Neuromuscular Electrical Stimulation and Biofeedback Therapy to Improve Endometrial Growth in Patients with thin Endometrium: A Randomized Controlled Study

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**Abstract**

To evaluate the efficacy of noninvasive Neuromuscular electrical stimulation (NMES) in thin endometrium treatment, 115 patients (endometrium thickness ≤7mm) were recruited and randomly allocated to two groups. NMES group received NMES 3 to 4 times from day 9 to 10 and in comparison, a similar group received aspirin. Pre and post-treatment endometrium thickness, endometrial volume and Power Doppler Angiography (PDA) related parameters were measured by three-dimensional ultrasound. The endometrium was thicker in the NMES group compared with that in aspirin group [8.00 versus 7.72; P=0.028]. The endometrial and sub-endometrial volumes at final point also differ significantly between groups [2.58 versus 2.28; P=0.008 and 1.40 versus 1.21; P=0.001 for endometrial volume and sub-endometrial volume respectively. Endometrial flow index (FI), sub-endometrial vascularization index (sub-VI), sub-endometrial flow index (sub-FI) and sub-endometrial vascularization flow index (sub-VFI) differed statistically between groups (P=0.032, P=0.022, P=0.006 and P=0.018 respectively). In conclusion, NMES group showed better endometrial thickness, volume and vascularization than aspirin group.

**Keywords:** Thin endometrium, neuromuscular electrical stimulation, endometrial vascularization

**RCT Registration number:** ChiCTR-TRC-11001787

**I. Introduction**

In every day clinical practice, clinicians often see infertile patients with complex and unusual problems. One of the most challenging and frustrating problems to deal with is that of the patient with a poor endometrium or a thin uterine lining. Thin endometrium at the time of ovulation can be a concern and may be a factor in failure of implantation (Check, Nowroozi et al. 1991), poor placental development and miscarriage (Demirol and Gurgen 2004, Tan, Vandekerckhove et al. 2005). Normally, in response to estrogen, the uterine lining or endometrium grows about 1-2mm every other day. Thin endometrium more commonly occurs when the basal germinal endometrium, from which the full endometrial layer develops, is compromised in its response to estrogen by damage or reduced blood flow. Many studies have been reported that a poor uterine receptivity in women with thin endometrium is associated with the impairment of blood flow impedance through the endometrium(Hsieh, Tsai et al. 2000, Sher and Fisch 2002, Khairiy, Banerjee et al. 2007). Adjuvant therapies are often used to improve endometrial development in women with thin lining during assisted reproductive technologies (ART)(Chen, Yang et al. 2006) (Hsieh, Tsai et al. 2000, Ledee-Bataille, Olivennes et al. 2002, Sher and Fisch 2002, Qublan, Amarin et al. 2008, Acharya, Yasmin et al. 2009, Dirckx, Cabri et al. 2009, Ho, Huang et al. 2009, Takasaki, Tamura et al. 2010, Gleicher, Vidali et al. 2011). In a pilot study published in 2011, we have shown that neuromuscular electrical stimulation (NMES) could be an effective option to manage women with thin endometrium (Bodombossou-Djobo, Zheng et al. 2011). NMES is the application of electrical current to the pelvic floor muscles. NMES combined with biofeedback may be useful in that the electrical stimulation provides a passive contraction that increases awareness of pelvic floor muscles contractions in general. Applying a low grade electrical current to pelvic floor muscles stimulates the pelvic muscles to contract. The purpose of this study was to investigate the effectiveness of the new therapy in a randomized controlled study and use three-dimensional ultrasound to objectively assess the response to therapy. The hypothesis was that by stimulating uterine smooth muscle to repeated contraction and relaxation, there will be an increased in muscle strength and blood supply towards the whole endometrial and the sub-endometrial regions that leads to peripheral tissue tropicity. By this hypothetical mechanism, NMES will likely correct the impairment of uterine blood flow and will increase the endometrial thickness.

**II. Methods**

The study was reviewed and approved by the Ethical Review Board of the Memorial Hospital of Sun Yat-Sen University. This was an open label, randomized controlled trial, interventional study, parallel assignment, comparing NMES with aspirin which was carried out from late December 2011 to May 2012 in Memorial Hospital of Sun Yat-Sen University. Pilot study publication (August 2011). After an observational study from September 2010 to April 2011, we were able to calculate a sample size. April 2011 to December 2011: sample size calculation after random table, decision of parallel treatment (Vitamin E, Estrogen or Aspirin), acquisition of three dimensional ultrasound equipment for objective assessment of endometrium in randomized control trial, screening for eligibility, concealment. Aspirin was retained after searches of medical literature reporting that Aspirin does not have a proliferative effect on endometrium.

The registration on December 2011. The patients’ enrolment effectively started after registration, on late December (December 2001). Every patient gave a written informed consent prior to participating in the study (RCT Registration number: ChiCTR-TRC-11001787).
II.1 Study population
Women consulting for infertility at IVF center. Memorial Sun Yat-Sen Hospital of Sun Yat-Sen University were screening for eligibility, especially those undergoing timed intercourse on ovulation induction (OI) on Clomiphene citrate 50mg per day, from, D5 orally for 5 days or Letrozole 2.5 mg per day, from D5, orally for 5 days) or on natural cycle (NC, no fertility drug was used), intrauterine insemination (IUI) on OI or on NC and frozen-thawed embryo transfer (FET) on NC, OI cycle or on HRT(Estradiol valerate, Progynova; Bayer Schering Pharma, France) was used for endometrial preparation, (see the pilot study for details on the endometrial preparation).

II.2 Inclusion and exclusion criteria
Women aged 20 through 39 years old were recruited into this study only if they were recorded at least 2 previous assisted reproductive treatment cycles failures in which the optimum endometrium thickness was ≤7 mm and signed the informed consent.

Women were excluded from participation if they have/were undergoing IVF/ICSI, a medical history that included pelvic cancer, severe endometriosis, Asherman’s syndrome, sub-mucous myoma, adenomyosis, or congenital uterine anomalies by hysteroscopy, vaginitis, previous surgery in the pelvis, smokers and alcohol drinkers, neurologic disorders, systemic diseases, hypertension or diabetes mellitus, a use of an intrauterine device, and had previous use of long term hormonal contraception or other medication(s) which may have affected the uterus during the last 3 months or chronic use of any medication including nonsteroidal anti-inflammatory agents. Exclusion based on physical examination by the nurse practitioner (the physical therapist) occurred if women had vaginal wall prolapse, skin breakdown around the perianal region, rectal or vaginal bleeding, or absolute contraindications for pelvic neuromuscular electrical stimulation such as complete denervation of the pelvic floor (will not respond), dementia, cardiac pacemaker, unstable or serious cardiac arrhythmia, unstable seizure disorder, pelvic pain and swollen, painful hemorrhoids. Contraindications for aspirin such as women who were suffering from platelet dysfunction, thrombopenia, gastrointestinal ulcers, recurrent gastritis, aspirin hypersensitivity or who were on treatment with anticoagulants or aspirin were also considered for exclusion. We excluded women whose conditions warranted treatment with aspirin such as thrombophilia.

II.3 Study design
Screenings conformed to pre-assisted reproductive technologies (ART) protocols; hormones profile (day (D) 1-3 Serum PRL, FSH, LH, E2, and T) and pelvic ultrasound were completed.

II.4 Randomization
The sample size was calculated based on our pilot study. Randomization scheme has been constructed by using computer generated random numbers. Participants have been randomized to two study groups. Allocation to groups was by concealment. The concealments were made by a research assistant. A total sample size of 47 randomized subjects per treatment group was planned, with an additional 20 subjects (20%) to compensate for discontinued subjects. The enrollment of patients and follow-ups began on late December 2011.

II.5 Intervention
Group 1: NMES group underwent NMES therapy on D 9 or D10 for 3 to 4 times consecutively (qd for 20-30 minutes). PHENIX neuromuscular electrical stimulation therapy system USB 4 (Guangzhou Shanshan medical apparatus and instruments industry CO. LTD, Guangzhou, China) was used according to the manufacturer’s recommended protocol for 20 to 30 minutes of intermittent vaginal electrical stimulation on the treatment days. The settings and steps of NMES have been detailed in our previous pilot study.

Group 2: Aspirin group received aspirin 100mg/day started from D 9 or D 10 until the day of urinary β-HCG test or serum β-HCG test.

Follow-up were done by ultrasound monitoring, using a 4D sonographic scanner (Voluson 730/ Voluson E8, GE Medical Systems, Kretz Ultrasound, Zipf, Austria) equipped with an automatic 6-12 MHz 4D probe, on D9-10, on the day of HCG injection (when lead follicles≥18mm or greater in diameter) or Serum E2≥200 pg/ml per follicle or D0, the start of progesterone supplementation for FET in the two groups), D16-18 to confirm ovulation, 2 weeks after HCG day for urine pregnancy test and up to 12 gestational weeks if pregnancy occurs.

II.6 Outcome Measures
Primary outcome measures assessed in this study were endometrial thickness and endometrial volume at the end of the treatment cycle.

Secondary outcome measures were endometrial and sub-endometrial vascularization by 3D PDA and the resistance index (RI), pulsatility index (PI) and eventually pregnancy rate.

II.7 Data analysis
Mean and standard deviation were used for description of variables which followed a normal distribution. Median and inter-quartile were used for description of variables which showed skew distribution and categorical variables were described as a percentage. Univariate analysis was performed with two sample t-tests for the continuous variables showing the normal distribution of data (Kolmogorov-Smirnov). The Mann–Whitney U-test was used for variables which were not normally distributed. For Categorical variables, statistical significances in frequency differences between groups were evaluated by using the chi-square test. Statistical analysis was performed with SPSS software, versions 16.0 (SPSS Inc., Chicago, IL, USA), with P<0.05 as the limit of significance.
III. Results

III.1 General characteristics of the study population

122 women were eligible to take part of the study. After exclusion and taking into account a dropout of +20% of included patients, we included 115 patients with 61 and 54 in NMES and aspirin group respectively. 12 of them (6 in the NMES group and 6 in the aspirin group) did not go through the treatment. In aspirin group, 3 women did not receive the treatment.1 woman was by random allocated to aspirin group, could not have the treatment because she has been taking the same treatment for 2 cycles of treatment and she required NMES therapy and conceived in that cycle (not included in the analysis). 2 refused to take part of the study after randomization and 3 did not come back for follow-up. In NMES group, 1 woman for lack of means, did not have NMES therapy, 2 did not start the treatment for unknown reasons. 2 were lost to follow-up on time due to the distance (from another hospital in cities close by).1 did not have a dominant follicle during monitoring and discontinued the intervention. A total of 55 and 48 women were randomized to NMES therapy and aspirin treatment groups respectively and effectively participated to the study and were further analyzed.

The general characteristics of the study subjects are shown in Table 1. The mean age of the study population was 30.74 ± 4.52 (range 21-39). The women in this study had mixed diagnosis. 51/103(50%) had primary infertility. 45 women out of 103 were diagnosed polycystic ovary syndrome (PCOS). 42 had tubal occlusion, and 71 with male factor. Their mean ages were 30.32 ± 4.57 and 31.23 ± 4.47 years for NMES and aspirin group respectively. Their mean body mass indexes (BMI) were 20.78 ± 3.24 and 21.82 ± 2.92 kg/m2 for NMES and aspirin respectively. The mean age, BMI, baseline hormones profile, endometrial thickness and endometrial volume at baseline (D 9-10) showed no significant difference between the two groups.

III.2 Primary outcome

After NMES therapy and aspirin treatment, the endometrium became thickened in the NMES group compared with that in aspirin group [8.00(6.66-9.22) versus 7.72(6.51-8.44); P=0.028] which was statistically significant. 32/55(58%) developed endometrial thickness equal to or more than 8 mm after NMES therapy in the NMES group and 16/48(33%) in aspirin group. The endometrial and sub-endometrial volume at final point also differ significantly between groups [2.58(1.90-3.45) versus 2.28(1.39-2.85); P=0.008 and 1.40(1.23-1.64) versus 1.21(0.92-1.44); P=0.001 for endometrial volume and sub-endometrial volume respectively] (Table 2).

III.3 Secondary outcome

The two groups did not differ significantly regarding endometrial vascularization index (VI) and vascularization flow index (VFI) at final point. But in another hand, endometrial flow index (FI), sub-endometrial vascularization index (sub-VI), sub-endometrial flow index (sub-FI) and sub-endometrial vascularization flow index (sub-VFI) differed statistically between NMES and aspirin groups (P=0.032, P=0.022, P=0.006 and P=0.018 respectively) (Table 3).

III.4 Pregnancy rate

Regarding the clinical pregnancy, there were 12 clinical pregnancies (12/53 or 23%) in the NMES group versus 7 (7/47 or 15%) in the aspirin group. This difference was not significant (P =0.445). The overall pregnancy rate was 19% (19/100). 2 women cancelled their cycles (1 in NMES and 1 in aspirin).

IV. Discussion

To our knowledge, this is the first randomized, open label controlled trial examining the effect of NMES compared to aspirin on endometrium thickness. Our main outcome of interest was the change in endometrial thickness and volume along with associated vascularization indices in the two groups. The data in this study have showed that NMES improved endometrial thickness, endometrial volume and endometrial vascularization in women with thin endometrium. NMES involves electrical stimulation of nerves and muscles with continuous short pulses of electrical current (Kobetic, Triolo et al. 1997). NMES of the pudendal nerve (the nerve that innervates the pelvic floor muscles) operate at relatively high frequencies of 50 Hz. Our main outcome of interest was the change in endometrial thickness, sub-endometrial thickness and sub-endometrial volume in women with thin endometrium.

Aspirin has been also proposed for the treatment of infertility. 45 women were diagnosed as infertility. After NMES therapy and aspirin treatment, the endometrium became thickened in the NMES group compared with that in aspirin group [8.00(6.66-9.22) versus 7.72(6.51-8.44); P=0.028] which was statistically significant. 32/55(58%) developed endometrial thickness equal to or more than 8 mm after NMES therapy in the NMES group and 16/48(33%) in aspirin group. The endometrial and sub-endometrial volume at final point also differ significantly between groups [2.58(1.90-3.45) versus 2.28(1.39-2.85); P=0.008 and 1.40(1.23-1.64) versus 1.21(0.92-1.44); P=0.001 for endometrial volume and sub-endometrial volume respectively] (Table 2).

The two groups did not differ significantly regarding endometrial vascularization index (VI) and vascularization flow index (VFI) at final point. But in another hand, endometrial flow index (FI), sub-endometrial vascularization index (sub-VI), sub-endometrial flow index (sub-FI) and sub-endometrial vascularization flow index (sub-VFI) differed statistically between NMES and aspirin groups (P=0.032, P=0.022, P=0.006 and P=0.018 respectively) (Table 3).

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During the last decade, the endometrium has been receiving increasing attention. A thin endometrial have been associated with a low pregnancy rates in many studies (Richter, Bugge et al. 2007, El-Toukhy, Coomarasamy et al. 2008, Miwa, Tamura et al. 2009). In our previous study (pilot study), we have shown that NMES could be an effective option to manage women with thin endometrium. It showed that pelvic floor NMES significantly enhanced endometrial thickness in patients with thin endometrium (Bodomboossou-Djibo, Zheng et al. 2011). In the present study, we found that NMES have a positive effect on endometrial thickness, endometrial volume and endometrial and sub-endometrial vascularization. These findings are in agreement with the hypothesis we suggested in the earlier report. Decreases in voluntary muscle activation may negate increases in muscle size. Many studies have shown increased voluntary muscle activation with NMES (Gondin, Gruet et al. 2005, Gabriel, Kamen et al. 2006). NMES-induced muscle contraction to generate sufficient muscle contraction for adequate exercise or functional purposes.

Aspirin is a salicylate drug, one of the most famous, cheapest, available and widely used drug in the world in patients with a wide range of therapeutic uses. Aspirin is often used as an analgesic to relieve minor aches and pains, as an antipyretic to reduce fever, and as an anti-inflammatory medication. Research on the use of aspirin during ART has yielded mixed results. Some studies suggest that aspirin therapy improves pregnancy rates (Weckstein, Jacobson et al. 1997, Rubinstein, Marazzi et al. 1999, Wadenstrom, Hellberg et al. 2004), others suggest it may increase the risk for miscarriage(Pakkila, Rasane et al. 2005, Stern and Chamley 2006). Aspirin has been also proposed for the treatment of thin endometrium (Khairy, Banerjee et al. 2007) but seemed to be useless and inefficient from an evidence-based...
In this present study, instead of measuring uterine arteries pulsatility index and resistance index, we tried to measure the spiral arteries Doppler indices and our goal was to measure the vessels which were responsible for vasodilatation and an improved blood perfusion in many organs. The above-mentioned facts have led to the hypothesis that low-dose aspirin may improve uterine and ovarian perfusion and that aspirin might enhance endometrial receptivity and ovarian responsiveness as well (Rubinstein, Marazzi et al. 1999), which could result in better implantation and pregnancy rates after IVF or ICSI treatment. In this data, we did not attempt to compare the pregnancy rates between the two groups because of the heterogeneity in treatment protocols. Since our sample size was not chosen to analyze pregnancy rates, there could be a possible bias regarding the results. In a study by Khairy et al, there was an improvement in uterine artery pulsatility index in patients taking low-dose aspirin (Khairy, Banerjee et al. 2007). However, it has been reported that the uterine arteries are not representatives of endometrium (Aytoz, Ubaldi et al. 1997, Salle, Bied-Damon et al. 1998). In this present study, instead of measuring uterine arteries pulsatility index and resistance index, we tried to measure the spiral arteries Doppler indices and our goal was to measure the vessels which are closer to the endometrium. But in some patients, we experienced the complete absence of blood flow signals which made it impossible for us to have complete and uniform records about these indices. From the data we obtained, there was no consistent decrease in impedance to uterine spiral arteries blood flow from baseline to final point in aspirin group patients. In contrast to these findings, there was a decrease in PI and RI values after NMES therapy in NMES group patients. This makes us believe that NMES not only improved endometrial thickness but also decreased PI and RI in patients with thin endometrium. Moreover, it has been shown that high blood flow impedance of uterine radial arteries and decreased in vascular endothelial growth factor (VEGF) expression which is a major mechanism of action of aspirin. The above-mentioned facts have led to the hypothesis that low-dose aspirin may improve uterine and ovarian perfusion and that aspirin might enhance endometrial receptivity and ovarian responsiveness as well (Rubinstein, Marazzi et al. 1999), which could result in better implantation and pregnancy rates after IVF or ICSI treatment. In this data, we did not attempt to compare the pregnancy rates between the two groups because of the heterogeneity in treatment protocols. Since our sample size was not chosen to analyze pregnancy rates, there could be a possible bias regarding the results. In a study by Khairy et al, there was an improvement in uterine artery pulsatility index in patients taking low-dose aspirin (Khairy, Banerjee et al. 2007). However, it has been reported that the uterine arteries are not representatives of endometrium (Aytoz, Ubaldi et al. 1997, Salle, Bied-Damon et al. 1998). In this present study, instead of measuring uterine arteries pulsatility index and resistance index, we tried to measure the spiral arteries Doppler indices and our goal was to measure the vessels which are closer to the endometrium. But in some patients, we experienced the complete absence of blood flow signals which made it impossible for us to have complete and uniform records about these indices. From the data we obtained, there was no consistent decrease in impedance to uterine spiral arteries blood flow from baseline to final point in aspirin group patients. In contrast to these findings, there was a decrease in PI and RI values after NMES therapy in NMES group patients. This makes us believe that NMES not only improved endometrial thickness but also decreased PI and RI in patients with thin endometrium. Moreover, it has been shown that high blood flow impedance of uterine radial arteries and decreased in vascular endothelial growth factor (VEGF) expression which is a major mechanism of action of aspirin.
Grants

- Key project of research of National Ministry of Health (WGC [2010]039)
- The science technology research project of Guangdong Province (2012A030400010)

Conflict of interest

No conflict of interest

Acknowledgment

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VI. References


**Annexure:**

**Table 1 General characteristic of the two groups (NMES & Aspirin)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>NMES group (N=55)</th>
<th>Aspirin group(N=48)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.32 ± 4.57</td>
<td>31.23 ± 4.47</td>
<td>0.288</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.78 ± 3.24</td>
<td>21.82 ± 2.92</td>
<td>0.095</td>
</tr>
<tr>
<td>bFSH (IU/ml)</td>
<td>7.02 ± 1.93</td>
<td>8.50 ± 9.47</td>
<td>0.289</td>
</tr>
<tr>
<td>bLH (IU/ml)</td>
<td>5.89 ± 3.26</td>
<td>5.77 ± 3.68</td>
<td>0.851</td>
</tr>
<tr>
<td>bE2(ng/l)</td>
<td>50.14 ± 37.89</td>
<td>50.91 ± 42.04</td>
<td>0.922</td>
</tr>
<tr>
<td>bT (mmol/ml)</td>
<td>1.12(0.86-1.7)</td>
<td>1.35(0.73-2.00)</td>
<td>0.722</td>
</tr>
<tr>
<td>Infertility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>28(50%)</td>
<td>23(48%)</td>
<td></td>
</tr>
<tr>
<td>Tubal factor</td>
<td>24(41%)</td>
<td>18(38%)</td>
<td></td>
</tr>
<tr>
<td>Male factor</td>
<td>38(64%)</td>
<td>33(69%)</td>
<td></td>
</tr>
<tr>
<td>PCOS</td>
<td>24(41%)</td>
<td>21(45%)</td>
<td></td>
</tr>
<tr>
<td>Abortion history</td>
<td>19(33%)</td>
<td>15(31%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as number (percentage) N (%), mean ± SD, or median (inter-quartile range) and analyzed by Student t-test, Non-parametric test or Chi-square as appropriate. P< 0.05 was significant. bFSH: baseline Follicle Stimulating Hormone, bE2: baseline estradiol, bT: baseline Testosterone, BMI: Body Mass Index, PCOS: Polycystic Ovary Syndrome, NMES: Neuromuscular Electrical Stimulation.

**Table 2 Comparison of endometrial thickness, endometrial volume and sub-endometrial volume and pregnancy rate between the two groups**

<table>
<thead>
<tr>
<th>Variables</th>
<th>NMES group(N=55)</th>
<th>Aspirin group(N=48)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial thickness at baseline(mm)</td>
<td>4.79(3.89-5.68)</td>
<td>4.96(4.06-5.89)</td>
<td>0.237</td>
</tr>
<tr>
<td>Endometrial thickness between the 2 points</td>
<td>7.14(6.13-8.13)</td>
<td>6.89(5.49-7.77)</td>
<td>0.384</td>
</tr>
<tr>
<td>Endometrial thickness at hCG day(mm)</td>
<td>8.00(6.66-9.22)</td>
<td>7.72(6.51-8.44)</td>
<td>0.028</td>
</tr>
<tr>
<td>Endometrial volume at baseline(cm³)</td>
<td>1.08(0.74-1.71)</td>
<td>1.21(0.73-1.60)</td>
<td>0.833</td>
</tr>
<tr>
<td>Endometrial volume at hCG day(cm³)</td>
<td>2.58(1.90-3.45)</td>
<td>2.28(1.39-2.85)</td>
<td>0.008</td>
</tr>
<tr>
<td>Sub-endometrial volume at baseline(cm³)</td>
<td>0.85(0.70-1.16)</td>
<td>0.85(0.61-1.13)</td>
<td>0.968</td>
</tr>
<tr>
<td>Sub-endometrial volume at hCG (cm³)</td>
<td>1.40(1.23-1.64)</td>
<td>1.21(0.92-1.44)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pregnancy rate</td>
<td>12/53(23%)</td>
<td>7/47(15%)</td>
<td>0.445</td>
</tr>
</tbody>
</table>

Data are presented as median (inter-quartile range) and analyzed by Non-parametric test. P< 0.05 was significant. Between the 2 points: time between baseline point and hCG day point. P value was adjusted by Bonferonni correction.
Table 3 Comparison of endometrial and sub-endometrial angiographic indices between the two groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>NMES group (N=55)</th>
<th>Aspirin group (N=48)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial vascularization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Vascularization Index</td>
<td>1.11(0.32-4.65)</td>
<td>1.28(0.28-3.73)</td>
<td>0.663</td>
</tr>
<tr>
<td>3 Vascularization Index</td>
<td>3.47(1.69-5.71)</td>
<td>2.39(0.93-5.38)</td>
<td>0.068</td>
</tr>
<tr>
<td>1 Flow Index</td>
<td>25.70(22.31-27.95)</td>
<td>23.52(21.19-26.38)</td>
<td>0.058</td>
</tr>
<tr>
<td>3 Flow Index</td>
<td>25.75(24.08-28.37)</td>
<td>24.37(23.16-27.10)</td>
<td>0.032</td>
</tr>
<tr>
<td>1 Vascularization Flow Index</td>
<td>0.27(0.07-1.32)</td>
<td>0.29(0.06-1.07)</td>
<td>0.666</td>
</tr>
<tr>
<td>3 Vascularization Flow Index</td>
<td>0.96(0.43-1.50)</td>
<td>0.52(0.22-1.48)</td>
<td>0.056</td>
</tr>
<tr>
<td>Sub-endometrial vascularization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Sub-Vascularization Index</td>
<td>4.01(1.39-11.40)</td>
<td>2.09(1.28-7.51)</td>
<td>0.366</td>
</tr>
<tr>
<td>3 Sub-Vascularization Index</td>
<td>8.68(4.82-15.66)</td>
<td>5.92(1.55-11.84)</td>
<td>0.022</td>
</tr>
<tr>
<td>1 Sub-Flow Index</td>
<td>26.48(24.15-29.38)</td>
<td>23.89(22.21-26.99)</td>
<td>0.003</td>
</tr>
<tr>
<td>3 Sub-Flow Index</td>
<td>27.85(25.38-29.45)</td>
<td>26.22(23.81-28.31)</td>
<td>0.006</td>
</tr>
<tr>
<td>1 Sub-Vascularization Flow Index</td>
<td>1.11(0.36-3.19)</td>
<td>0.79(0.33-2.11)</td>
<td>0.42</td>
</tr>
<tr>
<td>3 Sub-Vascularization Flow Index</td>
<td>2.26(1.22-4.36)</td>
<td>1.57(0.39-3.26)</td>
<td>0.018</td>
</tr>
<tr>
<td>Doppler indices</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Pulsatility Index (PI)</td>
<td>1.14(0.96-1.47)</td>
<td>1.00(0.81-1.27)</td>
<td>0.009</td>
</tr>
<tr>
<td>3 Pulsatility Index (PI)</td>
<td>1.11(0.87-1.24)</td>
<td>1.00(0.82-1.16)</td>
<td>0.202</td>
</tr>
<tr>
<td>1 Resistance Index (RI)</td>
<td>0.65(0.59-0.75)</td>
<td>0.61(0.54-0.72)</td>
<td>0.290</td>
</tr>
<tr>
<td>3 Resistance Index (RI)</td>
<td>0.61(0.57-0.69)</td>
<td>0.61(0.55-0.64)</td>
<td>0.292</td>
</tr>
</tbody>
</table>

Data are presented as median (inter-quartile range) and analyzed by Non-parametric test. P< 0.05 was significant. 1: baseline (D8-10), 2: time between 1 and 2, 3: hCG administration day=final point.

Graph 1 Change of endometrial thickness means over time in the two groups.
1: baseline (D8-10), 2: time between 1 and 2, 3: hCG administration day=final point. Group1=NMES Group; Group2=Aspirin group.
Graph 2 Change of endometrial volume means over time in the two groups
1: baseline (D8-10), 2: time between 1 and 2, 3: hCG administration day=final point. Group 1=NMES Group; Group 2=Aspirin group