

Endocrine Aspects of Female Sexual Dysfunction

Susan R. Davis, MD, PhD,* André T. Guay, MD, FACE,[†] Jan L. Shifren, MD,[‡] and Norman A. Mazer, MD, PhD[§]

*NHMRC Centre of Clinical Research Excellence, The Jean Hailes Foundation and Monash University, Clayton, Vic, Australia; [†]Center for Sexual Function/Endocrinology, Lahey Clinic Northshore, Peabody, MA, USA; [‡]Department of Gynecology and Reproductive Biology, Harvard Medical School, Boston, MA, USA; [§]Watson Laboratories, Inc, Salt Lake City, Utah and Department of Pharmaceuticals, University of Utah, Salt Lake City, Utah, USA

Summary of Committee. For the complete report please refer to *Sexual Medicine: Sexual Dysfunctions in Men and Women*, edited by T.F. Lue, R. Basson, R. Rosen, F. Giuliano, S. Khoury, F. Montorsi, Health Publications, Paris 2004.

ABSTRACT

Introduction. Various endogenous hormones, including estrogen, testosterone, progesterone and prolactin, may influence female sexual function.

Aim. To provide recommendations for the diagnosis and treatment of women with endocrinologic sexual difficulties.

Methods. The Endocrine Aspects of Female Sexual Dysfunction Committee was part of a multidisciplinary International Consultation. It included four experts from two countries and several peer reviewers.

Main Outcome Measure. Expert opinion was based on committee discussion, a comprehensive literature review and evidence-based grading of available publications.

Results. The impact of hormones on female sexual function and their etiological roles in dysfunction is complex. Research data are limited as studies have been hampered by lack of precise hormonal assays and validated measures of sexual function in women. Sex steroid insufficiency is associated with urogenital atrophy and may also adversely affect central sexual thought processes. Systemic estrogen/estrogen progestin therapy alleviates climacteric symptoms but there is no evidence that this therapy specifically improves hypoactive sexual desire disorder (HSDD) in premenopausal or postmenopausal women. Exogenous testosterone has been shown in small randomized controlled trials (RCT) to improve sexual desire, arousal and sexual satisfaction in both premenopausal and postmenopausal women. However, as there is no biochemical measure that clearly identifies who to treat, use of exogenous testosterone should be considered only after other causes of HSDD have been excluded, such as depression, relationship problems and ill health. The clinical assessment of HSDD should include detailed medical, gynecologic, sexual and psychosocial history and physical examination including the external/internal genitalia. Hormonal therapy should be individualized and risks/benefits fully discussed, and all treated women should be carefully followed up and monitored for therapeutic side effects.

Conclusions. There is a need for prospective, multi-institutional clinical trials to define safe and effective endocrine treatments for female sexual dysfunction.

Conflict of Interest. S. Davis, Unrestricted research grant support from: Procter & Gamble, Servier, Solvay and Wyeth; Consultant/Advisory Board: Servier, Cellergy, Wyeth, Acrux, Procter & Gamble; Investigator for: Procter & Gamble, Servier, Acrux, Organon.

A. Guay, Research Protocol Participation: Vivus, Macrochem, NexMed, Pfizer, Biosante; Consultant/Advisory Board: Cellegy, Pfizer, NexMed, Lilly-Icos, Bayer; Speaker's Bureau: Pfizer, Unimed-Solvay, Lilly-Icos, Bayer.

J. Shifren, Research support from Watson Labs, Solvay Pharmaceuticals, Procter & Gamble; Pharmaceuticals, Eli Lilly & Co.; Scientific advisory board member for Watson Labs and Eli Lilly & Co.

N. Mazer, Employee and stockholder in Watson Pharmaceuticals, Inc., collaborator to Procter & Gamble Pharmaceuticals, stockholder in GeneLabs Technology, Inc.

Key Words. Endocrine Sexual Dysfunction; Hormone Therapy; Sexual Desire Disorder; Estrogen Therapy; Progesterone Therapy; Testosterone Therapy; Dehydroepiandrosterone Therapy

Background

Sexual activity in women involves interest and motivation, ability to become aroused and achieve orgasm, the pleasure of the experience and subsequent personal satisfaction. All components of the female sexual experience are interdependent and thus impairment of any specific aspect may affect others. Sexual problems experienced by women include:

- i) Low interest or motivation to engage in sexual activity (libido),
- ii) Diminished capacity for vaginal lubrication and arousal,
- iii) Difficulty achieving/or absent orgasm, and/or
- iv) Painful intercourse (dyspareunia).

Usually in the context of a sexual relationship these problems are associated with a decrease in the frequency and pleasure of sexual activity and can become a source of tension and distress for the individual and her partner.

The endogenous hormones that potentially influence female sexuality include estrogens, androgens, progesterone, prolactin, oxytocin, and glucocorticosteroids. These each interact with numerous neurochemicals within the central and peripheral nervous system. The latter include serotonin, catecholamines, dopamine, other neurotransmitters and other hormones. The factors that determine the outcome of these complex interactions include the absolute levels of each hormone, their absolute receptor content, the presence and levels of specific co-activator and co-repressor proteins that modify the transcriptional response and the up or down regulation of receptor levels by other hormones. Hormones also influence vascular function by both endothelium-dependent and independent mechanisms [1].

Conclusions and Recommendations

Clinical Assessment of a Woman Presenting with Lowered Sexual Interest

In defining the problem it is important to determine whether the problem of low libido is causing the women personal distress. The duration of decreased libido and when the women last felt she

had normal libido should be established. Assessment should be nonjudgmental as what is normal for one woman may not be acceptable to another. Evaluation of psychosocial factors as discussed elsewhere is vital; however, the presence of psychosocial components does not exclude a contributing organic component and should not exclude a woman from full biological assessment. All women should be carefully screened for depression as a cause of their sexual difficulties. Similarly the presence of chronic illness does not exclude a hormonal cause. Indeed a hormonal cause may be more likely in women with illness or therapy that causes adrenal suppression.

A complete gynecological history should be taken. History should also identify possible iron deficiency, thyroid disease and galactorrhea.

In premenopausal women adequacy of estrogenization should be evaluated by taking a menstrual history. In the presence of regular cycles (periods every 21 to 35 days) dysfunction of the hypothalamic-pituitary-ovarian axis is extremely unlikely, such that estrogen is usually adequate and prolactin is normal. Amenorrhea prior to the age of 40 years requires full assessment.

A general physical examination should include assessment of thyroid status, presence of anemia or galactorrhea. Gynecological examination should include a pelvic examination with attention to signs of vaginal atrophy, size of introitus, presence of discharge or evidence of infection, vulvodynia and deep tenderness. Evaluation of the vulvar and vaginal tissues on exam relates more closely to sexual function than estradiol levels.

Recommendations regarding the investigations are shown in Table 1. Based on a systematic review of the clinical trials evidence of hormonal therapies for treating sexual problems in women, we conclude the following using standard grading for levels of evidence:

1. The decision to institute any hormonal therapy must be individualized and the patient adequately informed about risks and benefits.
2. Specific therapies:
 - i. Vaginal estrogen preparations are effective and generally safe for ameliorating

- urogenital atrophy and can improve vaginal lubrication and reduce dyspareunia. The risk of endometrial stimulation with vaginal estrogen preparations while uncommon appears to be related to the dose and estrogen type used.
- ii. Systemic estrogen/estrogen progestin therapy alleviates vasomotor and other menopausal symptoms, but are only indicated in symptomatic women.

Oral estrogen increases the risk of venous thromboembolic events (VTE) in the initial years of use. Parenteral therapy appears to have less risk for VTE although this requires confirmation [2].

A set regimen of oral CEE+MPA is associated with an increase in breast cancer risk beyond 5 years use [3]. Oral estrogen alone does not appear to be associated with this risk (http://www.nhlbi.nih.gov/whi/e-a_advisory.htm).

Oral CEE+MPA is associated with an increase in cardiovascular events in the first years of use and this risk wanes over 4 years [4]. Other estrogen regimens and modes of administration and other steroids (tibolone) do not necessarily convey the same risk.
 - iii. Progestins appear to have little impact in either direction on the urogenital effects of estrogen, and have no proven benefit on other aspects of sexuality when given alone.
 - iv. There is increasing use of estrogen +/- progestin therapy after breast cancer.

Table 1 Basic biochemical investigations for women presenting with low libido

General:
• TSH, iron stores
Specific:
"Premenopausal" and amenorrhea:
• Estradiol + FSH (for diagnosis of hypothalamic amenorrhoea/premature ovarian failure)
• Prolactin
Androgen profile:
• SHBG
• Free T by equilibrium dialysis (gold standard)
OR
Total T after organic solvent extraction and calculation of free T*
OR
Total T by RIA (with awareness of limitations) and calculation of free T*
• DHEA-S
• Early morning cortisol: if adrenal insufficiency suspected

* (or calculation of free androgen index: total T nM/SHBG nM × 100 if SHBG in normal range.)

Although there is no evidence that hormone therapy increases either recurrence or mortality from breast cancer, this therapy should be limited to moderate to severely symptomatic women, as for any therapy requires informed patient consent, and management of the patient should be in partnership with the physicians monitoring the woman's cancer.

Based on the available information it is not possible to recommend use of, or avoidance of, specific estrogen +/- progestin therapies, as availability varies considerably between countries, as does the preference of women and the cost. It could generally be recommended that the minimal dose that alleviates symptoms and avoids side effects should be prescribed, and that careful attention to cardiovascular, thrombotic and breast cancer risk and thorough examination should be undertaken before any treatment is prescribed.

- v. Testosterone (T), and its derivatives, appear to be useful in the short term for increasing libido, arousal and orgasm in oophorectomized women already treated with systemic estrogen [5,6]. There is some, but less data from RCTs for use in naturally menopausal women [7], but as the latter have similar T profiles to oophorectomized women when treated with estrogen, they can be considered a continuum of the same physiological state. Given the intracrinology of androgen action clinical outcome is difficult to predict from blood levels alone even if superior assays are available.
- vi. Long-term safety data for T therapy are lacking and long-term safety of exogenous T in women requires study before long term use can be recommended.
- vii. Safety data for the use of T in nonestrogen replaced postmenopausal women are lacking.
- viii. Further data on the use of T in premenopausal women are required.
- ix. Achieving physiological free T levels by transdermal delivery appears to be the best approach for minimizing the adverse effects of androgens. Contraindications to T therapy include androgenic alopecia, seborrhea or acne, hirsutism, pregnancy, lactation as well as a history of polycystic ovary syndrome. Androgen therapy is relatively contraindicated in women with hyperlipidemia or liver dysfunction. The

safety of androgen therapy in women with or at high risk for CVD, VTE or breast cancer is uncertain.

Based on available data no specific T therapy or dose can yet be recommended.

- x. The current evidence for the effectiveness of androgen precursors (DHEA and Andione) is inconclusive. DHEA appears to be less likely to cause virilizing side effects than Andione.
 - xi. Raloxifene appears to have no adverse or beneficial effects on sexual function in postmenopausal women [8].
 - xii. Tibolone may be an alternative to estrogen-androgen therapies for treating sexual problems in postmenopausal women. Further RPCT of the effects of tibolone on sexual function are required.
3. Clinical care: Expert opinion based on findings from various studies and understanding of hormone physiology and pathophysiology:
- Any woman treated with hormonal therapy requires ongoing monitoring which should include regular breast and pelvic examination, mammography and, in the presence of abnormal bleeding, endometrial biopsy.
 - When T is administered, continuation for longer than 6 months should be contingent on a clear improvement in sexual function and satisfaction. The clinician should be mindful of the substantial placebo effects found in all studies to date.
 - Physical examination at follow-up visits should include inspection of skin and hair for seborrhea, acne, hirsutism and androgenic alopecia. These may appear very gradually, even after a year or more of treatment.
 - Laboratory monitoring should include free/bioavailable T levels and SHBG with the goal of keeping these values at least within the normal range for premenopausal women to reduce the likelihood of side effects. Whether in fact a target level for older women should be even lower remains a matter requiring clarification.
 - Although no adverse effects on lipids have been found with short term parenteral therapies, a lipid profile, and, in the presence of a family history of diabetes or significant obesity, fasting insulin and glucose levels should be considered.
 - Additional biochemical investigations such as liver function tests should be based on clinical judgment.

In summary, the hormonal influences on female sexual function requires further investigation including validation of efficacy of T therapy in randomized placebo-controlled clinical trials and research into mechanisms of effects. The verification of female androgen insufficiency syndrome is required. Improved methods for total and free T measurement in the female range are urgently needed with an emphasis on methodology that can be put to routine use. Normal ranges for the various androgens in women by decade and ethnic background need to be established: this is currently being addressed in a large cross-sectional study being conducted in Australia.

Preparations of T specifically designed for use in women are required for use in research in this field and for therapeutic use if indicated. The long-term safety of exogenous T in women requires study before long term use can be recommended, specifically, the incidence and severity of effects on hair and skin need to be assessed by more sensitive measures, and their relation to T preparation and dose needs to be determined.

Acknowledgments

We wish to thank Dr Geoffrey Redmond, Dr James A. Simon and Dr Frank Stanczyk for their critical comments and Dr Henry Burger for his contribution.

Corresponding Author: Susan R. Davis, MD, PhD, Director, NHMRC Centre of Clinical Research Excellence, The Jean Hailes Foundation and Monash University, Clayton, Vic, Australia. E-mail: susan.davis@jeanhailes.org.au

Complete list of references on which these recommendations have been based is published in the full manuscript of the proceedings of 2nd International Consultation on Erectile and Sexual Dysfunctions, Paris, June 28–July 1, 2003.

References

- 1 Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999;340:1801–11.
- 2 Scarabin P-Y, Oger E, Plu-Bureau G, EStrogen and THromboEmbolic Risk Study Group. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. *Lancet* 2003;362:428–32.
- 3 Writing Group for Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 2002;288:321–33.

- 4 Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280:605–13.
- 5 Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, Burki RE, Ginsburg ES, Rosen RC, Leiblum SR, Caramelli KE, Mazer NA. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Eng J Med* 2000;343:682–8.
- 6 Sherwin BB, Gelfand MM. The role of androgen in the maintenance of sexual function in oophorectomized women. *Psychosom Med* 1987;49:397–409.
- 7 Davis SR, McCloud PI, Strauss BJG, Burger HG. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. *Maturitas* 1995;21:227–36.
- 8 Modugno F, Ness R, Ewing S, Cauley J. Effects of raloxifene on sexual function in older postmenopausal women with osteoporosis. *Obstet Gynecol* 2003;10:353–61.