

## Care of Women in Menopause: Sexual Function, Dysfunction and Therapeutic Modalities

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### Abstract

**Introduction:** The physiological changes that occur in menopause alter sexual function and affect well-being. Hormonal changes contribute significantly to reduced sexual function in older women and sexual dysfunction may well be amenable to treatment with exogenous hormones or other agents. **Materials and Methods:** Relevant clinical studies were identified by a computerised literature search. The collated data were presented to fellow gynaecologists for review, analysis of results and discussion in a series of meetings dedicated to finding the best evidence in menopause management. The evidence was assessed and used to prepare guidelines around the management of women who are affected by sexual dysfunction in menopause. **Results:** Hormone therapy benefits many women who have dyspareunia related to vaginal atrophy, reduced libido and decreased satisfaction, particularly if these symptoms adversely affect their quality of life. Alternative agents such as tibolone and sildenafil citrate can be useful adjuncts. **Conclusions:** It is increasingly important to recognise postmenopausal sexual dysfunction. Treatment of this syndrome must be individualised to the specific complaints of each woman. Hormones and other agents are relevant treatment options for properly-selected women.

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**Key words:** Androgen, Dyspareunia, Oestrogen, Postmenopause, Sex disorders

### Introduction

Menopause is a life change described by biological alterations occurring in the context of important social changes. There is an increasing appreciation for the role of sexual function in menopause and its importance for a woman's health and well-being.

A normal sexual response is a complex process dependent on a neurotransmitter-mediated response that causes increased pelvic blood flow, labial and clitoral engorgement and increased vaginal lubrication.<sup>1,2</sup> All physiological and psychological impairments that interfere with this process can lead to sexual dysfunction.<sup>3</sup>

Female sexual dysfunction (FSD) can be a challenging and complex medical problem. In the United States more than 40% of women suffer from FSD.<sup>4</sup> It is characterised by reduction of sex drive, aversion to sex, lack of arousal, inability to reach orgasm and pain during intercourse, and is often difficult to diagnose and treat due to the complex

intricacy of the female sexual response. A global survey of sexual problems over the age of 40 years found that a lack of interest in sex and inability to achieve orgasm were more prevalent in Asian women compared to their European counterparts.<sup>5</sup>

There is a tendency to assume that older women are less sexually active and have decreased sexuality, particularly after menopause. In a review of sex and ageing, Kaplan<sup>6</sup> concluded that most physically healthy men and women remain regularly sexually active well into advanced old age. However, physiological changes associated with the ageing process, coupled with the increasing prevalence of medical disorders in older age, play a significant role in the pathogenesis of sexual disorders. With the median age at last menstruation being 51 years<sup>7</sup> (the mean age of Singaporean women at menopause is 49 years)<sup>8,9</sup> and with the life expectancy of women in developed countries expected to exceed 70 years<sup>10</sup> a large number of women

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will spend a substantial proportion of their lives in the postmenopausal years. One may anticipate an increase in the incidence of sexual dysfunction. Hence, there is an increased demand for a greater understanding of the pathophysiology and treatment of FSD.

The primary change at the root of sexual dysfunction is the declining oestrogen level. The initial oestrogen deficiency accounts for diminished vaginal lubrication. Continued oestrogen loss is associated with muscular, vascular and urogenital alterations, and contributes to mood instability, disturbed sleep and impaired cognitive function. Thus, hypoestrogenism influences sexual function both directly and indirectly.<sup>11</sup>

Testosterone is an important hormone that affects the neurotransmitter systems involved in sexual behaviour.<sup>12-14</sup> Serum testosterone levels correlate positively with sexual desire and sexual behaviour.<sup>15</sup> In naturally menopausal women, serum androgen levels undergo a diverse rate of decline. Gambera et al<sup>16</sup> demonstrated a significant decline in androstenedione, dehydroepiandrosterone (DHEA) and DHEA-sulphate (DHEAS) during the first years of menopause, with testosterone and sex hormone-binding globulin only significantly lowered in the later years. This reduction is sometimes associated with a syndrome of specific changes in sexual desire and sexual response.<sup>17</sup>

After iatrogenic menopause (for example, following oophorectomy) only the adrenal glands continue to produce low levels of androgens, which further decline with age. Oophorectomised women are more likely to report a worsening of sexual function and sudden loss of sexual desire after hysterectomy compared to women whose ovaries are conserved. Adverse changes in libido, orgasmic response and psychological well-being are also more likely in oophorectomised women.<sup>18</sup>

Progestogens are known to contribute to sexual health and function, and the variability in the effects of specific progestogens are being increasingly appreciated.<sup>11,19</sup> Non-hormonal mediators of sexual function and well-being must not be overlooked. Comorbidities and psychosexual changes may manifest as sexual pain syndromes and contribute to lower self-esteem and diminished desire and responsiveness. We reviewed the clinical trials studying hormone and other therapy in menopausal women diagnosed with sexual dysfunction.

## Materials and Methods

We assessed the use of oestrogen or oestrogen plus progesterone alone, androgen alone, oestrogen and androgen, oestrogen plus progesterone and androgen. We also assessed the non-hormonal therapeutic agents tibolone and sildenafil citrate. A computerised literature search was performed to identify all relevant clinical studies in human

subjects. The studies reviewed involved naturally or surgically menopausal women with female sexual function as their primary outcome measure. These studies examined intervention with hormone therapy compared to placebo or nothing. The relevant literature was identified and retrieved from a search of PubMed, Medline and the Cochrane Database, using terms including but not restricted to menopause, postmenopause, hormone replacement, hormone therapy, sex hormones, oestrogen, androgen, progesterone, sex disorders, oophorectomy and hysterectomy. In addition, references from textbooks and published articles were used. After employing the search methods outlined above the reviewers selected the trials for consideration. Data regarding patient characteristics, hormone therapy, hysterectomy or oophorectomy history, and reported sexual dysfunction were extracted. The collated data were presented to fellow gynaecologists for analysis and discussion during a series of weekly meetings held at the Department of Obstetrics and Gynaecology, National University Hospital, Singapore. The gynaecologists attending the meetings were the clinical staff working in the department. At each meeting the individual studies were discussed, the data assessed and analysed and at the end of the series of meetings recommendations on management issues and practice guidelines were produced. The date of the latest literature review was 30 November 2006.

## Results

FSD is often difficult to define and diagnose. This is reflected in the use of varying parameters of sexuality to identify sexual dysfunction and the administration of multiple questionnaires across the various trials. We reviewed 38 trials that studied the effect of hormone and non-hormonal therapies on women with impaired sexual function. Some data demonstrated improved sexual function with therapy while other data showed no advantage.

The experience of the menopause varies across cultural and geographical zones.<sup>20</sup> Although the majority of data came from the study of women of Caucasian or African origin, the Asian women studied reported similar changes in sexuality following menopause. The common sexual problems among post-menopausal Thai women include loss of libido, orgasmic dysfunction, dyspareunia, decreased sexual desire and sexual activity, compared with the premenopausal period.<sup>21</sup> Results of a nationwide cross-sectional survey of multi-ethnic women in Singapore detailed the menopause experience of local women.<sup>9</sup> The mean age of natural menopause was 49.0 years, similar among Malay, Indian and Chinese women. Muscle and joint ache was the most common symptoms reported by 52.6% of respondents. Comparatively the prevalence of significant hot flushes was low in the general cohort (3.9

%), but more commonly reported by 14.6% of perimenopausal women. Hot flushes decreased with time from menopause ( $P = 0.007$ ) and were no longer present beyond the fifth year of menopause. Chinese women were significantly at lower risk of menopausal symptoms compared to women of other ethnicity.

A cross-sectional study by Gonzalez et al<sup>22</sup> on the prevalence of sexual dysfunction among South-American women demonstrated that diminished vaginal lubrication and pain during intercourse were most affected by menopause. The use of hormone therapy significantly improved orgasm, lubrication and vaginal pain.

In the oestrogen-only arm of the Women's Health Initiative (WHI),<sup>23</sup> the use of conjugated equine oestrogens in women without a uterus did not demonstrate a benefit with regard to sexual satisfaction at 1 or 3 years. Similarly, in women with an intact uterus, the combination of conjugated equine oestrogens and medroxyprogesterone acetate produced no significant improvement in sexual satisfaction compared to placebo, although genital dryness did improve significantly.<sup>24</sup> In Strickler's study<sup>25</sup> comparing oestrogen, raloxifene and placebo, scores for sexual behaviour and perceived attractiveness were unchanged across all groups. Hilditch et al<sup>26</sup> compared the efficacy of oral and transdermal oestrogen and found that both modes of therapy improved postmenopausal women's sexual scores on a quality of life scale to a similar degree.

Hypoestrogenism contributes to postmenopausal sexual dysfunction by causing vaginal epithelial atrophy, diminished vasocongestion and sensitivity. Reduced lubrication capability and tissue elasticity, in addition to shortening and narrowing of the vaginal vault, can lead to painful and unpleasant intercourse. At the same time, diminished sensory response may reduce orgasmic intensity.<sup>27</sup> Mainini et al<sup>28</sup> demonstrated the safety and efficacy of topical oestrogen application. More than 300 postmenopausal women with atrophic vaginitis were treated with 0.025 mg 17 $\beta$ -estradiol vaginal tablets for 24 weeks (once-daily application for 2 weeks followed by twice-weekly use for the following 22 weeks). The majority of subjects reported an improvement in symptoms following treatment. Raymundo et al<sup>29</sup> studied Asian women's response to vaginal conjugated equine oestrogens (0.625 mg/g cream) used once daily on days 1 to 21 of two 28-day cycles. The vaginal maturation index significantly improved from baseline and this benefit was maintained for 2 months.

The safety profile of intravaginal oestrogen has been reviewed.<sup>30</sup> Conjugated equine oestrogen cream may cause more breast tenderness and uterine bleeding compared to estradiol tablets. The occurrence of simple and complex endometrial hyperplasia has been reported with the vaginal ring and conjugated equine oestrogen cream, although the

incidence was not significant in the Cochrane systematic review. The estradiol-releasing vaginal ring and vaginal cream show equivalent efficacy when used for the relief of vaginal dryness,<sup>31</sup> although the vaginal ring was significantly more acceptable among the study population.

The data comparing the addition of testosterone to oestrogen or oestrogen-progestin suggested improved scores measuring sexual interest, satisfaction, frequency of activity and responsiveness. This improvement was greater than the scores reported by women on oestrogen therapy alone in many of the studies reviewed.<sup>32-41</sup>

Sherwin et al<sup>32</sup> demonstrated significantly higher scores for sexual fantasy, desire and arousal during each treatment phase with testosterone compared with placebo or oestrogen alone, but no significant difference in coital or orgasmic frequency between treatment and control groups. Castelo-Branco et al<sup>33</sup> concluded that the supplementation of oestrogen therapy with testosterone enhanced sexual activity to a greater degree than oestrogen alone. Shifren's et al<sup>34</sup> crossover trial demonstrated enhanced sexual activity with transdermal testosterone, particularly with regard to frequency of sexual activity and pleasure from orgasm. Lobo et al<sup>35</sup> showed a greater increase in baseline scores measuring sexual interest or desire and frequency of desire with the addition of testosterone to oral oestrogen. Penotti et al<sup>36</sup> and Dow et al<sup>37</sup> showed overall improvement in treatment groups over baseline scores for sexual interest and responsiveness, and sexual desire and satisfaction respectively, with no difference between those treated with oestrogen alone and those who received supplementary testosterone. The studies involving naturally and surgically menopausal women made little distinction between the effects of treatment combinations on either set of patients. Studies demonstrating the benefits of testosterone supplementation used intramuscular testosterone enanthate, oral methyltestosterone and testosterone undecanoate and testosterone patches.<sup>32-41</sup>

The addition of testosterone to oestrogen therapy is reported in oophorectomised women.<sup>41</sup> After 24 weeks of therapy oophorectomised women treated with oral testosterone undecanoate 40 mg plus estradiol valerate 2 mg daily showed an improved effect on interest in sex, enjoyment of sex and satisfaction with frequency of sexual activity, as well a greater improvement in the total McCoy's sex scale scores, compared to oophorectomised women treated with placebo plus estradiol valerate 2 mg daily ( $P < 0.05$ ). Total testosterone levels increased significantly from baseline levels after 24 weeks of testosterone-oestrogen treatment compared to oestrogen treatment alone (4.9 vs. 0.9 nmol/L,  $P < 0.001$ ). There were no significant adverse effects reported despite the fact that supraphysiological levels of testosterone were achieved in a significant

proportion of the women.

The data of Laughlin et al<sup>42</sup> demonstrate that the postmenopausal ovary remains a critical source of androgens throughout the lifespan of older women. Age-adjusted levels of both total and bioavailable testosterone were reduced by more than 40% ( $P < 0.001$ ) in hysterectomised women with bilateral oophorectomy compared to naturally menopausal women without history of pelvic surgery or hormone therapy, with intermediate levels observed in hysterectomised women with ovarian conservation. Androstenedione levels were 10% lower in women following hysterectomy, regardless of ovarian status, compared to naturally menopausal women ( $P = 0.039$ ). Levels of bioavailable estradiol, estrone, and SHBG did not differ by hysterectomy and oophorectomy status.

Oestrogen therapy may improve the general well-being in some groups of surgically menopausal women, and directly or indirectly alleviate a number of the symptoms associated with sexual dysfunction. Additional benefit may be derived from testosterone therapy in women who have the symptoms specifically related to androgen insufficiency; however, this seems to occur only at supraphysiological levels of total testosterone and physiological levels of free testosterone.<sup>43,44</sup>

The safety issues concerning the use of testosterone were analysed by Somboonporn et al, in a systematic review of testosterone therapy in peri- and postmenopausal women.<sup>45</sup> The adverse outcomes analysed included hirsutism, acne, mood alteration and lipid profile. There were no significant differences in hirsutism scores or mean acne scores among comparison groups in trials assessing oestrogen alone and oestrogen plus testosterone,<sup>34,35,41</sup> despite a significantly increased concentration of bioavailable testosterone in women using oestrogen and testosterone. Women using testosterone did not show an increased level of aggression or hostility.<sup>46</sup> There was no significant change in plasma viscosity, fibrinogen levels or haematocrit reported in the trials that reported these outcomes.<sup>34,41,47</sup> Several trials that employed oral and parenteral testosterone were analysed with respect to lipid profile at equal time points over a 24-month course of therapy. Meta-analyses found a significantly reduced level of high-density lipoprotein (HDL) cholesterol after treatment with oestrogen and testosterone compared to treatment with oestrogen alone, after 3 to 12 months of therapy,<sup>35,36,48</sup> a change that persisted at 24 months of treatment.<sup>40,47</sup> HDL cholesterol levels were significantly lower following combined oestrogen-testosterone therapy, and could be seen with both the testosterone implant and oral methyltestosterone.<sup>48,49</sup> Mean levels of low density lipoprotein (LDL) cholesterol, triglycerides and total cholesterol were not significantly different between treatment groups at any time point.

Women who develop secondary amenorrhoea before the age of 40, accompanied by sex steroid deficiency and elevated gonadotrophins, are diagnosed with premature ovarian failure, which may be caused by an underlying genetic defect,<sup>50</sup> chemotherapy, or prophylactic or therapeutic oophorectomy. These young women experience a range of hormone deficiency symptoms similar to postmenopausal women. Women with premature menopause, regardless of aetiology, represent a special group who may benefit greatly from a multidisciplinary approach comprising individualised hormone replacement and psychosexual therapy. Hormone therapy is indicated to compensate for the endocrine deficiencies in this group of women.

Premature menopause affects sexual function and sexual relationships, particularly if it is surgically-induced.<sup>51</sup> The loss of ovarian endocrine function can be highly distressing, although the experience is tempered by many factors, including achievement of child-bearing goals and the woman's relationship with her partner.

Surgically-menopausal women who are concurrent hormone users experience more vasomotor symptoms compared to premenopausal (non-oophorectomised) women, including sexual discomfort from vaginal dryness and dyspareunia, but fewer vasomotor symptoms compared with oophorectomised women who are non-users. The level of sexual functioning reported by oophorectomised women on hormone therapy was comparable to the level of sexual functioning in oophorectomised women not using hormones.<sup>52</sup> This data suggests that although hormone therapy can relieve iatrogenic vasomotor symptoms to some degree, its role might be less effective than often assumed. Vasomotor symptoms remained more prominent compared to non-oophorectomised controls without significant relief of sexual discomfort with hormone use.

In a placebo-controlled study of oophorectomised women with hypoactive sexual desire disorder, including young women in the reproductive age group, the efficacy of a testosterone patch (300 microgram/day) was assessed.<sup>53</sup> Subjects were on concomitant oral oestrogen therapy. With the testosterone patch applied twice a week over a 24-week period, the intervention group demonstrated a greater increase in frequency of satisfying sexual activity, greater improvement in sexual desire and diminished sexual distress compared to women on placebo, all of which were statistically significant.

The concurrent use of transdermal oestrogen and testosterone patches was studied in a similar cohort of surgically menopausal women of varying ages.<sup>54</sup> Subjects using oestrogen and testosterone patches reported a significantly greater increase in scores for sexual desire, arousal, orgasm and decreased distress compared to women

using oestrogen and placebo patches. There was a trend towards increased frequency of satisfactory sexual events. The testosterone patch was tolerated well by subjects in both trials when used in conjunction with oral or transdermal oestrogen, and no serious adverse events were reported.

Although long-term safety data regarding the use of oestrogen and testosterone in this population are lacking, both may be used judiciously where needed to alleviate symptoms of sexual dysfunction.<sup>51</sup>

Wu et al<sup>55</sup> studied the effect of tibolone on sexuality and quality of life in 48 postmenopausal Taiwanese women. Compared with continuous combined hormone therapy, tibolone was associated with improved sexual performance, satisfaction, arousal and orgasm as measured on the McCoy Sex Scale. Egarter et al<sup>56</sup> similarly found that tibolone used together with hormone therapy significantly improved women's satisfaction with their sexual lives and libido. In a prospective randomised trial of 72 postmenopausal women, Uygur et al<sup>57</sup> compared tibolone with conjugated equine oestrogen and medroxyprogesterone acetate on sexual desire, excitement and arousal, orgasm capacity, vaginal lubrication during sexual activity and dyspareunia before and after the treatment. Upon completing 6 months of treatment, women using tibolone had significantly higher scores for sexual desire, sexual excitement, intercourse frequency and vaginal dryness compared to women on oestrogen and progestin ( $P < 0.05$ ). The work of Hofling and colleagues<sup>58</sup> on circulating sex steroids and binding proteins in postmenopausal women demonstrates how tibolone affects serum androgen concentration, by reducing the level of sex hormone binding globulin by up to 50%, minimally affecting oestrogen concentration, and thus increasing the concentration of free testosterone.

Sildenafil citrate has been studied as a therapeutic agent for FSD. Berman et al<sup>59</sup> studied the safety and efficacy of this drug on naturally and surgically menopausal women with sexual arousal disorder in a placebo-controlled randomised trial. Significant improvements were found with sildenafil compared to placebo with regard to genital arousal during stimulation and satisfaction with intercourse, and was well-tolerated by subjects. Basson et al<sup>60</sup> studied the effect of sildenafil on genital responsiveness in postmenopausal women. Although there was no overall improvement in arousal or experience of orgasm in the study group, among the subjects with reduced vaginal pulse amplitude (measuring genital vasocongestion during arousal) there was a decreased latency to orgasm, and improved sexual arousal after treatment.

Few studies have assessed the direct impact of chronic disease on the sexual function of postmenopausal women. Because the experience of menopause in general is influenced by multiple lifestyle and societal influences,

women who require long-term treatment for chronic illness may experience a greater degree of sexual distress and dysfunction as a result of the illness or therapy,<sup>61-64</sup> the experience of which is tempered by interpersonal and psychosocial factors, all of which can impair the quality of life and sexuality.

A well-studied example is women with survivable breast cancer. Adjuvant chemotherapy suppresses ovarian endocrine function and patients may report vasomotor symptoms and sexual distress, often from vaginal dryness and dyspareunia.<sup>65</sup> The psychosocial impact on the woman's quality of life following diagnosis and treatment will be a strong modulator of sexual function.

In a small study reviewing the sexual function of breast cancer survivors, women who had undergone chemotherapy were 3 times more likely to report hot flashes ( $P = 0.02$ ) and decreased libido ( $P = 0.04$ ), and more than 5 times as likely to report vaginal dryness ( $P = 0.001$ ), dyspareunia ( $P = 0.003$ ), and difficulty achieving orgasm ( $P = 0.004$ ) compared to women not treated with chemotherapy.<sup>66</sup> Problems in sexual functioning were described by breast cancer survivors both in the short term (1 to 2 years)<sup>67</sup> and long term (at least 5 years)<sup>68</sup> following cancer treatment.

The specific symptoms reported by breast cancer survivors depend on the type of adjuvant therapy the women received. In a survey of over 1000 women who had treatment for early stage breast cancer, Ganz et al<sup>69</sup> found no difference in the global quality of life among women who received adjuvant chemotherapy or tamoxifen, or both, when compared with women who did not receive additional therapy. Women who were on tamoxifen reported hot flashes and night sweats more often, and vaginal dryness and dyspareunia occurred more often in survivors treated with chemotherapy.

Hysterectomy, with or without oophorectomy, is a common procedure performed for benign, and occasionally malignant, gynaecological conditions. Following an hysterectomy a woman may report improved sexual functioning, if the underlying gynaecological condition caused coital pain, or a diminution of any aspect of the sexual experience. There is evidence supporting both claims.

In a survey of almost 9000 women in Great Britain following surgical treatment for dysfunctional uterine bleeding, the prevalence of psychosexual dysfunction (loss of libido, diminished sexual arousal, vaginal dryness) was higher among women who had undergone a hysterectomy 5 years earlier, compared to women who had transcervical endometrial resection during the same period.<sup>70</sup> As expected the severity of symptoms was particularly pronounced among the women who had been oophorectomised. Hormone therapy had little benefit.

In a large survey of more than 1000 women in current

sexual partnerships, the prevalence of hypoactive sexual desire disorder (low sexual desire causing distress) was found to be higher in women who had undergone hysterectomy with bilateral oophorectomy compared to premenopausal and naturally menopausal women [odds ratio (OR), 2.1; 95% confidence interval (CI), 1.4-3.4;  $P = 0.001$ ].<sup>71</sup> Sexual desire scores correlated strongly with other aspects of sexual functioning including arousal, orgasm and pleasure ( $P < 0.001$ ). Low sexual desire was associated with lower frequency of intercourse and greater dissatisfaction with the partner relationship ( $P < 0.001$ ).

Andersen et al<sup>72</sup> compared sexual function among women treated for early stage gynaecological cancer with women who had treatment for benign gynaecological disease and women who were gynaecologically healthy. Although global sexual behaviour disruption did not occur, the decline in frequency of intercourse and in perceived sexual excitement was more evident in the subjects who were treated for gynaecological disease, both benign and malignant. The severity of symptoms were more pronounced in women who had malignant disease, possibly related to significant coital pain, premature menopause and the side effects of treatment.

In a study of matched groups of women following hysterectomy, subjects who had undergone bilateral oophorectomy, women complained of less pleasure from coitus, impaired libido and lubrication, compared to women whose ovaries were preserved at hysterectomy.<sup>73</sup> Oophorectomised women receiving oestrogen therapy reported similar distressing symptoms to oophorectomised women not receiving oestrogen, indicating that oestrogen therapy was of little benefit to the women in this trial.

In prospective study of perimenopausal women following hysterectomy for benign disease, Aziz et al<sup>74</sup> found no difference in psychological general well-being between women who had hysterectomy alone and those who had simultaneous oophorectomy, either at baseline or a year after surgery. Both groups of women showed increased positive well-being and decreased anxiety. Sexual satisfaction showed a positive correlation with the general psychological well-being, despite a reduction in ovarian sex steroid levels and the free androgen index in the oophorectomised women.<sup>75</sup>

In a long-term follow-up of over 1000 women with hysterectomy performed an average of 26 years earlier, the women reported having greater energy following an hysterectomy, with or without bilateral oophorectomy ( $P = 0.003$  and  $P = 0.001$  respectively).<sup>76</sup> More women with bilateral oophorectomy reported greater interest in sex ( $P = 0.007$ ) and an improved sense of well-being ( $P = 0.012$ ) compared to women in whom the ovaries were conserved.

The surgical approach to hysterectomy (by laparotomy or laparoscopy) does not have a significant impact on psychological well-being and sexuality 1 year after surgery.<sup>77</sup> Women who had total hysterectomy reported similar levels of sexual functioning compared to women who had subtotal hysterectomy.<sup>78</sup>

Significant predictors for satisfaction with sexual life after hysterectomy include preoperative satisfaction with sexual life (OR, 32; 95% CI, 10-125), a good relationship with the partner (OR, 50; 95% CI, 9-354), physical well-being (OR, 0.30; 95% CI, 0.09-0.88) and hormone replacement therapy (OR, 0.23; 95% CI, 0.06-0.78).<sup>79</sup>

Reviews of sexual partnerships among women who are surgically menopausal have found that a primary determinant of sexual satisfaction after surgery is the quality of the partner relationship preceding hysterectomy.<sup>79-81</sup> The only predictor of negative sexual experience of partners after hysterectomy was negative sexual experience before hysterectomy.

## Recommendations

No single therapeutic approach is appropriate for every woman with postmenopausal sexual dysfunction. Understanding of a woman's sexual health problems starts with a comprehensive evaluation of her sexual, medical and psychosocial history. Various modalities of treatment may be used simultaneously to achieve better sexual function such as treating chronic disease, optimising chronic medication dosage and supplementing with the most appropriate hormonal and non-hormonal therapy. The physician should bear in mind the low incidence of adverse events associated with the various therapeutic modalities available. Further research is required to establish optimal treatment regimens of the various agents discussed in this review, including dosage, forms of delivery and duration of treatment, for specific subtypes of sexual dysfunction.

## Conclusions

The menopausal transition and the ageing process bring about physical and psychological changes that can impair sexual functioning. The relative deficiency of oestrogen leads to vaginal epithelial atrophy and dryness that directly affect enjoyment of intercourse. In addition, sexual ageing can bring about a decline in sexual arousal and frequency of intercourse.

In symptomatic postmenopausal women, oestrogen therapy may have inconsistent benefits. The magnitude of effect depends greatly on the specific symptomology of the individual. Systemic oestrogen has not consistently improved sexual dysfunction symptoms in menopausal women. This may be attributed to the effect of systemic oestrogen on increasing circulating levels of sex hormone

binding globulin and reducing free testosterone.<sup>55</sup> However, women with complaints specifically related to vaginitis and atrophy (pain, diminished lubrication and genital responsiveness) will benefit particularly from topical oestrogen, which is a useful alternative for use in women wishing to avoid systemic oestrogen. Vaginal oestrogens should still be used with caution in a woman with an intact uterus, as there is a small risk of endometrial hyperplasia. This can be confirmed with a progesterone challenge test. Any woman with postmenopausal bleeding on hormone therapy must be fully investigated to exclude endometrial pathology.

Women with arousal disorders (libido, sexual satisfaction, frequency of sexual activity) may benefit from androgen therapy, either as an alternative or adjunct to oestrogen therapy, as androgens complement the actions of oestrogens. But instead of routinely using androgens in all postmenopausal women, this treatment should be used with caution and reserved for women with established androgen deficiency and related symptoms. Together with careful counselling and consideration of other covariates, oestrogen or testosterone therapy may be used judiciously, together or separately, in women with hormone deficiency-related sexual dysfunction.

As there is little data on the long-term effects of testosterone, its use should be restricted to the short-term. Additionally, close surveillance for a decrease in HDL-cholesterol becomes necessary for the duration of testosterone therapy. Surgically menopausal women are among the populations most likely to experience androgen deficiency.

Our understanding of FSD is somewhat limited by a lack of consensus about its definition and measurement. Moreover the definition of FSD continues to be expanded and revised.<sup>82-84</sup> Recently the American Foundation of Urologic Disease Consensus Panel established a new classification and diagnostic system which has since been used by gynaecologists and urologists to assist in identifying women with FSD.<sup>84</sup>

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#### REFERENCES

- Berman JA, Adhikari SP, Goldstein I. Anatomy and physiology of female sexual function and dysfunction: classification, evaluation and treatment options. *Eur Urol* 2000;38:20-9.
- Goldstein I, Berman JR. Vasculogenic female sexual dysfunction: vaginal engorgement and clitoral erectile insufficiency syndromes. *Int J Impot Res* 1998;10(Suppl):S84-90, S98-101.
- Read J. Sexual problems associated with infertility, pregnancy, and ageing. *BMJ* 2004;329:559-61.
- Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999;281:537-44. Erratum in: *JAMA* 1999;281:1174.
- Nicolosi A, Laumann EO, Glasser DB, Moreira ED Jr, Paik A, Gingell C; Global Study of Sexual Attitudes and Behaviors Investigators' Group. Sexual behavior and sexual dysfunctions after age 40: the global study of sexual attitudes and behaviors. *Urology* 2004;64:991-7.
- Kaplan HS. Sex, intimacy, and the aging process. *J Am Acad Psychoanal* 1990;18:185-205.
- Brambilla DJ, McKinlay SM. A prospective study of factors affecting age at menopause. *J Clin Epidemiol* 1989;42:1031-9. Erratum in: *J Clin Epidemiol* 1990;43:537.
- Chim H, Tan BH, Ang CC, Chew EM, Chong YS, Saw SM. The prevalence of menopausal symptoms in a community in Singapore. *Maturitas* 2002;41:275-82.
- Loh FH, Khin LW, Saw SM, Lee JJ, Gu K. The age of menopause and the menopause transition in a multiracial population: a nation-wide Singapore study. *Maturitas* 2005;52:169-80.
- Mathers CD, Sadana R, Salomon JA, Murray CJ, Lopez AD. Healthy life expectancy in 191 countries, 1999. *Lancet* 2001;357:1685-91.
- Graziottin A, Leiblum SR. Biological and psychosocial pathophysiology of female sexual dysfunction during the menopausal transition. *J Sex Med* 2005;2 Suppl 3:133-45.
- Bancroft J. The endocrinology of sexual arousal. *J Endocrinol* 2005;186:411-27.
- Schipper HM. Neurology of sex steroids and oral contraceptives. *Neurol Clin* 1986;4:721-51.
- Bernardi F, Pluchino N, Stomati M, Pieri M, Genazzani AR. CNS: sex steroids and SERMs. *Ann N Y Acad Sci* 2003;997:378-88.
- Riley A, Riley E. Controlled studies on women presenting with sexual drive disorder: I. Endocrine status. *J Sex Marital Ther* 2000;26:269-83.
- Gambera A, Scagliola P, Falsetti L, Sartori E, Bianchi U. Androgens, insulin-like growth factor-I (IGF-I), and carrier proteins (SHBG, IGFBP-3) in postmenopause. *Menopause* 2004;11:159-66.
- Basson R. Androgen replacement for women. *Can Fam Physician* 1999;45:2100-7.
- Shifren JL. Androgen deficiency in the oophorectomized woman. *Fertil Steril* 2002;77 Suppl 4:S60-2.
- Myers LS, Dixon J, Morrisette D, Carmichael M, Davidson JM. Effects of estrogen, androgen, and progestin on sexual psychophysiology and behavior in postmenopausal women. *J Clin Endocrinol Metab* 1990;70:1124-31.
- Gold E. Demographics, environmental influences, and ethnic and international differences in menopausal experience. In: Lobo RA, Kelsey J, Marcus R, editors. *Menopause: Biology and Pathobiology*. San Diego: Academic Press, 2000:189-201.
- Tungphaisal S, Chandeying V, Sutthijumroon S, Krisanapan O, Udomratn P. Postmenopausal sexuality in Thai women. *Asia Oceania J Obstet Gynaecol* 1991;17:143-6.
- Gonzalez M, Viafara G, Caba F, Molina E. Sexual function, menopause and hormone replacement therapy (HRT). *Maturitas* 2004;48:411-20.
- Brunner RL, Gass M, Aragaki A, Hays J, Granek I, Woods N, et al; Women's Health Initiative Investigators. Effects of conjugated equine estrogen on health-related quality of life in postmenopausal women with hysterectomy: results from the Women's Health Initiative Randomized Clinical Trial. *Arch Intern Med* 2005;165:1976-86.
- Barnabei VM, Cochrane BB, Aragaki AK, Nygaard I, Williams RS, McGovern PG, et al; Women's Health Initiative Investigators. Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. *Obstet Gynecol* 2005;105(5 Pt 1):1063-73.
- Strickler R, Stovall DW, Merritt D, Shen W, Wong M, Silfen SL. Raloxifene and estrogen effects on quality of life in healthy postmenopausal women: a placebo-controlled randomized trial. *Obstet Gynecol* 2000;96:359-65.
- Hilditch JR, Lewis J, Ross AH, Peter A, van Maris B, Franssen E, et al. A comparison of the effects of oral conjugated equine estrogen and transdermal estradiol-17 beta combined with an oral progestin on quality

- of life in postmenopausal women. *Maturitas* 1996;24:177-84.
27. Goldstein I, Alexander JL. Practical aspects in the management of vaginal atrophy and sexual dysfunction in perimenopausal and postmenopausal women. *J Sex Med* 2005;2 Suppl 3:154-65.
  28. Mainini G, Scaffa C, Rotondi M, Messalli EM, Quirino L, Ragucci A. Local estrogen replacement therapy in postmenopausal atrophic vaginitis: efficacy and safety of low dose 17beta-estradiol vaginal tablets. *Clin Exp Obstet Gynecol* 2005;32:111-3.
  29. Raymundo N, Yu-cheng B, Zi-yan H, Lai CH, Leung K, Subramaniam R, et al. Treatment of atrophic vaginitis with topical conjugated equine estrogens in postmenopausal Asian women. *Climacteric* 2004;7:312-8.
  30. Suckling J, Lethaby A, Kennedy R. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev* 2006;(4):CD001500.
  31. Ayton RA, Darling GM, Murkies AL, Farrell EA, Weisberg E, Selinus I, et al. A comparative study of safety and efficacy of continuous low dose oestradiol released from a vaginal ring compared with conjugated equine oestrogen vaginal cream in the treatment of postmenopausal urogenital atrophy. *Br J Obstet Gynaecol* 1996;103:351-8.
  32. Sherwin BB, Gelfand MM, Brender W. Androgen enhances sexual motivation in females: a prospective, crossover study of sex steroid administration in the surgical menopause. *Psychosom Med* 1985;47:339-51.
  33. Castelo-Branco C, Vicente JJ, Figueras F, Sanjuan A, Martinez de Osaba MJ, Casals E, et al. Comparative effects of estrogens plus androgens and tibolone on bone, lipid pattern and sexuality in postmenopausal women. *Maturitas* 2000 15;34:161-8.
  34. Shifren JL, Braunstein GD, Simon JA, Casson PR, Buster JE, Redmond GP, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 2000;343:682-8.
  35. Lobo RA, Rosen RC, Yang HM, Block B, Van Der Hoop RG. Comparative effects of oral esterified estrogens with and without methyltestosterone on endocrine profiles and dimensions of sexual function in postmenopausal women with hypoactive sexual desire. *Fertil Steril* 2003;79:1341-52.
  36. Penotti M, Sironi L, Cannata L, Vigano P, Casini A, Gabrielli L, et al. Effects of androgen supplementation of hormone replacement therapy on the vascular reactivity of cerebral arteries. *Fertil Steril* 2001;76:235-40.
  37. Dow MG, Hart DM, Forrest CA. Hormonal treatments of sexual unresponsiveness in postmenopausal women: a comparative study. *Br J Obstet Gynaecol* 1983;90:361-6.
  38. Braunstein GD, Sundwall DA, Katz M, Shifren JL, Buster JE, Simon JA, et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Arch Intern Med* 2005;165:1582-9.
  39. Sarrel P, Dobay B, Wiita B. Estrogen and estrogen-androgen replacement in postmenopausal women dissatisfied with estrogen-only therapy. Sexual behavior and neuroendocrine responses. *J Reprod Med* 1998;43:847-56.
  40. Davis SR, McCloud P, Strauss BJ, Burger H. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. *Maturitas* 1995;21:227-36.
  41. Floter A, Nathorst-Boos J, Carlstrom K, von Schoultz B. Addition of testosterone to estrogen replacement therapy in oophorectomized women: effects on sexuality and well-being. *Climacteric* 2002;5:357-65.
  42. Laughlin GA, Barrett-Connor E, Kritiz-Silverstein D, von Muhlen D. Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: the Rancho Bernardo Study. *J Clin Endocrinol Metab* 2000;85:645-51. Comment in: *J Clin Endocrinol Metab* 2001;86:1842-4.
  43. Kotz K, Alexander JL, Dennerstein L. Estrogen and androgen hormone therapy and well-being in surgically postmenopausal women. *J Womens Health (Larchmt)* 2006;15:898-908.
  44. Davis S. Androgen replacement in women: a commentary. *J Clin Endocrinol Metab* 1999;84:1886-91.
  45. Somboonporn W, Davis S, Seif MW, Bell R. Testosterone for peri- and postmenopausal women. *Cochrane Database Syst Rev* 2005;(4):CD004509.
  46. Sherwin BB. Use of combined estrogen-androgen preparations in the postmenopause: Evidence from clinical studies. *Int J Fertil Womens Med* 1998;43:98-103.
  47. Barrett-Connor E, Young R, Notelovitz M, Sullivan J, Wiita B, Yang HM, et al. A two-year, double-blind comparison of estrogen-androgen and conjugated estrogens in surgically menopausal women. Effects on bone mineral density, symptoms and lipid profiles. *J Repro Med* 1999;44:1012-20.
  48. Farish E, Fletcher CD, Hart DM, Azzawi FA, Abdalla HI, Gray CE. The effects of hormone implants on serum lipoproteins and steroid hormones in bilaterally oophorectomised women. *Acta Endocrinol (Copenh)* 1984;106:116-20.
  49. Raisz LG, Wiita B, Artis A, Bowen A, Schwartz S, Trahiotis M, et al. Comparison of the effects of estrogen alone and estrogen plus androgen on biochemical markers of bone formation and resorption in postmenopausal women. *J Clin Endocrinol Metab* 1996;81:37-43.
  50. Santoro N. Mechanisms of premature ovarian failure. *Ann Endocrinol (Paris)* 2003;64:87-92.
  51. Graziottin A, Basson R. Sexual dysfunction in women with premature menopause. *Menopause* 2004;11:766-77.
  52. Madalinska JB, van Beurden M, Bleiker EM, Valdimarsdottir HB, Hollenstein J, Massuger LF, et al. The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy. *J Clin Oncol* 2006;24:3576-82. Comment in: *J Clin Oncol* 2006;24:3519-21.
  53. Simon J, Braunstein G, Nachtigall L, Utian W, Katz M, Miller S, et al. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab* 2005;90:5226-33.
  54. Davis SR, van der Mooren MJ, van Lunsen RH, Lopes P, Ribot C, Rees M, et al. Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Menopause* 2006;13:387-96. Erratum in: *Menopause* 2006;13:850. Ribot, Jean [corrected to Ribot, Claude]. Comment in: *Menopause* 2006;13:328-30.
  55. Wu MH, Pan HA, Wang ST, Hsu CC, Chang FM, Huang KE. Quality of life and sexuality changes in postmenopausal women receiving tibolone therapy. *Climacteric* 2001;4:314-9.
  56. Egarter C, Topcuoglu A, Vogl S, Sator M. Hormone replacement therapy with tibolone: effects on sexual functioning in postmenopausal women. *Acta Obstet Gynecol Scand* 2002;81:649-53.
  57. Uygur D, Yesildaglar N, Erkaya S. Effect on sexual life – a comparison between tibolone and continuous combined conjugated equine estrogens and medroxyprogesterone acetate. *Gynecol Endocrinol* 2005;20:209-12.
  58. Hofling M, Carlstrom K, Svane G, Azavedo E, Kloosterboer H, Von Schoultz B. Different effects of tibolone and continuous combined estrogen plus progestogen hormone therapy on sex hormone binding globulin and free testosterone levels – an association with mammographic density. *Gynecol Endocrinol* 2005;20:110-5.
  59. Berman JR, Berman LA, Toler SM, Gill J, Haughie S; Sildenafil Study Group. Safety and efficacy of sildenafil citrate for the treatment of female sexual arousal disorder: a double-blind, placebo controlled study. *J Urol* 2003;170(6 Pt 1):2333-8.
  60. Basson R, Brotto LA. Sexual psychophysiology and effects of sildenafil citrate in oestrogenised women with acquired genital arousal disorder and impaired orgasm: a randomised controlled trial. *Br J Obstet Gynaecol* 2003;110:1014-24.
  61. Cayan S, Akbay E, Bozlu M, Canpolat B, Acar D, Ulusoy E. The prevalence of female sexual dysfunction and potential risk factors that may impair sexual function in Turkish women. *Urol Int* 2004;72:52-7.
  62. McInnes RA. Chronic illness and sexuality. *Med J Aust* 2003;179:263-6.

63. Heiman JR. Sexual dysfunction: overview of prevalence, etiological factors, and treatments. *J Sex Res* 2002;39:73-8.
64. Mooradian AD. Geriatric sexuality and chronic diseases. *Clin Geriatr Med* 1991;7:113-31.
65. Minton SE, Munster PN. Chemotherapy-induced amenorrhea and fertility in women undergoing adjuvant treatment for breast cancer. *Cancer Control* 2002;9:466-72.
66. Young-McCaughan S. Sexual functioning in women with breast cancer after treatment with adjuvant therapy. *Cancer Nurs* 1996;19:308-19.
67. Ganz PA, Coscarelli A, Fred C, Kahn B, Polinsky ML, Petersen L. Breast cancer survivors: psychosocial concerns and quality of life. *Breast Cancer Res Treat* 1996;38:183-99.
68. Broeckel JA, Thors CL, Jacobsen PB, Small M, Cox CE. Sexual functioning in long-term breast cancer survivors treated with adjuvant chemotherapy. *Breast Cancer Res Treat* 2002;75:241-8.
69. Ganz PA, Rowland JH, Meyerowitz BE, Desmond KA. Impact of different adjuvant therapy strategies on quality of life in breast cancer survivors. *Recent Results Cancer Res* 1998;152:396-411.
70. McPherson K, Herbert A, Judge A, Clarke A, Bridgman S, Maresh M, et al. Psychosexual health 5 years after hysterectomy: population-based comparison with endometrial ablation for dysfunctional uterine bleeding. *Health Expect* 2005;8:234-43.
71. Dennerstein L, Koochaki P, Barton I, Graziottin A. Hypoactive sexual desire disorder in menopausal women: a survey of Western European women. *J Sex Med* 2006;3:212-22.
72. Andersen BL, Anderson B, deProse C. Controlled prospective longitudinal study of women with cancer: I. Sexual functioning outcomes. *J Consult Clin Psychol* 1989;57:683-91.
73. Nathorst-Boos J, von Schoultz B, Carlstrom K. Elective ovarian removal and estrogen replacement therapy-effects on sexual life, psychological well-being and androgen status. *J Psychosom Obstet Gynaecol* 1993;14:283-93.
74. Aziz A, Bergquist C, Nordholm L, Moller A, Silfverstolpe G. Prophylactic oophorectomy at elective hysterectomy. Effects on psychological well-being at 1-year follow-up and its correlations to sexuality. *Maturitas* 2005;51:349-57.
75. Aziz A, Brannstrom M, Bergquist C, Silfverstolpe G. Perimenopausal androgen decline after oophorectomy does not influence sexuality or psychological well-being. *Fertil Steril* 2005;83:1021-8.
76. Kritz-Silverstein D, Goldani Von Muhlen D, Barrett-Connor E. Prevalence and clustering of menopausal symptoms in older women by hysterectomy and oophorectomy status. *J Womens Health Gend Based Med* 2000;9:747-55.
77. Ellstrom MA, Astrom M, Moller A, Olsson JH, Hahlin M. A randomized trial comparing changes in psychological well-being and sexuality after laparoscopic and abdominal hysterectomy. *Acta Obstet Gynecol Scand* 2003;82:871-5.
78. Zobbe V, Gimbel H, Andersen BM, Filtenborg T, Jakobsen K, Sorensen HC, et al. Sexuality after total vs. subtotal hysterectomy. *Acta Obstet Gynecol Scand* 2004;83:191-6. Comment in: *Acta Obstet Gynecol Scand* 2004;83:119-20.
79. Lonnee-Hoffmann RA, Schei B, Eriksson NH. Sexual experience of partners after hysterectomy, comparing subtotal with total abdominal hysterectomy. *Acta Obstet Gynecol Scand* 2006;85:1389-94.
80. Helstrom L, Sorbom D, Backstrom T. Influence of partner relationship on sexuality after subtotal hysterectomy. *Acta Obstet Gynecol Scand* 1995;74:142-6.
81. Penteado SR, Fonseca AM, Bagnoli VR, Assis JS, Pinotti JA. Sexuality in healthy postmenopausal women. *Climacteric* 2003;6:321-9.
82. Bachmann G, Bancroft J, Braunstein G, Burger H, Davis S, Dennerstein L, et al. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. *Fertil Steril* 2002;77:660-5.
83. Basson R, Leiblum S, Brotto L, Derogatis L, Fourcroy J, Fugl-Meyer K, et al. Definitions of women's sexual dysfunction reconsidered: advocating expansion and revision. *J Psychosom Obstet Gynaecol* 2003;24:221-9.
84. Basson R, Berman J, Burnett A, Derogatis L, Ferguson D, Fourcroy J, et al. Report of the international consensus development conference on female sexual dysfunction: definitions and classifications. *J Urol* 2000;163:888-93.