

# The Systemic Nature of Sexual Functioning in the Postmenopausal Woman: Crossroads of Psychiatry and Gynecology

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## Focus Points

- This article reviews the complex nature of sexual function in the postmenopausal woman.
- The four aspects impacting sexual function include interpersonal, psychosocial, psychological, and biological domains.
- The conceptual framework for viewing sexual function parameters as central/brain or peripheral/pelvic is provided.

## Abstract

*How is sexual function affected by menopause? Changes in circulating levels of estrogen and androgens during the peri- and postmenopausal years have a far-reaching impact on sexual symptoms in some women. Many factors influence whether or not a woman experiences a symptom and whether or not she finds it distressful. Likelihood of experiencing sexual symptoms depends on age and menopausal status. For those women who do experience sexual symptoms, and where these symptoms can be attributed to reduced levels of gonadal hormones, the use of estrogen or estrogen plus testosterone replacement therapy can be successful in improving sexual function. However, it is important to recognize that in addition to this biologic etiology of new-onset sexual symptoms in the postmenopausal woman, several nonbiologic domains influence sexual functioning as well. These domains could be thought of as being interpersonal, sociocultural or psychosocial, and psychological in nature. A woman's sexual function depends on the dynamic interplay of these factors. The clinician should identify sexual problems that are of new onset with the menopausal transition and causing distress to the woman; separate biologic from nonbiologic causes of symptoms; and design a treatment plan based on the dynamic interplay of these factors.*

## Introduction

Women seem to be less driven by traditional sexual goals, such as frequency of coitus and orgasm, and appear to be driven more by the interpersonal aspects of sexuality as a means for achieving intimacy.<sup>1</sup> Women also appear to be more distractible and less goal oriented in their sexuality.<sup>2-4</sup> This can make it challenging to diagnose new-onset sexual dysfunction in the menopausal woman and to develop treatment approaches for amelioration of the symptoms. The key to the differential diagnosis and treatment of the symptomatic woman is to understand the balance of factors that have resulted in a deterioration of the sexual function to which she has become accustomed. With this information the clinician may focus efforts on the avenues of treatment that have the highest probability of re-establishing the woman's pre-existing level of sexual functioning. Treatments may include biological

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interventions, such as hormone-replacement therapy, and/or mental health interventions, depending on the woman's individual presentation and evaluation of the critical factors that destabilized her previously satisfactory sexual relationship.

### Prevalence of Sexual Problems in Women

Female sexual dysfunction includes hypoactive sexual desire disorder, sexual aversion disorder, sexual arousal disorder, orgasmic disorder, and the sexual pain disorders, including dyspareunia, vaginismus, and noncoital sexual pain.<sup>5,6</sup> Sexual dysfunction is common, with 43% of females and 31% of males 18–59 years of age having some form of dysfunction as shown in a population-based survey.<sup>7</sup> Several other studies<sup>8–11</sup> have found similar results when the prevalence of the different sexual problems were combined. The prevalence rates for specific sexual problems examined in these studies were quite different, depending on the study methodology used. An important finding is that 33% to 50% of women who were defined as having a sexual problem regarded it as distressful.<sup>11</sup> The sexual problems noted in the studies appear to increase with menopause and age.<sup>12–15</sup> In their longitudinal study of menopausal women, Dennerstein and colleagues<sup>16</sup> found scores indicating that sexual problems are present in 42% of premenopausal women and 88% of postmenopausal women.

### Causes of Sexual Problems in the Aging Woman

What causes the increase in sexual problems that appears to come with age? Desire, drive, arousal, and vulvovaginal health appear to be affected by the neuroendocrine changes that occur with menopause and aging. One must also take into account that mood, general health, context, beliefs, and expectations<sup>17,18</sup> affect each woman irrespective of her gonadal hormone status. Additionally, the process of aging, type of hormone therapy, partner availability, relationship issues, presence or absence of psychiatric disorders, psychological barriers, cultural issues, general medical well-being, and previous sexual experience, all may influence sexual functioning in the postmenopausal woman.<sup>19</sup> The presence or absence of

psychiatric disorders requires emphasis, as 70% of patients with major depression report a decline in libido.<sup>20</sup> Additionally, eating disorders, histrionic personality disorder, and premenstrual syndrome all may impact sexual functioning.<sup>21</sup> Treatments for depression may further complicate this picture.<sup>21</sup>

### Hormonal Changes in the Menopausal and Aging Woman

Estrogen varies throughout the menstrual cycle with a low in the early follicular phase of about 50 picograms/mL and an average high in the late follicular, early luteal phase (mid-cycle) of approximately 250–300 pg/mL. After menopause, the primary source of estrogen production, the ovaries, cease to produce estrogen. The presence of estrogen in the circulation of postmenopausal women is a function of the conversion of androgens to estrogens at local tissue sites via aromatase activity and then leaking back into circulation. This form of ovarian production only brings the average woman's estrogen level to approximately 30 pg/mL postmenopausally—a level much lower than most women would be accustomed to premenopausally. However, some postmenopausal women may exceed this level, depending upon quantity of adipose tissue as well as other factors.

Total and free testosterone levels decline with age in premenopausal women from the early to mid reproductive years,<sup>22</sup> remain stable across the menopausal transition,<sup>23</sup> and then either continue to remain stable or decline with the gradual decline in adrenal function.<sup>24</sup> The secretion of adrenal androgens, namely androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate, also declines progressively with age.<sup>25</sup> This indicates that the normal physiological changes that occur with age result in the majority of women having low androgen levels by the time they reach menopause. This needs to be confirmed in large epidemiological studies of normal women.

Women who have undergone a hysterectomy with oophorectomy are likely to be testosterone deficient. This likelihood is increased in women closer to mid-life prior to the procedure. Women who have undergone unilateral or bilateral oophorectomy have lower ovarian androgen production than women who

have not had these procedures<sup>26</sup> and are likely to be testosterone deficient.

Other causes of diminished testosterone production in women are premature ovarian failure, chemo/radiotherapy, adrenal insufficiency due to adrenal failure or surgery, and combined hypopituitarism. Loss of testosterone is also iatrogenically induced by treatment with exogenous oral estrogen (oral contraception or oral postmenopausal hormone therapy) or chronic glucocorticosteroid therapy causing adrenal suppression.

### Impact of Hormonal Changes on Sexual Function

Studies have yet to clearly define a particular range of estrogen and testosterone levels that correspond to changes in desire and arousal that occur secondary to aging and/or with menopause. Research on desire and arousal does indicate an association between clinical symptoms (in the absence of interpersonal or psychiatric etiology) and lower levels of gonadal hormones. This research also shows that having symptoms and a low gonadal hormone level may predict a high degree of successful outcome with hormonal treatment.<sup>5,27,28</sup> Sexual problems associated with changing hormone levels in the aging woman can be described as either peripheral/pelvic or central/brain in origin. The following sections describe these changes using this conceptual framework.

#### Peripheral/Vulvovaginal and Pelvic Tissues

The genital and extragenital tissues are highly sensitive to the loss of ovarian hormones. Decreasing estrogen affects the tissues of the female reproductive tract, resulting in differing degrees of decline in vaginal lubrication, atrophic vaginitis, decreased blood flow, and vasocongestion with sexual activity.<sup>28</sup> Genital changes may include progressive ischemia, thinning of the barrier layers of skin and mucous membrane tissues, loss of subcutaneous fat, and decline in size of the introitus, labia minora, clitoris, labia major, vagina, and uterus.<sup>29</sup> Extragenital structures may exhibit loss of pelvic muscle tone, a decrease in intraurethral pressure, a decline in bladder size, and a thinning of the mucous membrane lining of the urethra and bladder.<sup>29</sup> Ovarian hormones influence sensory perception, central and peripheral nerve transmission and

discharge, peripheral blood flow, and the capacity to develop muscle tension.<sup>30</sup> Estrogen also enhances vibration sense, taste, and smell.<sup>31-33</sup> Kow and Pfaff<sup>34</sup> studied the touch receptor zones along the pudendal nerve—the nerve that innervates the clitoris—in an oophorectomized rat. These zones became smaller after oophorectomy and expanded with estrogen replacement. Postmenopausal women have been reported to have the symptoms of a peripheral neuropathy characterized by numbness, itching, clothing intolerance, and increased two-point discrimination thresholds.<sup>35</sup> The untreated clinical consequences of these physiologic changes secondary to hypoestrogenemia can be dyspareunia, vulvovaginal atrophy, and delayed or decreased orgasm, and the genital and extragenital symptoms listed above.

These changes in hormone levels and tissue integrity occur in a predictable manner with menopause and aging but remain highly variable from woman to woman, and from decade to decade. Sarrel<sup>27,28</sup> showed that estrogen levels <50 pg/mL (average level for a premenopausal woman during her follicular stage) may predict problems with vaginal dryness. While <10% of women with estradiol levels >50 pg/mL reported vaginal dryness or dyspareunia, approximately 40% of women with estradiol levels <50 pg/mL experienced vaginal dryness and approximately 30% experienced pain with penetration. The study did not evaluate the role of testosterone levels in this symptomatology.

Dennerstein and colleagues<sup>36</sup> reported similar findings for vaginal dryness with 50% of the women in their Longitudinal Melbourne Mid-Life Study exhibiting vaginal dryness at 3 years postmenopause. Both of these studies and others indicate that estradiol levels in combination with clinical presentation had clinical significance but that low estradiol levels alone in the absence of clinical symptoms may not be predictive of sexual symptoms.<sup>5</sup>

Reduced levels of testosterone may also have an impact on peripheral/pelvic sexual function by modulating the physiology of vaginal tissue and sexual arousal.<sup>37</sup> A correlation between genital responses/sensation and testosterone levels was found in a study comparing postmenopausal and premenopausal women.<sup>38</sup> Sarrel<sup>28,39</sup> and Traish and

colleagues<sup>37</sup> have proposed that blood flow during arousal is affected by estrogenization, but that androgens have an impact on this response.

Lastly, lubrication, classically thought to be estrogen dependent is actually partly estrogen dependent and partly androgen dependent. Vascular transudate and mucin production are both androgen dependent.<sup>37,40-43</sup> The role of androgens peripherally in the health of the epithelium and lubrication of the vulvovaginal tissues as well as clitoral blood flow and response has been implicated.<sup>37</sup> Thus, for some women, a complete return of vulvovaginal health and arousal may require replacement locally with both estrogen and androgen. This awaits further research.

#### **Central/Brain Factors in Sexual Function**

Rodent studies have been performed to study the effect of gonadal hormones on the brain. These studies have shown effects of estrogen and/or testosterone on the neurotransmitter systems serotonin, dopamine, acetylcholine, norepinephrine,  $\gamma$ -aminobutyric acid, vasopressin, oxytocin, neuropeptide Y, and cholecystokinin. These studies also show an effect in areas of the brain, such as the cortex, amygdala, hippocampus, and hypothalamus.<sup>44</sup> Rubirow and colleagues<sup>45</sup> concluded that “The vast array of proteins regulated through gonadal hormone genomic activity permits these hormones to influence virtually all aspects of neurotransmitter formation and activity.”

High concentrations of estrogen and testosterone are found in the brain, particularly in the hypothalamus and preoptic areas. Testosterone concentration is much greater than estrogen concentration in these sites, corresponding to high aromatase activity in these regions.<sup>46,47</sup> Androgens may act directly on the brain, or their action may be due to estrogen that has been aromatized from testosterone. Support for specific direct androgen actions within the brain comes from studies of the effects of cross-sex hormone therapy in transsexuals, where administration of androgens in female to male transsexuals leads to an increase in sexual motivation, whereas the combination of anti-androgens and high-dose estrogen given to male-to-female transsexuals has the opposite effect.<sup>48</sup>

#### **Evidence for Use of Estrogen/Androgen Hormone Replacement**

Observational and clinical trial studies have shown an impact of estrogen and estrogen plus androgen replacement on mood, hot flashes, desire, arousal, and frequency of coitus. Many of these studies do not reflect the entire postmenopausal population; instead, they reflect populations of women who appear to be symptomatic and benefit from this intervention. The results of the randomized control trials and how they affect the central/brain and peripheral/pelvic domains of sexual function are discussed in this section.

Estrogen replacement versus placebo after surgical or natural menopause has been examined by a number of authors. These trials either eliminated women with hot flashes or analyzed them the impact of hot flashes on sexual dysfunction. The inclusion criteria were characterized by no previous or current psychiatric problems, no situational stressors, and a stable unconflicted relationship. When estrogen was replaced in these women, improvements (compared to placebo) were seen in terms of desire,<sup>49</sup> fantasies,<sup>50</sup> enjoyment,<sup>49,50</sup> satisfaction,<sup>51</sup> orgasm/sexual activity/frequency of coitus,<sup>50</sup> masturbation frequency,<sup>52</sup> orgasm,<sup>49,52</sup> lubrication,<sup>49,50</sup> and maturation of vaginal cells.<sup>53</sup> In addition, both vaginal dryness<sup>50,54</sup> and pain<sup>50</sup> were decreased by estrogen replacement versus placebo.

Another set of trials with the same inclusion criteria examined the effect of testosterone therapy in the estrogen replete woman. When testosterone was added to estrogen replete women, the patients exhibited increased clitoral sensation,<sup>55</sup> orgasm,<sup>56</sup> desire,<sup>57,58</sup> libido,<sup>59</sup> fantasies,<sup>59</sup> arousal,<sup>60</sup> pleasure/orgasm,<sup>61</sup> pleasure,<sup>56</sup> pleasure with masturbation,<sup>52</sup> increased enjoyment,<sup>59</sup> satisfaction,<sup>56</sup> relevancy/importance of sexuality,<sup>56</sup> sexual activity/frequency of coitus,<sup>56,61</sup> and overall sexual function.<sup>62</sup>

Thus, many postmenopausal women with sexual complaints may benefit from local or systemic treatment with estrogen- and/or testosterone-replacement therapy. The criteria for whom to give such a therapy, the benefits of peripheral versus systemic, and what kind of peripheral or systemic therapies are most beneficial for different women is beyond the scope of this article. The choices for local

vulvovaginal estrogen would be cream, a twice-weekly vaginal tablet (ie, estradiol vaginal tablets), or an estradiol vaginal ring worn like a diaphragm that releases estrogen over a 3-month period. Less research has been done on local vulvovaginal testosterone therapy, which has variable absorption (none to excessive), and is usually compounded by a pharmacy at 2% testosterone propionate in petrolatum or cream and applied as two dollops to the vulva 2–3 times/week. Systemic estrogen therapies would include different oral estrogens with different pharmacologic compositions and half lives, patches or injections, and gels. Testosterone systemic therapy is limited at this time to a combined pill of estrogen and methyltestosterone, estratest half-strength and estratest, and two products currently under phase II and III trials, a testosterone gel and a testosterone patch. There are other forms of delivery that have been used outside the United States, such as injectables, but are not promoted inside the US. One problem with hormone injections is that they “depot” and the patient may experience an ever-increasing dose.

### Nonbiologic Factors Influencing Sexual Function

The terms drive, libido, desire, and arousal have been used in various ways with some overlap in the literature. When moving beyond a pure biological model one can begin to look at drive, libido, and the capacity for arousal as being driven by motivation, expectations, and interpersonal, psychological, and contextual variables.<sup>17,18</sup> It is the dynamic interaction of these variables that result in sexual activity when a woman is presented with an opportunity for sexual activity. Problems with any one of these domains may be sufficient to dampen the initiation or receptivity to the possibility of sexual activity, often referred to as her “motivation or willingness to engage in sexual activity.” For example, a woman may predominantly have interpersonal issues or stress but also have a diminished drive. She may have maintained sexual activity under the same influences when she was younger but postmenopausally, the change in gonadal hormones along with those same influences may have led to a change in her desire or libido.

Researchers<sup>1,3-5,11,63-66</sup> have developed various models to help guide clinicians

and researchers in clarifying the impact of the various domains of mental/central functioning on the individual's motivations to partake in sexual intimacy, and importantly, whether or not the woman considers these problems distressing. Despite the unresolved issues in the field, enough is known that some clinical recommendations can be made regarding differential diagnosis and treatment of the portion of postmenopausal women who present with sexual functioning problems.

### Clinical Applications

In order to attribute current sexual problems to the changes experienced with menopause, the clinician should confirm that the sexual problems are new in origin, are not caused by an untoward medical condition, and that the woman previously experienced good sexual functioning prior to her menopause. Next, the clinician should differentiate the influence of neuroendocrine change from those of psychosocial, interpersonal, and psychological factors.

The differential diagnosis could be conceived in terms of central sexual as well as central nonsexual symptoms impacting basic drive. Central sexual symptoms would include many of the consequences of a change in the level of drive/desire. These would include a decrease in sexual thoughts and fantasies, receptivity, initiation, relevancy, sexual activity, and frequency of coitus. Central nonsexual would include mood-dysphoria, motivation, energy, fatigue, vitality, well-being, and hot flashes affecting libido indirectly.

In addition to central sexual and nonsexual symptoms, the clinician should assess for peripheral/pelvic changes. With aging, a woman has the possibility of many changes in the pelvic region, some of which may affect her sexual response and comfort with coital relations. These would include clitoral sensitivity, sensation-sensory perception, lubrication, pain with sexual activity, pelvic vasocongestion, capacity to develop muscle tension, and postcoital bleeding.

Physicians should consider using estrogen and/or estrogen plus testosterone-replacement therapy in women whose symptoms appear to be caused by reduced levels of estrogen and/or androgen. The best candidates for this type of treatment are women who have symptoms consistent with low estrogen and/or

women who are estrogen replete but whose free-androgen levels are in the lowest quartile.<sup>67</sup> The absence of behavioral and interpersonal/contextual problems is important. Behavioral or cognitive therapy can be considered for problems that appear to be behavioral in origin. Some feel these need to be addressed prior to a biological approach, while others feel that a dynamic interaction exists between the decline in functioning due to biological changes along with interpersonal/behavioral problems in intimacy. For many cases a dual approach is warranted where the gynecologist or family practitioner replaces to the lowest necessary level of estrogen either peripherally or peripherally (local) and centrally (systemic) and observes for biological improvement concurrent with mental health interventions. The gynecologist or family practitioner would not move on to testosterone therapy unless there were indications that included failure of estrogen therapy alone, clear decline in central symptoms of drive/desire/arousal, vaginal symptoms attributable to hypotestosteronemia in a woman who is vaginally estrogen replete, and indications that the etiology of the sexual symptoms was partially biological despite behavioral problems in the couple.

### Conclusion

Some premenopausal women have operationally defined sexual problems, though not all are distressed by these problems. Many postmenopausal women are free of sexual problems for a significant number of years after menopause, prior to the onset of effects of aging on their sexuality. There is, however, a group of premenopausal and postmenopausal women who complain of sexual problems and these problems appear to be secondary to hormonal insufficiency and/or menopause and not attributed to aging alone. This group of women may present for care, which will require a full knowledge of the biological as well as the interpersonal, psychosocial, and psychological domains affecting their sexuality by the treating clinicians. A successful intervention for these women will require shared knowledge between specialties and more cooperation among specialties for successful outcomes. More research is needed to gain an increased understanding of the impact of gonadal hormones on the brain and the peripheral tissues; to know which

women most require hormonal intervention; and to recognize those in whom the benefit of hormone therapy does not outweigh the potential health risks.

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