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Biological and Psychosocial Pathophysiology of Female Sexual Dysfunction During the Menopausal Transition

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Abstract

Introduction
Although increasing age is a primary determinant of reduced sexual function in older women, changes in the hormonal environment that accompany menopause are also believed to be significant contributors to female (and couples') sexual dysfunction. It is important to explore current understanding of the specific contributions of biological and psychosocial factors on sexual function changes with age.

Aim
To analyze the most relevant biological, psychosexual and/or contextual factors that influence changes in women's sexuality during and after the menopause.

Method
Literature review plus clinical observations.

Results
Menopause is associated with physiological and psychological changes that influence sexuality. During menopause, the primary biological change is a decrease in circulating estrogen levels. Estrogen deficiency initially accounts for irregular periods and diminished vaginal lubrication. Continual estrogen loss is associated with changes in the vascular, muscular and urogenital systems, as well as alterations in mood, sleep, and cognitive functioning; these influence sexual function through both direct and indirect mechanisms. The age dependent decline in testosterone and androgen function, starting in the early twenties, may precipitate or exacerbate aspects of female sexual dysfunction; these effects are most pronounced following bilateral ovariectomy and consequent loss of greater than 50% of total testosterone. The contribution of progestogens to sexual health and variability in the effects of specific progestogens are being increasingly appreciated. Comorbidities, influenced by loss of sexual hormones, between mood and desire disorders and urogenital and sexual pain disorders are common and remain frequently overlooked in clinical practice. Physical and psychosexual changes may contribute to lower self-esteem, poorer self-image, and diminished sexual responsiveness and sexual desire. Other important non hormonal factors that affect sexuality are health status and current medications; changes in or dissatisfaction with the partner relationship; the partner's general health and/or sexual problems; socioeconomic status; and cultural attitudes towards sexuality and older women.

Conclusions
An interdisciplinary medical and psychosexual approach to postmenopausal sexual dysfunction must comprise an individualized hormone therapy and specific psychosexual and pelvic floor rehabilitative treatment. Determination of the best way to provide optimal management of sexual dysfunction associated with menopause requires additional controlled studies.

Key words

Menopause; Sexuality; Sexual hormones; Estrogens; Progestogens; Testosterone; Hormone replacement therapy; Female sexual disorders

Introduction

The menopausal transition has been identified as the nexus of a variety of hormonal, physiological, emotional, psychosocial and relational changes that are associated with an increased risk for sexual dysfunction.[1-3] While much current research and existing literature has been directed at characterizing patterns of sexual dysfunction following menopause, it remains extremely important to understand the biological and psychosocial changes that occur during the menopausal transition itself.

Improved knowledge of these changes can provide a better foundation for understanding the development of concurrent and subsequent sexual dysfunction, with regard to both epidemiology and treatment of the individual patient. Increased appreciation of the importance of changes in androgen levels and activity during menopause and in response to hormone replacement therapy, for example, has already increased efforts to more accurately characterize and treat arousal and desire disorders.[4,5]

From an overall management perspective, recognition of the nature of changes during the menopausal transition may enable practitioners to better prepare their patients who are undergoing menopause. Moreover, effective treatment of postmenopausal sexual dysfunction of any type must be based on consideration of the etiological basis for that dysfunction.

It is important to emphasize that sexual dysfunction is rooted in a wide range of *predisposing*, *precipitating*, and *maintaining* factors, which may be of biological or psychosexual origin. In addition, contextual factors that are specific to the patient's own life history and situation may act in important predisposing, precipitating or maintaining roles (Table 1).[6] As suggested by Table 1, it should be noted that a given factor, issue, or situation can act in a predisposing, precipitating, or maintaining sense, depending on the woman's menopausal and sexual status.

Predisposing factors comprise constitutional and developmental influences of biological, psychological and contextual origin that render a person susceptible to dysfunction. Important predisposing factors include preexisting medical conditions, which may involve congenital, hormonal, and/or metabolic disorders; and underlying psychosocial considerations, such as body/sexual self-image, relationship issues, and life goal fulfillment, as well as psychiatric disorders. Contextual predisposing factors are centered on cultural, ethnic, and religious messages about sexuality, as well as the meanings attached to menopause itself; basic socioeconomic and social factors also profoundly increase or decrease vulnerability to FSD.

Precipitating factors include events, situations and/or comorbidities that are more directly and causally linked to the development of dysfunction. Menopause itself may be a biological precipitating event, when the loss of reproductive functions, severity of side effects, and/or urogenital comorbidity contribute to the development of FSD. Vaginal dryness, secondary to the loss of estrogen, is an example of a sexual symptom frequently linked to menopause. Loss of desire may also be precipitated by menopause; this effect may be more rapid and distressing in premature iatrogenic menopause following ovariectomy. Women at menopausal age frequently contend with multiple life-stage challenges that act as contextual factors.

Maintaining factors act to prolong or intensify the dysfunctional state. One critical and frequently overlooked maintaining factor is "diagnostic omission," the failure or inability of providers to acknowledge or recognize the reality of FSD and its existence in a specific patient. Other important maintaining factors in FSD include lack of treatment or inappropriate treatment for hormonal decline and the loss of intimacy and changes in feelings toward the partner.[2,7,8]

The aging process and the perimenopausal period involve multiple events and transitions that represent potential precipitating factors for sexual dysfunction. This article reviews characteristic biological and psychosocial changes during the menopausal transition, and available data on how they contribute to altered sexual function during the perimenopausal and postmenopausal years. We focus primarily on changes associated with natural menopause; however, because some distinctive features of iatrogenic menopause and/or premature ovarian failure help shed light on the development of sexual dysfunction,[9] these are addressed as well where appropriate.

Biological Changes Affecting Sexual Function During Menopause

Endocrinology of Biological Changes

The biological changes traditionally associated with menopause do not occur in isolation, but against a backdrop of age-related changes in *all* body systems. While these broader aging effects are not considered in detail, it is important to remember they frequently interact with "purely menopausal" changes and in many cases may exacerbate their impact. However, the evidence is compelling that menopause *per se*, rather than more generalized changes due to aging, is a primary precipitating factor for changes in sexual function; this is much more evident in premature, iatrogenic menopause.[1,9]

The characteristic trigger of natural menopause is a decline in ovarian function, leading to a cessation of ovulation and a reduction in circulating levels of estradiol, from a range of 50 to 300 pg/mL (at the early follicular and late follicular phases of the menstrual cycle, respectively) to less than 30 pg/mL (Table 2). The small amount of circulating estradiol in postmenopausal women is thought to be the result of local tissue conversion of testosterone via aromatase activity.[10-12] The quantity of total estrogen still available depends on two factors: the intensity and rate of ovarian exhaustion (the degree and extent of estrogen depletion varies extensively between individuals); and the amount of adipose tissue, which functions as an endocrine gland. A higher body mass index is associated with increased production of estrone, via conversion of adrenal and residual ovarian androgens by aromatases in adipose tissue.

The complete passage from the reproductive years to postmenopause has recently been described, by the Stages of Reproductive Aging Workshop (STRAW), in terms of stages defined by menstrual cycle length and frequency (see article by Dennerstein in this supplement). Much current research and literature on postmenopausal sexual dysfunction has focused on comparing postmenopausal women to premenopausal women. However, it is important to emphasize that changes in the hormonal milieu, including reduction in circulating estradiol levels, as well as the resulting physiological responses and tissue effects, are most pronounced during the perimenopausal stage, comprising the early and late menopausal transition periods.[13,14]

The 5- to 10-fold reduction in circulating estradiol that occurs during perimenopause has profound structural and functional consequences for the reproductive tract and surrounding tissues. Loss of estrogen (in addition to a concurrent decline in circulating androgens) contributes to reduced overall blood flow and attenuated vasocongestion with sexual activity. Typical changes in external (labia minora, labia majora, clitoris) and internal (vagina, uterus) reproductive components include reduction in size, thinning of skin and mucous membranes, parallel involution of the corpus cavernosa, and loss of subcutaneous fat.[11,15]

These changes are accompanied by significant alterations in the urinary tract, including reductions in intraurethral pressure, bladder size, and thickness of the mucous membranes lining the bladder and urethra. In addition, there is significant reduction in pelvic muscle tone and in the resilience of connective-tissue support for urogenital structures (such as the uterosacral ligament), which is associated with increased risk for uterovaginal prolapse.[11, 16] An increasing degree of urogynecologic and sexual comorbidity with increasing age is an important feature in women, in addition to comorbidity with a range of dysmetabolic, neurologic, and immunologic disorders or dysfunction. In the epidemiological survey by Laumann and colleagues, the presence of urinary tract symptoms strongly increased the risk of both arousal disorders (RR=4.02; 95% CI 2.75 to 5.89) and sexual pain disorders (RR=7.61, 95% CI 4.06 to 14.26).[17]

Central and peripheral nervous system function is strongly affected by reduction in ovarian hormones; these changes may both drive and be driven by urogenital structural and functional alterations. Hormonal fluctuations during the menstrual cycle have been linked with significant variation in sensory capabilities and response, and studies in oophorectomized rats have revealed that the size of the pudendal-nerve response increases with exogenous estrogen.[18-20] In addition, multiple neurotransmitter systems in the brain, especially the areas known to regulate mood and desire (including the amygdala, hippocampus and hypothalamus) are heavily influenced by sex hormones.[21,22]

As shown in Table 2, the serum levels of testosterone and of proandrogens exceed that of estradiol, even during peak reproductive years, by several-fold to several thousand-fold.[10] In women, about half of circulating testosterone is secreted directly by the ovarian stroma and adrenal zona fasciculata in roughly equal quantities; the other half is derived from conversion of the proandrogen androstenedione, which is secreted by the same tissues. The proandrogen dehydroepiandrosterone sulfate (DHEAS) is produced entirely in the adrenal zona reticularis; conversion of DHEAS accounts for about 30% of circulating dehydroepiandrosterone (DHEA), with the remaining DHEA secreted by the adrenal zona reticularis and the ovarian theca.[23]

The role of androgens in maintaining urogenital health and sexual function during and after menopause (in addition to their importance in overall health, mood and sexual desire) is the subject of much current research, although interest in androgens as a component of gynecological care dates to the 1940s.[7,24,25] In contrast to the relatively sharp decline in circulating estrogens during natural menopause, androgen levels tend to peak when women are in their 20s and drop gradually with age; typical serum levels of testosterone and androstenedione at age 60 are about half those at age 40.[2,26,27]

Much of the current understanding of androgen effects in women has been derived from the symptomatology of women with androgen insufficiency (Table 3).[24] To some extent, progress in this area has been limited by difficulty in defining the “normal” range of androgen levels in women; it has not been possible to date to establish a threshold level for androgen insufficiency. In addition, the vagueness of these symptoms and the possibility that they potentially stem from a range of causative factors have made it difficult to firmly tie them to reduced androgen levels.[24]

However, the pattern of symptoms, and symptom frequency, following bilateral oophorectomy (surgical menopause) has validated their tie to androgen deficiency. In Figure 1, the secretory contributions of the ovaries, adrenals, and peripheral tissues for the principal proandrogens and androgens are compared for pre- and postmenopausal women. As can be seen, the proportion of testosterone contributed by the ovaries rises dramatically after menopause, from under

30% to about 50%; thus, oophorectomy removes a substantial source of circulating testosterone.[23,28] It has been reported that in contrast to the 50% of women who report severe symptoms following natural menopause, about 90% experience severe symptoms following surgical menopause, in which a primary source of androgens has been removed.[26]

In addition, women who have undergone chemotherapy or pelvic/whole body radiation therapy for cancer treatment may also experience iatrogenic androgen loss. Despite having ovaries in place, such therapies may irreversibly destroy not only follicles but the Leydig cells that are responsible for ovarian androgen production, leading to characteristic symptoms of androgen deficiency. These women constitute an often-unrecognized subgroup of iatrogenic menopause patients.[6]

Other research has shown that the prevalence of sexual desire disorders is also higher among women following surgical menopause. A recent European survey of 2467 women (in France, UK, Germany and Italy) showed that in the age cohort from 20 to 49 the percentage of women with low sexual desire is 19%, but is 32% in women who have undergone surgical menopause; this difference disappears when comparing naturally post-menopausal women (ages 50 to 70) and age-matched surgically menopausal women (46% and 48%, respectively). The percentage of women *distressed* by their HSDD was 27% in fertile women and 28% after surgical menopause in the age cohort 20 to 49, compared to 11% in women with natural menopause and 14% in those with surgical menopause in the age cohort 50 to 70.[29] Thus although the probability of HSDD increases with age, the *distress* associated with the loss of desire is inversely correlated with age.[30]

The recognition of androgen deficiency symptoms, in addition to research into the positive contribution of androgens, has led to the development of a list of putatively androgen-influenced health impacts in women (Table 4).[7,25,31] The levels of endogenous testosterone typically observed in healthy women are near or below the approximate threshold for testosterone deficiency in men, suggesting that at least certain of these effects may be more responsive to testosterone in women than in men. In addition, there is evidence that women may vary more extensively than men in the degree to which sexual physiology and behavior respond to androgens.[31]

In a small-scale study in naturally postmenopausal women with low sexual desire, testosterone augmentation of estrogen replacement therapy was associated with significantly greater improvement than estrogen therapy alone in measures of sexual interest, desire and frequency of desire.[5] Testosterone treatment in oophorectomized women has been found to increase sexual interest and enjoyment, pleasure and orgasm, and frequency of sexual activity when added to traditional estrogen-only therapy; in one study, the proportion of women engaging in sexual activity or having sexual fantasies at least once weekly increased 2- to 3-fold over baseline.[32,33]

The contribution of androgens to sexual health and function has important implications for traditional hormone replacement therapy (HRT) using conjugated estrogens (typically combined with progestogens). Estrogens down-regulate the expression of androgen receptors (and vice versa). Moreover, they appear to reduce the level of bioavailable androgens through another important mechanism.

Only 2% of circulating testosterone exists in the free state; of the remaining 98%, about one quarter is loosely bound to serum albumin, while three quarters is tightly bound to sex hormone-binding globulin (SHBG) or cortisol-binding globulin (CBG) and is generally unavailable for receptor binding. Similar patterns are also observed for dihydrotestosterone.[28] Oral estrogens strongly induce increased hepatic production of SHBG; this effect is not observed with transdermal administration, suggesting that it is dependent on first-pass metabolism.[34] The increased level of SHBG with oral estrogen therapy leads to increased sequestering, and reduced bioavailability, of testosterone and other androgens.[28]

The observed effect of HRT on androgen availability has led to recommendations that estrogens should be routinely augmented with androgens in postmenopausal women. In a randomized trial, combined estrogen-androgen therapy was associated with a significant reduction in menopausal vasomotor symptoms compared to estrogen therapy alone.[28,35] A study of transdermal testosterone therapy in surgically menopausal women showed a significant increase compared to placebo in sexual functioning and psychological well-being.[32]

The contributions of progesterone and progestogens to sexual health are being increasingly appreciated, in conjunction with more detailed understanding of the differential effects of different progestogenic hormones. Until recently, these hormones were considered to differ primarily with regard to potency, but are now understood to vary extensively with regard to spectrum of activity. Some of this variability is related to molecule of origin: 17-OH-progesterone, 19-nor-testosterone or 17-alfa-spironolactone. A summary of putative interactions between progesterone and progestogens and a variety of steroid receptors is provided as Table 5.[36-42]

Progesterone and progestogens, on balance, exert somewhat androgenic effects, through 3 separate mechanisms:

- Binding affinity to SHBG and CBG, which varies greatly among different progestogens; binding of progestogens may displace testosterone and other androgens, freeing the androgens for biological activity.
- Interaction with androgenic and other receptor types; progestogens may also interact with estrogenic, glucocorticoid, and mineralocorticoid receptors in both agonistic and antagonistic fashion (Table 5).[36-42]

- Direct interaction with intracellular enzymes, such as type 2 5-alpha reductase.

In addition, factors that influence differential progestogen effects include:

- Differential interaction with progestogen receptors PG-A (currently regarded as the primary progestogen receptor) and PG-B (which may act antagonistically to PG-A activation);
- Differences in interaction with other steroid membrane receptors, and differing activity and intracellular concentration of steroid-receptor complexes, which influence the ultimate effect of a given progestogen on gene expression;

Increasing understanding of these effects, as well as the ways in which pharmacokinetic behavior of specific progestogens is influenced by route of administration and extent of hepatic metabolism, should help practitioners further refine hormonal replacement approaches. The positive effects of the synthetic hormone tibolone on sexuality may derive significantly from the combination of androgenic, progestogenic and estrogenic properties in the same molecule.

In general, the observations regarding the importance of androgens in mediating the health of the reproductive tract, and the probable need to combine androgens with estrogens for complete hormonal supplementation following menopause, are analogous to the 30 years of clinical experience that demonstrated the need to supplement estrogens with progestogens to avoid endometrial hyperplasia and increased risk of endometrial cancer. The emerging appreciation of the importance of progestogens, and the variability in the effects of specific progestogens, is following a course similar to that observed with androgens.[43] Taken in total, these experiences point to the need to consider *all* ovarian hormones when planning replacement therapy.[26]

Endocrinological Drivers for Biological Correlates of Sexual Dysfunction

The changes in the hormonal milieu that occur during menopause are translated into increased risk of perimenopausal and postmenopausal sexual dysfunction through a variety of biological effects. The increasing appreciation of the complexity of female sexual response has led to a reappraisal and proposed revision of the classification of sexual disorders (see article by Dennerstein in this supplement). However, it is precisely this complexity that also makes it difficult to strictly tie the biological signs and symptoms of changes in the hormonal milieu to specific disorders.

Similarly, although the emerging consensus regarding the role of androgens in sexual health function has deepened our understanding of the complexity of hormonal influences, it has made the characterization of the specific etiology for a given biological effect more challenging. Estrogens and androgens act at times in opposition, and at other times in conjunction. An excellent example is in the vagina: both estrogens and androgens appear to be important in maintenance of vaginal blood flow, but androgens promote nonvascular smooth muscle relaxation while estrogens attenuate it.[25]

Nonetheless, it is possible to describe broad changes in biological structure and function, and in manifested symptoms, that are driven by hormonal influences during the menopausal transition. Figure 2 illustrates the characteristic time course of menopausal signs and symptoms; the most prominent features of the perimenopause (which is also characterized by the most significant drop in mean estradiol levels) include hot flushes/night sweats, urogenital symptoms (especially vaginal dryness) and sleep disturbances. The prevalence and severity of these symptoms vary somewhat across cultural and national boundaries, with Asian women reporting somewhat lower prevalence than Caucasian women.[44,45] However, across all groups, perimenopause has been consistently identified as the stage involving the highest incidence and greatest intensity of menopausal symptoms.[46-50]

For example, the prevalence of vaginal dryness increases dramatically from early to late perimenopause (Figure 3) and only gradually during postmenopause; vaginal tissue integrity and lubrication is affected by both estrogens and androgens.[25,48] The prevalence of dyspareunia (painful intercourse) also increases dramatically during this period and is significantly associated with vaginal dryness and low estradiol levels.[51]

Increased prevalence of lower urinary tract symptoms (LUTS) and urinary incontinence is associated with both systemic aging and with menopause.[52-55] Women with LUTS have more than a 7-fold greater risk for sexual pain disorders, and a 4-fold greater risk for sexual arousal disorders, than women without such symptoms.[17] Hypotonia and hypertonia of the pelvic floor muscles, which increase in prevalence with age, can also contribute to sexual pain.[7]

The decline in estrogens at menopause occurs concurrently with an increased risk for depression, which, as discussed below, is associated with high risk of sexual dysfunction.[56-58] Although several studies have demonstrated that this risk is driven by symptoms, especially vasomotor instability, and not by a direct effect of reduced estrogen on mood, some studies have also suggested that menopause may be associated with reduced endorphin levels.[59,60] The positive effects of tibolone on mood may in part derive from restoration of endorphin levels.[61]

It seems reasonable to conclude, based on the evidence available to date, that the precipitous drop in estrogen levels during the menopausal transition is the most important *underlying* biological precipitating factor for peri- and postmenopausal sexual dysfunction. Estrogen insufficiency is manifested through more immediate symptomatic factors

(vasomotor instability, vaginal dryness, urological symptoms) that contribute to arousal, desire and sexual pain disorders.

The gradual drop in androgen levels with age may also be a precipitating factor, and in surgical menopause the influence of androgen reduction may be comparable to or even greater than that of estrogen reduction. In natural menopause, androgens may also act as a predisposing factor; women with constitutionally low androgen levels (and/or those with limited responsiveness to androgens) may experience a "threshold effect" with the typical age-related reduction in androgen level. In addition, the role of progestogens on sexual well-being and other aspects of sexual function, overlooked until recently, should be more fully explored.

Psychosocial Factors Affecting Sexual Function and Dysfunction

The complex interplay of historical (predisposing) and current (precipitating, maintaining and contextual) factors can be especially hard to dissect with regard to psychosocial influences on sexual function and dysfunction. The subjective nature of these influences, as well as the challenges involved in their assessment and quantification, has limited the ability to conduct large-scale studies and to reach evidence-based conclusions. Moreover, it is clear that associations between many psychosocial factors (e.g., depression) and sexual dysfunction may be bidirectional in terms of causation.

Several studies, however, have demonstrated strong correlations between psychosocial factors and the prevalence for sexual dysfunction in women. As shown in Figure 4, the presence of a range of sexual symptoms and disorders is associated with elevated odds ratios, ranging from 2- to 6-fold, for anxiety and depression.[62] As noted above, bidirectional causation may drive these associations; directionality may differ between individual patients and may be cyclic in nature for many patients. In addition, treatment with certain antidepressants increases the risk of sexual dysfunction.

However, significantly increased odds for sexual arousal, desire and pain disorders have also been demonstrated for conditions for which causation is unlikely to be reciprocal, including poor overall health, emotional problems or stress, change in social status, and a history of sexual coercion (Figure 5).[17]

Aging and menopause bring on significant changes in body image that are driven by weight gain, body shape changes, changes in facial appearance, and self-consciousness about other health issues, such as incontinence. These may lead to an extended period of grief over lost youth and beauty, as well as increasing the risk of anxiety and depression. The partner is also undergoing changes of aging and may no longer elicit the same degree of sexual attraction or chemistry from the woman.

Partner issues and relationship dynamics are frequent contributors to sexual dysfunction. Partner availability can be a significant problem for aging women, because of divorce, partner death or chronic illness, partner sexual dysfunction (including both organic and psychological dysfunction), or extramarital affairs. Changes related to aging in both women and their partners frequently exacerbate preexisting relationship problems that may be marked by poor communication and mismatch of sexual "scripts" or sexual interest, especially in an era when men have been sexually rejuvenated by treatment for erectile dysfunction.

Both partners are likely to undergo decreased sexual responsiveness with aging, which can lead to "performance anxiety" and even boredom. Most relationships of long duration undergo a gradual diminution of sexual frequency, although this does not necessarily lead to decreased satisfaction. However, a history of infidelity or emotional detachment on the part of the partner can lead to anger, rage or disaffection, and ultimately to sexual "retirement." Low levels of relationship satisfaction, as well as low frequency of sexual activity and increased distress, have been strongly associated with attenuated sexual desire.[63,64] The importance of relationship issues as a driver of sexual dysfunction suggests that psychotherapy that addresses these issues as part of a global approach to dysfunction may enjoy more long-term success than strict attention to sexual issues.

Conclusions

As is the case with sexual function, sexual dysfunction involves the interaction of multiple developmental, historical, endocrinological and psychosocial factors in ways that differ profoundly between patients. Great progress has been made over the past 2 decades in clarifying and deciphering many of the hormonal and physiological influences on sexual dysfunction during and following natural and iatrogenic menopausal transition. These advances have already resulted in improved paradigms for addressing the biological drivers of sexual dysfunction.

At this point, the ways in which the complex web of psychosocial factors involved in the menopausal transition is transduced into increased or reduced risk of sexual function remain far less clear. However, continued study into the relationship between these factors and the development of various types of sexual dysfunction will undoubtedly result in better treatment approaches that facilitate improved patient outcomes.

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Table 1. Aetiology of Postmenopausal Sexual Dysfunction: Contributing Factors

I. PREDISPOSING FACTORS

A. Biological

- Endocrine disorders
- Menstrual cycle disorders / Premenstrual syndrome
- History of surgical intervention or medical illness
- Drug treatments affecting hormones or menstrual cycle
- Disorders associated with premature ovarian failure (POF):
    - Genetic: Turner's syndrome, Fragile X syndrome, mosaicism, deletions/inversions
    - Autoimmune: Systemic lupus erythematosus, rheumatoid arthritis
- Chronic disorders: renal or hepatic insufficiency, primary biliary cirrhosis
- Benign neoplasms (e.g., endometriosis) predisposing to iatrogenic menopause
- Iatrogenic menopause: bilateral ovariectomy, chemotherapy, radiotherapy
- Persistent residual conditions (e.g., dyspareunia/chronic pain associated with endometriosis)

B. Psychosexual

- Previous sexual experiences; quality of and satisfaction with sexual experiences during fertile years
- Life goal fulfillment (or lack of fulfillment) prior to menopause
- Body image issues/concerns
- Personality traits and temperament (inhibition vs. excitation, outgoing vs. shy)
- Attachment dynamics with partner and/or relatives
- History of sexual coercion, violence, or abuse
- Affective disorders (dysthymia, depression, anxiety)
- Coping strategies
- Social / Professional role(s)

C. Contextual

- Ethnic/religious/cultural messages, expectations, and constraints regarding sexuality
- Social meanings attached to menopause
- Cultural meaning of sexuality
- Socioeconomic status/access to medical care and facilities
- Support network

II. PRECIPITATING FACTORS

A. Biological

- Age at menopause
    - Premature ovarian failure (POF) – menopause before age 40
    - Premature menopause – menopause between age 40 and 45
- Biological vs. iatrogenic menopause (especially for premature menopause)
- Iatrogenic menopause
    - Androgen loss
    - Associated disorder/disease
- Extent and severity of menopausal symptoms
    - Impact on well-being, sexuality
- Current disorders
- Current pharmacological treatment
- Substance abuse (especially alcohol)

B. Psychosexual

- Relationship of fertility loss to fulfillment of life goals
- Unpleasant/humiliating sexual encounters or experiences

- Affective disorders (depression, anxiety)
- Loss of loving feelings toward partner

C. Contextual

- Relationship discord
- Life-stage stressors (e.g., divorce, separation, partner infidelity)
- Loss or death of close friends or family members
- Lack of access to medical/psychosocial treatment and facilities
- Economic difficulties

III. MAINTAINING FACTORS

A. Biological

- Multisystemic changes secondary to menopause
  - Hormonal
  - Vascular
  - Muscular
  - Neurological
  - Immunological
- Contraindications to hormone replacement therapy (HRT)
- Inadequacy of HRT in ameliorating biological symptoms
- Untreated or inadequately treated comorbities:
  - Urologic: Incontinence, LUTS, urogenital prolapse
  - Metabolic: Diabetes
  - Psychiatric: depression, anxiety, phobias
- Pharmacological treatments
- Substance abuse

B. Psychosocial

- Negative perception of menopause-associated changes
- Body image concerns and increased body changes (wrinkles, body shape/weight, muscle tone)
- Loss of sexual self-confidence or performance anxiety
- Diminished affection for, or attraction to, partner
- Affective disorders
- Distress (personal, emotional, occupational, sexual)

C. Contextual

- Omission of menopause and FSD from provider's diagnostic and therapeutic approach
- Lack of access to adequate care
- Partner general health or sexual problems or concerns
- Ongoing interpersonal conflict (with partner or others)
- Environmental constraints (lack of privacy, lack of time)

Adapted from:

Graziottin A.
Female sexual dysfunction: Assessment
in: Bø K. Berghmans B. Mørkved S. Van Kampen M. (Eds), Evidence-Based Physical Therapy For The Pelvic Floor - Bridging Science and Clinical Practice, Elsevier, Oxford, UK, 2007, p. 266-277

Table 2. Typical premenopausal and postmenopausal serum steroid hormone concentrations

	Typical Serum Level, pg/mL		
Steroid Hormone	**Reproductive Age**	**Natural Menopause**	**Iatrogenic Menopause**
Estradiol	100–150	10–15	10
Testosterone	400	290	110
Androstenedione	1900	1000	700
DHEA	5000	2000	1800
DHEAS	3,000,000	1,000,000	1,000,000

DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate.

(Adapted from Lobo RA, 1999.[10])

Table 3. Signs and symptoms associated with androgen deficiency in women

- Reduced sexual motivation, sexual fantasizing
- Reduced sexual enjoyment, sexual arousal
- Reduced vaginal vasocongestion
- Reduced bone and muscle mass
- Reduced quality of life (mood, affect, energy)
- Increased vasomotor instability (hot flushes)
- More frequent insomnia
- More frequent depression
- More frequent headache

(Adapted from Bachmann GA, 2002.[24])

Table 4. Putative effects of androgens in women

- Triggering of libido and central arousal
- Modulation of peripheral arousal
- Facilitation of nitric oxide–mediated smooth muscle relaxation
- Elevation of clitoral and nipple sensitivity and responsiveness
- Increase in sense of well-being and assertiveness
- Modulation of skin texture and scent

(Adapted from Graziottin A, 2004.[7])

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The Journal of Sexual Medicine 2005; 2 (suppl. 3): 133-145

Table 5. Putative Receptor Interactions of Progesterone and Selected Progestogens*

	Receptor Class				
Hormone	**Progestinic**	**Androgenic**	**Estrogenic**	**Glucocorticoid**	**Mineralocorticoid**
Progesterone	++	0 / -	0 / -	0 / +	0 / -
17a-hydroxyprogesterone-derived:					
Cyproterone acetate	++	---	0 / -	+	0
Medrogestone	++	-	0 / -	0	0
Medroxyprogesterone acetate	+++	0 / +	0 / -	+	++
Dydrogesterone	++	0 / -	0 / -	0	0 / -
19-nor progesterone-derived:					
Nomegestrol acetate	+++	--	0 / -	+	0
Megestrol	++	+	0 / -	+	0
19-nor testosterone-derived:					
Estranes					
Norethisterone	++	++	+	0 /-	0 / +
Norethisterone acetate	++	+++	+	+	+
18-ethylgonanes					
Levonorgestrel	+++	+++	0 / -	0	0 / +
Desogestrel	++	0 / -	0 / -	0 / +	0
Gestodene	+++	+	0 / -	+	-
Norgestimate	++	0 / -	0 / -	0	0 / -
17-α-spirinoloctone-derived:					
Drospirenone	++	---	0 / -	0	---

Legend: 0, no interaction/neutral; +, weakly agonistic; ++, moderately agonistic; +++, strongly agonistic; -, weakly antagonistic; --, moderately antagonistic; ---, strongly antagonistic.

***Based on a number of published studies and reviews, including:[36-42]**

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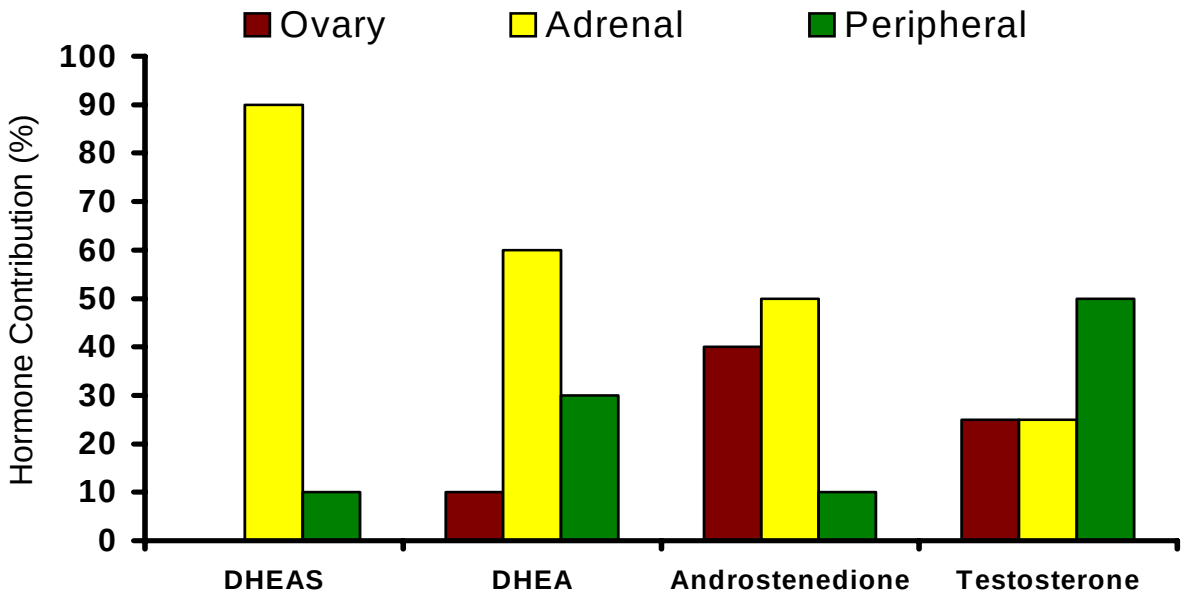
Figure 1. Androgen production: contribution from various tissues

(Top) Premenopause
(Bottom) Postmenopause (natural menopause)
(Adapted from Simon JA[28])



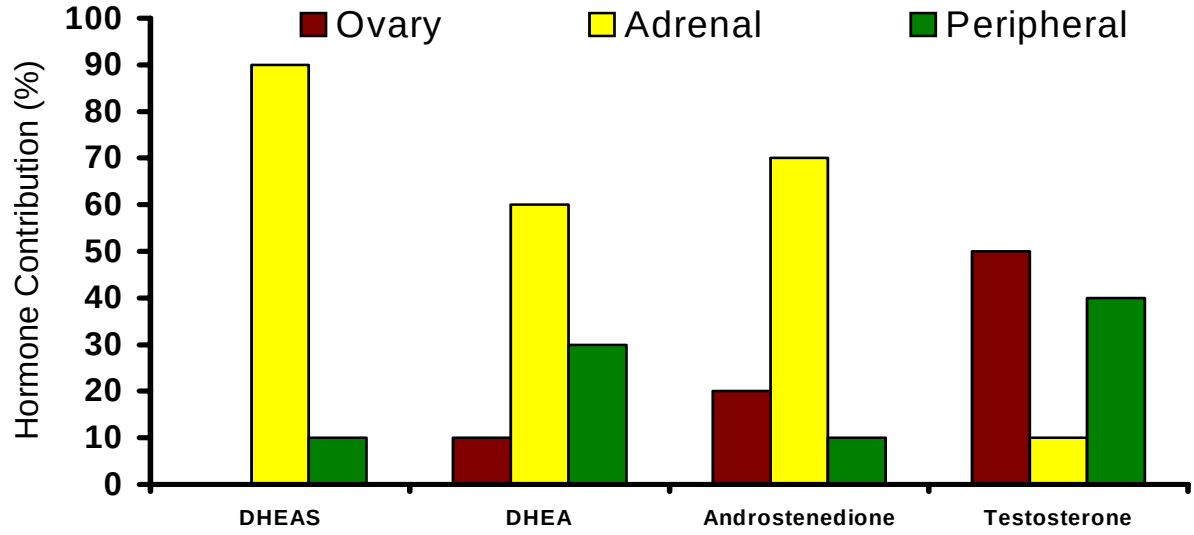


Figure 2. Temporal pattern of menopause-related symptoms

Modified from © JL Alexander, www.afwh.org

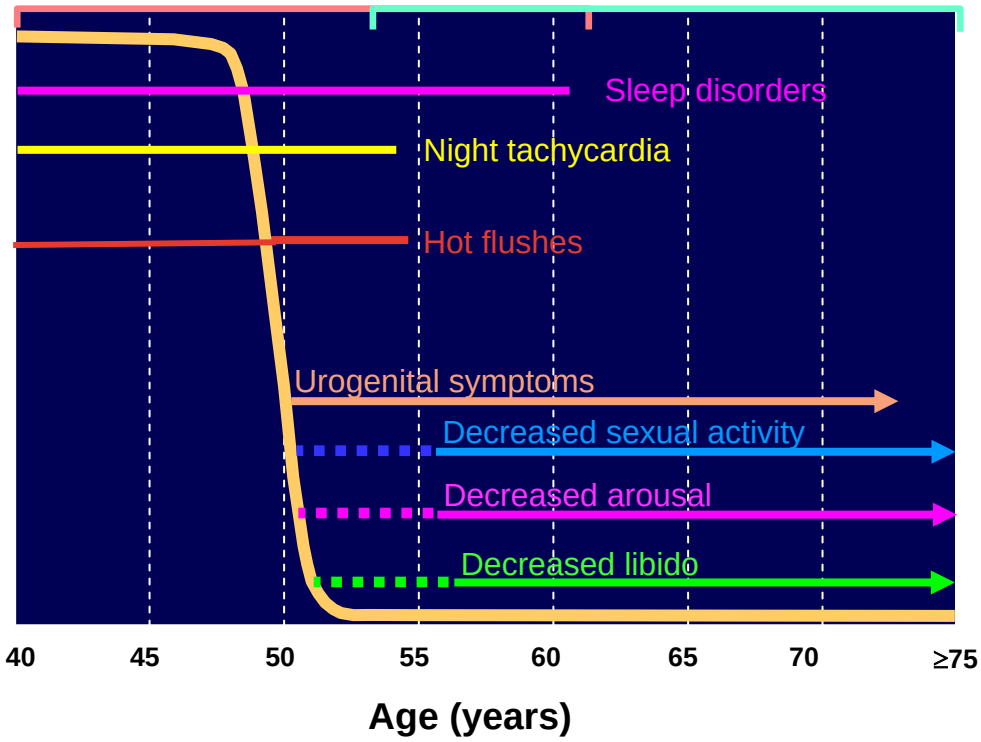


Figure 3. Prevalence of vaginal dryness during pre-, peri- and postmenopause

(Adapted from Dennerstein et al., 2000.[48])

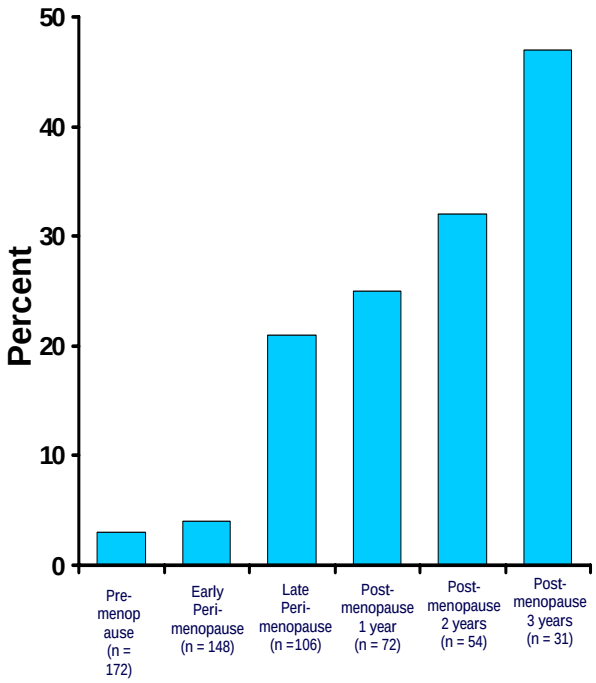


Figure 4. Association between anxiety and depression and sexual dysfunction

(Adapted from Dunn KM, 1999.[62])

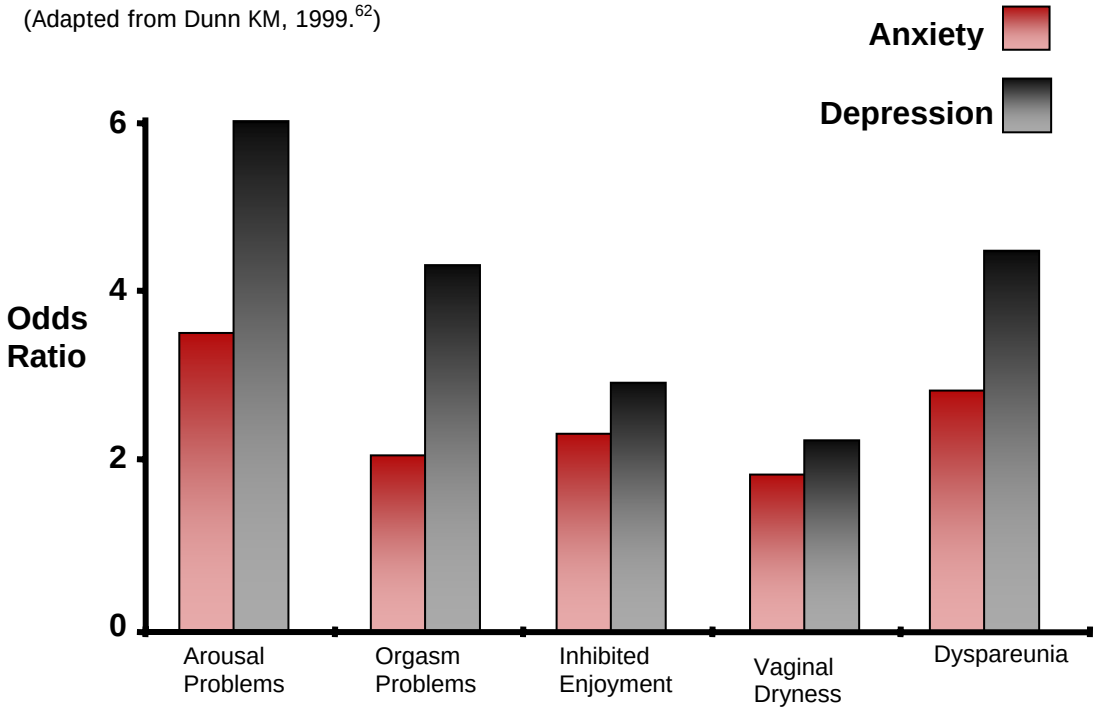


Figure 5. Association of sexual dysfunction with psychosocial factors

(Adapted from Laumann et al., 1999.[17])