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Magnetic Resonance Imaging of Morphological and Functional Changes of the Uterus Induced by Sacral Surface Electrical Stimulation

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OGURA, T., MURAKAMI, T., OZAWA, Y., SEKI, K. and HANDA, Y. *Magnetic Resonance Imaging of Morphological and Functional Changes of the Uterus Induced by Sacral Surface Electrical Stimulation.* Tohoku J. Exp. Med., 2006, **208** (1), 65-73 —— The purpose of this study is to examine the morphological and kinematical changes of the uterus induced by electrical stimulation applied to the skin just above the second and fourth posterior sacral foramens (sacral surface electrical stimulation [ssES]) in 26 healthy subjects. Out of them, eight subjects who had severe pain subjectively during every menstruation received ssES just in menstruation. Morphological and functional changes of the uterus were examined by using T2-weighted magnetic resonance (MR) imaging and T1-weighted MR cinematography, respectively. Cyclic electrical stimulation for 15 min with 5 sec ON and 5 sec OFF was applied just before MR scanning. A decrease in thickness of the muscular layer of the uterus was observed in every subject after ssES for 15 min and was significant as compared with the thickness before ssES. Periodic uterine movement during menstruation was observed in the subjects with severe menstrual pain in MR cine and the power spectrum analysis of the movement showed a marked decrease in peak power and frequency after ssES treatment. We conclude that ssES causes a reduction of static muscle tension of the uterus in all menstrual cycle periods and suppression of uterine peristalsis during menstruation in the subjects with severe menstrual pain. Possible neural mechanisms for these static and dynamic effects of ssES on the uterus at spinal level are discussed. ———— sacral surface electrical stimulation; uterus; MRI; neuromodulation

The contractile component of the uterine wall is the myometrium which is composed of smooth muscles. The myometrium regulates tension of the uterine wall and peristaltic movements of the uterus under control of the autonomic nervous system. The pelvic organs are controlled by the hypogastric nerves (sympathetic) and pelvic nerves (parasympathetic) which are, in general,

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reciprocal for motor function of the pelvic organs. Detrusor muscle contraction of the bladder is triggered by excitation of the pelvic nerve arising from the second to forth ventral sacral spinal roots, resulting in urination. However, physiological function of these sympathetic and parasympathetic nerves innervating to the uterine muscles is still ill-defined.

It has been reported that urine incontinence due to overactive bladder could be improved by applying electrical stimulation to the skin just above the second and fourth posterior sacral foramens (sacral surface electrical stimulation [ssES]) (Yokozuka et al. 2004). SsES caused an apparent increase in volume and compliance and a decrease in uninhibited contraction in the bladder. These effects on the bladder may be attributed to neuromodulation by electrically-induced afferent volleys in the pudendal nerve, which is also one of the S2-S4 spinal nerves. The pudendal afferent inputs may suppress the pelvic neurons and simultaneously facilitate the hypogastric neurons in the spinal cord, and thus resulting in an inhibition of detrusor muscle overactivity.

This implies that ssES may also influence the contractile properties of uterine smooth muscles, since the uterus might be also regulated basically by the same autonomic and somatic nervous systems as the other pelvic organs even if distribution modality of these nerves is different.

Recently, development of magnetic resonance imaging (MRI) devices enables not only static analysis but also kinematical analysis of uterine contraction using MR cinematography (MR cine). Fujiwara et al. (2003) described peristaltic movement of the uterus during menstrual cycle phases including the menstruation phase using MR cine. Static and dynamic changes of the inner myometrium during menstruation in the subjects with dysmenorrhea were also detected by T2-weighted MR cine (Kataoka et al. 2005). Such quantitative analysis will clarify the static and dynamic configuration of the uterus under various kinds of conditions more precisely.

The purpose of this study is to examine the morphological changes of the uterus induced by ssES in healthy subjects in all menstrual cycle phases with T2-weighted MR imaging (T2WI). It is also the purpose to analyze kinematical changes of the uterus during menstruation before and after ssES in healthy subjects with severe menstrual pain with T1-weighted MR cine technique.

Materials and Methods

Subjects were 26 healthy females (Table 1). The age of these subjects ranged from 19 to 25 years old (21.0 ± 2.2 years, mean ± S.D.). None of the subjects had either history of pregnancy or organic diseases in their pelvis. We also checked the existence of organic abnormalities in their pelvic organs through MRI examination in advance.

Eighteen subjects out of 26 were randomly selected volunteers and the rest eight subjects were volunteers who had severe menstrual pain and took rest during the first day of menstruation (day 1) without taking analgesic agents. Menstrual cycle phases of eighteen subjects were periovulatory (n = 6), menstrual (n = 1, no menstrual pain) and luteal (n = 11) phases as shown in Table 1. The eight subjects with severe menstrual pain were just in menstruation period of day 2 or day 3 and complained mild menstrual pain during this study.

These subjects were divided into two groups. One was a subject group who received electrical stimulation (ES group, n = 18, 20.4 ± 1.8 years) and the other was a control group without receiving electrical stimulation (n = 8, 20.9 ± 1.7 years). The eight subjects with severe menstrual pain belonged to ES group but were distinguished as an ESmp group.

A portable electrical stimulator (Lintec prototype, Tokyo) was used for ssES. The electrode for surface stimulation was 5 × 10 cm (Lintec prototype, Tokyo). Electrodes were bilaterally and symmetrically put on the skin just above the posterior sacral foramens from S2 to S4.

Cyclic stimulation with 5 sec ON and 5 sec OFF was applied for 15 minutes in each subject of the ES group. Bidirectional rectangular pulses with 0.2 msec duration were used and frequency of the pulse train was 3 Hz in each direction. Stimulation intensity was set to the intensity just below pain threshold in each subject.

MR imaging was performed by using a 0.2-T permanent magnet system (GE medical systems Signa Profile, WI, USA) with a body-flex coil. We confirmed that exothermic reaction of the electrode during MR imaging could be perfectly disregarded and no danger did reach to the subjects. MR imaging including MR

TABLE 1. *Details of all Subjects in this study*

ES group

Case No.	Age	Menstrual phase			Pain
		Periovilatory	Menstrual	Luteal	
1	19	○			–
2	19	○			–
3	19	○			–
4	20			○	–
5	19			○	–
6	19			○	–
7	19			○	–
8	19			○	+
9	19			○	+
10	19		○		–
11	20		○		+
12	25		○		+
13	22		○		+
14	23		○		+
15	21		○		+
16	20		○		+
17	21		○		+
18	22		○		+

Control group

Case No.	Age	Menstrual phase			Pain
		Periovilatory	Menstrual	Luteal	
19	25	○			–
20	20	○			–
21	20	○			–
22	21			○	–
23	20			○	–
24	21			○	–
25	20			○	–
26	20			○	–

Left side shows ES group subjects and right side shows control group subjects. Shading part shows ESmp subjects in ES group.

Menstrual = day 2 or day 3.

Pain (+) = severe pain and take rest during day 1 without analgesics.

Pain (−) = no pain.

, ESmp subjects.

cine was obtained in the oblique sagittal plane along the long axis of the uterus. After localization of the uterus MR imaging, T2-weighted imaging (T2WI: fast spin-echo, TR = 3,200 msec, TE = 108 msec, thickness = 5 mm, slice-gap = 1 mm) and T1-weighted MR cine (SPGR, TR = 22.4 msec, TE = 7.3 msec, FA = 30 deg, thickness = 5 mm, 0.5 f/sec) were performed before and after ssES in ES group and rest in control group for 15 min. The imaging time of T2WI and T1-weighted MR cine were 6 min and 2 min, respectively.

In order to perform objective evaluation of the electrically-induced morphological changes of the uterus, the measurement using T2WI was carried out according to the following "Index Factor" (Fig. 1).

(1) Myometrium thickness: thickness of the muscular layer which includes the outer myometrium layer and junctional zone (inner myometrium layer) in the uterine body.

(2) Apsidal length of the cavity from the internal cervical os to the fundus in the uterine body.

(3) Normalized myometrium brightness: brightness

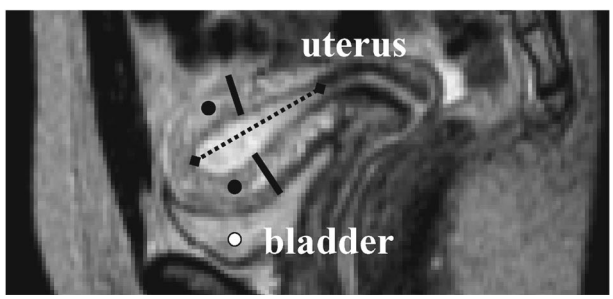

Fig. 1. Index factor.
Solid and dotted lines represent myometrium thickness and apsidal length of the uterine cavity, respectively. Normalized myometrium brightness (NMB) was obtained from the follow formula.

$$NMB = \left[\frac{\text{Myometrium brightness} \bullet}{\text{Bladder brightness} \circ} \right]$$

of the outer muscular layer normalized with brightness of the urinary bladder.

The measurements were performed with a randomized manner by two volunteers who did not know the purpose of this study in order to remove the prospective induction of the results. The averaged values measured by these two examiners were adopted.

The T1-weighted MR cine analysis was achieved after one or two days from the initiation of menstruation (day 2 or day 3) in the subjects of the ESmp group. First of all, the region of interest (ROI) with a diameter of 15 pixels, which never exceeded the uterine diameter, was fixed at the center of the uterine body being adjacent to the internal cervical os (Fig. 2). In T1-weighted MR imaging, the uterine wall is expressed as two layers of the myometrium and endometrium where MR brightness value of the myometrium shows a little bit higher than that of the endometrium. Cyclic movement of the myometrium within ROI was shown as sequential brightness changes of ROI in T1-weighted MR cine. Fast Fourier Transform of the brightness change was then performed and the power spectrum of the brightness changes corresponded with uterine peristalsis was analyzed.

The prior restriction of water intake was ordered for all subjects before 6 hours this study. Also, the urine voidance was carried out for all subjects just before study.

The research protocol was approved by the ethics committee of Tohoku University Graduate School of Medicine, Sendai, Japan. Subjects were informed of the purpose, protocol, anticipated results and safety of this study and signed an informed consent form before entering the study.

For statistic analysis, paired and unpaired *t*-test was used. The paired *t*-test was used to compare before and after ssES. On the other hand, unpaired *t*-test was used to compare two groups (control group and ES group).

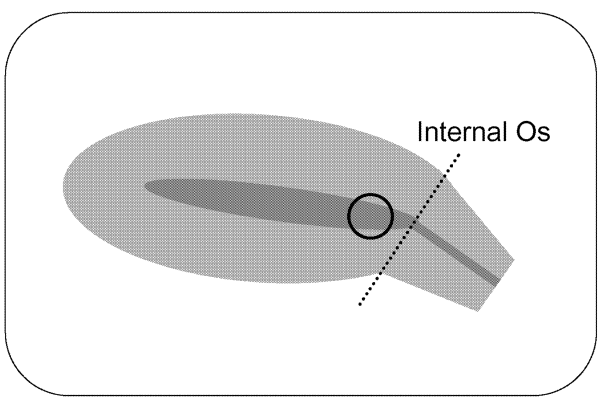

Fig. 2. Schematic illustration of uterine at T1-weighted MR imaging.
Dotted line indicates the level of internal os. The light gray and the dark gray area represent the myometrium and endometrium area, respectively. The circle of black line represents the region of interest (ROI).

Results

Myometrium thickness

Fig. 3 shows averaged data of myometrium thickness obtained from T2WI in ES group. The myometrium was significantly decreased in its thickness from 12.41 ± 2.03 mm before ssES to 11.04 ± 2.02 mm after ssES ($p < 0.01$: paired *t*-test). In control group, myometrium thickness was 12.89 ± 1.21 mm just before urination and 12.71 ± 1.06 mm after fifteen minutes rest. No significant difference was observed (paired *t*-test).

Thickness changes of the myometrium after ssES and the rest for fifteen minutes were –1.27 ± 1.19 mm and –0.18 ± 1.12 mm in ES and control groups, respectively. The change in ES group was significantly larger than in control group ($p < 0.05$: unpaired *t*-test).

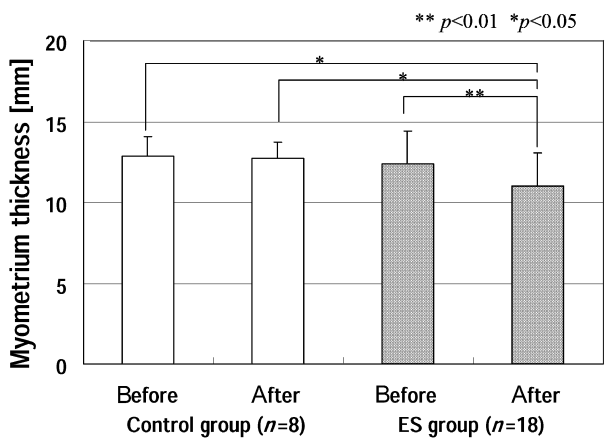

Fig. 3. Comparison of myometrium thickness.
White bars show the myometrium thickness change in control group before and after 15 min rest. Gray bars show the myometrium thickness change in ES group before and after ssES for 15 min. Significant difference was observed only before and after ssES for 15 min in ES group ($p < 0.01$: paired *t*-test).

Apsidal length of the cavity in the uterine body

Fig. 4 shows changes of apsidal length from the internal cervical os to the fundus in the uterine cavity before and after ssES. In ES group, the length of the cavity before and after ssES were 30.81 ± 8.28 mm and 32.34 ± 7.89 mm, respectively, and showed a significant increase ($p < 0.05$: paired *t*-test). In control group, the length just after urination and after fifteen minutes rest were 30.75 ± 8.95 mm and 32.81 ± 8.05 mm, respectively. It also showed a significant increase after fifteen minutes rest ($p < 0.05$: paired *t*-test). However, there was no significant difference between the lengths before ssES and the rest for fifteen minutes in ES and control groups, respectively (unpaired *t*-test). And the increasing rates of the length after the rest in control group and ssES in ES group was almost the same (unpaired *t*-test). There was no significant difference between the length changes of the uterine cavity in ES and control groups (unpaired *t*-test).

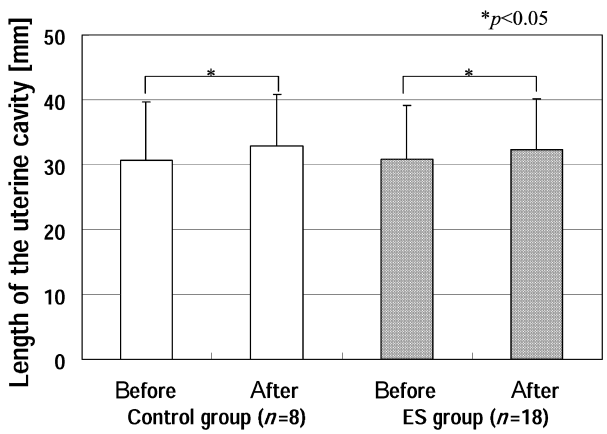

Fig. 4. Comparison of apsidal length of the uterine cavity.
White bars show the length of uterine cavity change in control group before and after 15 min rest. Gray bars show the length of uterine cavity change in ES group before and after ssES for 15 min.
There was no significant difference between the cavity length in ES and control groups.

Normalized myometrium brightness

Fig. 5 shows changes of normalized brightness of the outer myometrium layer. In ES group, normalized myometrium brightness before and after ssES were 0.70 ± 0.12 and 0.69 ± 0.14, respectively. In control group, normalized myometrium brightness just after urination and after fifteen minutes rest were 0.69 ± 0.12 and 0.69 ± 0.13, respectively. The significance was not observed among these data (paired and unpaired *t*-test).

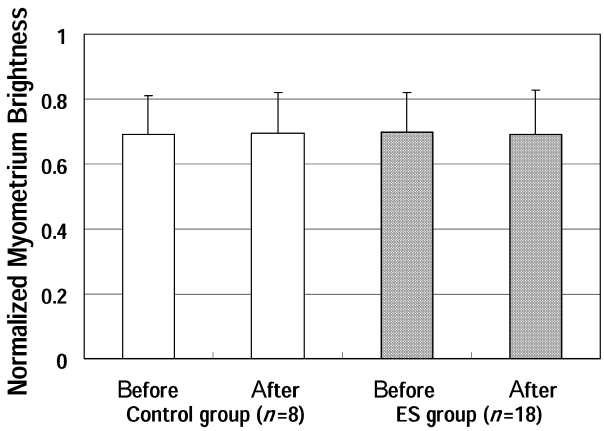

Fig. 5. Comparison of normalized myometrium brightness.
White bars show the normalized myometrium brightness change in control group before and after 15 min rest. Gray bars show the normalized myometrium brightness change in ES group before and after ssES for 15 min.
The significance was not observed among them.

T1-weighted MR cine

Fig. 6 shows sequential brightness changes of ROI within the uterine cavity for 120 sec obtained from T1-weighted MR cine before and after ssES in representative two subjects of ESmp group. Periodic brightness changes with an interval of around 30-40 sec were clearly observed before ssES (Figs. 6a and 6b). After ssES for 15 min, the interval increased to about 60 sec as shown in Figs. 6c and 6d. Concomitant with these changes, the amplitude of these waves was markedly decreased by applying ssES. Such an

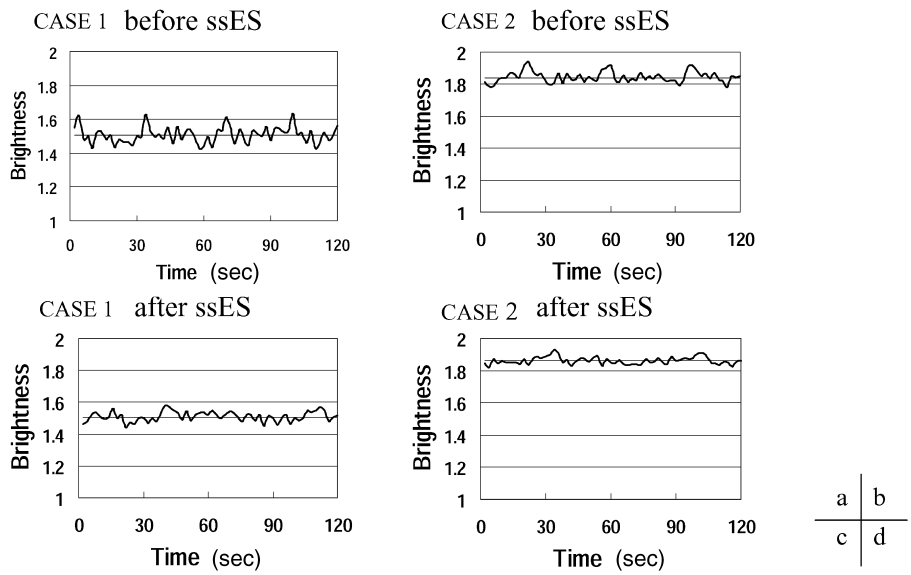

Fig. 6. Sequential brightness changes of ROI in 2 subjects of the ESmp group detected by T1-weighted MR cine.
Sequential brightness changes of ROI in case 1 and 2 before ssES (a, b) and after ssES (c, d), respectively.
Vertical axis: brightness of ROI.
Horizontal axis: the imaging time of T1-weighted MR cine (sec).

increase in interval accompanied by a decrease in amplitude of the periodic brightness changes induced by ssES was observed in all ESmp subjects.

Fig. 7 shows averaged power spectrum of the brightness changes of ROI before and after ssES in 8 subjects of ESmp group. The peak frequency and maximum power in the power spectrum were decreased after applying ssES.

Fig. 8a shows averaged data of peak frequency before and after application of ssES in ESmp group. The peak frequency was significantly decreased after ssES from 0.037 ± 0.004 Hz (2.2 ± 0.2 times/min) to 0.022 ± 0.005 Hz (1.3 ± 0.3 times/min) ($p < 0.01$: paired t-test).

Fig. 8b shows the change of maximum power at peak frequency before and after applying ssES in ESmp group. The maximum power was significantly decreased from 0.976 ± 0.263 before ssES to 0.566 ± 0.142 after ssES ($p < 0.01$: paired t-test).

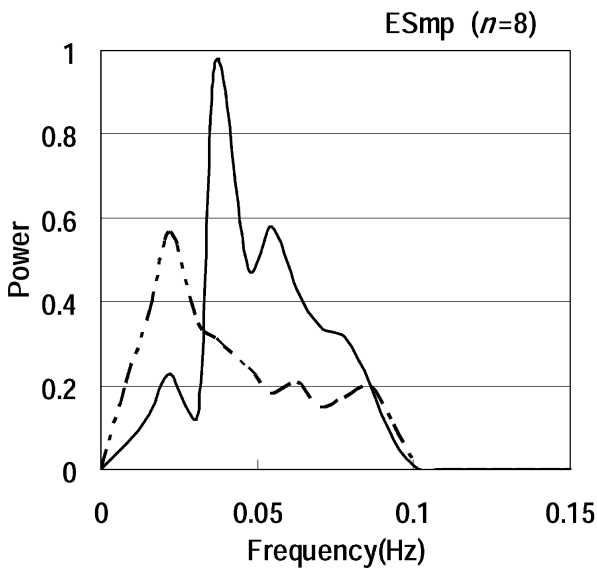

Fig. 7. Comparison of power spectrum in ESmp group before and after ssES.
The solid line shows the power spectrum before ssES and the two-point chain line shows the power spectrum after ssES for 15 min.
Vertical axis: the power.
Horizontal axis: the peak frequency (Hz).

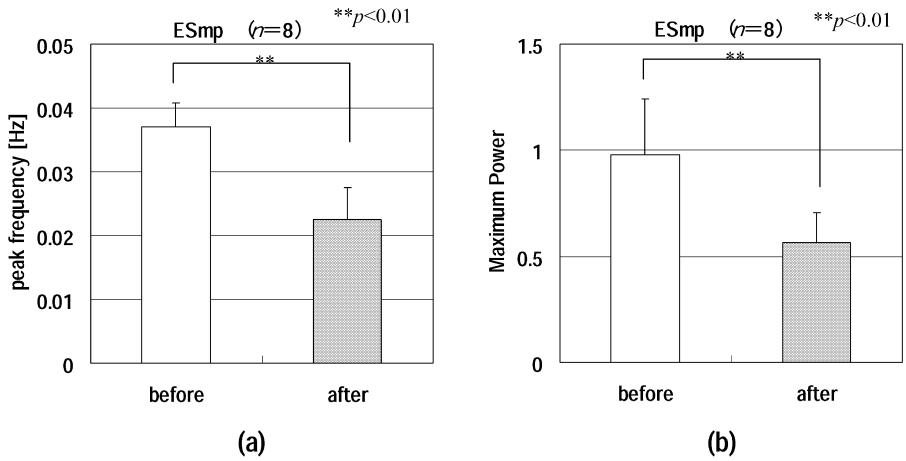

Fig. 8. Comparison of peak frequency and maximum power in ESmp group before and after ssES. Changes of averaged frequency (a) and maximum power (b) induced by ssES for 15 min. White and gray bars indicate the data before and after ssES, respectively.

Discussion

Morphological changes of the uterus induced by ssES in T2WI

The T2WI clearly demonstrated sagittal configuration of the uterus. Three layers of the uterine wall structure, the outer myometrium, inner myometrium which is called the junctional zone and endometrium could be distinguished. Therefore, a quantitative analysis of the structural changes of the uterus could be performed by the T2WI.

SsES caused a significant decrease in thickness of the myometrium composed of the outer and inner myometrium layers throughout all menstrual cycle phases. This change was independent of elevation in the uterine fundus and corpus due to an increase in bladder volume during study. In addition, normalized myometrium brightness with the brightness of the urinary bladder showed no change throughout the menstrual cycle phases. Neither diffuse nor focal thickness change more than 1 pixel (= 1.17 mm) in the inner myometrium layer, of which thickness ranged from 2 to 3 pixels in this digital measurement, was also observed throughout all menstrual cycle phases. It has been reported that the decrease in blood volume and water content in the myometrium lowers its signal intensity in T2WI (Togashi et al. 1993; Kataoka et al. 2005). Thus, it seems reasonable to say that the decrease in blood volume and water content was not responsible for the ssES-induced reduction of the myometrium thickness in either outer or inner myometrium layers.

Therefore, it is likely that such ssES-induced reduction of the myometrium thickness might be explained from a decrease in tension of whole uterine smooth muscles in any menstrual cycle phases.

Dynamic changes of the uterus induced by ssES in T1-weighted MR cine during menstruation day 2 and day 3

Spontaneous uterine contraction under resting condition with a frequency of 1 time/min was present in four uterine stages of the proestrus, estrus, metestrus and diestrus in the rat (Sato et al. 1996). Nakai and Togashi (2003) reported that peristaltic movements of the myometrium were observed in the ovulation and menstruation phases in healthy women by using the True FISP (fast imaging with steady state free precession) MR cine imaging. They described that frequency of the peristaltic movement of the uterus in healthy subjects was 0.5 times/min in the menstruation phase.

In the present study, averaged frequency of brightness changes of ROI which seemed to

reflect peristaltic uterine movement was 0.037 ± 0.004Hz (2.2 ± 0.2 times/min) during menstruation in the subjects with severe menstrual pain (Fig. 8a). Such high frequency peristalsis of the uterus in the menstruation phase has only been observed during the periovulatory phase in healthy subjects (Fujiwara et al. 2003). After applying ssES, both of the peak frequency and peak power of the uterine peristalsis showed significant reduction of 40% after ssES in the ESmp group. Thus, cyclic peristaltic movement of the uterus during menstruation in the subjects with severe menstrual pain was apparently suppressed in its frequency and amplitude by ssES which might stimulate the ventral rami of the sacral spinal nerves from S2 to S4.

It has been reported that transcutaneous electrical nerve stimulation (TENS) are effective to relieve pain in the subjects with primary dysmenorrhea (Lunderberg et al. 1985; Dawood and Ramos 1990; Kaplan et al. 1994). Milsom et al. (1994) showed that TENS to the lower part of the abdomen and the back in the subjects with dysmenorrhea resulted in reduction of menstrual pain without intrauterine pressure change. They mentioned that a cause of severe pain in dysmenorrhea is ischemia of the uterus and TENS might improve uterine circulation without interfering with uterine muscular activity. Namely, contractile properties of the uterus were not influenced by TENS. Therefore, it is reasonable to speculate that the effect of ssES on uterine activity differs from that of TENS.

Electrical stimulation to efferent fibers of the pudendal nerve results in contraction of the pelvic floor muscles and external sphincter muscles of the urethra (Lindstrom et al. 1984). On the other hand, afferent volleys induced by pudendal nerve stimulation caused neuromodulatory effects on overactive bladder via inhibition of the pelvic neurons and/or facilitation of hypogastric neurons in the spinal cord. Thus, urine incontinence in overactive bladder was markedly improved by an increase in maximum vesical capacity through a decrease in uninhibited contraction of the detrusor muscles (Ishigooka et al. 1994; Bosh and Grosen 1995; Shaker and Hassouna 1998). It has been reported that the same therapeutic effects were also obtained in the patients with refractory urine incontinence due to overactive bladder by ssES (Namima et al. 1999; Takahashi et al. 2001; Yokozuka et al. 2001). They described that ssES caused simultaneous stimulation of both efferent and afferent components of the pudendal nerve through the posterior sacral foramens from S2 to S4. Namely, ssES resulted in an increase in urethral pressure through activation of efferent fibers of the pudendal nerve while caused an increased in bladder volume by activation of its afferent fibers. They also described, however, that ssES might simultaneously stimulate the S2-4 pelvic nerves though higher voltage would be required for its activation because the fiber diameter of the parasympathetic pelvic nerve is considerably smaller than that of the somatic pudendal nerve.

In the present study, the same sacral area as in ssES for urine incontinence therapy was stimulated using a similar electrode and stimulation system. Therefore, it seems likely that ssES in the present study activated the afferent component of the pudendal nerve. Simultaneously, it may be difficult to exclude the possibility of direct pelvic nerve activation by ssES. Moreover, different from the bladder and bowel, the definite neural network model and its role in the spinal cord regulating uterine function are not still established. In addition, different speculations have been proposed as for the distribution and its function of the sympathetic hypogastric and parasympathetic pelvic nerves in the uterus. In some texts, it is described that the hypogastric nerve contracts the uterus and the pelvic nerve relax it while the others described the opposite. It is also mentioned that either sympathetic or parasympathetic efferent fibers distribute to the uterine body and relax the uterine smooth muscles (Sato et al. 1996). The present study was not performed to obtain enough data for speculating such neural mechanism of the uterus. Accordingly, it suffice to say that the suppression of static and dynamic contraction of the uterine smooth muscles by ssES might be achieved by neuromodulatory effects of the central and peripheral neural networks regulating uterine contraction via direct activation of

the anterior branches of spinal nerves from S2 to S4, i.e., the pudendal and pelvic nerves. This possible mechanism is thought to play an important role in the decrease in the myometrium thickness throughout all menstrual cycle phases and peristaltic movement during menstruation in the uterus.

The limitation of this study is thought that MR cine analysis using T1-weighted MR cine is not sufficient for analyzing dynamic changes of outer and inner myometrium layers independently. It was almost impossible for this method to examine the peristaltic movement of the junctional zone which was demonstrated by T2-weighted MR cine analysis (Masui et al. 2001; Kataoka et al. 2005). Further investigations will be conducted in due consideration of T2-weighted MR cine analysis.

In conclusion, this might be the first study which showed the static and dynamic changes of the uterine myometrium by ssES, i.e., a decrease in myometrium thickness throughout all menstrual cycle phases and, in the subjects with severe menstrual pain, weakening in peristaltic movement of the uterus during menstruation. MR imaging and MR cine techniques are powerful non-invasive tools for quantitative analysis of morphology and function of the internal organs.

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