Int J Clin Exp Med 2019;12(8):10478-10485
www.ijcem.com /ISSN:1940-5901/IJCEM0095143

Original Article

Effects of pelvic floor bionic electrical stimulation on outcomes of frozen embryo transfer and improvement of endometrium in patients with thin endometrium tissues

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Received April 10, 2019; Accepted June 10, 2019; Epub August 15, 2019; Published August 30, 2019

Abstract: Objective: The aim of the current study was to investigate the effects of pelvic floor bionic electrical stimulation on pregnancy outcomes of frozen embryo transfers (FET), as well as endometrium improvements, in patients with thin endometrium tissues. Methods: Medical records of 115 patients with thin endometrial tissues, undergoing frozen embryo transfers, were prospectively analyzed. Patients were randomly divided into the experimental group (N=57) and control group (N=57). The experimental group received pelvic floor bionic electrical stimulation therapy, combined with artificial cycle treatment. The control group received artificial cycle treatment. Endometrial thickness levels and improvement statuses of the two groups of patients at LH peak day were compared before and after treatment. Endometrial blood flow arterial resistance index (RI) and pulsation index (PI) levels were measured, before and after treatment, and the average value was calculated. Next, this study compared pregnancy outcomes of the two groups of patients. Pregnancy outcomes included embryo implantation rates and clinical pregnancy rates. This study also compared improvements in endometrial thickness levels in the experimental group of patients with different frequencies of electrical stimulation. Result: After treatment, endometrial thickness levels of the experimental group were significantly thicker than those of the control group ($P<0.05$). Degrees of improvement in PI and RI indexes in the experimental group were significantly higher than those in the control group ($P<0.05$). Embryo implantation rates and clinical pregnancy rates of the experimental group were significantly higher than those of the control group ($P<0.05$). After treatment, endometrial thickness levels of the low frequency group were significantly lower than those of the medium frequency group and high frequency group ($P<0.05$). Conclusion: Application of pelvic floor bionic electrical stimulation in patients with thin endometrium tissues can effectively improve endometrial thickness levels and blood perfusion. It can also improve embryo implantation and clinical pregnancy rates.

Keywords: Pelvic floor bionic electrical stimulation, thin endometrium, frozen embryo transfer, pregnancy outcomes

Introduction

Embryo transfer includes a complex process of multiple links. Implantation of fertilized eggs has been related to endometrial receptivity and embryo quality. A major reason for embryo transfer failure is poor endometrial growth [1]. Studies have shown that, for frozen embryo transfers (FET), one of the necessary elements of success is proper endometrial receptivity. Endometrial receptivity has been shown to be related to endometrium thickness levels, affecting embryo implantation and pregnancies [2, 3]. At present, there are no uniform criterion for thin endometrium tissues caused by poor endometrial growth [4]. Clinical treatment of thin endometrium tissue aims to achieve endometrial thickness growth by improving endometrial blood flow, mainly using drugs, including small doses of aspirin or estrogen replacement therapy. However, efficacy levels have not been satisfactory [5-7]. Some scholars have attempted to mechanically stimulate local endometrium to increase thickness levels [8, 9]. However, this operation is invasive and susceptible to infections. Thus, it is not suitable

for clinical promotion [10]. Therefore, methods of effectively improving endometrial receptivity are urgently needed.

Bionic electrical stimulation is a kind of activation or inhibition of biological tissues by electrical stimulation. One of the important features is the production of exciting effects of nerve muscular tissues by stimulating the polarized state of the membrane. This promotes blood circulation and restores damaged muscles and nerve tissues. Finally, muscle function is improved [11]. Pelvic floor bionic electrical stimulation treatment aims to induce a functional response of damaged pelvic floor muscles by stimulating the pelvic floor muscles with different frequencies. Contraction and relaxation abilities of the pelvic floor muscles are stimulated. As a result, endometrial receptivity is improved [12].

Aiming to increase pregnancy rates of patients with thin endometrium tissues through FET, the current study compared improvements in endometrium tissues and success rates of pregnancy using pelvic floor bionic electrical stimulation, combined with artificial cycle treatment.

Materials and methods

General information

A prospective analysis of 114 patients with thin endometrial tissues, undergoing FET, was carried out. The average age of the patients was (33.48±3.15) years. Patients were randomly divided into the experimental group (N=57) and control group (N=57). The experimental group received pelvic floor bionic electrical stimulation, combined with artificial cycle treatment. The control group received simple artificial cycle treatment. Thirty patients had infertility caused by obstruction of the fallopian tube, 39 patients had infertility caused by pelvic adhesions, and 46 patients had infertility caused by endometriosis. No significant differences were observed in age and BMI between the two groups.

Inclusion criteria: Patients with thin endometrium tissues diagnosed by imaging and related tests; Patients with infertility; Patients that underwent endometrial FET procedures.

Exclusion criteria: Patients with severe liver and kidney dysfunction or tumors; Patients with other genital organ diseases; Patients with long-term use of steroid drugs; Patients with abnormal endocrine function. The patients/families agreed to participate in the test and provided informed consent. This study was approved by the Ethics Committee.

Treatment methods

The two groups of patients received 6 mg/d estradiol valerate from the 2nd day of menstruation before the frozen embryo transfer. After 9 days of continuous administration, uterus examinations were conducted, examining endometrial thickness levels with vaginal ultrasounds. When endometrial thickness was ≥8 mm and the LH peak appeared, transplantation conditions were satisfied. Patients in the experimental group were treated with pelvic bionic electrical stimulation and French PHENIX USB8 therapeutic apparatus. They adopted the supine position, with a sterile probe placed into the vagina. The groins of both sides and lumbosacral joints were connected to the other 4 channels. Eight electrode slices, with a frequency of 40 HZ and a pulse width of 250 μs, were used. Intensity levels were adjusted according to patient tolerance. One treatment was conducted per day from the 9th day of menstruation. Each treatment lasted for 30 minutes. Treatment was terminated when vaginal ultrasounds detected the LH peak day. Next, this study compared the effects of different frequencies of electrical stimulation therapy on endometrial thickness levels.

Outcome measures

(1) Endometrial thickness levels and improvement statuses of the two groups of patients at LH peak day were compared, before and after treatment, via diasonography; (2) Endometrial blood flow arterial resistance indexes (RI) and pulsation indexes (PI), before and after treatment, were measured and the average value of the two measurements was calculated; (3) Pregnancy outcomes of the two groups, including embryo implantation and pregnancy rates, were compared. On the 14th day after embryo transfer, blood HCG ≥5 U/L indicated biochemical pregnancies. On the 25th day after embryo transfer, gestational sac and yolk sac indicated clinical pregnancies via vaginal ultrasonography. Clinical pregnancy rate = (Clinical pregnancy number/total number of transfer) × 100%. Implantation rate = (number of implantation

Table 1. General information table

Factor	Experimental group n=57	Control group n=57	t/X^2	P
Age			0.035	0.851
≥33	30 (52.63)	29 (50.88)		
<33	27 (47.37)	28 (49.12)		
BMI			0.036	0.850
≥23	32 (56.14)	33 (57.89)		
<23	25 (43.86)	24 (42.12)		
Do you drink alcohol			0.035	0.851
Yes	28 (49.12)	29 (50.88)		
No	29 (50.88)	28 (49.12)		
Causes of infertility			0.050	0.975
Fallopian tube obstruction	19 (33.33)	18 (31.58)		
Pelvic adhesions	21 (36.84)	22 (38.60)		
Endometriosis	17 (29.82)	17 (29.82)		
Coagulation function				
APTT s	28.31±2.11	28.28±2.08	0.076	0.939
PT s	11.62±1.22	11.83±1.17	0.938	0.350
FIB g/l	3.17±0.22	3.20±0.21	0.745	0.458
TT s	14.62±1.49	14.59±1.53	0.106	0.916
Infertility time (years)	2.35±1.26	2.29±1.28	0.246	0.806
Quality embryos	2.11±0.43	2.09±0.48	0.252	0.801
Renal function (μmol/L)				
Creatinine	64.89±3.79	65.21±4.11	0.432	0.667
Urea	5.48±0.79	5.51±0.82	0.199	0.843
Uric acid	271.35±12.45	275.09±13.83	1.517	0.132

Table 2. Improvements in endometrial thickness in the two groups before and after treatment (mm)

Time	Experimental group	Control group	t	P
Before treatment	5.31±0.46	5.42±0.49	1.236	0.219
After treatment	9.64±0.62	7.92±0.58	15.3	<0.001
t	9.24	11.23		
p	<0.001	<0.001		

embryos/total number of transplantation embryos) × 100%; and (4) Comparison of endometrial thickness improvements with different frequencies of electrical stimulation in the experimental group.

Statistical methods

SPSS 18.0 software was used for statistical analysis. Chi-square tests were used for enumeration data. Measurement data are expressed by mean ± SD. Paired t-tests were used to compare parameters before and after treatment in the two groups. Independent t-tests were used for comparisons between the two groups. One-way ANOVA, followed by post-hoc Bonferroni's testing, was used for comparisons among groups. P<0.05 indicates statistical significance (**Table 1**).

Results

Improvement of endometrial thickness after treatment

There were no significant differences in endometrial thickness between the two groups before treatment (P>0.05). After treatment, endometrial thickness levels of both groups were thicker than those before treatment, respectively. After treatment, the endometrial thickness level of the experimental group was (9.64± 0.62) mm, significantly thicker than that of the control group (7.92± 0.58) mm (P<0.05) (**Table 2** and **Figure 1**). Results indicate that pelvic floor bionic electrical stimulation can effectively improve endometrial thickness levels of patients.

Comparison of PI and RI of endometrial blood flow before and after treatment at LH peak day

There were no significant differences in blood flow PI and RI between the two groups before treatment (P>0.05). After treatment, PI and RI indexes of both groups were increased. PI and RI indexes in the experimental group were significantly higher than those in the control group, respectively (P< 0.05) (**Tables 3**, **4**).

Comparison of pregnancy outcomes between the two groups of patients

A total of 103 embryos were transplanted into the experimental group. The number of implan-

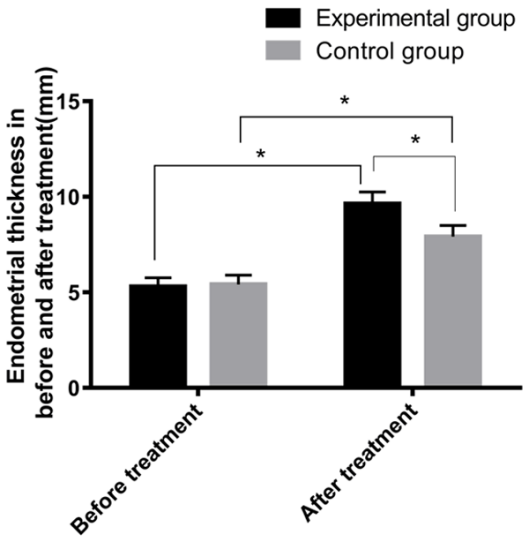

Figure 1. Improvements in endometrial thickness, before and after treatment, in the two groups. There were no significant differences in endometrial thickness between the two groups before treatment (P>0.05). After treatment, endometrial thickness levels of the experimental group were significantly thicker than those of the control group. Differences were statistically significant (P<0.05). Note: *indicates P<0.05.

tation embryos was 38 and the implantation rate was 38.897%. A total of 10 embryos were transplanted in the control group. The number of implantation embryos was 18 and the implantation rate was 17.48 %. The embryo implantation rate of the experimental group was significantly higher than that of the control group (P<0.05). There were 30 clinical pregnancies in the experimental group, with a clinical pregnancy rate of 52.63%. There were 14 clinical pregnancy in the control group, with a clinical pregnancy rate of 24.56%. The pregnancy rate of the experimental group was significantly higher than that of the control group (P<0.05) (**Table 5** and **Figure 2**). Results suggest that pelvic floor bionic therapy can significantly improve embryo implantation and pregnancy rates.

Effects of different frequencies of electrical stimulation on endometrial thickness

The experimental group was divided into a low frequency group (<3 times), medium frequency group (4-5 times), and high frequency group (>6 times), according to different frequencies of electrical stimulation. After treatment, endometrial thickness levels of the low frequency group, medium frequency group, and high frequency group were (8.97±1.25) mm, (9.89±0.06) mm, and (9.61±0.57) mm, respectively. Endometrial thickness levels of the low frequency group were significantly lower than those of medium frequency group and high frequency group (P<0.05). There were no significant differences in endometrial thickness levels between the medium frequency group and high frequency group (P>0.05) (**Table 6** and **Figure 3**).

Discussion

In the current society, with extreme lifestyle changes, incidence of infertility has increased rapidly. Thin endometrium tissues are a common cause of female infertility. The main reason for the failure of embryo implantation is poor endometrial receptivity [13]. Endometrial receptivity is affected by endometrial blood perfusion. It often directly reflects the microenvironment of the embryo implantation, affecting successful implantation of fertilized eggs [14, 15]. In a study by Takasaki [5] and his team, it was found that the expression quantity of CD34 and VEGF in vascular epithelial cells of patients with thin endometrium tissues was significantly lower than that of women with normal endometrium tissues. Blood flow resistance of endometrium tissues was also significantly greater than that of normal women. It has been suggested that patients with thin endometrium tissues have vascular dysplasia and high endometrium blood flow resistance. At present, the main treatment methods for thin endometrium tissues include estrogen therapy and corpus luteum support [16, 17]. However, it is not possible to improve endometrium thickness levels in the ovulation induction cycle or hormone replacement cycle [18]. Another treatment is to increase endometrial thickness through mechanical stimulation. The main mechanism is to promote the proliferation and differentiation of epithelial and stromal cells by mechanical removal of local lesions. Mechanical stimulation is invasive and cannot be performed repeatedly. Thus, it is not suitable for clinical promotion [19, 20]. In recent years, various studies have reported that electrical stimulation therapy can effectively improve endometrial thickness and endometrial perfusion [21]. Therefore, the current study

Table 3. Comparison of blood PI and RI indexes before treatment in the two groups of patients

Index	Experimental group n=57	Control group n=57	t	P
PI	0.73±0.04	0.72±0.05	1.179	0.241
RI	0.55±0.03	0.54±0.04	1.510	0.134

Table 4. Comparison of blood flow PI and RI indexes between LH peak days after treatment in the two groups of patients

Index	Experimental group n=57	Control group n=57	t	P
PI	0.98±0.13	1.33±0.34	7.259	<0.001
RI	0.68±0.11	0.57±0.09	5.843	<0.001

Table 5. Comparison of pregnancy outcomes between the two groups of patients [n, (%)]

Project	Experimental group n=57	Control group n=57	X^2	P
Embryo implantation	38/103 (38.89)	18/102 (17.48)	9.561	<0.050
Clinical pregnancy rate	30 (52.63)	14 (24.56)	9.475	<0.050

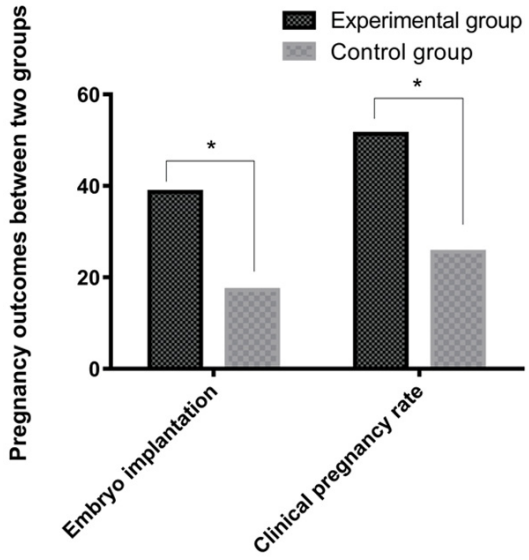

Figure 2. Comparison of embryo implantation rates and clinical pregnancy rates of the two groups of patients. Embryo implantation and clinical pregnancy rates of the experimental group were significantly higher than those of the control group (P<0.05). Note: *indicates P<0.05.

divided 115 cases of thin endometrial patients into two groups for pelvic floor bionic electrical stimulation and conventional treatment. This study also compared embryo transfers and endometrial improvements between the two groups. This study first compared improvements in endometrial thickness levels, after treatment, in the two groups. Results showed that endometrial thickness levels of the experimental group, after treatment, were significantly thicker than those of the control group. Differences were statistically significant (P<0.05). Results suggest that pelvic floor bionic electrical stimulation can effectively improve endometrial thickness levels in patients. Studies have shown that endometrial thickness and endometrial blood perfusion of patients with thin endometrium tissues after bionic electrical stimulation were significantly improved, compared to the control group [22]. This is consistent with present findings. The mechanism may be that bionic electrical stimulation can promote blood circulation to the endometrium and endometrial muscles. It also improves the nutritional status of the tissues, promoting a thickening of the endometrium. Next, the current study compared PI and RI levels of endometrial blood flow between the two groups, before and after treatment, at LH peak day. Results showed no significant difference in blood flow PI and RI between the two groups before treatment. After treatment, improvements of PI and RI indexes in the experimental group were significantly higher than those in the control group. Results suggest that pelvic floor bionic electrical stimulation can effectively improve patient endometrial blood flow. Endometrial receptivity was also significantly improved. PI and RI are indicators of endometrial perfusion, reflecting patient blood flow. Some studies [23] have indicated that pelvic floor bionic electrical stimulation can effectively improve the perfusion of thin endometrial patients. Electrical stimulation therapy promotes blood circulation by stimulating contraction and relaxation of uterine vascular muscles. This also confirms and explains present conclusions. The current study also compared embryo implantation and pregnancy

Table 6. Effects of different electrical stimulation frequencies on endometrial thickness

Time	Low frequency group n=19	Intermediate frequency group n=20	High frequency group n=18	F	P
Ninth days of menstruation	5.39±0.41	5.40±0.43	5.41±0.41	0.011	0.989
Transplant day	8.97±1.25	9.89±0.06*	9.61±0.57*	6.883	0.012

*indicated P<0.05 compared with low frequency group.

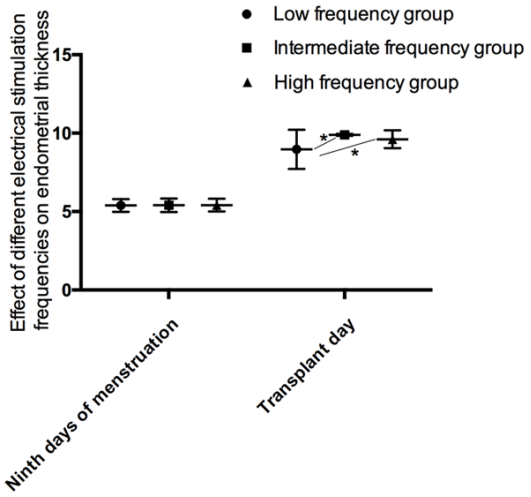

Figure 3. Effects of different frequencies of electrical stimulation on endometrial thickness. Endometrial thickness levels in the low frequency group were significantly lower than those in the medium frequency group and high frequency group. Differences were statistically significant (P<0.05). There were no significant differences in endometrial thickness between the medium frequency group and high frequency group (P>0.05). Note: *indicates P<0.05.

rates between the two groups. Results showed that embryo implantation rates and clinical pregnancy rates of the experimental group were significantly higher than those of the control group. Results suggest that pelvic floor bionic electrical stimulation can also effectively improve embryo implantation and pregnancy rates. Some studies [21] believe it is beneficial for embryo implantation when the endometrial proliferative phase is maintained at 13-15 days. Other studies [2] have shown that, when endometrial perfusion is significantly improved, endometrial receptivity is promoted. Thus, embryo implantation rates and clinical pregnancy rates are increased. This is also consistent with present conclusions. Some studies [24] have suggested that endometrial thickness levels provide predictive effects on pregnancy outcomes. Finally, the current study divided the experimental group into a low frequency group, medium frequency group, and high frequency group, according to different frequencies of electrical stimulation. This study compared endometrial thickness levels of the three groups of patients on the 9th day of menstruation and embryo transfer day after treatment. Results showed that endometrial thickness levels of patients in the low frequency group were significantly lower than those in the medium frequency group and high frequency group. Differences were statistically significant (P<0.05). However, there were no significant differences in endometrial thickness between the medium frequency group and high frequency group (P>0.05). Results suggest that, when electrical stimulation frequencies are increased, endometrial thickness can be significantly improved. The ideal number is 4-5 times. When frequencies continues to increase, endometrial thickness improves slightly. There were no significant differences, compared with the medium frequency group. However, in the current study, the mechanisms of pelvic floor bioelectrical stimulation therapy were not explored in depth. The safety of pelvic floor biosimilar therapy was not analyzed and discussed. These should be addressed in future studies.

In summary, application of pelvic floor bionic electrical stimulation therapy in patients with thin endometrium tissues can effectively improve endometrial thickness and blood perfusion levels of patients. It can also improve embryo implantation rates and clinical pregnancy rates. Thus, it is worthy of clinical promotion.

Disclosure of conflict of interest

None.

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