSDD (Grade A).
- Long-term safety data for T therapy are lacking, so additional safety data are required before long-term use of T therapy in women can be recommended (Grade C).
- Current data are not adequate to support the use of T therapy in premenopausal and perimenopausal women (Grade A).
- Achieving physiological free T levels by transdermal delivery appears to be the best approach for minimizing the adverse effects of androgens (Grade C).
- Relative contraindications to T therapy include androgenic alopecia, seborrhea or acne, and hirsutism (Grade C).
- T therapy is relatively contraindicated in women with hyperlipidemia or liver dysfunction (Grade C).
- T therapy is contraindicated in women with, or at high risk for, breast cancer, endometrial cancer, or cardiovascular disease, pending additional safety data. The safety of T therapy in women with or at high risk for cardiovascular disease, venous thrombotic event, or breast cancer is unknown (Grade C).

Based on expert opinion, findings from various studies, and understanding of hormone physiology and pathophysiology, we conclude the following:

- Any woman treated with androgen therapy requires ongoing monitoring, which should include annual breast and pelvic examinations, annual mammography, and evaluation for any abnormal bleeding. When T therapy is given, continuation for longer than 6 months should be contingent on a clear improvement in sexual function and satisfaction and absence of any adverse effects, considering the substantial PL effects found in all studies to date. Women must be informed that data on long-term safety are lacking. Physical examination at follow-up visits should include inspection of skin and hair for seborrhea, acne, hirsutism, and androgenic alopecia which may appear very gradually. Laboratory monitoring should include total T and SHBG levels, and a calculated value for FT, with the goal of keeping these values within the normal range for premenopausal women. Whether a lower target level for older women should be advised remains unknown. Although no adverse effects on lipids have been found with short-term parenteral therapies, a lipid profile and metabolic screening should be considered.

Endocrine Disorders: Effects on Female Sexual Function

Hypopituitarism (Level 2 Evidence)

Evidence that Supports the Influence of Pituitary Hormone Deficiencies on FSD

Hypopituitarism is defined as multiple pituitary hormone deficiencies, either genetic or commonly after removal of a pituitary and/or hypothalamic tumor or radiation [136]. Combination of sex hormone, thyroid hormone, glucocorticoid and/or growth hormone deficiency may occur and require physiologic replacement. There are limited studies concerning sexual function in these patients. A 12-month randomized study in 51 women with hypopituitarism demonstrated improvements in mood and sexual function in addition to increased bone density, fat-free mass, quality of life but not cognitive function in women randomized to T patch [136]. These women had variable forms of estrogen replacement with either oral contraceptives or low dose ET. Side effects included one-third with hirsutism and 65% with skin irritation caused by the patch. Thirty-eight

women with hypopituitarism on standard hormonal replacement were randomized to DHEA (30 mg/day if <45 and 20 mg/day if >45) or PL for 6 months [137]. Women on DHEA had improved alertness, stamina, and initiative as perceived by their partners and a trend toward improved sexual relations ($P = 0.06$). Increased interest in sex or activity at 6 months was noted in 50% of women receiving DHEA 30 mg/day but none receiving 20 mg/day. These data support a modest effect of aromatizable androgens or androgen and estrogen precursors (i.e., DHEA) on sexual function in women with hypopituitarism after optimization of standard hormonal therapies. Whether the effects are caused by androgenic, estrogenic actions, or both is unknown.

Recommendations

Women with hypopituitarism have profound estrogen and androgen deficiency and should be considered for therapy with ET and T therapy at least until the age of natural menopause, unless medically contraindicated (Grade B).

Hyperprolactinemia (Levels 2 and 3 Evidence)

Evidence that Supports the Influence of Elevated Levels of Prolactin on FSD

Hyperprolactinemia may be caused by physiologic, pharmacologic, or organic causes [138]. Elevated levels of prolactin (PRL) inhibit gonadotropin-releasing hormone pulsatility and thus ultimately decrease ovarian hormone secretion (estrogens, androgens). Hyperprolactinemia is observed in primary hypothyroidism and commonly with medications that inhibit dopamine tone such as the antidepressants and serotonin reuptake inhibitors [138,139]. Elevated prolactin may alter libido via direct neuroendocrine effects (impaired negative dopaminergic and positive serotonergic control of PRL release) and indirect endocrine mechanisms (i.e., secondary effects of hypoestrogenism) [140]. Although menstrual disturbances are a more common symptom than sexual dysfunction, hyperprolactinemic women without depression or other hormonal disorders reported lower scores for sexual desire, arousal, lubrication, orgasm, and satisfaction in comparison with controls [141]. Hulter et al. observed that 79.2% of 48 women with pituitary disease had a decrease in sexual desire, whereas problems with lubrication and orgasm were reported in 64.6% and 68.7%, respectively [142]. However, neither prolactin or T levels, but instead a normal pattern of menses, young age and intra-sellar tumor cor-

related with normal sexual desire and sexual function. In 109 women with hypothalamo-pituitary disorders, 62.4% had decreased sexual desire [142]. Altered sexuality was reported in 84.1% of the hyperprolactinemic women, but only in 32.6% of women with normal serum prolactin. Despite these observations, PRL-normalizing agents (bromocriptine, cabergoline) have not been evaluated as to potential beneficial effect on FSD [143].

Antipsychotic and neuroleptic drugs reduce sexual drive and may cause anorgasmia, in part related to drug-induced hyperprolactinemia, as demonstrated by less sexual dysfunction in patients treated with the so-called PRL-sparing drugs in comparison with those with a higher incidence of PRL elevation [144,145]. Antidepressant agents such as SSRIs may induce hyperprolactinemia and therefore impact negatively on sexual function [146,147]. Decreased sexual drive and orgasmic disorder [148,149] have been reported. These studies are limited by few containing proper control groups, variable dosages of agents, and variability in underlying mood disorder.

Recommendations

Women with hyperprolactinemia may develop sexual dysfunction, especially loss of sexual drive and impaired orgasm, but it is unclear if these symptoms are independent of associated estrogen deficiency (Grade B). Studies are lacking to prove that lowering circulating prolactin levels improve sexual function in women.

Thyroid Dysfunction and FSD

Although the literature is replete on the effects of both hypo- and hyperthyroidism on menstrual cyclicity and fertility [150–152], there are no clinical studies on the effect of thyroid disorders on female sexual function. This is an area for future research.

Effects of Adrenal Disease on Sexual Function

Adrenal Prohormones

DHEA is produced by the ovaries and adrenal glands whereas its sulfate ester, DHEAS is produced primarily by the zona reticularis of the adrenal cortex [30,153]. Together, DHEA and DHEAS are the most abundant steroids in plasma, providing a large precursor reservoir for the intracellular production of androgens and estrogens in nonreproductive tissues. Thus DHEA and DHEAS are not androgens (i.e., bind to the androgen receptor to activate transcription) but are precursor hormones that are metabolized to

androgens and estrogens in the brain, bone, breast, and adipose tissue [154]. Serum levels of both DHEA and DHEAS decline with age in women independent of menopausal age [56].

Adrenal Insufficiency and Sexual Dysfunction (Level 4 Evidence)

Primary adrenal insufficiency is characterized by abnormally low, serum concentrations of DHEA and DHEAS. Secondary adrenal insufficiency is caused by the loss of pituitary ACTH production and may be isolated or with low T levels because hypopituitarism results in combined ovarian and adrenal insufficiency [155]. Adrenal insufficiency, irrespective of cause, has been associated with impaired quality of life, low libido, and lack of well-being. However, there are no data comparing sexual function in women with adrenal insufficiency with normal age-matched controls using validated questionnaires.

Clinical trials of DHEA Therapy in Adrenal Insufficiency (Level 1 Evidence)

There are few, small studies of DHEA treatment to improve sexual well-being in women with adrenal insufficiency. In Addison's disease [156,157]. An RCT of DHEA 50 mg/day vs. PL in 24 women demonstrated no improvement in sexual function [156]. Arlt et al. randomized 24 women with primary (N = 14) and secondary (N = 10) adrenal insufficiency to treatment with either 50 mg oral DHEA daily for 4 months or PL in a double-blind, crossover trial [158]. Improvements in sexual function (thoughts, interest, and satisfaction measured by a visual analog scale) and mood were reported. However, more recent randomized studies have not shown benefit. A randomized controlled trial of DHEA 50 mg/day vs. PL for 12 months in 62 women showed no improvement in sexual function measured by a visual analog scale [157]. Similarly, other groups reported no benefit of DHEA, 25 mg/day for 9 months, on sexual function using the Norwegian version of the McCoy's Sex Scale Questionnaire in a PL-controlled, parallel group trial involving 39 women with primary and secondary adrenal insufficiency [159]. A PL controlled trial for 6 months followed by a 6-month open-label phase of 38 women with hypopituitarism and secondary adrenal insufficiency suggested that 20–30 mg of DHEA/day increased sexual interest and activity only during the open-label phase with no significant change in quality of life in either phase of the trial [137]. No effect of DHEA 50 mg/day on

sexual function was found in a double-blind crossover study of 15 patients with secondary adrenal insufficiency [160].

Recommendations

DHEA therapy is not currently recommended for women with primary or secondary adrenal insufficiency: the majority of clinical trials of DHEA replacement in women with primary or secondary adrenal insufficiency do not show any benefits on sexual function (Grade A).

Evidence from Women with Androgen Insensitivity Syndrome (Level 4 Evidence)

There are limited data concerning the sexual function of XY males with androgen insensitivity caused by the mutations in the androgen receptor [161,162]. These subjects are phenotypically female with normal breast development, but variable shallow vaginal development which may impair sexual performance. Limited retrospective case series suggest these subjects have a heterosexual orientation and normal libido and orgasmic response under the influence of high estrogens with complete or partial absence of androgen action at all target tissues. This model suggests that androgens are not necessary for normal sexual function.

Hormonal Excess States

Polycystic Ovarian Syndrome (PCOS); Level 3 Evidence

Current State of the Field

PCOS is the most common cause of female hyperandrogenism, occurring in 5–10% of premenopausal women [163]. Clinical manifestations of androgen excess (e.g., hirsutism, acne, seborrhea, alopecia, etc.) together with obesity and infertility may cause emotional distress, but data are limited concerning psychosocial and sexual functioning in PCOS [164]. An increased risk for depressive disorders, particularly in women with higher BMI and evidence of insulin resistance, has been recently outlined. Anxiety, vulnerability to distress, abnormal eating attitudes coupled to body dissatisfaction and low self-esteem, and quality of life have been also reported. In addition, PCOS women seemed to be less satisfied with their sex life and found themselves less attractive, presumably because of being frequently overweight and suffering from cosmetic androgen-related symptoms [165,166]. The relationship between androgen excess in PCOS and

sexual function has been difficult to study, probably as a consequence of the comorbid conditions that confound outcome measures. Indeed, PCOS women display a similar partner status and frequency of sexual intercourse in comparison with controls [167].

A recent study by Battaglia et al. [168] failed to demonstrate any significant difference in clitoral circulation between women with PCOS and controls. Moderate hirsutism and hyperandrogenism in these women did not induce a sense of loss of feminine identity and had no impact on sexual self-worth and sexual satisfaction. Treatment of women with androgen excess using antiandrogens has produced mixed results in a small case series of women presenting with hirsutism (increased desire in six women and decreased desire in 13 women) [169], whereas the use of the insulin sensitizer, metformin, improved the psychosocial, emotional, and psychosexual situation of PCOS women [170], presumably because of the reduction in other clinical symptoms.

Recommendations

Overweight women with PCOS may have an increased incidence of sexual dysfunction mainly because of emotional difficulties related to clinical manifestations of androgen excess and obesity (Grade C/D). These data have not been confirmed in lean PCOS women, suggesting that moderate hyperandrogenism alone may not significantly modulate sexual function. Further research is needed to understand if normalizing androgen excess and/or insulin resistance would improve sexual function in PCOS women.

Sex Hormone-Producing Tumors (Levels 3 and 4 Evidence)

Many kinds of ovarian tumors produce estrogens or androgens. Sertoli-Leydig cell tumors is an example of an androgen-producing tumors that cause virilization [171]. Conversely, granulosa cell tumors and thecomas are well-known estrogen-producing tumors. Pediatric or postmenopausal women with estrogen-producing tumors present with postmenopausal bleeding or isosexual precocity. Other forms of sex hormone producing tumors are extremely rare [172]. Androgen excess from these tumors might be expected to result in a state of hypersexuality in women, but no studies on sexual function are available in women with sex hormone producing tumors [173]. Thus, this is an area for further research.

Congenital Adrenal Hyperplasia (CAH; Levels 2 and 3 Evidence)

CAH refers to a family of inherited disorders in which defects occur in one of the enzymatic steps required to synthesize cortisol from cholesterol in the adrenal gland [174]. In 21-hydroxylase deficiency (21OHD), responsible for 90–95% of CAH cases, accumulation of precursors immediately proximal to the 21-hydroxylation step in the pathway of cortisol biosynthesis are shunted into androgen precursor pathway. Three forms of 21OHD CAH can be distinguished by clinical, hormonal, and molecular criteria: the classical salt-wasting, classical simple-virilizing, and nonclassical forms. Postnatal androgen excess leads to various hyperandrogenic signs that manifest from childhood to adulthood, depending on the severity of the 21OH enzyme deficiency [174]. Meyer-Bahlburg and coworkers [175] reviewed the sexual orientation in women with classical or nonclassical CAH and reported that most women were heterosexual. The rates of bisexual and homosexual orientation in their subjects were increased above controls in women with classical and nonclassical CAH, and correlated with the degree of prenatal androgenization. Limitations of this report include that this patient cohort was derived from a specialized referral base and may represent a biased group of subjects and lack appropriate controls. Importantly, the sexual functioning of women with non classical 21OHD did not differ from that of controls, unlike women with classical CAH who showed impaired sexual functioning, presumably as a consequence of disturbed body image, repeated genital examination, and surgery [176,177]. Retrospective qualitative data revealed a history of discomfort and social stress related to their extent of masculinization prior to treatment.

Recommendations

Caring for women with CAH requires careful individualized management, including appropriate therapy for their signs and symptoms of androgen excess as well as psychosexual counseling when needed (Grade C).

Chronic Endocrine Disorders

Diabetes (Levels 2 and 3 Evidence)

Current State of the Field

Women with diabetes have many factors potentially contributing to their risk of sexual dysfunction, including vascular, neurogenic, metabolic,

sex hormone, and psychologic abnormalities. Data on the incidence of FSD in diabetic women was recently reviewed by Bhasin and Basson [143]. The literature is limited by few studies with control groups, the poorly validated types of tools used to diagnose FSD, and the changing definitions of FSD from older to newer studies. The authors noted rates of decreased desire ranged from 9–60% in controls to 17–85% in female diabetics, and of decreased arousal from 41% in controls to 76%. Reduced lubrication was about twofold more common in diabetic in all but one study; pain and orgasmic difficulties were more prevalent in diabetics than nondiabetics. Overall dissatisfaction with sexual function ranged from 7–37% in controls to 42–52% in diabetics. A careful dissection of any differences in the incidence of or etiologies of sexual dysfunction in Type 1 compared with Type 2 diabetics was not examined in most studies. Importantly most studies did not separate pre- vs. postmenopausal women and estrogen status was not controlled. Sexual dysfunction was consistently linked to comorbid depression [143].

Several other studies have been published showing similar increased risks of sexual dysfunction in various populations [178,179], suggesting the incidence is independent of cultural norms. Studies have postulated altered reactive oxygen species activity in the mechanism underlying both male and FSD in diabetes [180]. A recent review of the literature of 400 citations concluded that research on sexual function in women with diabetes is limited, but multiple reports suggest that abnormalities in sex hormone levels contribute [181]. In contrast to men with diabetes and erectile dysfunction where the diabetic control and length of the disease correlate with incidence of impotence, no such correlation has been observed in women diabetics with sexual dysfunction. No intervention studies are available concerning changes in sexual function with aggressive treatment of vascular or metabolic derangements in women with diabetes. The impact on sexuality of living with a chronic, serious medical illness, and the confounding effects of obesity in many Type 2 diabetics should not be underestimated.

Recommendations

Women with Type 1 and Type 2 diabetes have an increased incidence of sexual dysfunction that may be caused by metabolic, vascular, neurogenic, hormonal as well as psychological etiologies (Grade

C). No studies are available concerning the impact of improved glucose lipid or hypertensive control or hormonal therapies on the sexual dysfunction in these patients. Thus, these women should be screened for sexual dysfunction. Further research is needed.

Obesity and MetS (Levels 2 and 3 Evidence)

Evidence that Obesity Influences Sexual Function

The MetS is a constellation of findings including central adiposity, insulin resistance, hypertension, and various other clinical features. The International Diabetes Federation consensus definition for MetS includes a waist circumference >80 cm in addition to two of the following factors: triglyceride >150 mg/dL (1.7 mmol/L), decreased high density lipoprotein cholesterol <50 mg/dL (0.9 mmol/L) or treatment for lipids, elevated blood pressure or treatment for hypertension, and/or elevated fasting serum glucose \geq 100 mg/dL (5.6 mmol/L) or known Type 2 diabetes [182]. Esposito initially described an independent effect of the MetS on the incidence of FSD in 100 premenopausal women with MetS compared with controls matched for age and BMI [183]. Sexual function was measured by the FSFI. Ponzolzer and coworkers recently performed a modified German FSD questionnaire on 538 women (mean age 44 years, 61% pre- and 39% postmenopausal women). Of the group, 18% had MetS [184]. FSD prevalence was 4.8% for disorders of low satisfaction and 39% for HSDD. The rate of these disorders increased with transition to menopause. There was no increased risk of disorders of arousal, pain, or orgasm in this cohort. Impaired desire was present in 59% in premenopausal women with MetS compared with 32% of controls. In postmenopausal women, however, there was no effect of MetS on the incidence of FSD. Thus, although age increases the risk of FSD overall, the concomitant presence of MetS had a more profound effect on premenopausal women. No data are available concerning interventions to reverse MetS and incidence of FSD.

Recommendations

Women with MetS may have an increased incidence of sexual dysfunction, which may be caused by vascular, metabolic, neurogenic, hormonal, or psychosocial causes (Grade C). We recommend screening women with MetS for sexual dysfunction and study of treatment interventions; none are currently available in these patients.

Summary and Conclusions

This review has summarized the scientific evidence supporting the mechanisms by which hormonal changes associated with aging and endocrine disorders contribute to sexual dysfunction in women. Data on the impact of hormonal therapies in female sexual disorders has been discussed. Many studies suggest that plasma T and/or E2 concentrations do not correlate with female sexual function or dysfunction. However, the limitations of past and current sex steroid hormone assays and normal reference ranges for women suggest additional studies are needed. The potential importance of intracrinology, i.e., local production and action of hormones, on sexual function and the well-documented age-related decline in substrate precursor hormones remains unclear.

Natural and surgical menopause and endocrine disorders that alter estrogens and androgen precursors may impact female sexual function. The consequences of hormone therapies in these states including, hypothalamic amenorrhea, POF, surgical and natural menopause and chemically induced estrogen deficiency with SERMs and AIs is variable but is indicative of benefits of low dose HT in individual patients. Hypopituitarism, hyperprolactinemia, thyroid disorders, and adrenal insufficiency alter a variety of hormones, each to a variable extent. Data are limited on the effects of therapies with estrogens, T and DHEA in each of these disorders, but they may provide additional model systems for future interventional trials. Studies on the effects of hormonal excess observed in PCOS, hormonally active ovarian or adrenal tumors, CAH and obesity-induced hyperandrogenism do not suggest that excess androgens and/or estrogens per se promote normal or hypersexuality, suggesting that an optimal balance of hormonal milieu is critical to normal sexual functioning. Information on the effects of diabetes and MetS on FSD suggest that the disorder is common in these populations, but no interventional trials have been performed show that improved metabolic control alters female sexual function.

Most importantly, the available literature emphasizes that hormones are only one component of the many factors that contribute to normal sexual function in women. It is hoped that this review of the state of the field will spur new research into the impact of hormones and endocrine disorders on FSD and additional research into the benefits and risks of hormonal therapies for these patients.

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Conflict of Interest: Dr. Wierman has nothing to declare; Dr. Nappi is a consultant to or researcher for Bayer-Schering Pharma, Boehringer-Ingelheim, Merck-Theramex, Novo Nordisk, Procter & Gamble Pharmaceuticals, Schering-Plough/Organon; Dr. Avis has no conflict of interest; Dr. Davis is a consultant to or researcher for Acrux Australia, Astra Zeneca, Bayer-Schering Pharma, Novartis, Procter & Gamble Pharmaceuticals and Schering-Plough/Organon; Dr. Rosner has nothing to declare; Dr. Shifren serves on a scientific advisory board for New England Research Institutes, receives research support from Procter & Gamble Pharmaceuticals, and serves as a research study consultant for Boehringer Ingelheim and Eli Lilly & Co.

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