



Literature Review: Menopause and Sexual Disorders

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ABSTRACT

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Menopause is a permanent termination of the menstrual cycle caused by the loss of activity of ovarian follicles which is enforced when experiencing amenorrhea for 12 months. The mean age for women to stop menstruating was 51.5 years. The cause of menopause is a decrease in ovarian hormones. When the ovaries stop working and estrogen levels drop, a woman will experience several complaints such as changes in menstrual patterns, vasomotor, somatic, and psychological complaints, sleep disorders, sexual disorders, urogenital disorders, osteoporosis, and cardiovascular disease. Physical, psychological, social, and cultural factors are factors that influence women's sexual function. The ageing process is known to increase the prevalence of sexual dysfunction. Female sexual dysfunction prevalence is quite high, range from 38% to 85.2%. Sexual disorders can take many forms and clinical symptoms. Circulating estrogen levels have been shown to influence sexual desire, activity, experiences, and problems in sexually active postmenopausal women. Deficiency of estrogen will cause vaginal atrophy which can affect sexual dysfunction. Many factors influence sexual dysfunction, both biological and psychological, in postmenopausal women. The goal of managing sexual disorders in postmenopausal women is to maintain age-related function. Vulvovaginal complaints should be managed individualized and depend on the severity of symptoms, medical history, and lifestyle of the patient.

Background

According to data from the statistical agency, the increase in the number of Indonesian women who experienced menopause in the period 1995–2005 was around 14 million, with a population of women aged 50–60 years and over 15.9 million, and it is estimated that in 2025 it will reach 60 million women who experience menopause.

During the climacteric period, there is a rapid decrease in gonadal hormones, which causes neuroendocrine changes in various brain regions. Chronic hypoestrogenism due to postmenopausal conditions is very important in the pathogenesis of mood and cognitive disorders. Steroid sex hormone receptors have been identified in several regions of the central nervous system. It is contribute to changes in mood, behavior, and nociception in menopausal women [1].

Menopause

Definition

Menopause is a natural phase in a woman's life which is marked by the end of the menstrual cycle and the fertile period, which occurs because the ovaries do not produce or do not produce estrogen [1], [2], [3].

Epidemiology

The average age of women who stop menstruating is at the age of 51.5 years, about 5% stop between the ages of 40 and 45 years (early menopause), and 5% occur at the age above 55 years (late menopause), and another quarter continues menstruating until past the age of 50 years. According to data from the statistical agency, the increase in the number of Indonesian women who experienced menopause in the period 1995–2005 was around 14 million, with a population of women aged

50–60 years and over 15.9 million, and it is estimated that in 2025 it will reach 60 million women who experience menopause [3], [4], [5]

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Etiopathogenesis

Death, which induces a decrease in ovarian hormones and a rise in the pituitary gonadotropin hormone, triggers menopause. There are only a few primordial follicles which have to be stimulated by FSH and LH at around 45 years of age; as the number of primordial follicles reaches zero, the development of estrogen from the ovaries decreases. It will no longer inhibit the production of FSH and LH gonadotropin when the production of estrogen falls below a critical value. In comparison, FSH and LH (especially FSH) gonadotropins are released in large and continuous amounts after menopause, but when the remaining primordial follicles become atretic, the ovaries actually drop to zero caused by the estrogen [4], [6], [7].

Climacteric phase

Climacteric is a transition period from the reproductive phase to the old age phase (selenium) which occurs due to decreased sexual and endocrinological functions of the ovaries (Figure 1) [8]. The climacteric phase consists of 4, namely the premenopausal stage, the perimenopause stage, the menopause stage, and the post/postmenopausal stage (Figure 2) [9], [10].

Clinical symptoms

When the ovaries not working and reduce the estrogen levels, several complaints will experienced such as menstrual disorders, vasomotor instability, hot flushes, night sweats, arthralgia, myalgia, mood

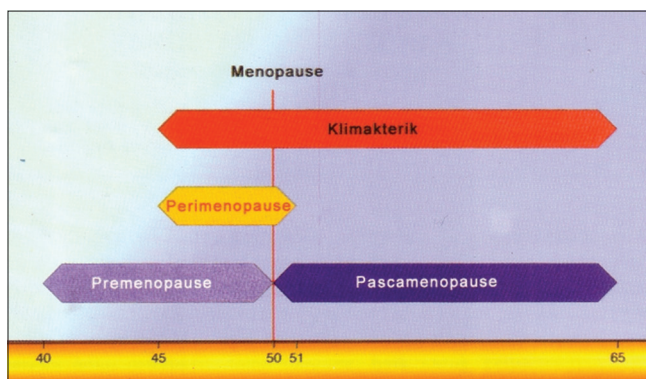


Figure 1: Climacteric phase [8]

disorders, sexual dysfunction, and short-term memory problems, psychological disorders (e.g., sleep disorders, mood lability, and depressive symptoms), which can affect the quality of life [11], [12], [13].

There are two types of symptoms: vasomotor disorders consisting of hot flushes and night sweats, occurring in 75% of postmenopausal women with varying degrees of severity and urogenital symptoms as a result of estrogen deficiency causing urethral and vaginal atrophy. The vaginal wall will thin and atrophy of the vaginal glands will occur, resulting in reduced lubrication and causing dyspareunia [14].

The effect of menopause on the central nervous system

During the climacteric period, there is a rapid decrease in gonadal hormones, which causes neuroendocrine changes in various brain regions. Chronic hypoestrogenism due to postmenopausal conditions is very important in the pathogenesis of mood and cognitive disorders. Steroid sex hormone receptors have been identified in several regions of the central nervous system [15].

Some studies have shown that neuroendocrine control of the thermoregulatory center in the hypothalamus involved by opioid neuropeptide. In addition, menopause is also associated with decreased levels of endorphins- β (β -EP), whereas vasomotor symptoms are associated with sudden increases in β -EP due to activation of the hypothalamic-pituitary (GnRH, LH, FSH) axis during hot flushes. Menopause also induces changes in the synthesis and secretion of β -EP which contribute to changes in mood, behavior, and nociception in menopausal women [15].

Menopause and Depression

There are several depressions that are associated with hormonal reproductive changes in

		Final Menstrual Period (FMP)								
		-5	-4	-3	-2	-1	0	+1	+2	
Terminology:		Reproductive			Menopausal Transition		Postmenopause			
		Early	Peak	Late	Early	Late*	Early*	Late		
							Perimenopause			
Duration of Stage:		Variable			Variable		a	b	Until demise	
							1 yr	4 yrs		
Menstrual Cycles:		Variable to Regular	Regular		Variable cycle length (>7 days different from normal)	≥ Skipped cycles and an interval of amenorrhea (≥60 days)		None		
						Amenorrhea ≥ 12 mos				
Endocrine:		Normal FSH		↑ FSH		↑ FSH		↑ FSH		
		*Stages most likely to be characterized by vasomotor symptoms					↑ = elevated			
<small>Source: Scharge JO, Schaffer J, Halverson LM, Hoffman BL, Bradsher KD, Cunningham FG: Williams Gynecology: http://www.accessmedicine.com. Copyright © The McGraw-Hill Companies, Inc. All rights reserved. The stages of reproductive aging. (Redrawn from Soules, 2001, with permission).</small>										

Figure 2: Reproductive cycle and menopause [10]

women in the form of: Premenstrual dysphoria, including premenstrual syndrome and premenstrual dysphoric disorder, postpartum depression, and depression during perimenopause [16].

Perimenopausal depression includes a variety of symptoms. The symptoms of perimenopause can fluctuate depending on the severity, thus increasing the difficulty of making the diagnosis. It is important to check the physical health of women with perimenopausal depression to rule out other causes of the symptoms, such as thyroid disorders and autoimmune disorders [17]. Management for perimenopausal depression usually includes antidepressants and hormone therapy [18].

Menopause and anxiety

The prevalence of symptoms of anxiety is high among middle-aged women. Studies show that in the last 2 weeks, up to 51% of women aged 40–55 years experience anxiety or irritability and 25% of them experience high-frequency symptoms. Selective Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors are the first-line medications used in the treatment of anxiety disorders [19].

Insomnia and menopause

Sleep disturbances often occur during perimenopause, menopause, and postmenopause. Women who experienced sleep disturbances during menopause ranged from 28% to 63%. Complaints tended to indicate lower total sleep time and arousal levels compared to laboratory sleep studies. Overall, studies have consistently shown an increased likelihood of sleep problems during the menopausal transition, which is closely related to the appearance of flashes and sweating [20].

The basic principles that contribute to a healthy life in general can help reduce sleep disorders such as exercise, healthy eating, managing stress, maintaining healthy relationships and being socially active, and intellectual stimulation [20].

Sexual Disorders in Menopause Woman

Definition

In any phase of sexual response (e.g., desire/excitement, orgasm, sexual satisfaction) or pain during sexual intercourse that causes interpersonal stress, sexual dysfunction has been identified as a disturbance. It is known that the ageing phase raises the prevalence of sexual dysfunction. The transformation process

after menopause, however, has a greater effect on the incidence of sexual dysfunction in females. Decreased sexual desire, decreased vaginal lubrication, anorgasmia, and dyspareunia are the major changes that occur in sexual function in menopausal women [21].

Epidemiology

The prevalence of female sexual dysfunction is very high, ranging from 38% to 85.2% [14], [21]. The lack of clear diagnostic criteria to assess sexual disorders in postmenopausal women also leaves the prevalence of their occurrence unclear. A cross-sectional study found that 55% of sexually active women aged 40–65 years had sexual dysfunction with a population of sexually active postmenopausal women (n = 1480). Other observational studies have indicated that 32–41% of postmenopausal women have dyspareunia and a similar percentage report that lubrication function has been compromised [21], [22].

Etiology

Estrogen deficiency can lead to vaginal atrophy in postmenopausal women and can contribute to postmenopausal sexual dysfunction. The North American Menopause Society (NAMS) reports that there are signs of vaginal atrophy in about 10–40% of postmenopausal women. Two thousand two hundred ninety postmenopausal women were included in a new survey, 45% of whom had signs of vulvovaginal atrophy [22].

Classification

Sexual disorders have various forms and clinical symptoms. Classification of sexual dysfunction in women can be seen in the following table: [23] (Figure 3).

Pathophysiology

Androgens and sex hormones in women are produced in the ovaries and adrenal glands, while in men in the testes. The main androgen hormones in women are adrenal androgens and testosterone. In women, 50% of the testosterone produced in the ovaries and adrenal glands will circulate in the blood. The production of testosterone in women comes from three sources, namely the ovaries, adrenal glands, and conversion from circulating androgens in the periphery. Testosterone levels decrease with age. This decrease is due to a combination of several factors, namely: The production of androgen hormones in the adrenal glands progressively decreases with increasing age, although the ovaries are still produced after menopause, the adrenal secretion of androstenedione decreases by about 50%. Low androstenedione levels result in a

Disorder*	Definition	Potential impact of postmenopausal estrogen deficiency
Sexual desire disorders		
Hypoactive sexual desire disorder	Persistent or recurrent deficiency or absence of sexual fantasies/ thoughts and/or desire for or receptivity to sexual activity	Association with vaginal atrophy, dryness, and dyspareunia, which may reduce sexual desire/receptivity or cause women to avoid sexual contact Estrogen levels may correlate with sexual desire
Sexual arousal disorder	Persistent or recurrent inability to attain or maintain sufficient sexual excitement, which may be expressed as a lack of subjective excitement or genital lubrication/swelling	Association with vaginal atrophy and dryness, which may impair the ability to attain or maintain genital lubrication Lack of interest in sexual contact because of vaginal symptoms may reduce subjective excitement Estrogen deficiency is associated with reduced blood flow and vasocongestion, key mechanisms for lubrication
Orgasmic disorder	Persistent or recurrent difficulty in, delay in, or absence of attaining orgasm following sufficient sexual stimulation and arousal	Estrogen deficiency is associated with decreased vasocongestion and blood flow Reduced estrogen levels may be associated with diminished vestibular sensation
Sexual pain disorder (dyspareunia, vaginismus, other sexual pain disorders)	Persistent or recurrent genital pain or involuntary vaginal spasms	Direct association between estrogen deficiency and dyspareunia because of its impact on vaginal atrophy Estrogen deficiency may be associated with hypersensitivity to vulvovaginal pain

*The disorder must cause personal distress to be considered a true disorder.²²

Figure 3: Classification of sexual dysfunction in women and its relationship to estrogen deficiency in postmenopause [23]

significant decrease in testosterone to conversion peripheral at menopause [23], [24] (Figure 4).

By converting testosterone to estrogen, ovaries produce estrogen. After menopause, when the ovaries decline in function, female adipose tissue becomes the main source of producing estrogen by converting adrenal androgens to estrogens in the adipose tissue. Testosterone and other hormones in the body (DHEA/DHEAS) are important for normal physiological functions of women [23].

Sexual function enters the menopausal transition phase characterized by decreased ovarian function. The most important physiological change during menopause is a 5–10-fold decrease in the amount of estradiol circulating in the blood vessels. Atrophy in the vaginal wall can be observed several weeks to several months after a decrease in estrogen concentration. Circulating estrogen levels have been shown to influence sexual desire, activity, experience, and problems in sexually active postmenopausal

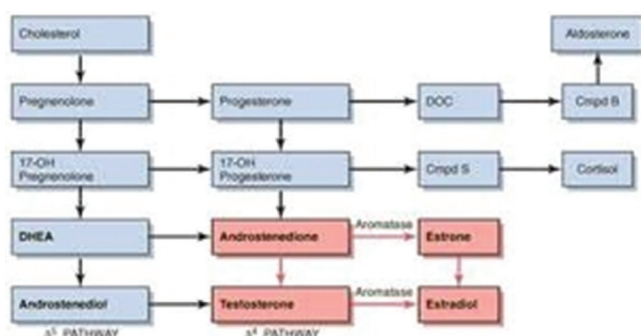


Figure 4: Testosterone synthesis [23]

women. In fact, data show a direct correlation between sexual complaints and estradiol levels <50 pg/mL [23].

The hormonal changes cause urogenital changes that affect sexual health. These include vaginal atrophy, changes in sexual desire, such as decreasing perfusion to the genital area, decreased vaginal lubrication, reduce muscle tension, and decreased uterine contractions [20]. According to research conducted by Arifianto at RSUP H Adam Malik Medan in 2017, there was a positive correlation with a decrease in serum estradiol levels along with a decrease in FSFI score (sexual dysfunction) with a correlation coefficient of $r = 0.600$ and $p < 0.001$. Based on the correlation of estradiol content with the Domain Desire/Libido, it is obtained a positive correlation where the correlation coefficient $r = 0.637$ and $p < 0.001$. It also shows that the strength of the correlation is strong ($r = 0.637$) [24].

Chronic progressive medical disorders due to hormonal changes in the vagina with symptoms such as dyspareunia and vaginal dryness are vulvar and vaginal atrophy (VVA). It is estimated that up to 40–50% of postmenopausal women are affected by VVA [25].

Decreased vaginal lubrication decreased blood flow and insufficient vaginal relaxation in people with estrogen deficiency due to loss of vaginal elasticity, which causes dyspareunia or discomfort during intercourse. A common cause of sexual dysfunction in postmenopausal women is loss of vaginal lubrication during sexual activity. Lack of estrogen in the vagina and adjacent tissues also induces reduced vascularity, contributing to decreased vaginal perfusion and postmenopausal swelling. There is diminished muscle tension in the pelvic floor after menopause and decreased uterine contractions, which can decrease the intensity of orgasm and also cause discomfort during uterine contractions. Lack of estrogen can also lead to decreased vestibular sensation and vibrational sensations, heat, and cold perception, which can contribute to decreased strength of orgasm [23], [26].

Clinical symptoms

In postmenopausal women, complaints of sexual disorders can stand alone or be accompanied by other disorders, such as disorders of the urinary tract. Both are called a genitourinary syndrome, which combines the condition of VVA and urinary tract dysfunction [27] (Figure 5).

Management

Problems related to the mind, body, and interpersonal relationships involved by sexual function by a complex and dynamic process. Many factors influence sexual dysfunction, both biological and psychological, in postmenopausal women. These include comorbid medical conditions and drugs

<p>Symptoms</p> <ul style="list-style-type: none"> Vulvar pain, burning, or itching Vaginal dryness Vaginal discharge Dyspareunia Spotting or bleeding after intercourse Dysuria, urinary frequency, urgency Recurrent urinary tract infections <p>Signs, external genitalia</p> <ul style="list-style-type: none"> Decreased labial size Loss of vulvar fat pads Vulvar fissures Receded or phimotic clitoris Prominent urethra with mucosal eversion or prolapse <p>Signs, vagina</p> <ul style="list-style-type: none"> Introital narrowing Loss of elasticity with constriction Thin vaginal epithelial lining Loss of mature squamous epithelium Pale or erythematous appearance Petechiae, ulcerations, or tears Alkaline pH (>5.5) Infection (yellow or greenish discharge) <p>Derived from D. J. Portman et al: Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. <i>Menopause</i>. 2014;21:1063–1068 (37), with permission.</p>
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Figure 5: Genitourinary syndrome in post-menopause [27]

as well as sexual, emotional, and interpersonal relationships [23].

The goal of managing sexual disorders in postmenopausal women is to maintain age-related function. Goldstein recommends a diagnostic algorithm and five-step management of women with sexual dysfunction [28] (Figure 6). Psychosexual counseling, in particular, is one of the main approaches and has an excellent success rate [24], [29].

The following are the therapeutic options needed to treat sexual dysfunction in postmenopausal women: [22], [23], [27].

- Vaginal moisturizers and lubricants vaginal moisturizers (e.g., polycarbophil, hyaluronic acid, and pectin-based moisturizers), when used regularly (at least twice a week), can provide an effective non-hormonal approach to relieve symptoms of vaginal atrophy
- Vaginal estrogen therapy
- A 2006 Cochrane meta-analysis of vaginal estrogens compared 19 agents in efficacy trials and found that all the products effectively relieved symptoms but could not yet differentiate between individual agents.

Low dose

Ten µg tablets provide a standard dose twice weekly for relief of vaginal symptoms for 8 weeks, and are effective for at least 52 weeks. Therapy was started with daily administration for 2 weeks and then twice a

Step 1	Identification of sexual health problem
Step 2	Client and partner education
Step 3	Modification of reversible causes
Step 4	First-line therapies consisting of self-help materials, vaginal lubricants and moisturisers, psychosexual therapy, devices and hormonal therapies
Step 5	Second-line therapies involving more invasive treatments, including surgical procedures

Figure 6: The five-step treatment of women with sexual dysfunction [28]

week thereafter. Vaginal tablets provide better results than moisturizing creams.

Moderate dose

Twenty-five gram estradiol tablet increased plasma estradiol from 3.1–0.83 to 19.8 ± 6.1 pg/mL for 7 days

Systemic dose of vaginal estrogen

CEE vaginal cream 0.625–2.5 mg, given daily, will produce a systemic effect as evidenced by the suppression of LH and FSH. Vaginal cream 2–4 g, given daily for 1–2 weeks, followed by a maintenance dose of 1 g, 1–3 times a week.

Other hormonal agents

Vaginal estriol preparations (gel and suppositories) are developed and controlled by the government in figures for countries outside the United States. Estriol is considered a low-affinity estrogen and is not considered to have a significant systemic effect, despite the rise in plasma concentration after repeated vaginal administration.

Although proven to give good results, estrogen therapy also has side effects, including endometrial hyperplasia, venous thromboembolism, and breast.

Ospemifene

This drug is used for the treatment of moderate to severe dyspareunia associated with vaginal atrophy in postmenopausal women and women with a history of breast cancer.

Ospemifene has a risk of developing vasomotor symptoms about 7.2%. Besides that, it can also increase the risk of cardiovascular disease due to arterial and venous thrombosis and thromboembolism.

Flowchart of management of sexual dysfunction disorders (Figure 7).

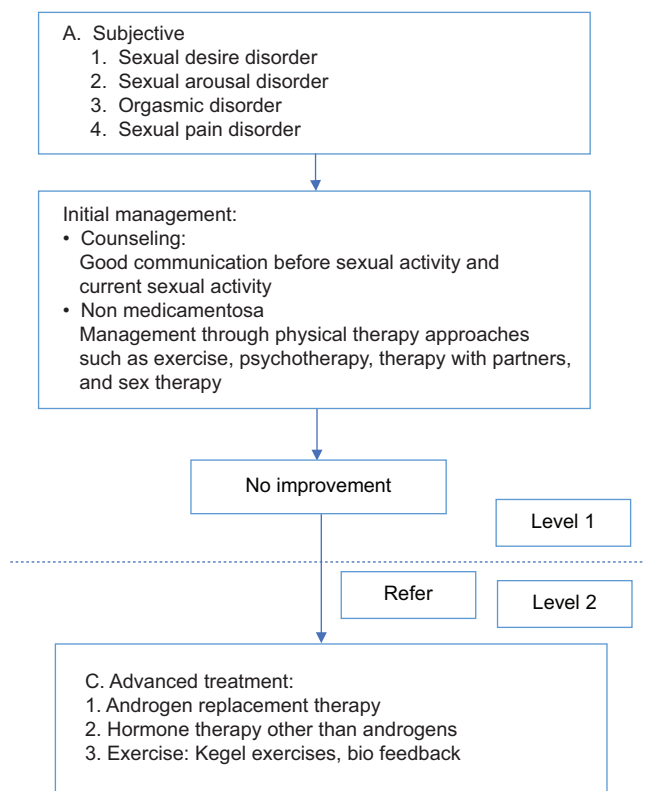


Figure 7: Flowchart of management of sexual dysfunction disorders

Description of Sexual Dysfunction Disorders Algorithm Sexual

A dysfunction disorder can be experienced by a woman at the age of menopause. The disturbance can be permanent or recurrent. Sexual dysfunction disorder can be described as a persistent or recurring condition. Sexual dysfunction disorder can be described as a condition in which a woman fails to react emotionally or physically to sexual stimulation as expected in healthy people in general or according to that person's standards of sexual response. Subjective Symptoms/Types of Sexual:

Sexual desire disorder

Hypoactive sexual disorders hypoactive sexual disorders: Deficiency or absence of sexual fantasies and desire for sexual activity and disorders of sexual aversion (sexual aversion disorders): Aversion or avoidance of genital sexual contact with a sexual partner.

Sexual arousal disorder

Sexual arousal disorders: Persistent or recurrent inability to achieve or maintain an adequate lubrication-inflammation response from sexual stimulation until the end of sexual activity and male erectile disorders: Also called erectile dysfunction and impotence, which is the inability to achieve or maintain an adequate erection until the end of sexual activity.

Orgasmic disorder

Female orgasmic disorders: Delay or absence of orgasm that persists or recurs after the normal phase of sexual arousal and male orgasmic disorders: Premature ejaculation is persistent or recurrent ejaculation at minimal stimulation before, on, or immediately after penetration and the patient's desire.

Sexual pain disorders

Dyspareunia as a persistent or recurrent genital pain associated with sexual intercourse in both men and women and vaginismus as an involuntary contractions/stiffness of the muscles in the outer third of the vagina which blocks penile insertion and sexual intercourse.

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