A FOGSI President's Initiative

TOG IPP

Infection Practice Points

By Dr. Nandita Palshetkar

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Dear FOGSIANs,

The theme of FOGSI this year is "We for Stree". I would like to thank every FOGSIAN who has helped making every woman Safer, Stronger and Smarter. Through various academic and social programs FOGSI aims to uplift the quality of care that is given to every woman who comes to us.

TOG IPP (Infection Practice Points) is one such conclave that brings to light some of challenging health issues like Vaginitis, Pelvic inflammatory disease (PID) and Urogenital infections.

I would like to thank Zuventus for their contributions towards the TOG IPP Conclave.

We, as clinical practitioners are always busy, therefore the TOG IPP that is released has been a quick and easy way to update you with the latest evidence in the field of Infections. This year we ask all FOGSIANs to focus on the Stree and help make them safer, smarter and stronger.

Select FOGSIANs across India came together to deliberate and create these practice points. I am sure that you will appreciate the efforts which has gone into preparing the Infection Practice Points and find them useful in your day to day practice.

Best wishes!

Nandita P. Palshetkar

Dr. Nandita Palshetkar

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President 2019 - Federation of Obstetrics & Gynecological Societies of India (FOGSI)

UROGENITAL ATROPHY
Evaluation and Management

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Panelists : **Dr. Kawita Bapat, Dr. Rahul Mayekar, Dr. Lila Vyas, Dr. Ritu Joshi, Dr. Sadhana Gupta, Dr. Swarnalatha S, Dr. Manju Gita Mishra, Dr. Anita Singh, Dr. Varsha Lahade, Dr. Jayam Kannan, Dr. Chandravati, Dr. Dinesh Salgaonkar**

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From left to right: Dr. Rohan Palshetkar, Dr. Pragya Mishra, Dr. Swarnalatha.S, Dr. Rahul Mayekar, Dr. Ameya Purandare, Dr. Dinesh Salgaonkar, Dr. Vinit Mishra, Dr. Lila Vyas, Dr. Varsha Lahade, Dr. Manju Gita Mishra, Dr. Chandravati, Dr. Nandita Palshetkar, Dr. Anita Singh, Dr. Jayam Kannan, Dr. Kawita Bapat

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UROGENITAL ATROPHY
Evaluation and Management

Vaginal infections in postmenopausal women

As the number of postmenopausal women is increasing, the interest in the role of effects of estrogen is also enhanced.[1] Profound atrophic and inflammatory changes in the vaginal tissues including modification in vaginal epithelial cytology, pH and microbial flora characterize the postmenopausal years.[2] Nearly 50% of postmenopausal women experience vaginal atrophy, thinning and inflammation of the vaginal walls. In postmenopausal women, vaginal thinning occurs secondary to a decline in estrogen and to some treatments like oophorectomy, pelvic radiation, certain chemotherapy drugs and by an increased vulnerability towards inflammation and infection. In addition, a decrease in estrogen affects vaginal flora, allowing overgrowth of bacteria and sometimes vaginal discharge. Reduction in estrogen may also contributes to dyspareunia, leading to a loss of sexual interest and sexual activity.[3]

Some women experience these modifications significantly affecting their quality of life with painful and sensitive vaginal symptoms such as vaginal dryness, itching, pain and/or discomfort during sexual intercourse. Most of the women who undergo transition through menopausal state (perimenopausal, early postmenopausal and late postmenopausal) express these various complaints in contrast to other menopausal symptoms (hot flashes or night sweats). Moreover, some women may experience long-term vaginal symptoms such as dryness, itching and painful intercourse after menopause, causing ongoing discomfort and distress in the elderly years.[2]

Till date, the main focus of clinical research on vaginal atrophy was measurements of the impact of estrogen deprivation on physical signs of atrophy and vaginal inflammation. Although the estrogen levels of all women during menopause declined dramatically and most elderly women develop some signs of estrogen deficiency in vaginal tissue, not all postmenopausal women develop serious or persistent vaginal symptoms.[2]

Hypoestrogenemia predisposes postmenopausal women to UTI

In the postmenopausal period, many women will spend one-third of menopausal period in hypoestrogenic state. Changes in vaginal pH and vaginal flora together with hypoestrogenemia may predispose postmenopausal women from developing urinary tract infection (UTI). Also, prolonged periods of transitional hypoestrogenism like during long-term breastfeeding or gonadotropin-releasing hormone (GnRH) analogue therapy can lead to serious vaginal atrophy or atrophic vaginitis.[1]

EXPERT OPINION

Prolonged periods of transitional hypoestrogenemia may induce severe vaginal atrophy and associated UTIs.

Vaginal atrophy

Vaginal or vulvovaginal atrophy is a common but poorly identified condition in perimenopausal and postmenopausal women. Vaginal atrophy may cause urogenital symptoms like itching,

burning, dryness, irritable bladder symptoms, reduced lubrication and painful intercourse.[4] As this condition causes both vaginal and urinary symptoms, medical specialists define vaginal atrophy and its related symptoms using the word 'genitourinary syndrome of menopause' (GSM).[5] Vaginal atrophy has a greater impact on quality of life and sexual health that increases with time rather than reducing, as with most other menopausal symptoms.[4]

A huge number of clinical data on vaginal atrophy issues has been collected in recent years. Up to 40% of postmenopausal women suffer from urogenital atrophy according to International Menopause Society (IMS).[1] Only 25% symptomatic women seek active therapy while 70% report that their physician rarely asks about vaginal symptoms.[5]

Vaginal dryness and atrophy is a silent epidemic affecting a large number of women who are certainly suffering in silence. This chronic and progressive disease affects up to 50%–60% of postmenopausal women, which are estimated by some healthcare providers to be lower than the actual incidence.[6]

Although postmenopausal vaginal atrophy is a prevalent condition, only few women seek therapy. This is probably because of one or several factors:[7]

- A belief that vaginal atrophy is a component of a woman's aging process
- Inhibitions to seek treatment that stem from religious beliefs
- Feelings of embarrassment with an incapacity to speak about the issue
- Lack of knowledge about medical service availability and potential for enhanced outcomes

According to Vaginal Health Insights Views & Attitudes (VIVA) study, 45% of participants reported having vaginal symptoms, 4% of them were attributed to vaginal atrophy, 63% failed to recognize vaginal atrophy as a chronic condition and 75% had an adverse impact on sex life.[7]

Several terms were used for describing this condition such as vulvovaginal atrophy (VVA), urogenital atrophy, symptomatic vaginal atrophy and atrophic vaginitis, etc. Recently a new terminology has been proposed for describing the complexity of typical urogenital signs and symptoms, namely GSM by American scientific societies (North American Menopause Society [NAMS] and the International Society for the Study of Women's Sexual Health).[5]

EXPERT OPINION

Vaginal atrophy is the thinning, drying and inflammation of the vaginal walls caused by decreased estrogen levels in the body.

Urogenital changes in menopausal women

After menopause, the physiological aging process of women accelerates, with modifications secondary to the cessation of estrogen production in the ovaries. This modification occurs especially in the genital tract (Table 1).[3]

A postmenopausal decline in estrogen affects the urinary tract, which can lead to thinning of the bladder and urethral linings, chronic dysuria and UTI. A woman's hormonal environment significantly affects the health of vaginal linings and urethral tissue.[3] In clinical practice, the diagnosis is done by clinical suspicion and the classical symptoms may include increasing vaginal dryness, itch, soreness, irritable bladder symptoms and dyspareunia. In postmenopausal women, up to 45% may develop these symptoms, that are often unrecognized by them or their partners.[4]

Table 1. Age-related changes in the female genital tract[3]	
Changes in estrogen	**Estradiol (17 β-estradiol)** The most potent estrogen produced and secreted by the ovary. In postmenopausal period, its secretion is minimal; although blood levels are reduced by 90%, it has 10 times greater biological activity than estrone, an important role in maintaining tissues that are hormone-dependent. **Estrone** A metabolite of estradiol with about one-third the estrogenic potency of estradiol; it is the major postmenopausal estrogen. Estrone is generated primarily from the conversion of androstenedione (produced in the ovaries and adrenal glands) in peripheral tissues. Postmenopausal levels are four times higher than in younger women. **Estriol** A metabolite of estradiol with significantly less potency than estradiol; does not play a significant role in postmenopausal period.
Anatomical changes	**Cervix** More flush with the vaginal vault; squamocolumnar junction recedes into the endocervical canal. **Ovary** Reduction in size; sclerotic; loss of follicular activity; cysts may be present. **Pelvic floor** Weakness; lack of support due to diminished collagen following the climacteric; nerve damage may be associated with parturition (childbirth) and uterovaginal prolapse. **Uterus** Marked reduction in size; fibrosis and thickened blood vessels in the myometrium; singular layer endometrium (cuboidal cells). **Vagina** Thinner, atrophic, less elastic; more vulnerable to trauma; reduced defenses against infection. **Vulva** Shrinkage of tissue; sparse graying pubic hair; thinner and keratinized epidermis.

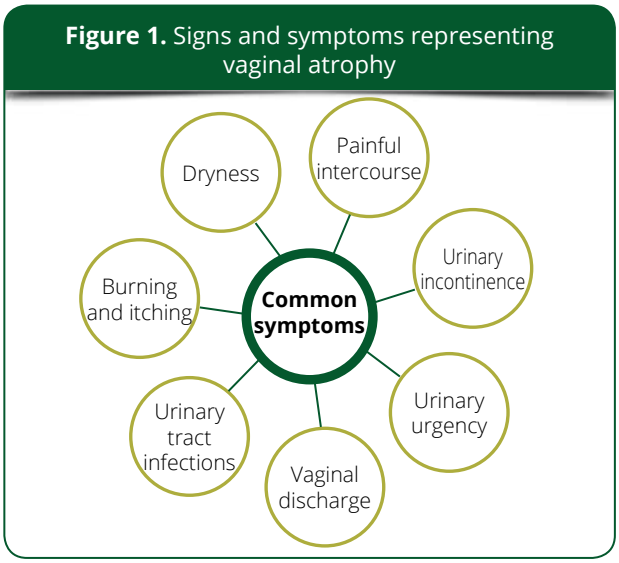
EXPERT OPINION

In postmenopausal period decline in estrogen increases the risk of UTIs in women with atrophic vaginitis.

Symptoms of vaginal atrophy

Classical signs and symptoms that represent vaginal atrophy are mentioned in Figure 1.[1,4]

Figure 1. Signs and symptoms representing vaginal atrophy



Causes and risk factors

In women, three forms of estrogen namely estradiol, estrone and estriol are produced in the ovaries. Estradiol is the most abundant and potent form in premenopausal women. During the transition phase between perimenopausal and postmenopausal years, estrone form of estrogen becomes the most prominent form which is less potent. This may cause estrogen deficiency and may lead to GSM symptoms. The cause of GSM is secondary to reduced levels of endogenous estrogen. Non-menopause related causes of estrogen deficiency that may mimic GSM sequelae like the systemic, hormonal and pharmacological therapies are mentioned in Table 2.[8]

Table 2. Causes of vaginal atrophy in premenopausal women or due to factors unrelated to menopause

Type	Cause
Systemic	• Hyperprolactinemia (during breastfeeding) • Postpartum estrogen deficiency • Hypoestrogenism (e.g., due to autoimmune disorders affecting ovaries, pituitary tumors)
Pharmacological	• GnRH agonist analogs » Leuprolide » Nafarelin • Selective estrogen receptor modulators • Tamoxifen • Aromatase inhibitors • Danazol • Medroxyprogesterone
Iatrogenic	• Bilateral oophorectomy (i.e., surgical menopause) • Ovarian failure secondary to pelvic radiation • Chemotherapy • Radiation therapy

GnRH: Gonadotropin-releasing hormone

Risk factors of vaginal atrophy or GSM[8]

Various risk factors in developing GSM that may contribute to reduced circulation and impaired receptor functions are mentioned below:

- Menopause
- Non-menopause hypoestrogenism
- Bilateral oophorectomy
- Cigarette smoking
- Alcohol abuse
- Decreased frequency of sexual activity
- Abstinence
- Ovarian failure
- Lack of exercise
- Absence of vaginal childbirth

Role of menopause in UTIs

The lack of estrogen leads to metabolic and trophic changes.[9] It has been well-established that endogenous estrogen has an impact on certain body structures such as bone and cardiovascular system. However, one particular area not highlighted is the effect on the urogenital tract, while the development of urogenital atrophy was a significant issue associated with menopause.[1] In postmenopausal women, lower urogenital tract disorders (vaginal atrophy, urethritis, dyspareunia, recurrent UTIs and urinary incontinence symptoms) are more common, attributing to the aging process as well as reduced estrogen levels.[9]

Pathophysiology of vaginal atrophy

Low production of estrogen following menopause or bilateral oophorectomy can cause vaginal atrophy. After estrogen withdrawal, vaginal atrophy is considered as a natural process. Menopause is the main cause of reduced circulating estrogen level. Despite this,

it can also occur in non menopausal women due to diminished ovarian estrogen production as a consequence of cancer treatments (radiation therapy and chemotherapy) and immunological disorders. In addition, lower estrogen levels in postpartum women combined with the loss of placental estrogen and antagonistic action of prolactin on estrogen production during lactation may lead to thinning of the vaginal lining.[10]

Estrogen helps to maintain the content of collagen in the epithelium and thereby influences its thickness and elasticity. It also helps to maintain mucopolysaccharides and hyaluronic acid that keep the surfaces of epithelium moist. Estrogen stimulation is responsible for the maintenance of a well-epithelialized vaginal vault during the reproductive years. This causes the nonkeratinized stratified squamous epithelium of the vagina to be thick, rugated and rich in glycogen (essential for rapid *lactobacilli* reproduction and maintenance).[10]

During the perimenopausal period, estrogen secretion mainly estradiol remains at about 120 ng/L. During menopause it reduces to 18 ng/L. This endogenous estrogen reduction leads the epithelium to become thin and glycogen content to decrease. Lack of glycogen helps to reduce the production of lactic acid and increases the vaginal pH, leading to overgrowth of nonacidophilic species and disappearance of *Lactobacillus* species.[11]

EXPERT OPINION

There is a gradual decrease in the estrogen level from peri-menopause to menopause.

In some patients, fresh flora with bacteria triggers a superficial infection in denuded areas and alters vaginal secretions. Moreover, the papillae of the vagina flatten and the rugae almost vanished, leaving the vagina relatively smooth when the estrogens are removed. The mucosa is gradually becoming thinner and eventually may become only a few cell layers thick. Some regions may have a moderately thick layer of intermediate cells, while others only have a raw of basal cells. Finally, the vagina becomes epithelium denuded.[11]

Potential complications

Vaginal infections

Vaginal atrophy increases a woman's risk of contracting vaginal infections as it causes changes in the acid balance of the vagina and making it easier for bacteria, yeast and other organisms to thrive and cause vaginal infections.[4]

Urinary problems

Vaginal atrophy involving visual changes may include redness, dryness, petechiae, phimosis of the clitoral hood, friability and stenosis. Further, stenosis or the contracture of the distal vagina may involve urethra caruncle formation or urethral mucosal prolapse and can reduce the size and fatty tissues of the vulva by affecting the tissues of endodermal origin. Moreover, the trigone of the bladder is also of endodermal origin and these physical changes correlate with the epidemiological increase in bladder symptoms and cystitis. Also, the urogenital sinus of endodermal origin is very sensitive to estrogens and results in urinary infections in women with vaginal atrophy due to reduced estrogen levels.[4]

Evaluation and diagnosing vaginal atrophy

Clinical presentation

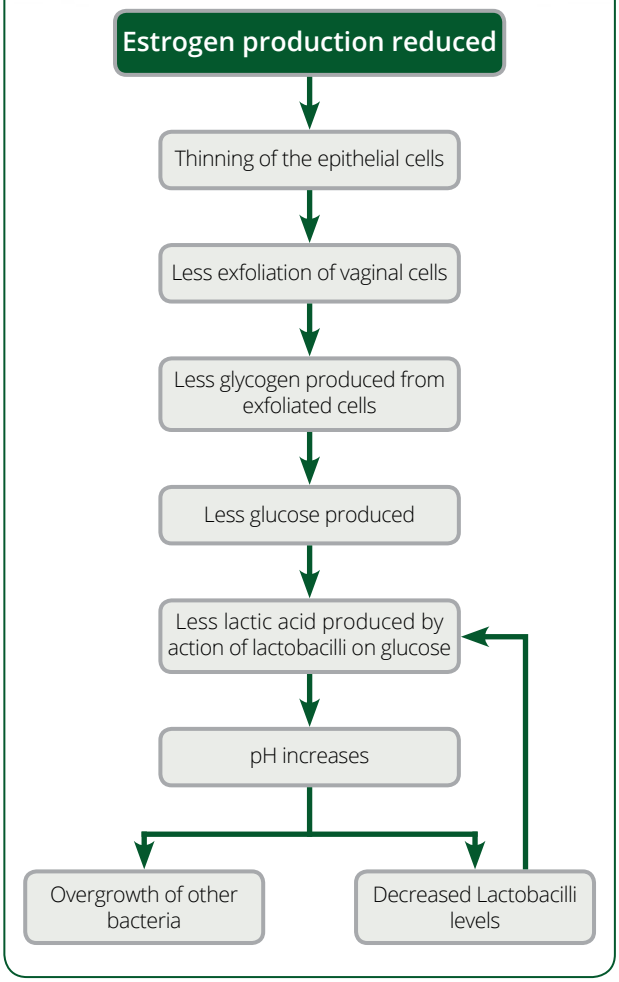
Atrophy of the labia majora and vaginal introitus is observed in most of the cases with vaginal atrophy. Also, the labia minora may recede. In a normal case without inflammation, the vulvar and vaginal mucosae may appear pale, shiny and dry.[12]

While in case if there is any inflammation they may appear reddened or pale with petechiae. Vaginal rugae may disappear and also the cervix may become flush with the vaginal wall and also a higher tendency of the vaginal shortening and narrowing is observed. The mechanism by which a series of effects takes place in vaginal atrophy are mentioned in figure 2.[12]

Vaginal atrophy can be diagnosed with a detailed history and comprehensive physical examination.[6]

- Vagina is dry, pale, frail tissue and lacks the normal mucosal ridges and folds
- Absence of expected elasticity and pliability associated with a well estrogenized vagina
- Minimal lubrication is present due to decreased vaginal blood flow and the tissues are easily traumatized with digital or pelvic examination
- Presence of petechiae or small hemorrhages on the vaginal lining
- Vaginal introitus is narrowed and the epithelial surface is typically very friable with or without ulceration
- Vulvar tissue appears diminished, obliterated, or even fused. Irritation and erythema are evident

Figure 2. Proposed mechanism for vaginal atrophy



- Pubic hair is diminished in most of the cases and there can be clitoral tissue shrinkage
- Apart from these, the pelvic organ prolapse is a very common symptom

Vaginal pH

As an adjunct to the physical examination, vaginal pH can be easily measured.[6] The pH of vaginal secretion varies between 3.8 and 4.5 and it remains within this range in healthy women even during the menstrual cycle. A pH of 4.5 or less signifies the absence of vaginitis, whereas a pH of more than 4.5 is classified as vaginitis.[13] It is typically greater than 5.0 in patients with atrophic vaginitis.[6]

Quick diagnosis tool[14]

Vaginal pH assessing gloves as Easy Quick diagnosis tool					
3.5	4.0	4.5	5.0	5.5	6.0
The normal vaginal pH is between 3.8 and 4.5. An altered vaginal pH is indicative of vaginal infection					
pH	≤ 4.5	< 4.5	> 4.5	≥ 5.0	
Vaginal discharge	+/-	+ (white, thick, clumpy discharge)	+ (white/grey, thin, clumpy discharge)	+ (Greenish-yellow, frothy discharge)	
Malodor	-	-	+	+	
Itching	-	+	-	+	
Burning	-	+	-	+	
	Normal	Candidiasis	Bacterial vaginosis	Trichomoniasis	

EXPERT OPINION

Vaginal pH assessing glove is an easy quick diagnosis tool which offers higher sensitivity and specificity in the detection of vaginal infections.

Vaginal atrophy scores

The vaginal atrophy score (VAS) is useful in the diagnosis of vaginal atrophy and also to determine the severity of the infection. Vaginal atrophy intensity can be determined using the five signs: vaginal dryness, rugae, pallor, petechiae and mucosal elasticity. Each sign was graded on a four-point scale (0=not present, 1= mild, 2=moderate, 3=severe) (Table 3).[7]

Additional testing

Cytology and wet mount smears can facilitate and substantiate the diagnosis. Some sexual healthcare specialists are now using high-resolution vulvoscopy for further examination of vulvar tissue to exclude possible underlying pathology. A biopsy of any suspicious lesion should be performed and the sample sent for comprehensive pathologic assessment.[6]

Differential diagnosis for vaginal atrophy

The differential diagnosis includes other conditions that may cause chronic vaginal and vulvar itching, discharge, or pain in the vagina (vaginal infections, irritants and vaginal dermatoses). In most cases, vaginal infections are caused by bacteria, viruses, protozoa and fungi. The three most common vaginal infections that can be misdiagnosed for vaginal atrophy are candida vulvovaginitis, bacterial vaginosis and trichomoniasis. Also, irritants that cause chronic vaginal itch including perfumes, any locally applied lubricant or moisturizer and soaps can cause vaginal atrophy. Vaginal

Table 3. Assessment of vaginal atrophy score[7]

	Not present (0)	Mild (1)	Moderate (2)	Severe (3)
Dryness	Normal lubrication	Slightly decreased	Minimal lubrication	Dry
Rugae	Normal number and depth	Reduced rugae	Rare rugae	Smooth vagina
Pallor	Normal pink	Light pink	Very pale	White/deep red
Petechiae	None	Bleeds on scraping	Bleeds on contact	Clearly seen
Mucosal elasticity	Normal	Decreased	None	Stenosis

Table 4. Differential diagnosis for symptoms of vaginal atrophy[12]	
Lesion	**Appearance**
Lichen sclerosis	Hypopigmented, crinkled, waxy-appearing tissue, with coalescing ivory and pink plaques, often in butterfly or figure-of-eight pattern involving labia majora and minora and clitoral hood and extending around anus; may result in labial agglutination.
Lichen planus	Painful, red plaques, or erosions, variably with white lacy edges or violaceous borders; may extend into vagina.
Lichen simplex chronicus (hyperkeratosis)	Thick, lichenified skin, often erythematous, caused by long-term rubbing or scratching.
Contact dermatitis (irritant or allergic)	Redness, swelling and itching, sometimes with blistering and painful, bright red swelling.
Vulvar intraepithelial neoplasm	Red, white, or dark raised or eroded lesions, multifocal.
Vulvar cancer	Commonly solitary ulcer with raised or indurated edge.
Extramammary paget disease	Brick red, scaly, eczematoid plaque with sharply demarcated border and sometimes a roughened surface.

dermatoses, including lichen sclerosus, lichen planus and lichen simplex chronicus, may cause similar symptoms. Cancer and precancerous lesions, including vulvar intraepithelial neoplasm, vulvar cancer and extramammary paget disease, are in the differential diagnosis of any localized areas of redness, thickening, or ulceration (Table 4). Biopsy should be performed if a malignancy is suspected or if the diagnosis is unclear.[12]

Relationship between estrogen, the vaginal flora and pathophysiology of UTI

The most common symptoms of UTIs in premenopausal women are urinary urgency, frequency and dysuria. Postmenopausal women with UTIs may report nocturia, malaise, urinary incontinence, or odorous urine.[15] Several guidelines have been proposed for the management of urogenital atrophy in relation to atrophic vaginitis. An agreement has been reached regarding the management of urogenital atrophy (Table 5).[1]

Treatment of vaginal atrophy, alone and in association with UTI

Prevention and lifestyle changes

All women, in particular for women with menopause, a regular sexual activity if desired is recommended. This helps to improve the

Table 5. Recommendations on the detection and management of urogenital atrophy[1]	
Lifestyle	Sexual exercise is recommended
Supplements	Remedies like byronia, lycopodium and belladonna
Lubricants	Other lubricants (compatible with latex condoms if safe sex is consideration)
Treatments	Chinese herbs, acupuncture and polycarbophilic gels
	Vitamin D and E oil, cream or capsule formulations
Drugs	Vaginal estrogen formulations or systemic hormone therapy

blood circulation and the seminal fluid contains prostaglandins, sexual steroids and essential fatty acids that serve as maintenance to the vaginal tissues.[1] Pelvic floor physiotherapy can also be recommended as it improves the tone, strength of the muscle fibres, elasticity and also increases the muscle mass that helps to overcome menopause symptoms.[16]

Non-prescription therapy: Lubricants

As we all are aware that atrophic vaginitis is commonly observed among postmenopausal women and only a few seek treatment. According to most of the clinical trials, an appropriate therapeutic solution is to use topically applied products. Estrogen-based treatments have been shown to be effective while most of the patients are reluctant to use such formulations for reasons like health concerns. Hence, there is a need to assess the efficacy of acceptable alternatives.[17]

Hyaluronic acid vaginal gel plays an important role in tissue repair in women with vaginal atrophy associated with extreme vaginal dryness

Hyaluronic acid vaginal gel offers hydrating properties that release water molecules to the vaginal tissues, thus alleviating the dry state of the vagina without irritating the vaginal mucosa.[17]

The efficacy of hyaluronic acid vaginal gel in the symptomatic treatment of vaginal dryness was evaluated in comparison to the estriol cream. The study included 144 women with extreme dryness and was randomized into two groups (test group and control group). The test group was treated with hyaluronic acid vaginal gel (72) and the control group was treated with estriol cream. Both the treatment gel and control cream were applied with a device, once daily for every 3 days to a total of 10 applications during 1-month period. The efficacy was evaluated by grading vaginal dryness and other three vaginal symptoms with a visual analog scale. All the assessments were performed at baseline, by telephone after the 3rd application and at the final visit of the patients.[17]

A significant improvement was observed in both the groups after 10 applications. Both hyaluronic acid vaginal gel and estriol cream significantly improved the clinical symptoms of vaginal dryness in postmenopausal women, with an improvement rate of 84.44% and 89.42%, respectively. The secondary parameters such as vaginal itching, dyspareunia and burning sensation were also similar in both the groups. Hyaluronic acid was found to be similar in efficacy, safety without any incidence of adverse events or discontinuation of the therapy. Hyaluronic acid vaginal gel was found to be as effective as estriol cream in the symptomatic treatment of vaginal dryness.[17]

EXPERT OPINION

Hyaluronic acid vaginal gel is clinically effective in relieving the symptoms of vaginal dryness.

Pharmacotherapy

The first-line treatment goal in patients with atrophic vaginitis must relieve symptoms, reverses or minimizes the physiological changes and improves quality of life. An individualized care must be considered during therapeutic management depending on the type of symptoms, medical history, lifestyle of the patient and treatment goals.[6]

Antibiotics for UTIs in association with vaginal atrophy

Empirical antimicrobial treatment

The causative pathogens, the severity of illness, local resistance patterns and potential for colonization with multidrug-resistant organisms must be considered when deciding an empirical antimicrobial treatment for therapeutic management of UTIs. The potential empirical regimens may include:[15,18-20]

- Monotherapy with a fluoroquinolone, aminoglycoside, third-generation cephalosporins or carbapenems[18]

Targeted antimicrobial treatment

Targeted antimicrobial therapy can be considered after doing culture and sensitivity testing. Based on the results, monotherapy or combination therapy can be started.

- Combination therapy with an aminoglycoside and third-generation cephalosporin[18]
- Combination therapy such as penicillin's and third-generation cephalosporin's in combination with β-lactam antibiotics (amoxicillin + clavulanic acid and/or cefditoren) can be considered in the treatment of UTIs[15,19,20]

Cefditoren is safe and effective in the treatment of uncomplicated cystitis

Cefditoren offers efficacious activity against urinary tract pathogens, especially against gram-negative bacteria. It shows good clinical and antimicrobial efficacy against UTIs, hence it is effective in the treatment of antimicrobial resistant UTI-causing pathogens, including fluoroquinolone non-susceptible *E. coli* with acute uncomplicated cystitis.[20]

To assess the clinical and microbiological efficacy of cefditoren in women with acute uncomplicated cystitis, a multicenter, randomized, open label study was considered. The study included 104 women with acute uncomplicated cystitis. All the patients were randomized to receive either 3-day dose (n= 51) or a 7-day therapy (n= 53) groups.[20]

During the 1st visit 94 bacterial strains were isolated from all the participants of which 81.7% (85/104) were *E. coli.* Clinical and microbiological efficacy was evaluated on 5-9 days following administration of the last dose. The clinical efficacy of the 3rd and 7th day therapy groups was 90.9% (40/44) and 93.2% (41/44), respectively (p=1.000). The microbiological efficacy was 82.5% (33/40) and 90.2% (37/41), respectively (p=0.349). There were no reports of any serious adverse events in both the groups. Cefditoren was found to be effective, safe and well-tolerated for uncomplicated cystitis, with no significant differences in clinical and microbiological efficacy among 3- and 7-day therapeutic regimens.[20]

EXPERT OPINION

Cefditoren is effective in the treatment of antimicrobial resistant UTI-causing pathogens, including fluoroquinolone non-susceptible *E. coli*.

Estrogen therapy: Indications and contraindications

Local, low-dose estrogen preparations can be considered as the first-line pharmacologic treatment for atrophic vaginitis. According to a recently published position statement from the North American Menopause Society (NAMS), an evidence-based conclusions and recommendations specific to the role of local estrogen preparations were considered for the treatment of vaginal atrophy in postmenopausal women.[6]

Phytoestrogens/Isoflavones as a 'New Frontier'

For the management of hypoestrogenic induced vaginal atrophy, vaginal gel containing soy isoflavones can be effective and safe in relieving symptoms of vaginal atrophy.[21]

Effective treatment of vaginal atrophy with Isoflavone Vaginal Gel[21]

Isoflavone (glycine) vaginal gel offer considerable reduction of symptoms in postmenopausal women with symptomatic vaginal atrophy. To evaluate the efficacy and tolerability of isoflavone vaginal gel, a double-blind, randomized, placebo-controlled trial was conducted. The trial included 99 postmenopausal women with symptomatic vaginal atrophy. The duration of therapy was 12 weeks. The treatment management included isoflavone vaginal gel (4%, 1 g/ day), conjugated equine estrogen cream (0.3 mg/day) and a placebo gel. The vaginal atrophy symptoms were classified at none, mild, moderate and severe. The vaginal cytology was evaluated to determine the maturation value at 4th week and 12th week. Evaluation of endometrial safety (by transvaginal ultrasonography) was evaluated at screening and at the end of study.[21]

Isoflavone vaginal gel was found to be effective in relieving the symptoms of vaginal dryness and dyspareunia. Also, there was an increase in the intermediate and superficial cells in the vaginal flora. The results were similar to the effects with the use of conjugated equine estrogens and superior to placebo gel. No changes were observed at the end of the study in endometrial thickness, sera follicle stimulating hormone and estradiol levels. Isoflavone vaginal gel on a daily basis in postmenopausal women showed improvements in vaginal atrophy symptoms and a significant increase in cell maturation values of the vaginal flora.[21]

EXPERT OPINION

Local application of Isoflavones gel offer relief of vaginal atrophy symptoms especially in women who have contraindications to the hormonal therapy.

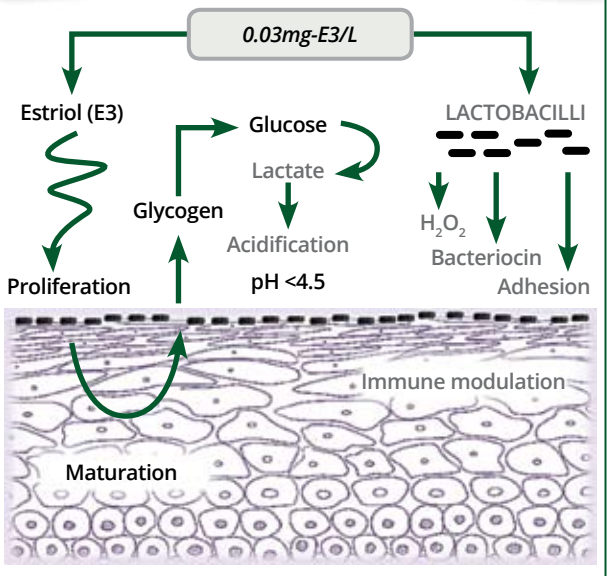
Vaginally administered probiotics for prevention and treatment of vaginal atrophy

Vaginally administered probiotics offer positive effects on the vaginal microflora composition thereby prevent vaginal infections in postmenopausal women by:

- Promoting the proliferation of beneficial microorganisms
- Altering the intravaginal microbiota composition

Vaginally administered probiotics also reduce the symptoms of vaginal infections (e.g., vaginal discharge, vaginal odor, etc.) and are helpful in the treatment and prevention of various vaginal infections such as vaginal atrophy.[22]

Figure 3. Mechanism of action with estriol-lactobacillus combination



H_2O_2: Hydrogen peroxide

Treatment of vaginal atrophy with estriol and lactobacilli combination

Dual mechanism of action is seen with estriol (0.03 mg) and *Lactobacillus acidophilus* (1 billion CFUs) combination (figure 3).

The use of ultra-low-dose estriol in combination with lactobacilli in the treatment of vaginal atrophy represents a modern medical concept. To restore and maintain a healthy vaginal system, both sufficient estrogen levels and colonization by lactobacilli are essential. A ultra-low-dosed estriol possesses no risk of endometrial proliferation, stimulates the vaginal epithelium and helps in the development of physiological flora.[5]

Vaginal lactobacilli tablet offers therapeutic efficacy by a variety of mechanisms to reinstate homeostasis by[5]

- Commensal colonization
- Blocking adhesion of pathogens
- Enhancing epithelial barrier function
- Influencing antimicrobial peptide secretion
- Maintaining the mucosal immunity of the human vagina

EXPERT OPINION

Estriol and lactobacilli combination could be considered as preferred option in the treatment of symptomatic vaginal atrophy in aging menopausal women.

Hence, estriol and lactobacilli combination displays synergistic action and considerably improves the clinical signs and symptoms along with the quality of life in women suffering from vaginal atrophy. This combination therapy is well-tolerated with lower incidence of side-effects and negligible estriol absorption.[5]

Lactobacilli vaginal tablet or the pH tablet is known to reduce cervico-vaginal proinflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). A comparative study including 67 women with bacterial vaginosis (BV) was carried out to evaluate the efficacy of probiotic lactobacilli vaginal tablets in women with vaginal infections. Fifty women with intermediate flora and 42 women with normal vaginal flora were randomized to receive either probiotic lactobacilli vaginal tablets (*L. brevis* CD2, *L. salivarius* subsp. *salicinius* and *L. plantarum*) or the vaginal pH tablet (active comparator). The concentrations of IL-1β, TNF-α and IL-6 were measured by using ELISA kit after collecting the cervico-vaginal lavage.[23]

Probiotic vaginal lactobacilli tablet was well-tolerated and safe without any side-effects or occurrence of adverse reactions. The clinical cure rate was found to be nearly 80%; i.e., 32% of the women restored normal vaginal flora and 47% of women showed improved nugent score. Only 20% of women did not clear the vaginal infection in the first follow-up (post 8 days of therapy). The pH lowering tablet resolved BV symptoms and restoration of normal vaginal flora in 74% and 26% women, respectively. Probiotic lactobacilli vaginal tablet was efficacious and superior in preventing BV and restoring the vaginal flora compared to the pH lowering tablet. Significant reduction in proinflammatory vaginal cytokines (IL-1β, IL-6 and TNF-α) was observed with the probiotic lactobacilli vaginal tablet, while the pH lowering tablet did not show any effect.[23]

Vaginally administered probiotic lactobacilli vaginal tablets containing at least 1 billion viable lactobacilli (*L. brevis* CD2, *L. salivarius* subsp. *salicinius* and *L. plantarum*) is effective in reducing the symptoms of vaginal infection and significantly restores the vaginal flora to normal flora.[23]

EXPERT OPINION

Vaginally administered probiotic lactobacilli in the form of vaginal tablet is effective in reducing the symptoms of vaginal infection and to restore the normal vaginal flora.

SUMMARY

- Nearly 50% of postmenopausal women experience vaginal atrophy, thinning and inflammation of the vaginal walls
- Some women experience these manifestations with painful and sensitive vaginal symptoms such as vaginal dryness, itching, or pain/ discomfort during sexual intercourse, significantly affecting their quality of life
- A postmenopausal decline in estrogen affects the urinary tract, which can lead to thinning of the bladder and urethral linings, chronic dysuria and UTI
- UTIs are experienced by almost 50% of postmenopausal women who have atrophic vaginitis
- Vaginal atrophy increases the risk of GSM such as frequency or urgency of urination or a burning sensation during urination
- pH assessing gloves as easy quick diagnosis tool offers higher sensitivity and specificity in the detection of vaginal infections
- A water-soluble vaginal lubricant can be beneficial and used to moisten the tissues and in the prevention of painful sexual intercourse
- Hyaluronic acid could be a suitable alternative to estroil therapy in women with complications of vaginal atrophy associated with UTIs
- Combination therapy such as penicillin's and third-generation cephalosporin's in combination with β-lactam antibiotics (amoxicillin + clavulanic acid and/or cefditoren) can be considered in the treatment of UTIs
- Cefditoren is effective in the treatment of antimicrobial resistant UTI-causing pathogens, including fluoroquinolone non-susceptible *E. coli*
- Local application of isoflavones offer relief of vaginal atrophy symptoms especially in women who have contraindication to the hormonal therapy
- Estriol and lactobacilli combination could be considered as preferred option in the treatment of symptomatic vaginal atrophy in aging menopausal women
- Vaginally administered probiotic tablets containing at least 1 billion viable lactobacilli (*L. brevis* CD2, *L. salivarius* subsp. *salicinius* and *L. plantarum*) is effective, safe and well-tolerated in reducing the symptoms of vaginal infections and restoring the vaginal flora to normal flora

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