The Impact of Radiofrequency on Pelvic Floor Distress, Restoration, and Sexual Function Among Women Suffering from Pelvic Floor Disorders

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ABSTRACT

Background & Objective: Pelvic floor disorders (PFDs) are common devastating situations among women globally. The present study aimed to evaluate the clinical efficacy of radiofrequency (RF) on pelvic floor distress, restoration, and sexual function among women with PFDs.

Materials & Methods: This pre-post intervention study was performed on forty-three women with PFDs, who referred to a teaching pelvic floor clinic. Patients underwent RF three times fortnightly. Women were examined at three time points of baseline, one month post-intervention, and in a three months follow-up. In addition, a biofeedback evaluation was performed by a physiotherapist at the first session and follow-up. All women were asked to complete the Female Sexual Function Index and Pelvic Floor Distress Inventory questionnaires at the first session and in follow-up assessments. Descriptive statistics, the paired samples t-test, and the Friedman test were used to analyze the data.

Results: The mean and standard deviation of the age and gravidity of participants were 40.3±8.01 years and 2.65±1.3, respectively. We observed that 81.4% of women had a history of vaginal delivery. A significant improvement was found in the levator muscle tonicity by manual examination in the three-month follow-up (P<0.001). Moreover, maximal pelvic floor contraction measured by biofeedback improved (P=0.075). There were significant improvements in female sexual function and pelvic floor distress, including pelvic organ prolapse, colorectal-anal distress, and urinary distress after RF therapy (P<0.001).

Conclusion: The findings of the current investigation showed that RF could be applied for pelvic floor restoration and is likely to improve sexual function and pelvic floor distress.

Keywords: Pelvic floor, Pelvic floor disorders, Radiofrequency Therapy, Sexual Function

Introduction

Pelvic floor disorders (PFDs) or pelvic dysfunctions include pelvic organs prolapse, urinary and fecal incontinence, feeling of vaginal swelling, as well as sexual symptoms, such as extreme vaginal laxity (1, 2). Previous studies have shown that many factors, including stroke, menopause, intra-abdominal increased pressure, ascites, a history of pelvic surgery, limited physical activity, hormone therapy, parity, vaginal delivery, age, race, body mass index, and congenital factors might be associated with PFDs (3, 4, 5).

The prevalence of at least one pelvic floor disorder is 23% that increases with age (3, 6). In Iran, Eftekhar et al. found 42% of women to have pelvic floor dysfunction (e.g., fecal and urinary incontinence, as well as pelvic organs prolapse) (1). The PFDs impose excessive costs on healthcare systems (7). In addition, PFDs can generate abundant problems in social relations, quality of life, and sexual dysfunction. Studies have demonstrated that sexual function and strength of pelvic floor muscles have a positive
correlation. As we know, the pelvic floor muscles have a significant role in producing involuntary contractions, facilitating blood flow to the genitalia, and better sensitivity during sexual activity (8, 9).

Various invasive and non-invasive therapies have been applied for pelvic floor restoration. Invasive treatments entail different types of surgeries and non-invasive therapies are pelvic floor muscle exercise (Kegel exercise) (10), biofeedback (11), laser (12), and radiofrequency (RF) (13).

The RF is an energy-based device used to improve genital appearance, sexual function, stress urinary incontinence, lubrication, vaginal laxity, Genito-pelvic sensation, bowel incontinence, pelvic organ prolapse (POP), and chronic pelvic pain (13-16).

RF induces an inflammatory process through generating the heat of 40°C-45°C and stimulates fibroblasts leading to the proliferation of the glycogen-enriched epithelium, neovascularization, and collagen formation (13). Therefore, it is believed that RF is a safe and effective intervention for the management of PFDs as measured by several outcome measures, including the Pelvic Floor Distress Inventory (PFDI-20) and Female Sexual Function Index (FSFI-6). With this background in mind, the present study aimed to identify the clinical efficacy of RF on sexual function, pelvic floor restoration, and distress among women with PFDs. Furthermore, the patient satisfaction index after treatment was assessed based on the improvement of sexual, colorectal-anal, and urinary symptoms.

Materials and Methods

Study Design and Participants

This pre-post study was conducted on a study population of women, who referred to a pelvic floor clinic affiliated to Tehran University of Medical Sciences, Tehran, Iran during December 2019-July 2020.

Sample Size and Sampling

First, a sample size of 40 women was considered based on a previous study (13). A power of 80% at a 5% significance level was estimated for the present study. Consequently, in practice, 43 women were enrolled in the study. All women with PFDs were assessed and those meeting the inclusion criteria were entered into the study. The inclusion criteria entailed signing informed consent, being married, at least having one PFD, such as urinary incontinence, lower gastrointestinal tract problems (e.g., constipation, fecal or gas incontinence, splitting, and digitation) vaginal laxity, and sexual problems. The exclusion criteria were having uncontrolled conditions, such as diabetes mellitus and severe psychological disorders, having prosthesis or intrauterine devices, being a smoker, active infection, and severe prolapse needing surgery. All participants were asked to respond to the study questionnaires both at baseline and at three-month follow-up.

Measures

1. Demographic and medical information: A short questionnaire was used to collect data concerning the age, education, employment status, and medical history of patients, including the number of pregnancies, mode of delivery (vaginal or caesarian section), history of pelvic floor surgery, history of rectal tears and episiotomy. In addition, weight, height, chief complaint, urinary symptoms, colorectal symptoms, and sexual symptoms were recorded.

2. Clinical examination: The participants were examined three times by a urogynecologist for the tonicity of the levator muscle by vaginal exam pre-treatment, as well as one and three months post-treatment. They were classified into three grades the low, medium, and normal.

3. Biofeedback evaluation: We used electromyographic biofeedback for measuring the three indices of muscle contractions. An expert pelvic floor physiotherapist assessed the power average (µV), rest average (µV), and endurance (sec) of contractions. Biofeedback evaluation was performed at the first session and the three-month follow-up.

4. PFDI-20: The PFDI-20 contains three subscales with six, eight, and six questions regarding the inconvenience of the prolapse (POP Distress Inventory-POPDI), complications of defecation (Colorectal-Anal Distress Inventory-CRADI), and difficulties in urination (Urinary Distress Inventory-UADI), respectively. Primarily, all questions have yes and no answers. The answers are scored based on a Likert scale of 0-4 with 0 for “No” and 1-4 for “Yes”. The score could be derived from the mean of the answered items in any subscales multiplied by 25 (rang: 0-100). The lower scores indicate lower distress. The total score is obtained as the sum of sub-scores (range: 0-300) (6). The Iranian version of the PFDI-20 showed acceptable validity and reliability (17).

5. FSFI-6: The FSFI-6 is a measure for assessing sexual function among females based on the following subscales: sexual desire, arousal, lubrication, orgasm, satisfaction, and pain. Sexual desire and satisfaction are scored based on a Likert scale with a range of 1-5. Moreover, arousal, lubrication, orgasm, and pain have a range of 0-5. The total score could be obtained by computing six sub-scores. The total score ranges from 2 to 30 with higher scores indicating better sexual performance. Scores less than 19 demonstrate the need for further interventions (18). The psychometric properties of the Iranian version of FSFI-6 are reported elsewhere (19).

Intervention

The Higgs device made by the Maya Slim Company was used for intervention. One disposable applicator (IQA: Intra Quadratic Applicator) was allocated to
each patient. We used two programs for standard therapy, the first of which was the endothermy program that generates homogeneous heat inside the body between applicator and grounding pad leading to increased blood circulation in that area. This program endures 15 min with a device power of 10 W without pulling out IQA from the patient’s body. The second program was Endogym Areeo, which stimulates aerobic exercises that endure 30-40 min at 35 W. Patients underwent Higgs treatment three times fortnightly based on the protocol provided by the same company.

**Statistical Analysis**

Descriptive statistics, including mean, standard deviation, frequency, and percentage were used to describe the data. The paired samples t-test was used to compare pre- and post-intervention in terms of pelvic floor distress, sexual function, and biofeedback results. In addition, the Friedman test was used for pre-post comparisons because a physical exam was performed by a gynecologist and the data were ordinal. The SPSS software version 23 (SPSS Inc., Chicago, IL., USA) was used for data analysis. The significance level was considered P-value< 0.05.

**Ethics**

The Review Board of the Tehran University of Medical Sciences approved the study (IR.TUMS.IKHC.REC.1398.294).

**Results**

**Patients**

Descriptive data, including demographic characteristics and the medical history of women, are shown in **Table 1**. The mean age of participants was 40.3±8.01 years. Thirty-eight patients (88.37%) were unemployed and twenty (46.51%) had under-diploma education. About surgical history, only one patient had a history of sphincter tears and none of the individuals had a history of fourth-degree laceration. Seven women had a history of medical diseases, such as diabetes mellitus or blood hypertension, which were well controlled. Elevated body mass index was observed in thirty-five (81.31%) people, 15 (34.8 %) of whom were obese.

**Table 1. The characteristics of the participants**

|                          | Mean (SD) | No. (%) |
|--------------------------|-----------|---------|
| Age (years)              | 40.30 (8.01) |         |
| Education status         |           |         |
| Under diploma            |           | 20 (46.51) |
| Diploma                  |           | 19 (44.18) |
| Academic                 |           | 4 (9.3) |
| Job status               |           |         |
| Employed                 |           | 5 (11.6) |
| Unemployed (housewife)   |           | 38 (88.37) |
| Body Mass Index          | 27.85 (3.51) |         |
| 18.5-24.9                | 8 (18.6)  |         |
| 25-29.9                  | 20 (46.51) |         |
| ≥30                      | 15 (34.8) |         |
| Gravidity                | 2.65 (1.3) |         |
| Vaginal Delivery         | 1.46 (1.0) | 35 (81.4) |
| History of pelvic floor surgery | 6 (13.95) |         |
| History of episiotomy    | 35 (81.4) |         |
| Chief complaint          |           |         |
| Urinary symptoms         | 31 (72.1) |         |
| Colorectal symptom       | 15 (34.9) |         |
| Sexual symptom           | 33 (76.7) |         |
| Patient Satisfaction Index after treatment (1-10) | | |
### Levator Muscle Tonicity

The results of the Friedman test are shown in Table 2. A significant improvement was found in the levator muscle tonicity in clinical examination by the urogynecologist pre-, as well as 1 and 3 months post-test ($P<0.001$). There were no side effects after RF treatment among participants.

#### Table 2. Clinical exam results by urogynecologist.

|                          | Baseline          | Follow-up (1 Month) | Follow-up (3 months) | P-value |
|--------------------------|-------------------|---------------------|----------------------|---------|
|                          | Mean (SD)         | Mean (SD)           | Mean (SD)            |         |
| Tonicity of levator (0-2)| 0.67 (0.47)       | 0.88 (0.39)         | 1.13 (0.60)          | $<0.001^a$ |
| Low No. %                | 14 (32.6)         | 6 (14)              | 5 (11.6)             |         |
| Medium No. %             | 29 (67.4)         | 36 (83.7)           | 27 (62.8)            |         |
| Normal No. %             | 0                 | 1 (2.3)             | 11 (25.6)            |         |

* Derived from Friedman test

### Pelvic Distress, Sexual Function, and Biofeedback Evaluation

The results of the paired t-test are summarized in Table 3. There were significant improvement in female sexual functioning (0.84 points augmentation) and pelvic floor distress (29.7 points decrease), including POP (10.66 points), colorectal-anal distress (5.08 points), and urinary distress (13.96 points) after RF therapy ($P<0.001$). Moreover, maximal pelvic floor contraction measured by biofeedback improved ($P=0.075$). However, there was no significant improvement in biofeedback results, namely maximal pelvic floor contraction, resting pelvic muscle tonicity, and the endurance of contraction.

#### Table 3. Comparing pelvic floor distress inventory, female sexual function and biofeedback results, derived from Paired Sample t test

|                          | Baseline          | Follow-up (3 months) | P-value |
|--------------------------|-------------------|----------------------|---------|
|                          | Mean (SD)         | Mean (SD)            |         |
| Pelvic floor distress inventory-20 |                 |                      |         |
| Pelvic Organ Prolapse Distress Inventory | 40.69 (18.5) | 30.03 (17.5) | $<0.001$ |
| Colorectal-Anal Distress Inventory | 18.16 (19.4) | 13.08 (14.5) | $<0.001$ |
| Urinary Distress Inventory | 50.00 (27.15) | 36.04 (20.7) | $<0.001$ |
| Total Pelvic Floor Distress Inventory | 108.86 (46.6) | 79.16 (38.4) | $<0.001$ |
| Female sexual function inventory | 20.67 (3.55) | 21.51 (3.68) | $<0.001$ |
| Biofeedback               |                   |                      |         |
| Maximal pelvic floor contraction ($\mu V^*$) | 11.48 (4.67) | 12.40 (4.08) | 0.075 |
| Resting pelvic muscle tone ($\mu V$)       | 1.70 (0.65)      | 1.76 (0.57)        | 0.474   |
| Endurance of contraction (s)               | 3.03 (1.76)      | 3.15 (1.16)        | 0.455   |

* Micro Volt
Discussion

The findings of the current study showed a significant improvement in the tonicity of levator muscle contraction assessed in manual examination by a urogynecologist. We found that maximum pelvic floor muscle contraction increased as measured by biofeedback. However, the elevation was not statistically significant. This could be due to the small sample size, which was not sufficient for a significant variation.

Our results revealed no significant change in resting pelvic muscle tone or the endurance of maximal contraction. However, the resting tone was in the normal range from the beginning. A similar observation was reported in a previous retrospective study that used RF among postpartum patients for pelvic floor restoration where no changes in resting pelvic muscle tone were observed. The latter investigation also reported improvement in the maximal pelvic floor contraction (13).

The findings of the present study showed that pelvic floor distress, including POP distress, colorectal-anal distress, and urinary distress improved after RF. This is comparable with a study that applied a non-invasive RF for the management of stress urinary incontinence and vulvovaginal laxity, where both symptoms and sexual satisfaction were improved (20). Similarly, another research showed that RF improved fecal incontinence and the quality of life sustained for 12 months without delayed morbidity (21). However, a study reported that the clinical impact of RF was negligible for most of the patients. The mentioned study concluded that RF should not be recommended for patients with fecal incontinence if we do not know about patient-related factors associated with treatment success (22).

Our findings indicated that female sexual function improved after RF. This might be due to the increased levator muscle tone that resulted in diminished vaginal laxity and improved sexual satisfaction. Consistently, studies have shown that RF procedure reduced vaginal laxity (23, 24) that improved sexual function and satisfaction (24). As we know, vaginal laxity can decrease sexual satisfaction via lowering physical sensation during sexual intercourse. Likewise, it might diminish the quality of sexual relationships (25). Furthermore, the patient satisfaction index specified that women had improvement in urinary, sexual, and colorectal-anal symptoms after three RF sessions.

We found that the majority of participants were overweight or obese. Previous studies showed that obesity was associated with PFDs (26) and weight loss in many cases causes a problem for surgical treatment (27). Zhu et al. studied a group of 5300 women and observed that obesity was a strong risk factor for urinary incontinence. Obesity could influence urinary incontinence, which is likely to occur due to an increase in intra-abdominal pressure leading to the weakening of pelvic floor muscles and fascia (27).

Limitations and Strengths

To the best of our knowledge, it is the first study on RF implication for pelvic floor distress in Iran. Secondly, the present study benefits from two evaluation approaches, namely biofeedback and manual examination of muscle contractions. However, there were also some limitations. Firstly, due to special conditions caused by the COVID-19 pandemic, some women could not participate in therapeutic sessions and were excluded from the investigation. Secondly, we utilized convenience sampling which limits the generalizability of the results. Thirdly, we did not evaluate some psychological variables that might interfere with sexual function, such as depression or anxiety. Further studies with a larger sample size and longer follow-ups are recommended.

Conclusion

The findings of the current investigation showed RF to be a safe procedure, which could be applied for pelvic floor restoration and is likely to improve sexual function and pelvic floor distress among women with PFDs.

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Conflict of Interest

The authors declared no conflict of interest.

References

1. Eftekhar T, Ghanbari Z, Kalantari F, Shariat M, Haghollahi F. The frequency of pelvic floor dysfunctions and their risk factors in women aged 40-55. J Family Reprod Health 2012; 6: 59-64.

2. Mattsson NK, Nieminen K, Heikkinen AM, Jalkanen J, Koivurova S, Eloranta ML, Suvitie P, Tolppanen AM. Validation of the short forms of the pelvic floor distress inventory (PFDI-20),
pelvic floor impact questionnaire (PFIQ-7), and pelvic organ prolapse/urinary incontinence sexual questionnaire (PSIQ-12) in Finnish. Health and quality of life outcomes 2017; 15: 88. [DOI:10.1186/s12955-017-0648-2] [PMID] [PMCID]

3. Nygaard I, Barber MD, Burgio KL, et al; Pelvic Floor Disorders Network. Prevalence of symptomatic pelvic floor disorders in US women. JAMA 2008; 300: 1311-1316. [DOI:10.1001/jama.300.11.1311] [PMID] [PMCID]

4. Subramanian D, Szwarczenski K, Mauskopf JA, Slack MC. Rate, type, and cost of pelvic organ prolapse surgery in Germany, France, and England. Eur J Obstet Gynecol Reprod Biol. 2009; 144: 177-81. [DOI:10.1016/j.ejogrb.2009.03.004] [PMID]

5. Jelovsek JE, Moher C, Barber MD. Pelvic organ prolapse. Lancet 2007; 369: 1027-38. [DOI:10.1016/S0140-6736(07)60462-0]

6. Barber MD, Walters MD, Bump RC. Short forms of two condition-specific quality-of-life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7). Am J Obstet Gynecol 2005; 193: 103-13. [DOI:10.1016/j.aajog.2004.12.025] [PMID]

7. Bahrampour T. The Hidden Medical Epidemic Few Women Have Been Willing To Talk About, Until Now. 2015. Accessed 27 August 2018.

8. Pourkhiz Z, Mohammad-Alizadeh-Charandabi S, Mirghafourvand M, Haj -Ebrahimi S, Ghaderi F. Effect of pelvic floor muscle training on female sexual function during pregnancy and postpartum: A randomized controlled trial. Iranian Red Crescent Medical Journal 2017; 19. [DOI:10.5812/ircmj.63218]

9. Martínez CS, Ferreira FY, Castro AA, Gomide LB. Women with greater pelvic floor muscle strength have better sexual function. Acta Obstet Gynecol Scand 2014; 93: 497 -502. [DOI:10.1111/aogs.12379] [PMID]

10. Cakmakci S, Kokanali MK, Topcu HO, Aksakal OS, Doğanay M. Effect of home-based Kegel exercises on quality of life in women with stress and mixed urinary incontinence. Journal of Obstetrics and Gynaecology 2015; 35: 407-10. [DOI:10.3109/01443615.2014.960831] [PMID]

11. Herderschee R, Hay-Smith EJ, Herbisson GP, Roovers JP, Heineman MJ. Feedback or biofeedback to augment pelvic floor muscle training for urinary incontinence in women. Cochrane Database of Systematic Reviews 2011 (7). [DOI:10.1002/14651858.CD009252] [PMID]

12. Fisitonić N, Fisitonić I, Guštek ŠF, Turina IS, Marton I, Vižintin Z, Kažić M, Hreljac I, Perhavec T, Lukač M. Minimally invasive, non-ablative Er: YAG laser treatment of stress urinary incontinence in women-a pilot study. Lasers in medical science 2016; 31: 635-43. [DOI:10.1007/s10103-016-1884-0] [PMID] [PMCID]

13. Dayan E, Ramirez H, Westfall L, Theodorou S. Role of Radiofrequency (Votiva, InMode) in Pelvic Floor Restoration. Plastic and Reconstructive Surgery Global Open 2019;7: 1-7. [DOI:10.1097/GOX.0000000000002203] [PMID] [PMCID]

14. Qureshi AA, Tenenbaum MM, Myckatyn TM. Nonsurgical vulvovaginal rejuvenation with radiofrequency and laser devices: a literature review and comprehensive update for aesthetic surgeons. Aesthet Surg J 2018; 38: 302-311. [DOI:10.1093/asj/sjx138] [PMID]

15. Hashim PW, Nia JK, Zade J, Farberg AS, Goldenberg G. Noninvasive vaginal rejuvenation. Cutis 2018; 102: 243-6.

16. Eftekhar T, Hajibabaee M, Pourali L, Vizheh M, Montazeri A. The Impact of Higgs Radiofrequency on Pelvic Organ Prolapse and Sexual Function Among Women Suffering from Vaginal Laxity. Journal of Obstetrics, Gynecology and Cancer Research (JOGCR). 2021; 10;6:128-33. [DOI:10.30699/jogcr.6.3.128]

17. Hakimi S, Hajebrahimii S, Bastani P, Aminian E, Ghana S, Mohammadi M. Translation and validation of the pelvic floor distress inventory short form (PFDI-20), Iranian version. BJM open. 2017;7(Suppl 1).

18. Isidori A, Pozza C, Esposito K, Ciotola M, Giugliano D, Morano S, Lenzi A, Jannini EA, Development and validation of a 6-item version of the female sexual function index (FSFI) as a diagnostic tool for female sexual dysfunction. Journal of Endocrinological Investigation 2006; 29: 22.

19. Ghassami M, Rahmati N, Mogadam A, Shaeiri MR. The study of the psychometric properties of the 6-item version of the female sexual function index (FSFI-6) amongst Iranian women. The Journal of Urmia Nursing and Midwifery Faculty 2014; 12: 532-43.

20. Lalji S, Lozanova P. Evaluation of the safety and efficacy of a monopolar nonablative radiofrequency device for the improvement of vulvo-vaginal laxity and urinary incontinence. J Cosmet Dermatol 2017; 16: 230-234. [DOI:10.1111/jocd.12348] [PMID]

21. Ruiz D, Pinto RA, Hull TL, Efron JE, Wexner SD. Does the radiofrequency procedure for fecal incontinence improve quality of life and incontinence at 1-year follow-up?. Diseases of the
22. Visscher AP, Lam TJ, Meurs-Szojda MM, Felt-Bersma RJ. Temperature-controlled delivery of radiofrequency energy in fecal incontinence: a randomized sham-controlled clinical trial. Diseases of the Colon & Rectum 2017; 60: 860-5. [DOI:10.1097/DCR.0000000000000861] [PMID]

23. Millheiser LS, Pauls RN, Herbst SJ, et al. Radiofrequency treatment of vaginal laxity after vaginal delivery: nonsurgical vaginal tightening. J Sex Med 2010; 7: 3088-3095. [PMID] [DOI:10.1111/j.1743-6109.2010.01910.x]

24. Sekiguchi Y, Utsugisawa Y, Azekosi Y, Kinjo M, Song M, Kubota Y, Kingsberg SA, Krychman ML. Laxity of the vaginal introitus after childbirth: nonsurgical outpatient procedure for vaginal tissue restoration and improved sexual satisfaction using low-energy radiofrequency thermal therapy. Journal of Women's Health 2013;22: 775-81. [DOI:10.1089/jwh.2012.4123] [PMID]

25. Krychman ML. Vaginal laxity issues, answers and implications for female sexual function. The journal of sexual medicine 2016; 13: 1445-7. [DOI:10.1016/j.jsxm.2016.07.016] [PMID]

26. Wasserberg N, Haney M, Petrone P et al: Morbid obesity adversely impacts pelvic floor function in females seeking attention for weight loss surgery. Dis Colon Rectum 2007; 50: 2096-103 [DOI:10.1007/s10350-007-9058-6] [PMID]

27. Pomian A, Lisik W, Kosieradzki M, Barcz E. Obesity and pelvic floor disorders: a review of the literature. Medical science monitor: international medical journal of experimental and clinical research 2016; 22: 1880. [DOI:10.12659/MSM.896331] [PMID] [PMCID]

28. Zhu L, Lang J, Wang H et al: The prevalence of and potential risk factors for female urinary incontinence in Beijing, China. Menopause 2008; 15: 566-69. [DOI:10.1097/gme.0b013e31816054ac] [PMID]