

## LASER users' expert opinion in response to "The clinical role of LASER for vulvar and vaginal treatments in gynecology and female urology: An ICS/ISSVD best practice consensus document"

We read with interest "*The clinical role of LASER for vulvar and vaginal treatments in gynecology and female urology: An ICS/ISSVD best practice consensus document*" by Preti et al.<sup>1</sup> While we welcome efforts to improve research quality in any field of our discipline, we were disappointed by the methodological confusion and incorrect statements presented. It is inappropriate to incorporate different clinical and cosmetic indications treated with LASER technology in a consensus document. The data is not presented in as an impartial fashion as one would expect for a consensus document representing two prestigious societies.

Examples of inappropriate and inaccurate statements regarding LASER therapy for women with Genitourinary Syndrome of Menopause (GSM) are listed as follows:

1. It is unacceptable to include GSM and "vaginal rejuvenation" in the same category, as GSM is a true disease state, while "vaginal rejuvenation" is a poorly defined term that implies an aesthetic or cosmetic treatment.

2. The authors stated that the inclusion criteria of the study by Athanasiou et al<sup>2</sup> was insufficient by including women with "at least one moderate or severe symptom of GSM." However, additional requirements including "objective evidence of menopause" and a visual analog scale to quantify GSM severity were required.<sup>2</sup> The authors emphasized that only 1/3 of patients achieved vaginal pH below 4.5 and criticized inaccurate techniques used for lactobacilli estimation. However, lactobacillus colonization does not always correspond to a pH below 4.5, while Nugent scoring and Hay-Ison criteria allow for weighted microorganism estimation using the overall abundance of Lactobacillus. According to the 2018 European (IUSTI/WHO) Guideline on the management of vaginal discharge, Gram stain with wet mount microscopy remains the gold standard for diagnosis of bacterial vaginosis or aerobic vaginitis.<sup>3</sup> In regard to concerns over an improved vaginal maturation index without an increase in leukocytes<sup>1</sup> it should be noted that an increase in epithelial cells provides a substrate for growth and corresponds to lactobacilli proliferation,

while unchanged proportions of leukocytes indicate an absence of inflammation.

3. In regard to the proposed mechanism of action of LASER, the authors described that the "*most superficial layer of the vaginal mucosa is made up of stratified squamous epithelium but, unlike the skin epidermis, is devoid of keratinocytes and is therefore non-keratinized.*" However, the authors failed to mention other substantial differences between skin and vaginal mucosa in premenopausal women, such as the vaginal epithelium's ability to synthesize, store, and release glycogen at the epithelial surface. The authors stated "*It is unclear ... if these histologic changes following LASER treatment can be directly correlated with the improvement of clinical symptoms, as no control group was used.*" In the referenced histological study, pretreatment specimens were used as internal controls for comparison with posttreatment biopsies.<sup>4</sup>

4. The referenced article from Zerbinati et al<sup>4</sup> illustrated "*epidermal thickening with acanthosis, and some show parakeratosis and increase in dermal chronic inflammatory cells. These changes are consistent with repair, as might be seen in lichen simplex chronicus, and alone do not indicate functional remodeling.*" The acanthosis represents glycogen filled cells, and inflammatory cells are stimulated fibroblasts which represent proper functional remodeling of lamina propria and epithelial layers.

5. The authors questioned histological findings of LASER treatments, such as "*denuding of the epithelium and different degrees of tissue coagulation, which are consistent with thermal injury.*" This histologic study aimed to determine the safest and most appropriate of five different LASER settings in an ex vivo model, which explains the variable degrees of tissue effects observed.<sup>5</sup>

6. The authors noted the limited duration of follow-up for the majority of laser studies, however there is available data at 2-year follow-up to confirm the safety and efficacy profile of LASER treatment for GSM.<sup>6,7</sup> This length of follow up is longer than available studies reporting outcomes of estrogen and ospemifene.<sup>8-11</sup>

7. The authors state that “the majority of LASER research carried out so far has been industry-funded, leading to a significant risk of bias.” This is false because the majority of published studies on fractional CO<sub>2</sub> LASER for GSM were investigator-initiated without industry funding.


We strongly believe that this joint society consensus statement lacks balance, creates significant confusion, and potentially creates inaccurate perceptions that can negatively impact this very promising technology. To be objective and free of bias, such analyses need to be truly comprehensive, especially if practice recommendations are made. On the basis of published data and vast clinical experience worldwide, Fractional CO<sub>2</sub> LASER treatment appears to be an effective nonhormonal option for GSM that will be strengthened by ongoing level 1 research. We acknowledge this is a very attractive market for many companies producing different energy-based devices, and welcome regulatory oversight regarding safety and efficacy.

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