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Standards of care and future directions in vaginal atrophy

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ABSTRACT

Vaginal atrophy (VA) affects about half of the female population in post-menopause, a rate that justifies the growing interest in research, and is due to an estrogen deficiency. This involves dryness, thinning of the epithelium, and a concomitant loss of glycogen in epithelial cells with progressive reduction in the number of glycogen-feeding acidophiles *Lactobacilli*. The lack of *Lactobacilli* in turn causes pH alterations and less resistance to infections. If left untreated over the years, VA progresses from mild to moderate and severe forms. Current management is based on hormone replacement therapy (HRT), with the vaginal route of administration being preferred, as it shows fewer side effects and is in direct contact with the mucosa; selective estrogen receptor modulators, particularly ospemifene; selective estrogen enzyme modulators, an example of which is tibolone; and non-HRT interventions. The last ones represent the standards of care in mild VA to be started as early as possible, and a first-line treatment in moderate to severe forms not complicated by osteoporosis as part of a step-up approach. A focus on innovative techniques such as laser, radiofrequency combined with electroporation, and ozone-oxygen therapy is here carried out, together with an excursus on products of proven efficacy virtually free of side effects, i.e., hyaluronic acid, fat-soluble vitamins (vitamins A and E), probiotics (*Lactobacilli*), polynucleotides, exosomes, phytoestrogens (soy isoflavones), monocots (*Aloe vera, Triticum aestivum*), and platelet-rich plasma. Future directions for therapeutic intervention specifically aim to protect women's health and well-being by encouraging research in the field of non-HRT, and its integration with hormonal treatments; in this way, it will be possible to further reduce the minimum effective dose of hormones to be taken, if necessary, by moving from low to ultra-low doses for an increasingly shorter period of time.

Keywords: Vaginal atrophy; genitourinary syndrome of menopause; hormone replacement therapy; selective estrogen receptor modulators; phytoestrogens; laser; radiofrequency; electroporation; ozone-oxygen; hyaluronic acid; *Lactobacilli*; polynucleotides; exosomes; platelet-rich plasma

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INTRODUCTION

The term vaginal atrophy (VA) refers to the post-menopausal involution of the vagina due to estrogen deficiency; it is estimated that half of the female population suffers from it after menopause. Menopause can be achieved physiologically following the exhaustion of the follicular reserve, or it can be induced by bilateral oophorectomy, hypothalamic-pituitary dysfunctions, and pelvic chemoradiotherapy; a decrease in estrogen levels also occurs in breast cancer survivors treated with antiestrogens, in primary ovarian insufficiency, and during postpartum lactation. Cigarette smoking is another well-known risk factor that compromises vaginal trophism.[1]

Estrogen deficiency unleashes three main changes in the vagina (Figure 1). At first, it causes a thinning of the epithelium and a decline in subepithelial collagen, with loss of vaginal elasticity and increased susceptibility to trauma and bleeding during sexual penetration. Secondly, it influences vaginal hemodynamics resulting in reduced secretions; this event is related to the onset of intimate dryness and loss of lubrication during sexual intercourse, which then becomes painful (dyspareunia). Third, it causes a reduction of glycogen in epithelial cells, and a consequent decrease in the number of glycogen-feeding *Döderlein bacilli*. Through the production of lactic acid, these commensal bacteria are responsible for maintaining an acidic pH (3.5-5.0) in the vagina, which prevents the growth of pathogenic microorganisms; with the lack of *Lactobacilli* the pH becomes less acidic (6-7) or basic (7-8), a condition that favors vaginal infections, smelly discharge, unpleasant odors, burning, and itching.[1]

When vaginal inflammation overlaps with atrophy, we are referring to atrophic vaginitis that, together with vulvovaginal atrophy and atrophic dysfunction of the urethra and bladder, constitutes the genitourinary syndrome of menopause (GSM); while vasomotor symptoms of climacteric tend to regress over time, VA progressively worsens if left untreated.[1]

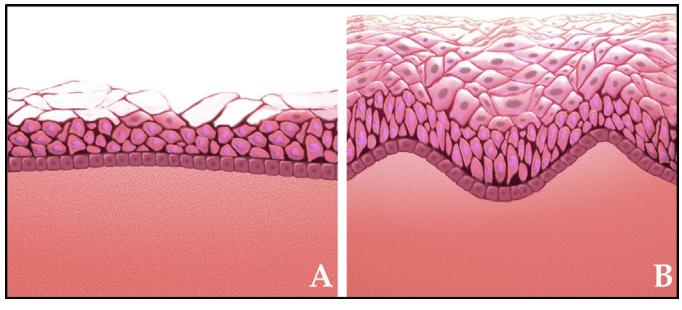

Figure 1. Atrophic vaginal epithelium of menopause (A) compared to epithelium of reproductive age (B): note the reduction in thickness, the loss of roughness, and the empty glycogen lacunae on the surface (by courtesy of Blausen Medical Communications, Inc.)

The following analyses the therapies currently available in an attempt to combat it, and the future directions of research.

Hormone Replacement Therapy

Hormone replacement therapy (HRT) is a form of hormone therapy to treat symptoms associated with menopause, including osteoporosis, hot flashes, and VA. Contraindications to HRT are represented by: history of breast or ovarian cancer; endometrial or breast hyperplasia; ongoing female malignancy; uterine leiomyomas; undiagnosed vaginal bleeding; hypercholesterolemia/hypertriglyceridemia; decompensated diabetes mellitus or uncontrolled arterial hypertension; angina; coronary stenosis; venous thrombosis; pulmonary embolism; coagulation defects; liver, gallbladder, and/or kidney diseases; stroke; migraines; dementia; epilepsy; otosclerosis; systemic lupus erythematosus; porphyria; angioedema; asthma; allergy to excipients or active ingredients; thrombophilia or genetic predisposition to endometrial, ovarian, and/or breast cancer; a body mass index >30 kg/m^2.[2]

In an effort to increase tolerability and reduce side effects, among which spotting, breast tenderness, headache, fluid retention and weight gain, gastric discomfort, lipid profile alterations, thrombosis, ictus, hormone-dependent cancer/hyperplasia, cognitive or mood decline, visual disturbances, and skin manifestations, bioidentical HRT has gained popularity in the 21st century. It consists of artificial compounds with exactly the same chemical and molecular structure as hormones produced by women. However, it also requires careful monitoring through weight and blood pressure measurement and gynecological examination with transvaginal ultrasound after the first three months to assess adverse effects, symptom relief, and ensure proper dose; long-term follow-up should be annual and include blood tests, Pap smear, breast assessment and, if necessary, a bone mineral density scan.[3]

The main routes of HRT administration are oral, vaginal, transdermal, subcutaneous, and intramuscular, of which the first three are by far the most used. Oral HRT can be considered the standard of care for moderate to severe VA in patients who have been postmenopausal for more than one year, with osteoporosis, vasomotor symptoms, and no contraindications to treatment.

Oral HRT

Over the years, estrogen-only pills have been replaced by those that also contain progesterone, since unopposed estrogen promotes endometrial hyperplasia and significantly increases the risk of cancer in non-hysterectomized patients. Estradiol is the primary female sex hormone, but its synthetic derivative

ethinylestradiol, when administered orally, is about 100 times more potent than estradiol or conjugated equine estrogens (CEEs), so its unit dose is reduced to 1/100, i.e., 0.0025 mg or 0.005 mg per tablet instead of 0.25 mg or 0.5 mg (Table 1). Among the progestins used in combined pills there are: drospirenone, dydrogesterone, medroxyprogesterone, nomegestrol, norethisterone, and norgestimate (Table 1).

Vaginal HRT

Vaginal HRT can improve VA with fewer systemic effects than oral HRT, as it is not subject to first-pass metabolism through the liver. In this way, coagulation cascade is not activated, which may explain why oral HRT is associated with a higher risk of thromboembolism, stroke, and heart attack. For this reason and because of direct contact with the mucosa, vaginal HRT is preferable to oral HRT in the absence of osteoporosis and vasomotor symptoms, and it is available in the form of suppositories, creams, and vaginal rings or pessaries. The ovules contain 0.004 mg or 0.01 mg, depending on the needs, of bioidentical estradiol; one is applied in the evening before going to bed for fifteen consecutive days, and then continue with two maintenance applications per week. Suppositories based on the synthetic estrogen promestriene are also available at a dosage of 10 mg, to be used for 3 week treatment cycles; it does not appear to convert into estradiol and therefore has negligible systemic effect. The ring is an interesting option as it releases 0.0075 mg of bioidentical estradiol daily and lasts for three months. Suppositories containing prasterone (dehydroepiandrosterone) are also available on the market at a unit dose of 6.5 mg to be inserted at bedtime; the exact reason why prasterone is effective in treating VA is still unknown, although it may be due to its local aromatization to estrogen.[4]

Transdermal HRT

Similar to vaginal HRT, transdermal HRT does not undergo first-pass metabolism; it is available in gel, spray or patches. The last ones can contain only estradiol delivered at a daily dose of 0.025 mg, 0.0375 mg, 0.05 mg, 0.06 mg, 0.075 mg, or 0.1 mg for a duration of one week per patch, or a combination of estradiol (0.045 mg or 0.05 mg) and levonorgestrel (0.015 mg) or norethindrone (0.14 mg or 0.25 mg), to be applied once or twice a week on clean, dry skin, avoiding the breast and the same previous area.[5]

Phytoestrogens

Phytoestrogens are plant-derived xenoestrogens, such as soy isoflavones; without significant health risks, they can attenuate

Table 1. Active ingredients, unit doses, and posology of the oral HRT available on the market for the treatment of VA

Active ingredients	Unit doses (mg)	Posology
Estradiol	0.5, 1 or 2 (per tablet)	1 per day (for 21 days then 7 days off)
Estradiol + drospirenone	0.25+0.5, 0.5+1 or 1+2 (per tablet)	1 per day (continuous)
Estradiol + dydrogesterone	1+5, 1+10 or 2+10 (from 15th to 28th tablet)[1]	1 per day (continuous)
Estradiol + medroxyprogesterone	2+10 (from 12th to 21st tablet)[1]	1 per day (for 21 days then 7 days off)
Estradiol + nomegestrol	1.5+2.5 or 1.5+3.75 (from 1st or 11st to 24th tablet)[1]	1 per day (continuous or for 24 days then 4 days off)
Estradiol + norethisterone	0.5+0.1 or 1+0.5 (per tablet)	1 per day (continuous)
Estradiol + norgestimate	1+0.09 (from 4th to 6th, 10th to 12nd, so on in sequence per tablet)[1]	1 per day (continuous)
Estradiol + progesterone	1+100 (per tablet)	1 per day (continuous)
Estradiol[2]/estrone[2]/equilin[2]	0.3, 0.45, 0.625, 0.9, 1.25 or 2.5 (per tablet)	1 per day (for 21 days then 7 days off)
Estradiol[2]/estrone[2]/equilin[2] + medroxyprogesterone	0.3+1.5, 0.45+1.5, 0.625+2.5 or 0.625+5 (per tablet)	1 per day (continuous)
Ethinylestradiol + norethisterone	0.0025+0.5 or 0.005+1 (per tablet)	1 per day (continuous)

[1]: the other tablets contain only estradiol at the same unit dose; [2]: conjugated equine estrogens (CEEs); HRT: hormone replacement therapy; VA: vaginal atrophy

VA but to a lesser extent than animal-derived estrogens. They are available both in the form of suppositories and supplements, the former to be preferred for the treatment of VA. Depending on the case, they should be considered as a first-line treatment before switching to vaginal HRT.[6]

Selective Estrogen Receptor/Enzyme Modulators

Selective estrogen receptor modulators (SERMs) are a class of tissue-specific drugs that act on estrogen receptors (ERs), selectively stimulating or inhibiting estrogen-like action in various tissues. On the other hand, selective estrogen enzyme modulators (SEEMs) are drugs that do not directly stimulate or inhibit ERs, but whose metabolites act selectively on ERs in various tissues; they therefore first require enzymatic metabolism. SERMs/SEEMs have similar indications and contraindications as oral HRT, although this class of drugs also includes active ingredients used in the treatment of luminal breast cancer, so fewer side effects on mammary tissue are expected.[7]

By virtue of this, they can be considered the standard of care for moderate to severe VA in patients who have been postmenopausal for more than one year, with osteoporosis, vasomotor symptoms, and no contraindications to treatment or at low risk of developing breast cancer. Some of these molecules are of particular interest in the treatment of VA.

Ospemifene

Ospemifene is a synthetic SERM with agonist action on the vagina and bone tissue, with mixed action on the endometrium, and with antagonist action on the breast, which gives it a possible chemoprevention on mammary tumor. It binds ERs-α and ERs-β with similar affinity; both are present in the vagina during reproductive age, but only ERs-α are found in the vagina even after menopause. For this reason, ospemifene can be used in the treatment of VA, particularly when associated with moderate to severe dyspareunia, at a unit dose of 60 mg per daily tablet to be taken continuously until the symptom is relieved.[8]

Tibolone

Tibolone is a synthetic SEEM whose two major active metabolites, 3α-hydroxytibolone and 3β-hydroxytibolone, act as potent, fully activating agonists of the ERs, with a high preference for ERs-α; hence its usefulness in the treatment of VA. Since it also has a weak progestogenic and androgenic action, it is available alone at a unit dose of 2.5 mg per daily tablet to be taken continuously until the symptom disappears. Androgenic activity is responsible for possible side effects, such as acne and increased hair growth.[8]

Bazedoxifene

Bazedoxifene is a synthetic SERM with agonist action on bone, and antagonist action on the breast and endometrium. Classically used for the prevention of osteoporosis in post-menopause, it is also commercially available in combination with 0.45 mg CEEs at a unit dose of 20 mg per tablet to be taken daily; since CEEs are active on the vagina, this combination may be used off-label in the treatment of VA.[9]

Lasofoxifene

Lasofoxifene is a synthetic SERM with agonist action on bone, and antagonist action on the breast and endometrium. Recently, two phase III trials enrolling 444 and 445 women have shown significant benefits at twelve weeks on VA through oral lasofoxifene at unit doses of 2.5 mg or 0.5 mg daily, compared to placebo. In 2025, a further study in 72 patients with metastatic breast cancer has confirmed its usefulness in the treatment of VA at a dosage of 5 mg per day.[10,11]

Non-hormone Replacement Therapy

Non-HRT includes all treatments that do not exploit hormones and can be effectively used as a replacement therapy in VA patients who are unwilling or unable to take hormones (e.g., breast cancer survivors, ovarian cancer survivors). Non-HRT can be considered the standard of care in mild VA to be started as soon as possible, and a first-line treatment in moderate to severe forms not complicated by osteoporosis as part of a step-up approach.

Laser

Fractional carbon-dioxide (CO_2) laser is able to activate fibroblasts which are stimulated to synthesize new collagen and, to a lesser extent, elastin, both fundamental proteins of the extracellular matrix. In addition, it can also reactivate microcirculation, thus promoting the hydration process of the matrix. The result is a rejuvenating effect on vaginal tissues, including the epithelium. Fractional CO_2 laser is a minimally invasive outpatient technique that exploits an intravaginal probe capable of releasing the laser beam in a controlled radial manner at a depth of less than 5 mm. After placing the patient in the lithotomy position and applying an inserter that acts as a guide, a graduated probe with an open end is inserted deep into the vagina (Figure 2A); once the probe has been positioned deeply, the first automatic 360° scan is performed for 1-5 seconds. The scanning can be repeated at the physician's discretion by rotating the probe 45° first to the left and then to the right, in order to direct the beam uniformly. On the market, there are also probes with 90° closed ends that

allow the laser beam to be directed into a single quadrant of the vaginal canal. The probe is then retracted one notch, and the scan is repeated once or twice again in a checker-board motion; this procedure continues until the entire vagina has been treated based on individual length. Normally a session lasts 15-20 minutes, and three sessions spaced one month apart are required; during the first session it is recommended to use a lower power (20-30 W) to let the tissues get used to it, and then move on to a higher power (40 W) in subsequent sessions. After a session, mild swelling, redness, and slight bleeding may occur, which generally resolves within 24-48 hours. A couple of days before the session the patient must avoid ovules or creams that could interfere with the laser emission, while after the sessions hydrating and nourishing substances can be applied, avoiding vaginal intercourse for a week. Adding oral supplementation with bioactive collagen peptides offers significant benefits over laser treatment alone, and 1-2 maintenance sessions are recommended one year after the treatment cycle. Patients with active infections (*Candida, Herpes, Papilloma, Chlamydia, Ureaplasma, Mycoplasma, Gardnerella, Klebsiella, Gonococcus, Streptococcus, Staphylococcus, Treponema, Trichomonas, Haemophilus, Escherichia*, etc.) or dysplastic/neoplastic changes cannot undergo treatment unless the problem has been resolved; it is therefore necessary to screen patients with a Pap smear, papilloma test, and with a set of cervico-vaginal swabs. Further contraindications to treatment are recent pelvic surgery performed within one year, uterine prolapse of grade ≥2, and ongoing antihormonal or anticoagulant/antiplatelet therapy; mesh erosion or extrusion are absolute or relative contraindications depending on the case.[12]

Erbium-doped yttrium aluminum garnet (Er:YAG) laser has emerged as a promising alternative for VA treatment as well. Unlike CO_2 laser which delivers high-speed pulses up to a wavelength of 10.6 μm, Er:YAG laser emits infrared light with a typical wavelength of 2.94 μm; for this reason, it can be chosen

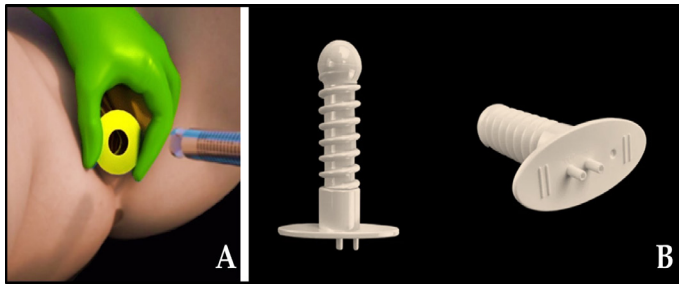

Figure 2. A graduated laser probe with an open end and its inserter in place at the vaginal entrance as guidance (A), compared to a threaded O3-O2 probe with a double connection at the base for vaginal insufflation and the safety device (B)

when even more superficial applications, and consequently a quicker recovery, are desired.[13]

Radiofrequency

Fractional radiofrequency (RF) exploits electromagnetic waves capable of generating heat in depth to stimulate fibroblasts and promote neocollagenesis with subsequent mucosal remodeling. As in laser technology, fractional energy is distributed from the endovaginal handle to equidistant points, producing only microscopic columns of thermal lesions that allow for faster re-epithelialization. However, RF uses even lower power than laser and the risk of operator-dependent adverse events is quite low.[14]

In order to maximize its effectiveness, especially in cases of vaginal laxity, it can be combined with electroporation (EP), which can transiently increase the permeability of the mucosa by means of electrical impulses. The treatment plan includes one session per week for seven consecutive weeks, avoiding vaginal intercourse; each session lasts 20 minutes, including 10 min of RF and 10 min of EP, during which a 2% hyaluronic acid solution is delivered. A booster session is recommended after six months. The treatment is absolutely contraindicated in patients with pacemakers; the other contraindications are the same as those of the laser. According to a 2025 randomized controlled trial on 48 postmenopausal women, both RF and laser are effective treatments for the symptoms of GSM. In light of what emerged from a further 2025 study on 62 breast cancer survivors receiving adjuvant therapy, both treatments produced significant improvements in VA comparable to those achieved with promestriene. Another prospective randomized open-label clinical trial conducted with 62 postmenopausal women from 2024 reached an overlapping conclusion. In the same year, a descriptive study of 48 postmenopausal women has concluded that both RF and CO_2 laser are valid alternatives to vaginal estrogen creams, and, in a randomized clinical trial of 32 women, RF has demonstrated similar efficacy to vaginal estrogen administration.[14-18]

Ozone-oxygen (O_3-O_2)

Similarly to fractional laser, O_3-O_2 has a rejuvenating effect on tissues, combined with antiseptic properties; for this reason, it is also indicated for patients with active infections, including *Candida*, *Herpes*, *Papilloma*, *Chlamydia*, *Gardnerella*, and *Trichomonas*. It can be effectively delivered into the vagina via lipogel or ovules, made from ozonated sunflower oil, or by insufflation; this latter route of administration has the advantage of diffusing O_3-O_2 in a uniform manner along the entire length of the vagina. Initially, vaginal irrigation with saline solution is performed to remove any mucus buildup. Subsequently, a

lubricated probe made of O_3-resistant material that does not release phthalates is inserted deep into the vagina; the base of the probe is equipped with two connections, one central and one lateral, to which two silicone tubes must be connected (Figure 2B). The opposite end of the central cannula is connected to an O_3 generator, while the lateral tube is connected in series with a liquid collector and an O_3 destructor to avoid gas leaks in the room. The concentric multi-ring thread of the vaginal probe is also designed to prevent O_3 leakage during treatment (Figure 2B). After placing the patient in the lithotomy position under the control of a pulse oximeter to monitor vital parameters, proceed with the insufflation of the O_3-O_2 mixture at a concentration between 10-30 µg/mL with constant flow, gradually extracting the probe ring by ring, for 5-10 min per day or every other day or per week. The volume of O_3-O_2 mixture to be used varies between 1-2 L; in total, ten procedures are recommended once a year or more, depending on the clinical scenario. Prolonged concentrations above 30 µg/mL should be avoided due to the increased risk of suppression of the saprophytic flora, and to avoid excessive local oxidative stress with irritation of the mucous membranes. The procedure must be stopped immediately in case of alteration of the patient's vital parameters (<90% SpO_2; >100 bpm), due to a possible remote risk of air embolism. It is recommended to lubricate the vagina immediately after the procedure with synthetic mucus based on hyaluronic acid, and to restore the *Lactobacilli* flora with vaginal ovules to be applied in the evening before bed; sexual penetration should be avoided for one week after the end of the entire treatment cycle. Contraindications to treatment include: coagulation disorders, cardiovascular instability, decompensated hyperthyroidism, seizures, substance abuse, alcohol intoxication, hepatolenticular degeneration, hemochromatosis, current use of antihormonal drugs, iron or copper supplements, anatomical abnormalities, and favism. A glucose-6-phosphate dehydrogenase test is therefore required prior to any O_3-O_2 therapy; if the patient suffers from favism, it is possible to opt for treatments without O_3 and based on intravaginal hyperbaric O_2.[19]

Hyaluronic Acid

Hyaluronic acid is another of the main components of the extracellular matrix able to absorb significant amounts of water, giving turgor to the tissues. It is available both in lubricating creams and in ovules to be applied preferably before going to bed for long periods of time (12 weeks), in order to obtain concrete benefits. Two recent systematic reviews evaluated its use in VA, concluding that it shows an efficacy profile comparable to vaginal estrogens, but with higher safety and tolerability.[20,21] Therefore, hyaluronic acid can be considered a valid alternative to vaginal estrogens in patients who cannot or do not want to undergo hormonal therapies, and a first-line treatment for mild VA virtually free of side effects; treatment requires boosters as needed depending on the clinical picture.

Fat-Soluble Vitamins

Among the fat-soluble vitamins useful in the topic treatment of VA are vitamins A and E. Vitamin A maintains the homeostasis of epithelium and mucosal membranes through its metabolites, while vitamin E acts as an antioxidant protecting them from free radicals and reactive O_2 species. Both are available in the form of ovules, also in combination with hyaluronic acid, virtually devoid of side effects. An 8 week study in 42 patients found benefits from the use of suppositories containing 1 mg (2.22 IU) of vitamin E compared to placebo, while another 8 week trial enrolling 40 patients showed that the benefits obtained with 5 mg hyaluronic acid ovules were greater than those of 1 mg vitamin E, taken separately. Therefore, the preferred formulation is the one in combination with hyaluronic acid for 8-12 weeks, to be repeated as needed. Two other 12 week studies in 52 patients each found no difference between the use of high vaginal doses (100 IU) of vitamin E and vaginal estrogens, findings suggesting its efficacy in VA.[22]

Moreover, receptors for vitamin D, another well-known fat-soluble vitamin, are expressed in the superficial layers of the female urogenital tract, and, in addition to playing a role in the prevention and treatment of postmenopausal osteoporosis, vitamin D may help support urogenital health in women with GSM. In 2023, a randomized, double-blind clinical study in 64 patients compared a CEEs vaginal cream with a vaginal cream based on vitamins D and E, concluding, after twelve weeks of treatment, that it is a suitable alternative to vaginal estrogens.[23]

Lactobacilli

As previously reported, *Lactobacilli* are essential in the vaginal microbiota and form a biofilm in women of reproductive age, which protects them from infections by producing lactic acid. In addition to lactic acid, they release hydrogen peroxide and butyric acid which inhibit the growth of *Candida albicans*. The dominant strains of *Lactobacilli* in healthy women are: *Lactobacillus crispatus*, *Lactobacillus gasseri*, *Lactobacillus iners*, *Lactobacillus jensenii*, and *Lactobacillus plantarum*. Restoring the vaginal flora with probiotic ovules is therefore a key moment in the treatment of VA, virtually free of side effects, to be associated with other therapeutic options. Recent findings suggest that not only vaginal HRT but also laser therapy, both with CO_2 and

Er:YAG lasers, helps restore its balance in favor of *Lactobacilli*. To maintain the vaginal microbiome, oral dietary supplements are available on the market.[24,25]

Monocots

Among the monocots of interest in the treatment of VA there are *Aloe vera* and *Triticum aestivum (Triticum sativum, Triticum vulgare)* for their hydrating properties. The latter, available in ovules, cream, or vaginal solution, is made up of starch, glycolipids, and phospholipids that create a surface film that prevents fluid loss and promotes re-epithelialization. A 6 week study in 60 patients compared *Aloe vera* vaginal cream to an estrogen cream, finding that both treatments significantly improved symptoms of VA, but the *Aloe vera* group showed superior results in terms of fluid volume without side effects.[26,27]

Polynucleotides

Polynucleotides are biopolymers composed of nucleotide monomers covalently linked in a chain, very well tolerated in regenerative and aesthetic medicine. They are now available as vaginal ovules or intradermal injections to promote, at the doctor's discretion, the physiological repair mechanisms in atrophic-dystrophic conditions of the vagina or vulva.[28]

Exosomes

Exosomes are extracellular vesicles ranging in size from 30 to 150 ηm that are produced in the endosomal compartment of most eukaryotic cells, including vaginal ones; they have in fact been detected in human vaginal fluid. Mesenchymal stem cells-derived exosomes are now being exploited in cosmetics, and studied for tissue rejuvenation and reconstruction. Still at the experimental level, a promising line of research is evaluating the usefulness of exosomes derived from human umbilical cord mesenchymal stem cells to also ameliorate VA.[29]

Platelet-rich Plasma (PRP)

As a concentrated source of autologous platelets and plasma proteins, PRP contains multiple growth factors that can stimulate tissue regeneration and healing, including vaginal abrasions and ulcers. Still in the experimental phase, PRP appears to give promising results in the treatment of VA and GSM.[30]

CONCLUSION

There are currently several therapeutic options available for the management of VA; when the clinical picture allows it, treatments that do not expose patients to side effects and health risks are preferable. Future directions for therapeutic intervention aim to protect women's health and well-being by encouraging research in the field of non-HRT, and its integration with hormonal treatments; in this way, it will be possible to further reduce the minimum effective dose of hormones to be taken, if necessary, by moving from low to ultra-low doses for an increasingly shorter period of time.

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FOOTNOTES

Contributions

Surgical and Medical Practices: L.R., D.S., Concept: L.R.; Design: L.R., Data Collection or Processing: L.R., Analysis or Interpretation: L.R., D.S., Literature Search: L.R., D.S., Writing: L.R.

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