Int J Clin Exp Med 2017;10(1):760-766
www.ijcem.com /ISSN:1940-5901/IJCEM0034619

Original Article

Improvement of pelvic floor neuromuscular electrical stimulation (nmes) on endometrial thickness and blood perfusion of infertile women with thin endometrium

Yi-Ping Luo, Li Xiao, Jian-Hao Liang, Wei Lian

Department of Gynecology of The First People's Hospital of Shunde, Foshan 528300, Guangdong, China

Received June 28, 2016; Accepted September 5, 2016; Epub January 15, 2017; Published January 30, 2017

Abstract: Objective: Neuromuscular Electrical Stimulation (NMES) has been used in clinical treatment of problems related to gynaecology and obstetrics department, including stress urinary incontinence (SUI), low back pain, sexual dysfunction, pelvic pain, and constipation. However, its effect on endometrial thickness and blood perfusion in infertile women with thin endometria is still unknown. We aimed to evaluate the effect of pelvic floor neuromuscular electrical stimulation (NMES) therapy for improving endometrial thickness and blood perfusion in infertile women with thin endometria through different current intensity and duration of NMES current. Methods: 284 patients with infertility and thin endometria were recruited and divided into two groups, both of which were continuously monitored in regard to endometrial thickness and endometrial vascular resistance index (RI) during mature follicles days of two menstrual cycles. The control group of 134 patients was treated with estradiol valerate. The experimental group of 150 patients was treated with estradiol valerate and pelvic floor NMES. Endometrial thickness and RI were measured during the mature follicles days. Results: The mean endometrial thickness and RI were higher after NMES in the experimental group than in the control group; the difference was statistically significant ($P<0.05$). Further, the mean endometrial thickness, RI and luteinizing hormone (LH) were increased followed by the increased current intensity ($P<0.05$). Whereas the mean of endometrial thickness, RI and luteinizing hormone (LH) were unchanged when the patients were treated with different duration of NMES current. Also, we found that the endometrial thickness was related to the time of the electric stimulate $P<0.05$, and the longer is the treatment time, the thicker is the endometrial thickness. However, the intensity of the current is not associated with endometrial thickness, $P>0.05$. Conclusion: This study suggests that pelvic floor NMES not only increases endometrial thickness, but also improves endometrial perfusion. Therefore, NMES therapy may be effective for patients with thin endometria.

Keywords: Pelvic floor neuromuscular electrical stimulation, thin endometrium, endometrial thickness, endometrial blood flow

Introduction

Pregnancy is closely related to whether or not ovulation occurs and whether or not the embryo implants after fertilization [1]. Likewise, whether the implantation of the embryo is associated with endometrial thickness and blood supply for adequate endometrial thickness contribute to the implantation of an embryo and achievement of pregnancy [2]. Endometrial factors directly determine the success of pregnancy [2, 3]. Perfusion of the micro-environment of the endometrium influences the endometrial thickness and its blood flow. Endometrial blood flow deficiency often indicates a poor uterine environment [4]. Improving endometrial blood flow, and thereby improving endometrial receptivity, can increase the success rate of embryo implantation, which attracts significant public attention [5].

Currently, thin endometrium is defined as an endometrial thickness less than 7 mm or 8 mm when measured via ultrasonography on the human chorionic gonadotropin day or a natural menstrual cycle luteinizing hormone (LH) peak day with assisted reproductive technology [6]. Thin endometrium, a common cause of infertility, contributes to more than 60% of embryo implantation failure in all women. Further, clinical treatment of thin endometrium is difficult [7]. At present, the primary treatment methods include estrogen replacement therapy, application of drugs that improve local microcirculation, and mechanical stimulation of the endometrium, as well as the use of traditional Chinese medicine and drugs [8]. Although various methods have been employed to regulate the blood flow of uterine arteries and increase the thickness of the endometrium, there is still no consistently effective treatment option available. Thus, an ideal therapeutic agent is needed as soon as possible.

Neuromuscular electrical stimulation (NMES) has been extensively applied to groups of muscles to improve activities of daily living by using electric impulses generated by a device and delivered through electrodes on the skin, which directly stimulate the muscles [9]. Recent reports have found that it could be used in gynaecology and obstetrics department during pregnancy and the postpartum period, especially for treatment of stress urinary incontinence (SUI), low back pain, sexual dysfunction, pelvic pain, and constipation [9-13]. So far, few studies have assessed the effect of pelvic NMES for reproductive medicine at home or abroad. Additionally, reports regarding the effectiveness of electrical stimulation have been controversial. Therefore, the objective of the present study was to effect of pelvic floor neuromuscular electrical stimulation (NMES) therapy for improving endometrial thickness and blood perfusion in infertile women with thin endometria.

Materials and methods

Clinical information

The study was reviewed and approved by the Ethical Review Board of the First People's Hospital of Shunde. Written informed consent was obtained from all patients. All patients were randomized in a hospital setting.

The 284 patients were selected as research subjects from May 2012 to September 2014 in our hospital in the infertility specialist outpatient department. Ages ranged from 24-39, with an average of 30.2±3.0 years of age. The patients were made to undergo a variety of tests, including genetics check, thyroid and adrenal B-ultrasonography, uterine cavity ultrasound, uterine lining biopsy, and sex hormone tests to exclude congenital disease, uterine lesions, intrauterine adhesion, hydrosalpinx, polycystic ovary syndrome, and anti-estrogen hormone drug treatment. All accepted patients had to meet the following criteria: continuous observation of 3 natural ovulations, ultrasound endometrial thickness ≤7.0 mm on LH peak day, and no history of hormone medication in the previous 3 months.

Research methods

Two hundred and eighty-four patients who were infertile were divided into control and experimental groups. The control group, consisting of 134 patients, began the treatment of oral estradiol valerate 3 mg taken 2 times/day on the 5th day of menstruation. A color Doppler ultrasound monitored follicular diameter of the patients when the urine LH test got the highest value, test LH value with blood check, monitor the endometrial thickness and RI. The experimental group was further divided into two groups. All 150 experimental patients began oral estradiol valerate on the 5th day of their menstrual cycles, taken 2 times/day, to the follicle maturation day; this oral medication method was the same as that of the control group. The first experimental group tested treatment time dependence: three days after the end of their menstrual cycles, the patients received pelvic NMES treatments every other day. Treatment days included five applications of NMES in 10, 20, 30, 40, and 50 min sessions. The specific operation was as follows: the patients take supine bit, then disinfected probes were inserted into the patients' vaginal canals, posted electrode tablets in the center of pelvic, then connected with PHENIX USB8 neural-muscle electric stimulus treatment instrument; adjusted treatment instrument parameters: frequency: 40 Hz, pulse wide: 250 us, current intensity: 25 mA. The second group varied by intensity of treatment: In menstrual end 3rd days up every other day, make neural muscle electric stimulus in each 30 min, specific operation following: the patients take supine bit and sterile bacteria probe was inserted patients vaginal; posted electrode tablets in pelvic Center, and connected PHENIX USB8 neural-muscle electric stimulus treatment instrument; then adjusted the treatment instrument parameters: frequency 40 Hz, pulse wide 250 us, current intensity respectively for 15, and 20, and 25, and 30, and 35 mA; treatment time: from menstrual 8th days began until LH peak day, daily 1 times, each 30 min, about

Table 1. Baseline characteristics of experiment group and control group

	Control group (N=134)	Experimental group (N=150)	*t*	*P*
Age (year)	28.32±2.87	28.27±1.98	0.079	0.938*
Infertility Age (year)	3.52±0.65	3.23±1.46	0.969	0.338*
Endometrial Thickness (mm)	5.60±0.39	5.48±0.37	1.181	0.243

*Due to the unequal variance distribution ranging in age and infertility between the control group and experiment group, student t test was employed.

Table 2. Results before and after therapy between experiment group and control group

	Control group (N=134)	Experiment group (N=150)	*t*	*P*
the increases of endometrium after treatment (mm)	2.04±0.30	3.12±0.39	-11.573	<0.001*
The changes of RI after treatment	0.32±0.12	0.20±0.10	-4.088	<0.001
LH	35.15±13.93	39.92±14.53	-1.249	0.217

*Due to the unequal variance distribution ranging in the increases of endometrium after treatment between the control group and experiment group, student t test was employed.

Table 3. Comparison of therapeutic results in different times

Time (min)	10	20	30	40	50	t	p
The increases of endometrium after treatment (mm)	1.82±0.26	2.13±0.15	2.55±0.21	2.96±0.33	3.23±0.35		<0.05
The changes of RI after treatment	0.17±0.14	0.20±0.13	0.24±0.15	0.28±0.11	0.33±0.16		<0.05
LH	35.10±11.85	36.19±12.47	37.32±13.15	38.68±12.93	39.97±13.58		<0.05

Table 4. Comparison of therapeutic results in different current

Current (volt)	15 (n=30)	20 (n=30)	25 (n=30)	30 (n=30)	35 (n=30)	F	p
The increases of endometrium after treatment (mm)	3.08±0.24	3.14±0.35	3.11±0.37	3.13±0.41	3.10±0.35		>0.05
The changes of RI after treatment	0.31±0.15	0.31±0.10	0.29±0.14	0.34±0.15	0.31±0.14		>0.05
LH	39.89±13.98	39.32±14.11	38.91±15.01	39.34±14.22	39.75±14.53		>0.05

5~6 times. On patients' follicle maturation days, we checked blood LH values and used color Doppler ultrasound to measure uterine lining thickness and RI situation. We compared these measurements with those taken before treatment.

Clinical criteria

The film thickness of uterine and the blood flow signal were detected in patients LH peak day, the patients take bladder rock cutting bit, and the ultrasound specialist physician used Japan Alokal 400 ultrasound diagnostic instruction and adjust vaginal probe frequency to 5.0 MHz, put the probe in vaginal dome part to make the ultrasound check, and measured the uterine thickness, and show the blood flow signal in most obviously spectrum part. Ultrasound instrument automatically get uterine film blood flow RI. The above determination is observed continuously in at least 3~5 one cardiac cycle, make the average of the 2 times values as final value of the measuring.

Statistical analysis

SPSS 19.0 software was used for statistical analysis. Comparisons between the different groups were assessed by a Student's *t*-test and a one-way ANOVA analysis. P<0.05 shows that the difference was statistically significant. The data was analyzed based on the intention-to-treat principle. Substituted secondary outcome measures were substituted when primary outcome measures were missing.

Results

The baseline characteristics of both the groups and the statistical difference between them are shown in **Table 1**. After two sets of treatments and complete color Doppler ultrasound monitoring of 2 menstrual cycles, comparison of

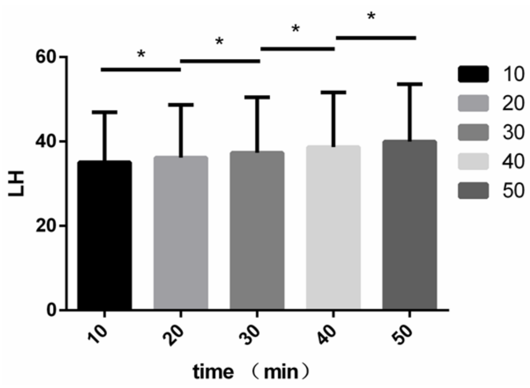

Figure 1. The LH after treatment in different times.

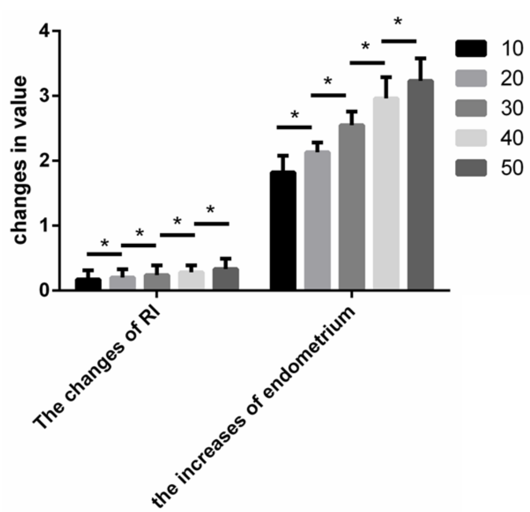

Figure 2. The increases of endometrium and RI after treatment in different times.

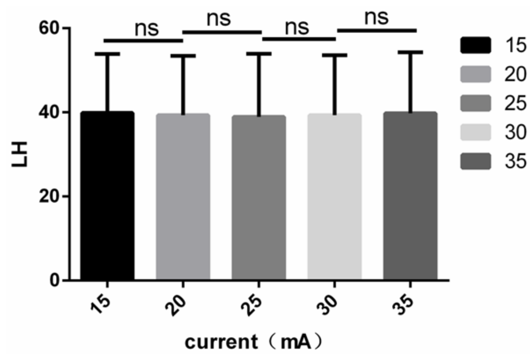

Figure 3. The LH after treatment in different current.

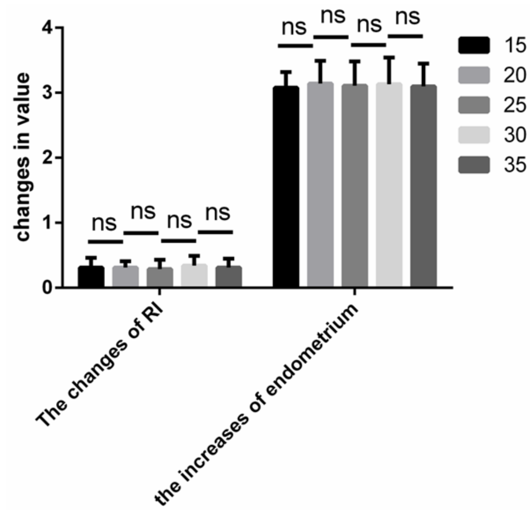

Figure 4. The increases of endometrium and RI after treatment in different current.

endometrial thickness and RI changes are shown in **Table 2**. The changes of endometrial thickness after different NMES current intensities and durations are presented in **Tables 3** and **4**, respectively.

Based on the above results, the control group and the experimental group were comparable in terms of age, infertility, and endometrial thickness distribution, with P>0.05 indicating that the differences were not statistically significant: functionally, there are no differences in baseline information between the two groups. The endometrial changes and RI of the experimental group and the control group before and after treatment, P<0.05, shows that there was a statistically significant change in endometrial thickness and RI of the two groups after treatment. Comparing just the LH value of the test group and the control group before and after treatment, P>0.05, shows that the difference was not statistically significant for that variable.

Further, we research the time and current intensity dependence of the endometrial thickness. As vividly shown in **Figures 1** and **2**, we found that the endometrial thickness was related to the time of the electric stimulate P<0.05, and the longer is the treatment time, the thicker is the endometrial thickness. Similarly, the changes of RI and LH were also increased following the increased time of electric stimulate. However, from **Figures 3** and **4**, we can see the intensity of the current is not associated with endometrial thickness, P>0.05, and the changes of RI and LH were not associated with endometrial, too. Based on these results, we could conclude that the pelvic neuromuscular electrical stimulation had no effect on the preovulatory LH peak for the experimental group. We also found that the link between NMES current and endometrial thickness for *P* value is less than 0.05. Therefore, there is no significant connection between the intensity of NMES current but the time of treatment with endometrial thickness.

Discussion

Pregnancy is closely related to whether or not ovulation occurs and is dependent on the implantation of the embryo after fertilization. To that end, LH peak is necessary for follicular maturation and discharge, which is the foundation of a successful pregnancy [14]. The success of embryo implantation depends on uterine capacity and embryo quality. One of the factors that contribute to a successful pregnancy is uterine thickness being ≥7 mm, and 2/3 of embryo implantation failure is associated with insufficient uterine lining capacity [15]. Better uterine lining blood perfusion often indicates better uterine lining capacity, and the uterine lining blood flow situation directly reflects the microenvironment of embryo implantation, and so influences the success of embryo implantation [16]. In recent years, thin endometrium has been another challenge for clinicians. There are many treatments used for thin endometrium, such as active treatment of the primary disease, hormone replacement therapy, and improving local microcirculation with medications [17, 18]. These kinds of treatments are used because the womb is the target organ for estrogen and progesterone [19]. Estrogen and progesterone are the driving force of growth, so most people with thin endometria can be improved after active treatment [20]. However, in clinical work, there is a segment of thin type uterine patients who, after undergoing a variety of treatments, still cannot achieve a satisfactory uterine lining thickness [21]. In addition, the application of female hormones can also have defects: in early follicles, the application of large doses of female hormones can inhibit follicle-stimulating hormone (FSH) secretion and effect egg quality. Furthermore, female hormones that promote uterine lining growth are time-dependent, not dose-dependent [22, 23]. Therefore, we can conclude that many attempts at the treatment of thin endometrium have been made, but they are generally ineffective; we still need to explore new and more effective treatment strategies.

Currently, there are some studies using pelvic neuromuscular electrical stimulation (NMES) to treat the patients with thin endometrium with different results, but no effects on ovulation have been reported [24]. In 2011, Bodombossou-Djobo showed that pelvic neuromuscular electrical stimulation increases endometrial thickness in thin endometria, but it did not increase the pregnancy rate. In the study, the uterine blood flow was not measured [25]. Previous studies also found that endometrial blood flow and vascular resistance index were improved, but intima-media thickness after NMES treatment was not reported [26, 27]. Likewise, other studies found that pelvic dysfunction therapy machines can improve endometrium RI and endometrial blood flow, but found no significant effect in the thickness of endometrium [28, 29].

150 infertile patients with thin endometria were treated with neuromuscular electrical stimulation, and we found that pelvic neuromuscular electrical stimulation not only increases endometrial thickness, but also improves endometrial blood perfusion, and did not affect the preovulatory LH peak in patients' blood. These results indicate that pelvic neuromuscular electrical stimulation is effective in the treatment of thin endometrium. The mechanism may be that electrical stimulation accelerates blood flow, maintaining the decreased blood flow resistance and increased pelvic, vaginal, endometrial, and uterine blood circulation in muscles, while also increasing blood supply, to promote the growth of the endometrium through the control of vascular smooth muscle contraction and relaxation.

Further, in order to detect whether current intensity has an effect on endometrial thickness, we checked the changes of endometrial thickness through a different current gradient. Interestingly, we found that the current promotion of endometrial hyperplasia was a time-dependent factor. Likewise, we tested various durations of current to explore whether or not it had an impact on endometrial thickness. However, it was not dose-dependent in that manner.

In conclusion, endometrial thickness and sufficient endometrial blood flow are prerequisites for successful pregnancy. In addition, the promotion of NMES current for endometrial thickness is time-dependent, but not dose-dependent. Pelvic neuromuscular electrical stimulation in the treatment of infertility for thin endometrium patients is safe, non-invasive, simple, and economical, and offers a new approach in thin endometrium treatment. However, further studies are needed to evaluate its mechanism.

Acknowledgements

The authors thank Dr. Xiao Li for critical appraisal of the manuscript and technical instruction in pelvic floor neuromuscular electrical stimulation (NMES) on Endometrial Thickness. This investigation was supported by medical science and technology research project in Foshan 201208207.

Disclosure of conflict of interest

None.

Address correspondence to: Yi-Ping Luo, Department of Gynecology of The First People's Hospital of Shunde, Foshan 528300, Guangdong, China. E-mail: luoyiping1188@sina.com

References

[1] Badreldin N, Kuller J, Rhee E, Brown L, Laifer S. Pregnancy Management After Bariatric Surgery. Obstet Gynecol Surv 2016; 71: 361-8.
[2] Gupta SK. Embryo Implantation and Pregnancy: Immunologic Intricacies and Strategies for its Success. Am J Reprod Immunol 2016; 75: 205-7.
[3] Thouas GA, Dominguez F, Green MP, Vilella F, Simon C, Gardner DK. Soluble ligands and their receptors in human embryo development and implantation. Endocr Rev 2015; 36: 92-130.
[4] Doren M, Suselbeck B, Schneider HP, Holzgreve W. Uterine perfusion and endometrial thickness in postmenopausal women on long-term continuous combined estrogen and progestogen replacement. Ultrasound Obstet Gynecol 1997; 9: 113-9.
[5] Zeng X, Pang H, Li X, Luo S, Jin S, Li S. Impact of obesity on endometrial blood flow in women without polycystic ovarian syndrome during intracytoplasmic sperm injection. Reprod Biol Endocrinol 2013; 11: 57.
[6] Check JH, Cohen R, Choe JK. Failure to improve a thin endometrium in the late proliferative phase with uterine infusion of granulocyte-colony stimulating factor. Clin Exp Obstet Gynecol 2014; 41: 473-5.
[7] Dain L, Bider D, Levron J, Zinchenko V, Westler S, Dirnfeld M. Thin endometrium in donor oocyte recipients: enigma or obstacle for implantation? Fertil Steril 2013; 100: 1289-95.
[8] Willmann C, Budik S, Walter I, Aurich C. Influences of treatment of early pregnant mares with the progestin altrenogest on embryonic development and gene expression in the endometrium and conceptus. Theriogenology 2011; 76: 61-73.
[9] Chen CC, Chuang YF, Yang HC, Hsu MJ, Huang YZ, Chang YJ. Neuromuscular electrical stimulation of the median nerve facilitates low motor cortex excitability in patients with spinocerebellar ataxia. J Electromyogr Kinesiol 2015; 25: 143-50.
[10] Park JS, Oh DH, Hwang NK, Lee JH. Effects of neuromuscular electrical stimulation combined with effortful swallowing on post-stroke oropharyngeal dysphagia: a randomised controlled trial. J Oral Rehabil 2016; 43: 426-34.
[11] Giggins O, Fullen B, Coughlan G. Neuromuscular electrical stimulation in the treatment of knee osteoarthritis: a systematic review and meta-analysis. Clin Rehabil 2012; 26: 867-81.
[12] Gerovasili V. Neuromuscular electrical stimulation appears to be useful in people with severe chronic obstructive pulmonary disease. J Physiother 2012; 58: 270.
[13] Coghlan S, Crowe L, McCarthypersson U, Minogue C, Caulfield B. Neuromuscular electrical stimulation training results in enhanced activation of spinal stabilizing muscles during spinal loading and improvements in pain ratings. Conf Proc IEEE Eng Med Biol Soc 2011; 2011: 7622-5.
[14] Gulland A. Pregnant women are too cautious about risk of medicines. BMJ 2016; 353: i3135.
[15] Matorras R, Matorras F, Mendoza R, Rodríguez M, Remohí J, Rodríguez-Escudero FJ, Simón C. The implantation of every embryo facilitates the chances of the remaining embryos to implant in an IVF programme: a mathematical model to predict pregnancy and multiple pregnancy rates. Hum Reprod 2005; 20: 2923-31.
[16] Esteller-Vico A, Liu IK, Vaughan B, Steffey EP, Brosnan RJ. Effects of vascular elastosis on uterine blood flow and perfusion in anesthetized mares. Theriogenology 2015; 83: 988-94.
[17] Takasaki A, Tamura H, Taketani T, Shimamura K, Morioka H, Sugino N. A pilot study to prevent a thin endometrium in patients undergoing clo-

miphene citrate treatment. J Ovarian Res 2013; 6: 94.
[18] Gleicher N, Vidali A, Barad DH. Successful treatment of unresponsive thin endometrium. Fertil Steril 2011; 95: 2123, e13-7.
[19] Vohra P, Buelow B, Chen YY, Serrano M, Vohra MS, Berry A, Ljung BM. Estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expression in breast cancer FNA cell blocks and paired histologic specimens: A large retrospective study. Cancer Cytopathol 2016; [Epub ahead of print].
[20] Ghazvini H, Khaksari M, Esmaeilpour K, Shabani M, Asadi-Shekaari M, Khodamoradi M, Sheibani V. Effects of treatment with estrogen and progesterone on the methamphetamine-induced cognitive impairment in ovariectomized rats. Neurosci Lett 2016; 619: 60-7.
[21] Takasaki A, Tamura H, Miwa I, Taketani T, Shimamura K, Sugino N. Endometrial growth and uterine blood flow: a pilot study for improving endometrial thickness in the patients with a thin endometrium. Fertil Steril 2010; 93: 1851-8.
[22] Ganderton C, Semciw A, Cook J, Pizzari T. The effect of female sex hormone supplementation on tendon in pre and postmenopausal women: A systematic review. J Musculoskelet Neuronal Interact 2016; 16: 92-104.
[23] Engel KC, Stökl J, Schweizer R, Vogel H, Ayasse M, Ruther J, Steiger S. A hormone-related female anti-aphrodisiac signals temporary infertility and causes sexual abstinence to synchronize parental care. Nat Commun 2016; 7: 11035.
[24] Sun Z, Zhu L, Lang J, Wang W, Shi H, Pang H, Shi X. [Continuous improvement of portable domestic pelvic floor neuromuscular electrical stimulation on the pelvic floor function of patients with urinary incontinence]. Zhonghua Fu Chan Ke Za Zhi 2015; 50: 937-41.
[25] Bodombossou-Djobo MM, Zheng C, Chen S, Yang D. Neuromuscular electrical stimulation and biofeedback therapy may improve endometrial growth for patients with thin endometrium during frozen-thawed embryo transfer: a preliminary report. Reprod Biol Endocrinol 2011; 9: 122.
[26] Joo JK, Jeong JE, Kim CW, Lee KS. Quantitative Assessment of Endometrial Volume and Uterine Vascularity and Pregnancy Outcome in Frozen-Thawed Embryo Transfer Cycles. J Reprod Med 2016; 61: 133-8.
[27] Son JB, Jeong JE, Joo JK, Na YJ, Kim CW, Lee KS. Measurement of endometrial and uterine vascularity by transvaginal ultrasonography in predicting pregnancy outcome during frozen-thawed embryo transfer cycles. J Obstet Gynaecol Re 2014; 40: 1661-7.
[28] Polackwich AS, Shoskes DA. Chronic prostatitis/chronic pelvic pain syndrome: a review of evaluation and therapy. Prostate Cancer Prostatic Dis 2016; 19: 132-8.
[29] Anderson RU, Wise D, Sawyer T, Nathanson BH, Smith JN. Equal Improvement in Men and Women in the Treatment of Urologic Chronic Pelvic Pain Syndrome Using a Multi-modal Protocol with an Internal Myofascial Trigger Point Wand. Appl Psychophys Biof 2016; 41: 215-24.