Authors’ reply re: Vaginal Er:YAG laser application in the menopausal ewe model: a randomised estrogen and sham-controlled trial

Sir,

We thank colleagues Tamer Erel and Oz civit for their comments on our experimental assessment of the effects of vaginal Er:YAG laser application in menopausal ewes and are happy to clarify some details.

First, our colleagues were surprised that our findings did not match those of a recent study by Gaspar et al., who reported a 2.4-fold increase in vaginal epithelial thickness (base line: 45 ± 33 μm to 153 ± 45 μm) 3 months after second non-ablative Er:YAG laser) and a three-fold increase in vaginal cell layers. We included that study in our discussion, also reporting an increase in glycogen and neo-angiogenesis. This study included ten women used as their own control; it lacked definition of primary and secondary end points, nor did it have a power calculation, or details on the pathology methods used. Apart from that, to better understand how those results would compare to our findings, the inclusion of a sham control and/or estrogen-exposed group would be necessary.

Further, we wholeheartedly agree with Tamer Erel and Oz civit, who have ample clinical experience with clinical laser application, that animal models have their limitations, hence also the ewe. These animals are often used to study menopause-associated disorders, including genito-urinary atrophy as described in our manuscript. More precisely, ewes have vaginal dimensions close to that of women, and when they undergo ovariectomy, their vaginal epithelium thins to 34–118 μm, which is perhaps not identical, but is close to the range observed in women (50–180 μm). We agree that the vaginal pH is not comparable and that this may have consequences on vaginal secretions and the microbiome, which unfortunately were not studied in our experiment.

Although animal models are not a perfect representation of a human, our observations prompt the need for properly controlled clinical trials, which – wherever ethically acceptable – include outcome measurements that permit comparison and understanding of these experimental findings. We, as well as others, are currently running such studies and would suggest reaching formal conclusions from them (clinical trial gov number: NCT04021966).

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Re: Vaginal Er:YAG laser application in the menopausal ewe model: a randomised estrogen and sham-controlled trial

Sir,

As authors of several published clinical studies using the same technology for the treatment of genitourinary syndrome of menopause (GSM) in women, we read with interest the recently published study from Mackova et al.

We compliment the authors on the sophisticated design and methodology used in the study; however, we believe that the sheep model is simply not adequate to investigate GSM symptom relief, for several obvious reasons, the two most important being:

• A sheep is an animal without natural menopause; therefore, it is impossible to compare the symptoms of induced menopause after ovariectomy in sheep with those of menopause in women.
• It is impossible to measure quality of life-related symptom severity, nor their relief after treatment, in sheep.

Genitourinary syndrome of menopause (GSM) is a complex condition affecting 70% of postmenopausal women, who suffer from several symptoms severely affecting their quality of life.

Let us illustrate the complexity of the condition by focusing on only one of the symptoms of GSM: vaginal dryness. The physiology of vaginal lubrication is strongly connected to sexual pleasure and regulated by a complex interplay of different psychological and physiological factors. In premenopausal women, this is orchestrated by circulating estrogen. Vasodilatation caused by an upstream signalling mechanism leads to increased capillary pressure and liquid flow to the vaginal mucosa. As always in nature, there are different pathways to achieve the same result, and to compensate for the absence of estrogen, the master regulator, new treatments are finding.
ways to achieve similar results independently of estrogen. The Er:YAG laser with SMOOTH mode stimulates tissue turnover and also induces vasodilatation and angiogenesis, resulting in increased vaginal lubrication and better tissue quality. Several published studies have shown that multiple GSM symptoms are greatly reduced when using the Er:YAG SMOOTH laser and that the results are comparable and last longer than local vaginal estrogen.\(^2\)–\(^5\) Even with no change in vaginal epithelial thickness, the treated women reported excellent symptom relief, which should be the ultimate goal of any GSM treatment. However, we have also shown that treatment with the same Er:YAG laser that was used in the Mackova et al. animal study does in fact greatly increase epithelial thickness in women. Our most recent published study has shown a threefold increase in epithelial thickness, measured 3 months after completed laser treatment, in a group of women with severe vaginal atrophy.\(^3\) They have reported a significant decrease in GSM symptoms, including vaginal dryness, which was reduced from 8.5 at baseline to 1.8 at the 3-month follow-up, as measured on a 0–10 visual analogue scale (VAS) scale. The women were extremely satisfied with the result, and the reduction of symptoms significantly improved their quality of life. Although the thickness of their vaginal epithelium was greatly increased, we cannot say that this is the only reason for the relief of their symptoms, as there are probably other factors at play, such as an increase in angiogenesis and blood flow, and improved vasodilatation. The mechanisms of action of the Er:YAG SMOOTH laser are still not completely clear. But what we know so far is that it is a safe treatment that greatly benefits women.

One must remember to be extra careful when extrapolating the results of animal model studies to human conditions, especially with respect to conditions that significantly affect quality of life. Instead, we should trust the women.

**Data availability statement**

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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**Authors’ reply re: Vaginal Er:YAG laser application in the menopausal ewe model: a randomised estrogen and sham-controlled trial**

*Sir,*

We thank colleagues Gaspar and Gambacciani for their compliments and comments\(^1\) on our experimental study assessing the effects of vaginal Er:YAG LASER application in menopausal ewes.\(^2\) Though they accept the comprehensive methods used, they question the experiment’s relevance. They state that in sheep, menopause induced by ovarectomy is not comparable to naturally occurring menopause. Indeed, our ewes were castrated at approximately 8 years of age, but we have demonstrated earlier that the atrophic changes in the ovine vagina then parallel those described in menopausal women, which is logical given the distribution of estrogen receptors in the lower genital tract.\(^3\)\(^,\)\(^4\) In the actual experiment, the ewes were of advanced age and multipurpos, and the interval between castration and laser application was 6 months; therefore their vagina was deeply atrophic.

We concur with our colleagues that indeed in sheep, and most likely any other animal, it is probably impossible to study the subjective impact of genitourinary syndrome of the menopause (GSM), as well as the relief of it by medical interventions. This should, however, not preclude attempts to study the mechanisms of human diseases or their treatment in species that do simulate all other measurable findings one can observe in women. This limitation is extensively discussed in the manuscript.\(^2\) Conversely, we took advantage of the possibilities in an animal experimental model to conduct a controlled trial and a comprehensive set of outcome measurements, which clinically would not be acceptable, though it should permit the determination of findings that have been clinically claimed, and the understanding thereof. The latter is at present lacking, as Gaspar and Gambacciani acknowledge in their letter.\(^1\)

We do not doubt at all that our experimental findings need to be complemented by clinical studies that include the above subjective symptoms. In that respect, Gaspar and Gambacciani refer to their recent report\(^5\) in which they describe a significant decrease in GSM symptoms concurring with a 2.4-fold increase in vaginal epithelial thickness (ET; from 45 ± 33 µm to 153 ± 45 µm 3 months after LASER). We actually