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ORIGINAL STUDY

Interferential current: a new option for the treatment of sexual complaints in women with premature ovarian insufficiency using systemic hormone therapy: a randomized clinical trial

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Abstract

Objective: The aim of the study was to evaluate the efficacy of interferential current (IC) in the sexual function of women with premature ovarian insufficiency (POI) using systemic hormone therapy (HT), compared to topical estriol.

Methods: A randomized clinical trial with 40 women with POI using systemic HT, who were sexually active and referred for dyspareunia and reduction of lubrication. The women were divided into two treatment groups for 4 weeks: IC group (eight electrotherapy sessions twice a week); or E group (estriol vaginal cream, daily application, 0.5 mg/d). The Female Sexual Function Index was used to evaluate pre-/posttreatment sexual function.

Results: Mean age was 37.13 ± 7.27 years and mean treatment time with HT was 8.20 ± 8.73 years, similar data for both groups. There was an improvement in global sexual function, lubrication, and pain domains for both treatments. The differences between the pre-/posttreatment lubrication scores were respectively 0.75 ± 3.31 ($P = 0.014$) for IC and 1.16 ± 1.22 ($P < 0.001$) for estriol, whereas for dyspareunia the differences were 1.00 ± 1.47 ($P = 0.005$) for IC, and 0.68 ± 1.30 ($P = 0.006$) for estriol. There was no pre-/posttreatment difference for the desire and arousal domains. Only in the IC group did orgasm (difference 0.90 ± 1.42, $P = 0.010$) and satisfaction improve (difference 0.70 ± 1.28, $P = 0.021$).

Conclusion: The use of perineal IC seems to be a new option for women with POI using systemic HT and presenting with sexual complaints, leading to an improvement in pain, lubrication, satisfaction, and orgasm.

Key Words: Estriol vaginal cream – Genitourinary syndrome – Interferential current – Premature ovarian insufficiency – Sexual function.

Premature ovarian insufficiency (POI) is a condition that is associated with hypergonadotropic hypogonadism due to the impairment of ovarian function in women younger than 40 years of age. Both spontaneous and iatrogenic causes (genetic, enzymatic, autoimmune causes, and radiotherapy, chemotherapy, and surgical procedures), may induce POI but most POI cases are idiopathic. POI has repercussions in the short and long term. Sexual dysfunctions are among the various repercussions of hormone deficiency,[1,2] with decreased desire, arousal, worsening of lubrication, dyspareunia, reducing satisfaction, and hindering the ability to achieve orgasm. The reported prevalence of sexual dysfunction is 62%.[3,4]

Studies suggest the importance of promoting trophism of the vaginal wall, epithelial proliferation, and neovascularization, which can be obtained by systemic hormone therapy (HT) for complaints of pain during intercourse and decreased lubrication.[1,5-11] Systemic HT, the treatment of choice for POI, contributes to minimize such repercussions.[5] There is evidence that, despite the improvement in cytology and

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vaginal flora, with beneficial effect on the surface of the mucosa, many women complain about different domains of sexual function.[3,4,12-14] In this situation, a therapeutic option is the use of vaginal estrogen cream, which is seen to be better in relation to systemic HT. Topical estriol is, however, generally evaluated as an alternative to the use of systemic hormonal therapy, with insufficient data for its concomitant use. In addition, adherence to topical treatment is low, usually due to discomfort associated with increased vaginal discharge.[15]

Thus, few adjunct options for HT have been evaluated, especially for young women with loss of ovarian function.[16] This clinical trial was developed to evaluate the use of a physiotherapeutic current, interferential current (IC), compared to the use of topical estriol in the treatment of both dyspareunia and reduction of vaginal lubrication and in the improvement of the sexual function of women with POI using systemic HT.

MATERIALS AND METHODS

Study design and participants

A randomized nonblind clinical trial was carried out with women diagnosed with POI and treated with HT, presenting complaints of reduced lubrication or pain during intercourse, to compare two types of treatment: IC or topical estriol. The participants were recruited at the Endocrine Gynecology Outpatient Clinic of the Department of Gynecology and Obstetrics of the School of Medical Sciences at University of Campinas - UNICAMP in January, 2018.

This study was approved by the ethics committee of the institution, number CAE 06124512.6.2001.5404. This study followed the CONSORT guidelines for a randomized clinical trial and was registered in the Brazilian Registry of Clinical Trials (REBEC), number RBR-74zbms. All the women signed the informed consent after being advised on the study aims before their inclusion.

Studied population

A total of 40 women with a diagnosis of POI were treated with systemic HT and who presented with complaints of reduced lubrication or pain during sexual intercourse. POI diagnosis was reached by the presence of amenorrhea or long menstrual cycles lasting more than 120 days and with at least two levels of follicle-stimulating hormone above 25 mIU/mL before the start of hormone treatment. Registered women should be sexually active, in a heterosexual relationship, and report at least one sexual relationship in the last 4 weeks. Women with side effects from the use of IC, such as a pacemaker or metal implant in a lumbar or hip region; an acute infectious process or ulcer in the genital area; the presence of a systemic or localized allergic condition; or with chronic diseases (acquired immunodeficiency syndrome, kidney transplantation, lupus, tuberculosis, immunosuppression, pelvic/spine deformity, neoplastic diseases); or using vaginal estrogen cream, were excluded.

Complaints of pain and reduction of lubrication during sexual intercourse, and overall sexual function, were analyzed using the Female Sexual Function Index (FSFI), applied before the beginning of the treatment and at the end of the treatment, with a 4-week difference. The FSFI was self-administered by the participants who, if they had any doubts, could ask questions to an interviewer, who was blinded to the participant's treatment group. The frequency of sexual activity was also questioned immediately before initiation of treatment and subsequent re-evaluation. Participants were counseled not to use any other medication or treatment for these sexual complaints, such as nonhormonal lubricants, during the study.

Study interventions

Participants were randomly included into one of the two treatments described below and for concomitant use of systemic HT.

Interferential current

Eight sessions of electrotherapy were performed twice a week for 4 weeks. The treatment was performed individually, with the bipolar application of the IC using Dual Apparatus 961 – Manufacturer Quark medical products, Piracicaba, São Paulo, Brazil, ANVISA Registration No. 80079190022. The electrodes were bilaterally positioned on the labia majora, parallel and aligned with the vaginal introitus. A 4,000 Hz current was used; MPA: 50 Hz; slope: 1/1 with intensity calibrated according to the sensitivity of each woman, maintaining a current that triggered a ''strong but comfortable'' feeling. The therapy was maintained for 20 minutes.

Estriol vaginal cream

Local treatment was carried out using a prescription of an intravaginal estriol-containing cream applied every night, for 4 weeks, with the aid of a graduated applicator. A filled applicator, up to the mark for use, contains 0.5 g of cream, with 0.5 mg of estriol per application (Stele, Biolab, Taboão da Serra, Brazil). All the women in this group were contacted weekly by the main researcher by telephone, to check adherence to treatment and to check for any possible undesired effects.

Primary Outcome

The primary objective of the study was to promote an improvement of the complaints of dyspareunia and reduction of lubrication during intercourse, as well as to promote improvement of sexual function, evaluated immediately before and after treatment through the FSFI.

Questionnaire: Female Sexual Function Index

The FSFI contains 19 questions that assess sexual function, in the previous 4 weeks, in each component or domain: sexual desire; sexual arousal; vaginal lubrication; orgasm; sexual satisfaction; and pain/discomfort during sex. For each question, there are answer alternatives that receive scores between 0 and 5 in an increasing way in relation to the presence of the questioned function. Only in the questions about pain, is the

score defined in an inverted form, that is, the higher the pain, the lower the score. At the end, a score for each domain and a total score (ranging from 2.0 to 36.0) are presented, from which the sexual function of each woman was analyzed. Total score less than 26.5 indicates sexual dysfunction.[17,18]

Sample size calculation

Based on the study ''Função sexual de mulheres com vulvodínea localizada provocada após tratamento fisioterápico por eletroestimulação com corrente interferencial'' (Sexual function of women with localized provoked vulvodynia after physiotherapeutic treatment by electrical stimulation with IC),[19] and considering the mean scores of the FSFI before and after the intervention (19.01 ± 4.85 and 27.35 ± 3.64), with a 5% alpha and 10% beta error and a statistical significance level of 5%, the calculated sample size was 30 women, 15 for each treatment group (two in total). Because their is a potential risk of loss during follow-up, it was decided to increase the number to 20 women in each group.

Randomization

The 40 women with POI using systemic HT were blindly allocated 1:1 into two treatment groups: IC (study group) or topical estriol (E - control group) by a randomized draw using 40 sealed envelopes which were prepared before the beginning of the study. Each envelope had a piece of paper with the treatment to be performed. The women chose an envelope at the moment of the inclusion in the study. All women were instructed not to stop using HT during the study time.

Statistical analysis

To describe the profile of the sample, tables with absolute frequency (n) and percentage (%) values and descriptive statistics of numerical variables with mean values (standard deviation) were set up. The Mann-Whitney test was used to compare the numerical variables between the two groups, due to the absence of normal distribution of the variables. The Wilcoxon test for related samples was used to compare the numerical variables between the before and after treatment, due to the sample size and the absence of normal distribution of the variables. A sensitivity analysis using linear regression and adjusted for baseline values of each outcome was also conducted, with the baseline values changed to ranks due to absence of normal distribution. The significance level adopted for the statistical tests was 5%, that is, $P < 0.05$. SAS software for Windows version 9.2 was used.

RESULTS

A total of 85 women with POI were interviewed until reaching a total number of 40 women who met the inclusion and exclusion criteria and agreed to participate and were randomly placed in both treatment groups (Fig. 1).

The mean age of the 40 women was 37.13 (±7.27) years and the diagnosis of POI was made at approximately 27.90

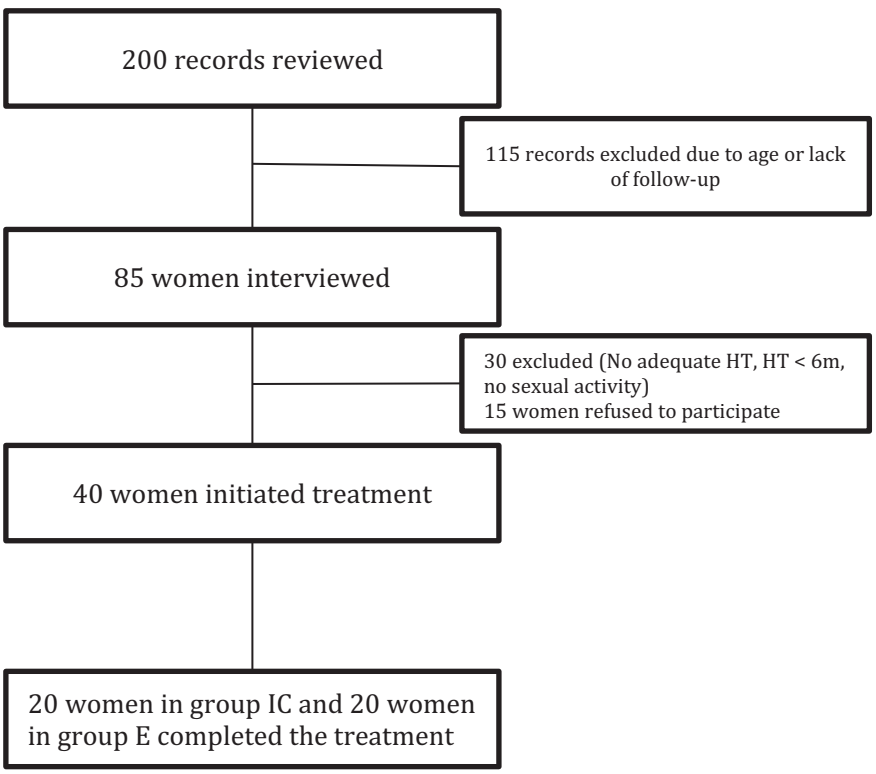

FIG. 1. Schematic representation of the inclusion of women in the study. IC group, interferential current group; E group, vaginal estriol group; HT, hormone therapy.

TABLE 1. *Characterization of the 40 women with premature ovarian insufficiency using systemic hormone therapy and according to the two treatment groups: interferential current (N = 20) and estriol vaginal cream (N = 20)*

	Total sample		Interferential current		Estriol vaginal cream		
	Mean	SD	Mean	SD	Mean	SD	*P*
Age	37.13	7.27	38.75	5.86	35.50	8.28	0.249
Age at diagnosis	27.90	8.68	29.45	7.39	26.35	9.75	0.323
POI time period	9.23	8.45	9.30	8.23	9.15	8.88	0.533
Age at treatment onset	28.93	8.80	30.45	7.49	27.40	9.90	0.357
HT time period	8.20	8.73	8.30	8.56	8.10	9.12	0.621
Parity	0.85	1.17	0.85	1.27	0.85	1.09	0.844

Mann-Whitney test for comparison between groups. HT containing conjugated estrogen or 17-beta-estradiol associated with a progestogen (77.5%), combined oral contraceptives (15%), tibolone (7.5%).
HT, hormone therapy; POI, premature ovarian insufficiency.

(±8.68) years. The time that elapsed between the date of diagnosis and inclusion in the study was 9.23 (±8.45) years. The onset of HT treatment was at 28.93 (±8.80) years and the mean treatment time for HT was 8.20 (±8.73) years. No differences were found between these variables (Table 1), in the comparison between the two groups. Systemic HT used was thus distributed: 77.5% of the women used conjugated estrogen or 17-beta-estradiol associated with a progestogen, 15% used combined oral contraceptives, and tibolone was used by 7.5% of them. Fifty-seven percent were nulliparous and 42.5% had one or more children; 32.5% were homemakers and 67.5% were engaged in some professional activity.

Both treatments, IC and topical estriol, were effective with an increase in the FSFI score and, therefore, an improvement in overall sexual function, with some differences in results in the different domains. In the comparison between them, IC and topical estriol provided an improvement in the lubrication and pain domains. Pre- and posttreatment lubrication scores, as well as the difference between the two moments were respectively 3.74 (±1.36), 4.49 (±1.42), and 0.75 (±3.31) ($P = 0.014$) for IC and 3.93 (±1.66), 5.09 (±1.08), and 1.16 (±1.22) ($P < 0.001$) for estriol. For the pain during intercourse domain, the pre- and posttreatment scores were 3.60 (±1.65) and 4.60 (±1.31), a difference of 1.00 (±1.47) ($P = 0.005$) for IC, whereas for the estriol group they were 4.42 (±1.80) and 5.10 (±1.22), a difference of 0.68 (±1.30) ($P = 0.006$) (Table 2 and Fig. 2). Desire and arousal were domains that showed no improvement with either treatment (Fig. 3).

Only in the group treated with IC was there significant improvement in the orgasm domain (pre- and postintervention, respectively, 3.52 [±1.58] and 4.42 [±1.42], a difference of 0.90 [±1.42], $P = 0.010$); and satisfaction (4.10 [±1.50] and 4.80 [±1.11], a difference of 0.70 [±1.28], $P = 0.021$). There was also an increase in the frequency of intercourse but only in the group treated with IC, whereas in the group that used estriol, this frequency had a small reduction ($P < 0.04$), according to this analysis (Table 2 and Fig. 3).

A sensitivity analysis using linear regression and adjusted for baseline values of each outcome was also conducted. The results from this analysis confirm those presented in Table 2, except for sexual frequency, where no significant differences were found after adjustment ($P = 0.064$).

DISCUSSION

Women with POI, although treated with systemic HT, often have sexual complaints. The therapeutic options for this situation are restricted. This clinical trial evaluated treatment using IC and its response in sexual function, compared to the

TABLE 2. *Female Sexual Function Index score (pre-, posttreatment and pre- and posttreatment differences) for the interferential current and estriol treatments in women with premature ovarian insufficiency using systemic hormone therapy (N = 20 in each group)*

	Interferential current		Topic estriol		
	Mean ± SD	P^a	Mean ± SD	P^a	P^b
Initial FSFI	21.39 ± 6.29		24.12 ± 7.49		0.074
Final FSFI	25.76 ± 6.29		26.89 ± 5.97		0.543
FSFI difference	4.37 ± 5.96	0.004	2.78 ± 5.04	0.001	0.291
Desire difference	0.45 ± 1.42	0.233	0.24 ± 1.00	0.353	0.782
Arousal difference	0.65 ± 1.43	0.102	0.38 ± 1.07	0.134	0.559
Lubrication difference	0.75 ± 1.31	0.014	1.16 ± 1.22	0.001	0.776
Orgasm difference	0.90 ± 1.42	0.010	0.20 ± 0.75	0.285	0.101
Satisfaction difference	0.70 ± 1.28	0.021	0.14 ± 0.98	0.892	0.096
Pain difference	1.00 ± 1.47	0.005	0.68 ± 1.30	0.006	0.301
Initial coitus frequency (per wk)	2.30 ± 1.49		2.45 ± 0.94		0.377
Final coitus frequency (per wk)	2.80 ± 1.74		2.30 ± 1.38		0.347
Coitus frequency difference	0.50 ± 1.85	0.176	−0.15 ± 1.23	0.344	0.041

FSFI, Female Sexual Function Index.
[a]*P* value for pre- and posttreatment comparison. Wilcoxon test.
[b]*P* value for comparison between the two types of treatment. Mann-Whitney test.

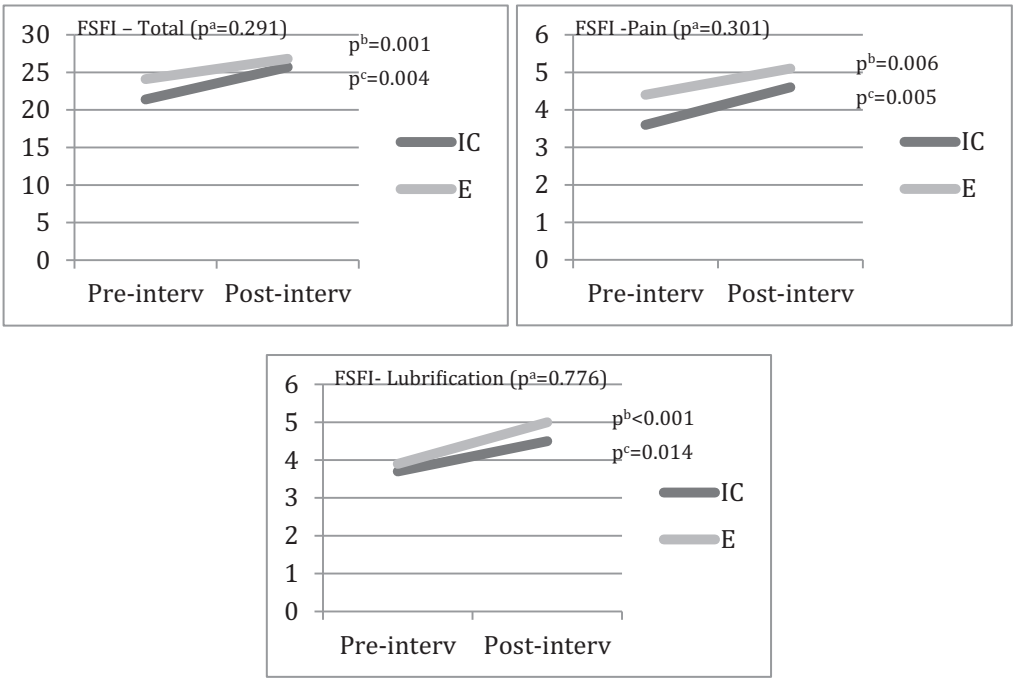

FIG. 2. Total FSFI, pain, and lubrication scores for women with premature ovarian insufficiency using systemic hormonal therapy (HT): comparison between pre- and posttreatment and between interferential current (IC) and estriol vaginal cream (E) interventions ($n = 20$ in each group). FSFI, Female Sexual Function Index; P^a, P value for the difference between the groups – Mann-Whitney test; P^b, P value for the difference between pre- and postintervention for the estriol group – Wilcoxon test; P^c, P value for the difference between pre- and postintervention for the interferential current group – Wilcoxon test; preinterv, preintervention; postinterv, postintervention.

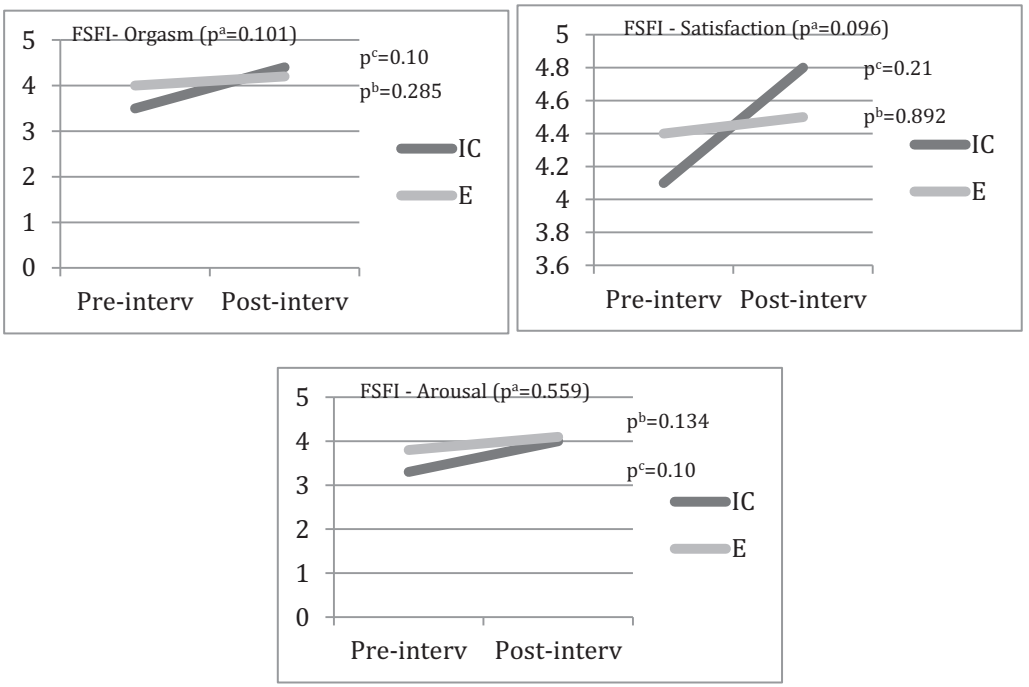

FIG. 3. Scores of the orgasm, satisfaction, desire, and arousal domains obtained through the FSFI, for women with premature ovarian insufficiency using systemic hormonal therapy: pre- and posttreatment comparison and between interferential current (IC) and estriol vaginal cream (E) interventions ($n = 20$ in each group). FSFI, Female Sexual Function Index; P^a, P value for the difference between the groups – Mann-Whitney test; P^b, P value for the difference between pre- and postintervention for the estriol group – Wilcoxon test; P^c, P value for the difference between pre- and postintervention for the interferential current group - Wilcoxon test; preinterv, preintervention; postinterv, postintervention.

use of topical estriol, considered the first therapeutic choice for these cases. Assessment using the FSFI questionnaire showed that both treatments were effective in promoting improved sexual function. Treatment with IC improves orgasm, satisfaction, and lubrication domains, and reducing pain during intercourse.

Sexual complaints are included within the set of symptoms and signs that make up the genitourinary syndrome (GUS), exhaustively studied for older, postmenopausal women, and which includes genital, urinary, and sexual symptoms associated with hypoestrogenism, with an estimated prevalence of at least 50% of these women.[20] The exact prevalence of GUS in women with POI is not well known, although the literature suggests that it may be minor, with the exception of complaints related to sexual function.[20] The choice of therapy depends on the severity of the woman's symptoms and preference, as well as the presence or absence of sexual activity. Such options include systemic and topical HT.[16,21] In a meta-analysis with a population of exclusively climacteric women, it was shown that topical estradiol may be superior to oral therapy.[22-24]

It is, however, necessary to consider that in POI there are great knowledge gaps to be filled. Our group has been studying the sexual function of women with POI and some characteristics need to be scored: they are relatively young women who mostly use systemic HT. Despite this, they present with involvement of several sexual function domains such as pain and reduced lubrication during the sexual act despite systemic HT. Moreover, systemic HT is sufficient to improve vaginal trophism, but it does not have the same result in improving sexual function.[14,25,26]

Thus, considering topical estriol as the main alternative for treatment when there is a persistent reduction of lubrication and dyspareunia, a comparative study with a new therapeutic approach using IC was carried out. The therapeutic approach of the pelvic floor using electric currents, electrotherapy, gained notoriety due to the strengthening effects of pelvic floor muscles and visceral analgesia and inhibition, causing improvement of symptoms and complaints related to chronic pelvic pain, urinary incontinence, sexual dysfunction, bladder hyperactivity, dysmenorrhoea, and vaginism.[27-30] Among the therapeutic currents used, IC is indicated to decrease pain, promote muscle relaxation, and improve local blood circulation. IC is an electrical current that overcomes the skin barrier and reaches the deeper tissues.[31] Increased blood circulation is referred to as the physiological effect of the current, as a consequence of a slight muscular contraction or action on the autonomic nervous system, decreasing the tone of the blood vessels and favoring the elimination of chemical substances responsible for the inflammatory process.[32] The main effects of ICs are the selective stimulation of myelinated afferent fibers (analgesia) and normalization of the neurovegetative balance (relaxation and improvement of circulation).[33]

Considering that the reduction in lubrication can cause pain during intercourse and may cause a decrease in the frequency of sexual intercourse, which in turn has an impact on all sexual functions, alternatives are needed to break this cycle.[6-8,10] The regularity of sexual activity has been attributed as a protective factor for vaginal atrophy, perhaps because of increased blood flow in the pelvic organs, maintaining the elasticity of the mucosa and vaginal walls.[34-36] This evidence was considered as the selection criterion for this clinical trial. Thus, to give homogeneity to the studied groups, only women referring to sexual activity were included. Also included were women with consistent adherence to HT. Thus, all the women included had systemic HT, had regular heterosexual sexual activity, but sexual dysfunction was found in 67.5% of the women in the group (FSFI total score <26.55). This result is similar to that obtained by our research team in another study 8 years earlier, with another group of women with POI.[3] At the end of both treatments, an improvement in sexual function could be seen, with a prevalence of sexual dysfunction reduced to 47.5%.

Evidence from literature shows that all SF domains can be compromised when ovarian function is lost prematurely[26] and that sexual fantasies and even masturbatory activity are reduced.[4] Considering that sexual function is evaluated based on the performance of various aspects or domains, the psychological-based domains such as desire, arousal and satisfaction have a stronger impact than the physical domains such as pain and lubrication.[3] Although with different weights, the improvement in pain and lubrication observed for both treatments used in this clinical trial showed a positive influence on sexual function. In the case of treatment with IC, it was direct by improving lubrication and dyspareunia, or indirect through the action of the current throughout the perineal region, providing an improvement in the satisfaction and orgasm capacity. Desire and sexual arousal did not change after treatment, either with vaginal cream or with IC, most likely because these parameters depend more on emotional and psychological aspects than on organic changes in the vaginal mucosa and/or the skeletal muscle framework of the pelvic floor.

The relevance of the results obtained for the IC treatment is that it presents a new therapeutic option to improve the sexual function of the women with POI, using systemic HT, and that it was not inferior to vaginal estriol cream, the commonly used treatment.

To the best of our knowledge, we can say that there is a lack of randomized controlled trials evaluating how much systemic HT used in POI is sufficient for GUS control, just as there are few studies in women of any age evaluating options when systemic HT is already used and is insufficient. Thus, although the relatively low number of participants, the impossibility of a double-blinded study, and the short follow-up time are the main limitations of our study, our results are relevant considering that they present a new alternative in the treatment of reduced lubrication and dyspareunia that impact the sexual function of women with POI. The strong point is that such results were obtained from a randomized clinical trial, with topical estriol as the control group, considered the standard treatment for this condition.

CONCLUSION

The treatment using perineal IC showed a therapeutic option in this subset of women with POI using systemic HT and who maintained sexual symptoms of urogenital syndrome with improvement in pain, lubrication, satisfaction, and orgasm, reflecting a better overall evaluation of sexual function without compromising the frequency of sexual intercourse.

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