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Original article

Cosmetic Gynecology: Present and Future Perspectives

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Abstract

Postmenopausal women and events like childbirth, and aging may cause structural and functional changes in women genitalia. The arising indications do not only cause psychological distress to women but negatively affect the sexual well-being and deteriorate the quality of their lives. Regenerative/ cosmetic gynecology procedures enable women to treat the functionality issues and modify the physical structure of vagina. This review discusses the latest developments in this field with regards to various kinds of procedures that are available, particularly the use of energy-based devices, and adipose tissue derived stem cells therapy for fat grafting which have revolutionized the regenerative gynecology procedures. These offer non-invasive modalities to treat the conditions like urinary incontinence among others which occur in high prevalence among women. Despite the advancements made in this field, it lacks regulatory guidelines and standardized procedures which imposes one of the biggest challenges of the field. Alongside, we have documented a procedure called Intimacell® which has been standardized for fat grafting procedures in vulvovaginal region.

Keywords: ***Cosmetic Gynecology, Vaginal Rejuvenation, Stem Cell in aesthetic gynecology, energy based devices.***

Introduction

Regenerative Gynecology is a branch of cosmetic and aesthetic surgery which comprises of surgical and non-surgical procedures to enhance the aesthetic appearance and functionality of the vulvo/vaginal region. Events like pregnancy, childbirth and ageing affect the structure of vagina thereby causing changes in its appearance and physical response to stimuli. Most commonly women are affected by birthing injuries, uterine prolapse, incontinence issues, vaginal atrophy, genitourinary syndrome of menopause, perimenopausal and menopausal changes, lichen sclerosus, sexual dysfunction, and vulvovaginal laxity. These indications not only affect sexual well-being of women but deteriorate the overall quality of life [3,4]. Cosmetic gynecology procedures enable pelvic floor toning and regain the integrity of the tissues, hence, giving an opportunity to women to achieve a better quality of life through increased comfort and sexual confidence [9]. Table 1 lists cosmetic gynecology procedures in practice.

Table 1: Overview of the procedures and treatments performed in cosmetic gynecology

Surgical Procedures	Labia minoraplasty Clitoral hood reduction (Hoodoplasty) Labia majoraplasty Vaginal caliber reduction Monsplasty Vaginoplasty Perineoplasty Colporineoplasty
Minimally Invasive Procedures	Platelet Rich Plasma therapy Lipofilling/Lipograft
Energy Based Devices	Surface cooled monopolar Radio frequency Cryogen cooled monopolar Radio frequency Erbium YAG laser therapy CO_2 laser therapy HIFU 1470 Diode Laser

Platelet Rich Plasma (PRP) therapy for vaginal rejuvenation

Over the last 20 years PRP has been used as an effective treatment for various indications including maxillofacial surgery, wound treatment, orthopedic, soft tissue injuries, gastrointestinal surgeries, scars, burns, gynecological disorders, and in cosmetic procedures [22-24]. PRP is enriched with several growth factors and cytokines [27,28] that are released in response to cellular damage and stimulate the process of fibroblast collagen synthesis Figure 1 shows separation of blood into three layers after centrifugation while PRP preparation.

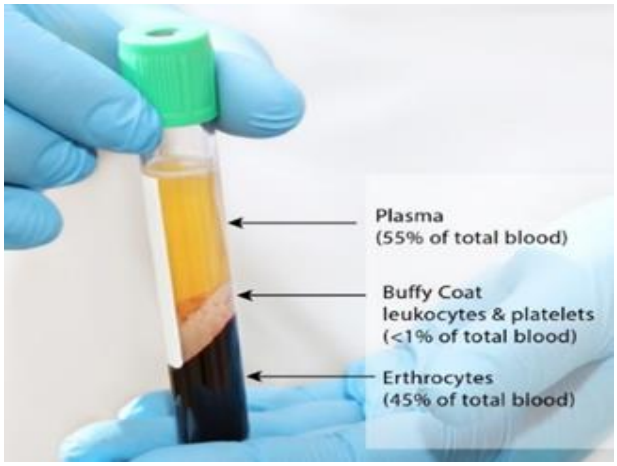

Figure 1: The separation of blood into three layers after centrifugation while PRP preparation

A study in 2017 conducted a pilot study with sixty eight women of ages between 32-90 years, to measure their responses to PRP therapy as a treatment for overactive bladder, stress incontinence, varying degrees of sexual dysfunction (orgasm, libido, and dyspareunia) and lack of lubrication. There were two sessions of PRP therapy was provided two months apart. The results revealed that 94% of women were satisfied and only 6% of them who had the indication of overactive bladder, did not show any improvement. The study concluded that the treatment is effective, and safe for women seeking changes in the vulvo-vaginal region[29].

Long et al in 2021 conducted a study to evaluate the effectiveness of autologous PRP injection as a therapy for women with SUI indication. Twenty women were enrolled in this study and PRP was injected at anterior vaginal wall. Follow up was done at the interval of 1 month and 6. Secondary outcomes including sexual function and treatment effect sorted by age were analyzed. They found that PRP treatment is effective in relieving SUI symptoms without significant adverse reactions at both 1 month and 6 month follow up. PRP is also used as an adjunct therapy along with energy-based devices procedures to enhance the efficacy of the treatment [30]. In another study by Willison F et al 2021, feasibility, safety, and efficacy of $FxCO_2$ (Fractional Microablative CO_2) vaginal laser treatment and PRP was evaluated in 62 women with refractory urge urinary incontinence (UUI) with urinary function and sexual function as secondary outcome measures. The participants underwent three sessions of transvaginal $FxCO_2$ laser and PRP which were administered at 4–6-week intervals. The 12-month follow up data revealed that the average severity of all self-reported measures of primary and secondary outcomes was significantly reduced and no adverse events were reported [31].

Role of Adipose Derived Stem Cells and Fat Transfer in Rejuvenation and Treatment of Female Genital Area

Stem cell therapy is a process of isolating autologous adult stem cells and injecting them at the site which requires healing or regeneration. Recent reports have identified that adipose contains the highest percentage of adult stem cells in the body [32,33]. The ADSCs harvested from the patient's own body fail to elicit an immunological response and therefore their administration into the targeted site does not lead to rejection [34]. It has a varied composition: mature adipocytes, ECM (extracellular matrix) and a stromal vascular fraction (SVF) which consists of a variety of cells including adipose derived stem cells (ADSCs), endothelial cells, erythrocytes, pericytes, fibroblasts, hematopoietic cells, vascular smooth muscle cells, and other immune cells [49,50].

Fat Transfer is performed for genital volume restoration, for rejuvenation of vaginal wall and vulvar skin, and vaginal recalibration by lipofilling technique. Lipofilling procedure consists of reducing the vaginal caliber by thickening the vaginal walls employing adipose tissue transplant. It is indicated for those patients who are concerned by the sensation of a wide vagina. The causes are often post gravid in multiparous women and a few times constitutional [58].

Protocol

For adipose tissue derived stem cell regenerative gynecology, we use an in-house developed methodology called Intimacell®. The protocol includes preparation of Klein solution (tumescent anesthesia) which consists of 500 mg- lidocaine, 0.5 mg-epinephrine, and 10 mEq-sodium bicarbonate in 1 L of normal saline; lipoaspiration followed by centrifugation at 1100 rpm for 4 mins, collecting the micro-fragmented adipose tissue, and homogenization by ultrasonication (**Figure 2**). The flowchart for Intimacell® methodology for SUI treatment is shown in **Figure 3**.

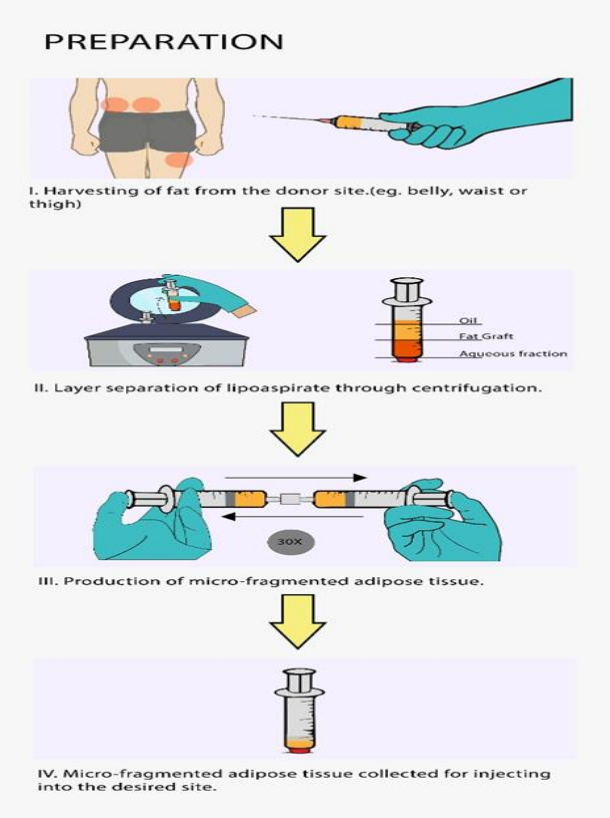

Figure 2: Graphical presentation of preparation of micro-fragmented adipose tissue

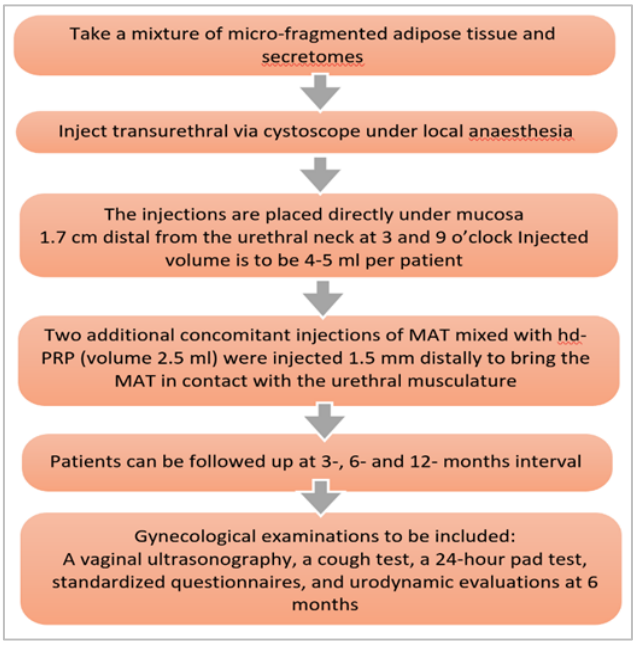

Figure 3: Intimacell® methodology for the treatment of Stress Urinary Incontinence

Energy Based Devices (EBD)

Energy-based devices are the latest development in this sector which has brought with it a promising approach to help alleviate vaginal concerns [68,69]. The EBDs apply thermal or nonthermal energy to the skin tissue which stimulates collagen formation, contraction of elastin fibres, neovascularization, induce tissue remodeling, and improve lubrication. The use of EBDs to vaginal tissue address genitourinary syndrome of menopause, vulvovaginal atrophy by increasing the proliferation of vaginal epithelium, stimulating neo-collagenesis, and increasing vascular and neural regeneration, thereby moving from pure aesthetics to functional gynecology applications [70]. The two types of lasers that are commonly used to treat vulvovaginal tissue are carbon dioxide (CO_2) and erbium:yttrium-aluminum-garnet (Er:YAG).

Carbon Dioxide Laser

The carbon di oxide (CO_2) laser emits light at wavelength of a 10,600 nm, which is greatly absorbed by tissue water and the depth of penetration is dependent on the water content while being independent of melanin and hemoglobin [73] The heat produced by CO_2 laser denatures the proteins and upregulates the expression of TGF-β which in turn activates the fibrogenic process (**Fig 1**).

CO_2 laser treatment has been found to be highly efficacious in rejuvenating the vulvovaginal tissues. Many studies had reported significant improvement in indications like, genitourinary syndrome of menopause, vaginal laxity, sexual function, and women's quality of life following treatment with CO_2 laser therapy [74-78]. One of the first studies performed by Cruz et al (2014) reported that CO_2 laser therapy improved a number of symptoms for genitourinary syndrome of menopause (GSM) as compared to the group that was subjected to vaginal estrogen therapy. 45 post-menopausal women with GSM were included in the study [79].

In 2011, Gaspar et al. conducted a study in which they observed that the women with GSM who underwent CO_2 laser treatment therapy, PRP, and pelvic exercises showed increased fibroblast activity, neogenesis in the ECM (Extracellular matrix), increased fibrillar components, improvement in vaginal epithelium and in glycogen concentration within the epithelium [80]. Furthermore, a study in 2015 reported that following CO_2 laser treatment vaginal epithelium thickness was increased as well as storage of glycogen, and fibroblast synthesis of collagen was increased [81]. Recently, Ruanphoo et al. conducted a randomized controlled trial with 88 postmenopausal women experiencing GSM. They found significant improvements in the VHI (Vaginal Health Index), which clinically evaluates vulvovaginal atrophy, and the VAS (Visual Analog Scale) which evaluates symptoms of GSM [82]. In a retrospective study conducted in 2020 found that vaginal CO_2 laser therapy emerged as the most cost-effective treatment as compared to vaginal estrogen therapy and ospemifene therapy [83].

Erbium:Yttrium-Aluminum-Garnet

The Er:YAG laser is a near-infrared ablative laser which is employed to induce tissue resurfacing. It emits light at a wavelength of 2,940 nm and yields an absorption coefficient which is 16 times higher than that of the CO_2 laser. The penetration depth of Er:YAG laser is confined to approx. 1–3 mm of tissue per J/cm2, in comparison to the 20–30 mm provided by the CO_2 laser [73]. This particular feature enables a more precise skin ablation, with very little thermal damage to the surrounding tissues. The use of Er:YAG laser may lead to a milder post-operative discomfort, edema, and erythema, and overall faster healing time as compared to theCO_2 laser [84]. This laser exposes the underlying collagen tissue to heat which leads to contraction of the collagen, thereby inducing the wound healing cascade which consequently stimulates fibroblasts to synthesize collagen [85-87].

The Er:YAG laser is employed for indications like vaginal laxity, and GSM and for SUI indications, it is more commonly used than CO_2 laser. A number of studies have reported the efficacy of the Er:YAG laser on rejuvenating and revitalizing the vulvovaginal tissue and its effectiveness in management of aforementioned conditions [85,86,88-90]. In a study by Lapii et al. [87] vaginal biopsies from 18 patients with SUI were analysed before and 1-2 months after the exposure. The results showed an increase in epithelial glycogen content and increased thickness of epithelial layer by 64.5%. They also observed an increase in active fibroblasts and neo-collagenogenesis apart from increased density of capillaries [87]. Recently, in a cohort study by Reisenauer et al. [90] with 30 patients who received two treatments of Er: YAG laser therapy, it was observed that the quality of life was significantly improved for the patients.

Radiofrequency (RF)

In RF therapy, a device emits focused electromagnetic waves which generates heat. This heat reaches a thermal dose threshold, beyond which the collagen fibers fold its triple helix structure and become thicker and shorter. This denaturation of collagen begins at 60˚C and it fully denatures at 70-75 ˚C. At 67 ˚C, partial denaturation of collagen elicits mild inflammatory response leading to the activation of fibroblasts for collagen and elastin synthesis [91-93] which occurs at a temperature at 40–45 ˚C thereby resulting in skin tightening [94]. However, if the surface temperature of the skin exceeds 45 ˚C, it is common to feel pain and have thermal burns during and after the RF treatment [95]. Till now, no thermal burns are reported in vaginal tissue treatment with RF up to 47 ˚C, but at approximately 55 ˚C, burns and blisters have been observed. The monopolar RF devices used currently for vaginal treatment employ mobile delivery, with target surface temperature at or below 45˚C.

In a study performed with 20 women, it was found that three RF treatments led to the increased concentration of collagen [96]. Various clinical studies have also shown the effectiveness of RF for treating for vaginal laxity, GSM, sexual dysfunction, and particularly SUI [97,98]. In a stud by Sarmento et al. in 2020, post-menopausal women diagnosed with GSM underwent three treatments with RF. Vaginal smears were obtained and assessed, throughout the treatment at different intervals. The results showed a significant decrease in the vaginal pH, an increase in the amount of parabasal cells and superficial epithelial cells, increase in the concentration of lactobacillus species, and improvement in VHI score and GSM [99].

HIFU

It stands for 'High Intensity Focused Ultrasound'. The first use dermatologic, aesthetic use of HIFU was reported by White et al. in 2008. HIFU was approved by the FDA (Food and Drug Administration) in 2009 for use in browlifting [100]. Currently, it is employed for facial rejuvenation, tightening lifting, and body contouring, which are regarded 'off-label' use [101-103]. The principle behind HIFU is that it generates instant microthermal lesions by accumulating high-frequency ultrasound beams at the target site without causing damage to the epidermis and surrounding tissue. This induces cellular damage and volume reduction of the target area which in turn aids in new collagen/ elastin formation and ECM. In a study by Sekiguchi et al 2018, safety and efficacy of HIFU treatment was evaluated for vaginoplasty for 29 patients with median age of 46 years. They concluded that HIFU vaginoplasty can improve quality of life for women who suffer from pelvic floor disorder. Other studies have also shown the effectiveness of HIFU for vaginal treatments [105].

According to a comparison study where neocollagenesis and neoelastogenesis were analyzed after the HIFU and RF sessions, it was found that monopolar RF led to neocollagenesis and neoelastogenesis in the papillary dermis layer along with upper, and deep reticular dermis whereas HIFU led to neocollagenesis in the mid and deep reticular dermis layer and neoelastogenesis in the deep reticular dermis. HIFU showed highest level of both processes, neocollagenesis and neoelastogenesis in the deep reticular dermis. It was concluded that although both HIFU and RF affect deep tissues but HIFU impacts focal regions and monopolar RF impacts diffuse regions [105]. A comparative analysis of the depth range of the energy-based devices is illustrated in **Figure 4**.

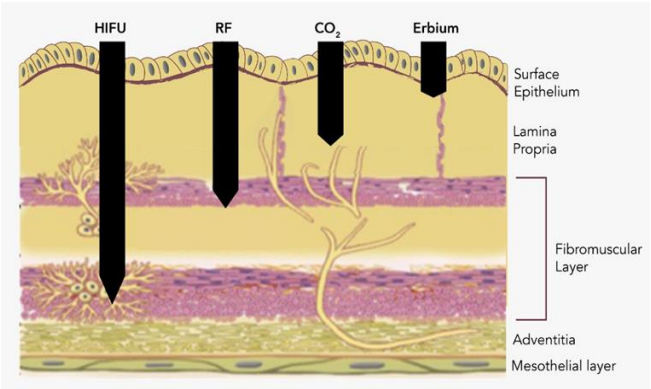

Figure 4: Illustration of depth range into the tissue of difference energy sources used in EBDs. This figure depicts that HIFU penetrates the deepest in the tissue layer as compared to the RF, CO_2, and Er:YAG.

For optimal results from the use of EBDs, it is recommended to include at least three sessions in the treatment which should be spaced 4 weeks apart followed by a touch-up session. EBDs also find their place as an adjuvant therapy to augment the results of other procedures that address sexual dysfunction or enhancements like G-spot or O-spot augmentation. The scope of services therefore sees an overlap not just to urogynaecology, but also to associated fields like urology, plastic surgery, and cosmetic dermatology.

Histological Effects

Following the ablative skin resurfacing using CO_2 and Er:YAG lasers, histological changes include the formation of collagen (neocollagenesis) at around 6 weeks post-treatment [106]. The studies reveal that post CO_2 laser elicited resurfacing, the facial skin of the patients showed upregulation of IL1β, TNFα, TGF-β1, procollagens I and III, metalloproteinases (**Figure 5**).

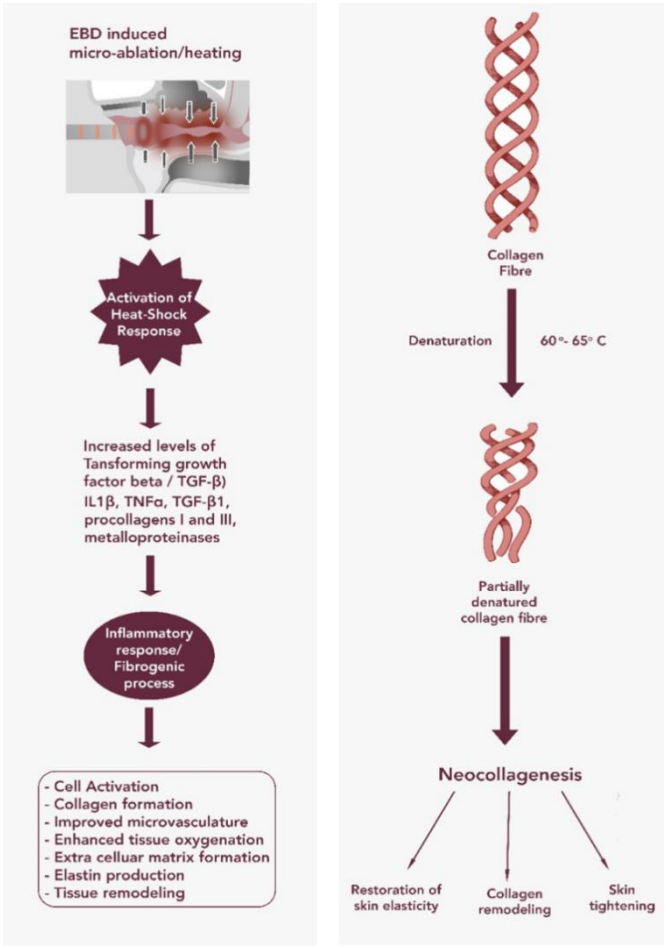

Figure 5: The mechanism of action behind tissue rejuvenation after the treatment with Energy based devices. [5A] The illustration represents the process inolved upon heating of the tissue which upregulates key factors in the cell. These factors elicit the inflammatory response and fibrogenic process which consequently leads to neocollagenesis, neoelastinogenesis, neovascularization, and formation of ECM. [5B] This figure depicts the effect of heat on underlying collagen fibers.

In a study following fractional CO_2 laser resurfacing, it was observed that 1-3 days posttreatment, the wound healing process showed granulation which was followed by dermal remodeling and neocollagenesis upto 30 days after the treatment. Neocollagenesis

was observed to continue for several months thereafter as it has been seen after the treatment with standard ablative CO_2 laser [107].

The effects of fractional CO_2 laser treatment on vaginal mucosa are increased thickness of squamous stratified epithelium, increased levels of glycogen and a huge number of glycogen-rich cells depositing at the epithelial surface. Increased ECM content which includes collagen and ground substance, and active fibroblasts were also observed in the connective tissue of the lamina propria. Additionally, undulated epithelium, newly formed connective tissue papillae, and blood capillaries penetrating inside the papillae were detected post treatment [79,81]. Similar results were obtained post treatment of vaginal mucosa by fractional Er:YAG laser. The study reveals that it led to increased cellularity and thickness of the epithelium and a compact lamina propria with dense connective tissue arrangement, increased elastin and collagen content [108]. With RF treatment, the creation of new dermal volume is extensively studied and is shown to improve mechanical characteristics of the skin and skin laxity [95].

Tissue ablation by light-based devices induces the process of collagen shrinkage induced by heat followed by neocollagenesis. This process occurs at 45-50˚C in the area surrounding the ablated tissue. The rise in temperature causes the activation of heat shock response (HSR) in the cells which leads to the upregulation of heat shock proteins (HSPs). Studies have shown that particularly HSP70 has a key role in coordinating the expression of growth factors like transforming growth factor- beta (TGF-β) which further elicits inflammatory response, and fibrogenic process leading to the formation of new collagen, elastin and ECM (**Figure 5**) [78]. The mechanism of action behind neocollagenesis is that any energy-based device application causes the collagen to denature and break into shorter collagen fibers. This partially denatured collagen stimulates the production of new collagen fibers which causes tissue tightening after skin-resurfacing procedures [109]. New elastin formation that is unique to RF, effectively treated vaginal laxity.

Excessive transfer of heat to dermis may however lead to adverse effects like scarring and permanent hypopigmentation. Since with age and due to hormonal influence, the vaginal tissue varies in its water content and cellular component, it should be noted that controlled power of the energy source must be used. The use of EBDs has been associated with wither no or minimal adverse effects which may include discomfort during treatment, dysuria, vaginal discharge, vaginal bleeding, edema, itching, and mild burn [110,72].

Recently in 2018, US FDA issued a public warning regarding the use of EBDs to perform vaginal cosmetic procedures or vaginal rejuvenation. FDA highlighted that although, the FDA is aware of the usage of such devices, it has not approved their usage for any specific gynecological condition. With this claim came another challenge for the medical practitioners, manufacturers, and the women who seek such procedures to use these devices. To overcome this issue American Urogynecologic Society (AUGS) released the clinical consensus statement in May 2020 on vaginal energy-based devices according to which a total of forty statements were assessed and divided into five categories: patient criteria, health care provider criteria, efficacy, safety, and treatment considerations [114].

Conclusion

The past decade has seen a substantial rise in technological advancements with the advent of new tools and procedures to reverse age-related tissue remodeling, and for tissue functional restoration. The implementation of these new modalities for vaginal rejuvenation has opened up a new dimension to explore cosmetic indications in conventional gynecology. The social acceptance and the formation of regulatory bodies for better practice of these procedures is long overdue. However, looking ahead, this field has emerged with immense potential and promise to improve the quality of life of the patients and has been successful in carving its own niche. The issues that are being addressed by the cosmetic gynecology procedures are among those which generally are not spoken about openly. Ironically, women do not even bring the symptoms up to be discussed with their doctors and partly it is due to the lack of awareness of such procedures and widely acceptance of these to get rid of the functionality issues or improving self-esteem by accentuating the aesthetic appearance. With this field rapidly evolving, it is vital for standardized procedures to come into place for a safer practice. Long-term studies are required to understand the outcome of the procedures and to validate the treatment using the novel approaches in this field.

Ethics approval and consent to participate

Not applicable

List of abbreviations

PRP: Platelet Rich Plasma
ADSCs: Adipose derived stem cells
EBD: Energy based devices
RF: Radiofrequency
HIFU: High Intensity Focused Ultrasound
ECM: Extracellular matrix

Data Availability

Not applicable

Financial support

None.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' contributions

PM conceptualized, designed and supervised the study, collected the data and performed the analysis. DM supervised the study, collected the data and performed literature review. NK was a major contributor in writing the manuscript, literature review and study design. MJ contributed towards data collection, analysis and writing of the manuscript. All authors read and approved the final manuscript.

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