Genitourinary Syndrome of Menopause: A Systematic Review

Sri Hayati[1,2], Tukimin Bin Sansuwito[3]
[1] *Department of Nursing & Public Health, Faculty of Nursing, Lincoln University College, Malaysia*
[2] *Department of Nursing, Universitas Adhirajasa Reswara Sanjaya, Indonesia*
[3] *Lecturer Ph.D. In Nursing and Public Health, Faculty of Medicine, Lincoln University, Malaysia*
**Corresponding Author: sri@ars.ac.id*

KEYWORDS
estrogen, menopause, phytoestrogen, sexuality, genitourinary syndrome

ABSTRACT
Genitourinary syndrome is the most common health problem experienced by postmenopausal women. Its pathogenesis is correlated with decreased estrogen levels, which results in thinner vaginal epithelium with a reduced proportion of superficial cells. In the vaginal wall, there is a decrease in the number of collagen fibers, a reduction in smooth muscle mass, and a decrease in vascularization. The consequences of these changes are that the vaginal wall experiences a decrease in size, elasticity, lubrication, and integrity of the mucosal layer. The most common symptom experienced is vaginal pain, which ultimately causes fear of engaging in sexual activity. Handling of genitourinary syndrome symptoms is important because the population of postmenopausal women is large and will continue to increase. The purpose of writing a literature review is to review the pathogenesis of genitourinary syndrome and various treatment options. Literature was obtained through a search on Google Scholar and PubMed database during 2022 and selected publications from the last 5 years, both in Indonesian and English. The keywords used are menopause, genitourinary syndrome, pathogenesis of genitourinary syndrome, genitourinary syndrome therapy, phytoestrogens, selective estrogen receptor modulators (SERM), and hormone replacement therapy. The results found that most cases are undiagnosed and only a few receive appropriate therapy. Most menopausal women self-treat the symptoms of genitourinary syndrome experienced with over-the-counter drugs and many cases are not treated. The main therapy for genitourinary syndrome is hormones given systemically or topically. One systemic therapy is SERM. Many topical therapy options include phytoestrogens, hyaluronic acid, moisturizers, lubricants, colostrum, vitamins, herbs, laser therapy, and radio frequency. Various types of therapy methods have different mechanisms of action, most of which have been proven effective in improving the structure and physiology of the vagina and can reduce symptoms of the genitourinary syndrome and also improve sexual function.

INTRODUCTION

The population of women entering menopause continues to increase, so health problems correlated with menopause are becoming very important. (1) Genitourinary syndrome symptoms are experienced by more than 50% of menopausal women and are one of the most disturbing symptoms of menopause. (2) Genitourinary syndrome is a change that occurs in the vagina due to estrogen deficiency with the main symptoms being vaginal dryness and pain during sexual activity. (3) Decreased estrogen levels cause changes in the vagina which include thinning of the epithelium, decreased maturation index of epithelial cells, decreased collagen fiber content, decreased smooth muscle mass, and decreased vascularization. (4)

Genitourinary syndrome often does not receive proper treatment because the symptoms are non-specific and some patients do not consult a doctor. Only a small proportion of menopausal women with symptoms of genitourinary syndrome take prescribed medication, most take over-the-counter medication and some do not take any treatment at all. (5) Hormonal therapy is the main option to reduce the symptoms of genitourinary syndrome because it has been proven to be effective, but its use is still limited because it is expensive and there are many concerns about side effects. (6)

Selective estrogen receptor modulators (SERM) such as tamoxifen, azotoxifene, raloxifene, bazedoxifene are systemic estrogen replacement therapies that have good effectiveness and have been proven not to cause dangerous side effects. There are many types of topical therapy to reduce the symptoms of the genitourinary syndrome, starting from those containing the hormone estrogen, phytoestrogen, hyaluronic acid, colostrum, and vitamins, as well as laser therapy. and radiofrequency. (3),(7) Various therapeutic options for genitourinary syndrome have different mechanisms of action in improving vaginal structure and physiology, some have been proven effective and some still need further research. This paper aims to review the pathogenesis of genitourinary syndrome and its various therapeutic options.(8)

METHOD

A literature search was conducted systematically online during the years 2019-2024 using Google Scholar and PubMed databases to find selected published articles in Indonesian and English from the last five years. The keywords used in the search were menopause, genitourinary syndrome, pathogenesis of genitourinary syndrome, genitourinary syndrome therapy, phytoestrogens, SERMs, and hormone replacement therapy.

RESULTS AND DISCUSSION

a. Prevalence of Genitourinary syndrome

A woman is said to have experienced menopause when she experiences amenorrhea for 12 consecutive months. Before a woman enters menopause, there is a transition period called perimenopause. During this period, a woman experiences irregular menstrual cycles until they finally stop. Menopause is characterized by changes in reproductive hormone levels that cause many symptoms such as vasomotor symptoms, insomnia, mood disorders, and symptoms in the genital organs. In addition, there is also an increased risk of suffering from several chronic

diseases such as osteoporosis and cardiovascular disease.(9) Genitourinary syndrome or also known as vulvogenitourinary syndrome describes the spectrum of changes that occur in the female genital organs during menopause. Since 2014, consensus has given this collection of symptoms a new term. International Society for the Study of Women's Sexual Health and the North American Menopause Society that is genitourinary syndrome of menopause.(3),(10) The prevalence of genitourinary syndrome in postmenopausal women is quite high. A survey involving 4246 women aged 55-65 years living in Sweden, Finland, England, the United States, and Canada found that 39% experienced genitourinary syndrome.(11)

b. Pathophysiology of Genitourinary syndrome

In a woman's body, three types of estrogen hormones regulate the structure and physiology of the reproductive organs: estradiol, estrone, and estriol. The ratio of the three types of estrogen hormones experiences dynamics during a woman's life. During premenopause, the highest estrogen levels are estradiol, which is the estrogen hormone with the greatest potential, while during menopause, estradiol levels decrease and the highest is estrone, which is the estrogen hormone with the weakest potential. Changes in the ratio of estrogen hormones cause hypoestrogen conditions in post-menopausal women. This hypoestrogen state causes dramatic anatomical and physiological changes in the vaginal organs, leading to genitourinary syndrome. This is because estrogen through its receptors spread across the four layers of the vaginal wall, namely the epithelium, lamina propria, muscle layer, and adventitia, plays a role in maintaining the anatomical structure of the vagina and also regulating its physiology. Changes in each layer of the vagina are as follows:(12)

1. Changes in the Vaginal Epithelium

The epithelium lining the vaginal mucosa is a stratified squamous epithelium. Stimulation of estrogen receptors located in the epithelium and stroma by the hormone estrogen causes increased proliferation and Epithelial stratification. Parabasal cells undergo differentiation, move upwards to the superficial layer of the epithelium, and undergo cornification. Decreased estrogen levels cause epithelial cells to be smaller with less cytoplasmic content and a decrease in the thickness of the vaginal epithelium.(13) During menopause, the vaginal epithelium is dominated by parabasal cells, intermediate cells decrease, and the proportion of superficial cells also decreases or even disappears. A decrease in the proportion of superficial cells results in a decrease in glycogen concentration in epithelial cells, this causes changes in the vaginal microbiome, namely a decrease in lactobacillus bacteria and an increase in vaginal pH.(14).On observation, the vaginal mucosa becomes pale and more fragile.

2. Changes in the Lamina Propria

In the vaginal lamina propria there are two important structures, namely collagen and elastic fibers, collagen fibers provide rigid properties while elastic fibers provide elastic properties to the vaginal wall. The structure of the lamina propria is maintained by a balance between the synthesis of matrix components by fibroblasts and their degradation.(15) Decreased estradiol levels during menopause cause decreased fibroblast function which causes decreased synthesis of matrix components that maintain the structure of the vaginal lamina propria, namely collagen fibers and elastic fibers. Hypoestrogen conditions also cause increased collagen degradation by matrix metalloproteinases. (MMP-2 and MMP-9) and cathepsin.

3. Changes in the Smooth Muscle Layer

The smooth muscle layer of the vaginal wall is located beneath the lamina propria, which consists of a circular layer on the inside and a longitudinal layer on the outside. The smooth muscle cells of the vaginal wall are embedded between collagen fibers. In postmenopausal women, there is a decrease in smooth muscle mass, redifferentiation of smooth muscle into myofibroblasts and also a change from type I collagen to type III collagen.(16)

4. Changes in Blood Vessels and Nerve Fibers

In the connective tissue layer of the vaginal wall are found large blood vessels accompanied by bundles of nerve fibers, smaller blood vessels, and nerve fibers that penetrate to the muscle layer, lamina propria, and the basement membrane. The blood supply to the vaginal wall is regulated by the levels of nitric oxide produced by the endothelium. In hypoestrogen conditions, there is a decrease in nitric oxide secretion which causes a decrease in blood supply to the vagina.(17)

5. Changes in External Genitalia and Urinary Organs

In menopausal women, changes in the external genitalia can also These symptoms are a consequence of decreased estrogen levels because estrogen receptors are not only found in the vagina but also spread to the vulva, pelvic floor muscles, endopelvic fascia, urethra, and trigone of the bladder be observed, including a decrease in the amount of pubic hair, a decrease in subcutaneous fat in the labia majora, and shrinkage of the labia minora and vestibular bulbs. In the urinary system, a decrease in the capacity and ability of the bladder to contract, a decrease in the function of the urethral sphincter accompanied by a decrease in the function of the pelvic floor muscles can be found(18).

c. **Symptoms of Genitourinary syndrome**

Symptoms of genitourinary syndrome vary from mild to severe. A Beijing study of 570 postmenopausal women who experienced genitourinary syndrome found that 175 people experienced mild symptoms, 68 people experienced moderate symptoms and 27 people experienced severe symptoms.(19)The most common symptoms of genitourinary syndrome were vaginal dryness (93.3%) and decreased lubrication during sexual activity (90.0%).2 Another symptom that is also quite often complained of is a burning/itching sensation in the vulva/vagina experienced by around 63.3% of postmenopausal women. Menopausal women who are still sexually active often complain of dyspareunia with a prevalence of 80%. Other complaints that are also often experienced are loss of libido, decreased sexual desire, and vaginal bleeding or spotting during or after intercourse. Vaginal symptoms can also be accompanied by urinary tract symptoms, including dysuria (29%), urgency and incontinence (28%), and recurrent urinary tract infections.(19) Symptoms of genitourinary syndrome that are chronic and tend to get worse as menopause progresses can have a huge impact on quality of life because they can interfere with intimacy with your partner. The results of a survey involving more than 3,000 menopausal women in the United States revealed that genitourinary syndrome symptoms affected sexual pleasure in 59% of respondents.(4)(20) Survey results in Turkey revealed that genitourinary syndrome symptoms significantly affect the ability to have sex (62%), the ability to enjoy sex (72%), and the ability to experience sexual spontaneity (66%). The survey also revealed that 51% of postmenopausal women who experienced genitourinary syndrome symptoms were still sexually active, but their sex drive was reduced.(20) Menopausal symptoms also cause emotional disturbances and reduce the comfort of life for menopausal women. The results of a survey involving more than 3,000 menopausal women in the United States revealed that 24% of respondents experienced sleep disorders, 23% experienced impaired comfort in life and 23% experienced emotional disturbances. A survey of postmenopausal women in Turkey found that 10.4% felt they had lost their feminine qualities, 9.1% felt sad, and 32.8% felt like they were getting old.(20)

d. Genitourinary syndrome Diagnosis

Diagnosing genitourinary syndrome in menopausal women is not easy because there are several obstacles both from menopausal women and from clinicians. The survey results found that most menopausal women are not aware of or know the symptoms of genitourinary syndrome and even though they are aware of the symptoms of genitourinary syndrome, many

menopausal women are reluctant to discuss it with health workers. Survey results from Women's EMPOWER are consistent with previous surveys that found that postmenopausal women are generally unable to recognize the symptoms of genitourinary syndrome and its chronic and progressive symptoms. The results of this survey also found that the majority of menopausal women are reluctant to discuss vaginal symptoms or sexual disorders experienced with doctors and health professionals. The reason why menopausal women are reluctant to discuss genitourinary syndrome is because menopausal women believe that the vaginal symptoms they experience are a normal part of the aging process and they only need to cope with the symptoms.(21) The survey results also revealed that menopausal women who experience symptoms of genitourinary syndrome expect their doctors to start asking about menopausal symptoms, and in fact, this is still rarely done.

e. **Use of Medication to Treat Genitourinary Syndrome Symptoms by Menopausal Women**

Genitourinary syndrome symptoms, although very disturbing, many are not consulted with a doctor so they do not get the right treatment. Most menopausal women treat their symptoms themselves by using over-the-counter drugs or non-hormonal drugs and only a small number use drugs prescribed by a doctor. Many menopausal women with genitourinary syndrome symptoms do not receive any treatment. (5) A survey of women's knowledge about the availability of medications for the treatment of genitourinary syndrome found that 42% of menopausal women were unaware that medications were available to reduce the symptoms of genitourinary syndrome. (14) There are several reasons why menopausal women are less interested in drugs to reduce the symptoms of genitourinary syndrome, namely because there is a feeling of discomfort when having to apply topical drugs to the vagina. Another reason is that some menopausal women consider the symptoms they experience to be not bothersome, while over-the-counter drugs are not very effective, in addition to the price of over-the-counter drugs which is a concern for menopausal women. Another problem that hinders the treatment of genitourinary syndrome symptoms with hormonal drugs is the concern about the side effects of hormonal drugs. Most postmenopausal women are concerned about the side effects and risk of cancer, thus limiting the use of topical vaginal therapies prescribed by doctors. (14) The survey results found that menopausal women were very concerned about the safety of drugs to reduce symptoms of genitourinary syndrome including increased risk of breast cancer and the possibility of systemic absorption. (21) There are many therapeutic options available to reduce the symptoms of genitourinary syndrome in postmenopausal women. Therapies that can be used include hormonal or nonhormonal, either applied locally or systemically. The choice of therapy for genitourinary syndrome symptoms must be individualized by considering the severity of symptoms, potential side effects and personal preferences of the patient.(22)

f. **Laser and Radio Frequency Therapy**

Laser therapy for the treatment of genitourinary syndrome, although recently introduced, has shown effectiveness and high levels of patient satisfaction. The first laser therapy procedure was published in 2014. (23)The mechanism of action of laser therapy is by increasing the vascularization of the vaginal mucosa, stimulating the synthesis of new collagen and matrix material in the connective tissue, thickening the vaginal epithelium with the formation of new papillae, increasing glycogen content in the vaginal epithelium, so it can restore the health of the vaginal mucosa that occurs during menopause. Khadijah al reported that laser therapy can also improve the quality of life and improve sexual activity in menopausal women.(24)

g. **Herbs**

Herbal ingredients are often used to relieve menopausal symptoms and are effective in treating menopausal syndrome. Some herbs that are often used in treating menopausal symptoms are Actaea racemosa, Evening Primrose Oil, Foeniculum vulgare, Ginkgo biloba, Glycyrrhiza glabra, Hypericum perforatum, Medicago sativa, Melissa officinalis, Panax ginseng, Passiflora

incarnata, Pimpinella anisum, Salvia officinalis, Trifolium pretense, Trigonella foenum, Valerian officinalis, And Vitex agnuscastus. These herbal ingredients are usually available on the market as supplements so they often do not have standards in terms of quality, safety, and purity that can vary between brands. These compounds can also interact with prescription drugs, so caution should be taken when used in conjunction with medications prescribed by a doctor.(9)

CONCLUSION

Genitourinary syndrome is one of the symptoms of menopause with high prevalence and can cause sexual dysfunction. Decreased estrogen levels cause symptoms of genitourinary syndrome during menopause, so hormone therapy is the main choice. The use of hormones, both systemic and local, needs to pay attention to the safety of the emergence of dangerous side effects. In addition to hormone therapy, there are many other therapy options available to reduce the symptoms of genitourinary syndrome, either systemically or locally. Other therapeutic options other than estrogen that are effective include SERMs, phytoestrogens, moisturizers and lubricants, hyaluronic acid, colostrum, and vitamins D and E. Some therapies that are being developed include laser therapy and radiofrequency. Probiotic therapy also has the potential to be developed but requires further research, while herbal therapy needs to be standardized and ensure there is no interaction with other drugs.

REFERENCES

1. Elfaki SH. Genitourinary syndrome of menopause exploring the history, updates and treatment. Int J Reprod Contraception, Obstet Gynecol. 2024;13(7):1891–6.
2. Moral E, Delgado JL, Carmona F, Caballero B, Guillán C, González PM, et al. Genitourinary syndrome of menopause. Prevalence and quality of life in Spanish postmenopausal women. The GENISSE study. Climacteric [Internet]. 2018;21(2):167–73. Available from: https://doi.org/10.1080/13697137.2017.1421921
3. Angelou K, Grigoriadis T, Diakosavvas M, Zacharakis D, Athanasiou S. The Genitourinary Syndrome of Menopause: An Overview of the Recent Data. Cureus. 2020;12(4).
4. Kagan R, Kellogg-Spadt S, Parish SJ. Practical Treatment Considerations in the Management of Genitourinary Syndrome of Menopause. Drugs and Aging [Internet]. 2019;36(10):897–908. Available from: https://doi.org/10.1007/s40266-019-00700-w
5. Nappi RE, Martini E, Cucinella L, Martella S, Tiranini L, Inzoli A, et al. Addressing Vulvovaginal Atrophy (VVA)/Genitourinary Syndrome of Menopause (GSM) for Healthy Aging in Women. Front Endocrinol (Lausanne). 2019;10(August):1–11.
6. Pompei LM, Wender MCO, Kulak J, Pires I, Suvarna Y, Nappi RE. Impact of postmenopausal vaginal discomfort on sex and relationships in Brazil: the CLOSER survey. Climacteric [Internet]. 2021;24(6):593–9. Available from:

https://doi.org/10.1080/13697137.2021.1908988

7. Di Donato V, schiavi MC, iacobelli V, D'oria O, Kontopantelis E, Simoncini T, et al. Ospemifene for the treatment of vulvar and vaginal atrophy: A meta-analysis of randomized trials. Part I: Evaluation of efficacy. Maturitas [Internet]. 2019;121(November):86–92. Available from: https://doi.org/10.1016/j.maturitas.2018.11.016
8. Reid RL, Black D, Derzko C, Portman D. Ospemifene: A Novel Oral Therapy for Vulvovaginal Atrophy of Menopause. J Obstet Gynaecol Canada [Internet]. 2020;42(3):301–3. Available from: https://doi.org/10.1016/j.jogc.2019.10.039
9. De Franciscis P, Colacurci N, Riemma G, Conte A, Pittana E, Guida M, et al. A nutraceutical approach to menopausal complaints. Med. 2019;55(9):16–8.
10. Sarmento ACA, Costa APF, Vieira-Baptista P, Giraldo PC, Eleutério J, Gonçalves AK. Genitourinary Syndrome of Menopause: Epidemiology, Physiopathology, Clinical Manifestation and Diagnostic. Front Reprod Heal. 2021;3(November):1–6.
11. Alvisi S, Gava G, Orsili I, Giacomelli G, Baldassarre M, Seracchioli R, et al. Vaginal health in menopausal women. Med. 2019;55(10):1–13.
12. Statement FP. FEBRASGO POSITION STATEMENT Genitourinary Syndrome of Menopause. FEBRASGO POSITION STATEMENT. 2022;1(3):319–24.
13. Ye Z, Jiang P, Zhu Q, Pei Z, Hu Y, Zhao G. Molecular stratification of human fetal vaginal epithelium by spatial transcriptome analysis [Internet]. Vol. 1. 2024. p. 1–52. Available from: https://doi.org/10.1101/2024.03.20.585995
14. Faubion SS, Kingsberg SA, Clark AL, Kaunitz AM, Spadt SK, Larkin LC, et al. The 2020 genitourinary syndrome of menopause position statement of the North American Menopause Society. Menopause. 2020;27(9):976–92.
15. Rynkevic R, Ferreira J, Martins P, Parente M, Fernandes AA. Linking hyperelastic theoretical models and experimental data of vaginal tissue through histological data. J Biomech [Internet]. 2019;82(xxxx):271–9. Available from: https://doi.org/10.1016/j.jbiomech.2018.10.038
16. Li Y, Zhang QY, Sun BF, Ma Y, Zhang Y, Wang M, et al. Single-cell transcriptome profiling of the vaginal wall in women with severe anterior vaginal prolapse. Nat Commun [Internet]. 2021;12(1):1–13. Available from: http://dx.doi.org/10.1038/s41467-020-20358-y
17. Li X, Mao Z, Yang L, Sun K. Co-staining Blood Vessels and Nerve Fibers in Adipose Tissue Xin. Physiol Behav. 2020;176(5):139–48.

18. Ulhe SC, Acharya N, Vats A, singh A. Study of Vulvovaginal Atrophy and Genitourinary Syndrome of Menopause and Its Impact on the Quality of Life of Postmenopausal Women in Central India. Cureus. 2024;16(2):1–19.
19. Zhu Y, Wei J, Yang X, Zhu W, Zhang W. Investigation on prevalence and risk factors associated with genitourinary syndrome of menopause in middle-aged and older women in Beijing community: a cross sectional study. BMC Womens Health. 2022;22(1):1–8.
20. Selvi I, Baydilli N, Yuksel D, Akinsal EC, Basar H. Reappraisal of the Definition Criteria for "Genitourinary Syndrome of Menopause," and its Effect on Quality of Life in Turkish Postmenopausal Women. Urology [Internet]. 2020;144:83–91. Available from: https://doi.org/10.1016/j.urology.2020.07.025
21. Krychman M, Graham S, Bernick B, Mirkin S, Kingsberg SA. The Women's EMPOWER Survey: Women's Knowledge and Awareness of Treatment Options for Vulvar and Vaginal Atrophy Remains Inadequate. J Sex Med. 2019;14(3):425–33.
22. Scavello I, Maseroli E, Di Stasi V, Vignozzi L. Sexual health in menopause. Med. 2019;55(9):1–10.
23. Naumova I, Castelo-Branco C. Current treatment options for postmenopausal vaginal atrophy. Int J Womens Health. 2018;10:387–95.
24. Adabi K, Golshahi F, Niroomansh S, Razzaghi Z, Ghaemi M. Effect of the fractional CO2 laser on the quality of life, general health, and genitourinary symptoms in postmenopausal women with vaginal atrophy: A prospective cohort. J Lasers Med Sci [Internet]. 2020;11(1):65–9. Available from: https://doi.org/10.15171/jlms.2020.11