Maternal and foetal physiological response of sacral surface electrical stimulation during pregnancy: a preliminaly study

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New Findings:

What is the central question of this study?

The physiological response to sacral neuromodulation by pregnant women and foetuses has not been previously explored.

What is the main finding and its importance?

Sacral surface electrical stimulation had no adverse effect on pregnant women and foetuses at least 36 weeks of gestation. It may cause uterine relaxation resulting from decreased uterine artery pulsatility index and increased umbilical venous flow volume and thereby improve utero-placental perfusion and improve lower back pain.

ABSTRACT

This study aimed to examine the impact of sacral surface electrical stimulation on maternal and foetal physiology during pregnancy. Ten pregnant women at 36 weeks of gestation without multiple gestations, foetuses with malformations, foetal growth restriction, hypertensive disorders, polyhydramnios, or oligohydramnios were enrolled. This prospective study monitored maternal and foetal physiological responses before and after sacral surface electrical stimulation for single pregnancies. Sacral surface electrical stimulation was performed once per patient. Each parameter was measured directly before and then immediately after stimulation. Follow-up measurements were conducted at 12 h, 1 day, 2 days and 7 days after stimulation. Variables of interest were compared before and after the stimulation. Regarding the foetal Doppler measurements, significant differences were not found in the umbilical and middle cerebral artery pulsatility index. However, foetuses showed a significant increase in the umbilical venous flow volume. The uterine contraction frequency and the maternal uterine artery pulsatility index significantly decreased. Pregnancy outcomes, and rates of caesarean section, foetal distress, and neonatal asphyxia were not confirmed. In conclusion, sacral surface electrical stimulation had no adverse effects on pregnant women or foetuses at 36 weeks of gestation and might improve utero-placental perfusion and lower back pain.

ABBREVIATIONS

ss-ES: Sacral surface electrical stimulation

IRB: Institutional review board

UA-PI: Foetal umbilical artery pulsatility index

MCA-PI: Middle cerebral artery pulsatility index

UVFV: Umbilical venous flow volume

Ut-PI: Uterine artery pulsatility index

CTG: Cardiotocography

VAS: Visual analogue scale

INTRODUCTION

The pelvic and genital organs receive innervation from the sympathetic nervous system through the hypogastric nerves and from the parasympathetic nervous system through the pelvic nerves. The preganglionic axons of the parasympathetic nerves arise from the S2–S4 spinal segments (Yokozuka et al., 2004). Electrical stimulation for neuromodulation at S2–S4 is considered effective for the treatment of disorders that affect the pelvic organs and pelvis, such as lower urinary tract dysfunction and urinary and faecal incontinence (Abello, 2018; Alavi et al., 2015; Damaser et al., 2015; Liu et al., 2017; Wang & Zhang, 2012; Wang et al., 2017). Some women have undergone electrical stimulation therapy even during pregnancy for these disorders. Sacral neuromodulation implantation was shown to be effective for pregnant patients with bladder dysfunction or faecal incontinence and caused no maternal or foetal adverse effects (Agnello et al., 2021; Mahran et al., 2017; Yaiesh et al., 2016); however, electrical stimulation using sacral neuromodulation implantation is invasive. Sacral surface electrical stimulation (ss-ES) of the skin over the posterior sacral foramen is a non-invasive method for neuromodulation of the S2–S4 area and has produced similar effects (Yokozuka et al., 2004).

The physiological response to sacral neuromodulation by pregnant women and foetuses has not been systematically investigated. Therefore, we investigated the impact of ss-ES, a non-invasive sacral neuromodulation method, on maternal and foetal physiology during pregnancy.

MATERIALS AND METHODS

Ethical Approval

Written informed consent was obtained from all patients who underwent ss-ES. We warrant that the experiments described in this manuscript comply with the provisions of the Declaration of Helsinki. This study was approved by the Institutional Review Board (IRB) of Shiga University of Medical Science Hospital (IRB numbers: 27-87). This study is registered in UMIN Clinical Trials Registry (ID: 000025247; URL: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000024322).

Participants

Ten women at 36-weeks of gestation, who were managed at the Shiga University of Medical Science Hospital between February and September 2016, were recruited for the study. We excluded patients with multiple gestations, foetuses with malformations, foetal growth restriction, hypertensive disorders, polyhydramnios, and oligohydramnios.

Interventions

The ss-ES method used was in accordance with a method previously reported (Ogura et al., 2006). Electrodes were placed on the

skin bilaterally and symmetrically above the posterior sacral foramina between S2 and S4, 4 cm below the Jacoby line as the upper edge border and the apex of the sacrum as the lower edge border of the treatment zone in the sitting position (Figure 1). Cyclic stimulation (5 s on /5 s off) was applied for 15 min. Bidirectional rectangular pulses (0.2 ms duration) were used, with a pulse train frequency of 3 Hz in each direction. The stimulation intensity was set to a level immediately below the pain threshold of each subject (Ogura et al., 2006). Stimulation was performed in a semi-fowler's position only once per patient. An IFCα1 prototype with a 5×9 cm electrode (Nihon Medix, Chiba, Japan) (Figure 2) was used for this study.

Parameter Measurement

The foetal umbilical artery pulsatility index (UA-PI), middle cerebral artery PI (MCA-PI), umbilical venous flow volume (UVFV), and maternal uterine artery PI (Ut-PI) were measured. All Doppler measurements were obtained by a single experienced operator using a Voluson E8 ultrasound system (GE Healthcare, Tokyo, Japan) with a wall motion filter of 60 Hz and a gate size fitting within the blood vessels, evaluating five or more consecutive waveforms while confirming by palpation that there was no uterine contraction. The UA-PI was measured at a free-floating portion of the cord. For the Ut-PI, we measured the placental and non-placental sides, and obtained the average of both values. The MCA-PI and UVFV were measured in the direction of blood flow at < 10° to obtain accurate blood flow velocity values. To determine the UVFV, the umbilical vein was identified in each patient, and its diameter and mean blood flow velocity in

113 the vertical direction were measured. The values adjusted for the estimated foetal body weights were also recorded.

114 Furthermore, cardiotocography (CTG) was performed and subjective evaluations of lower back pain were obtained using the
115 visual analogue scale (VAS) during interviews. Foetal heart rate monitoring and uterine contraction frequency (times/30 min) were
116 estimated from the CTG. Foetal heart rate monitoring results were classified as category I (normal), II (indefinite), or III (abnormal) in
117 accordance with the 2008 National Institute of Child Health and Human Development Guidelines (Macones et al., 2008). The values were
118 evaluated on a VAS scale from 0 to 10.

119 Each parameter was measured directly before and then immediately after stimulation. Follow-up measurements were conducted at
120 12 h, 1 day, 2 days and 7 days after stimulation. CTG was also performed during stimulation.

121 In addition, we recorded the number of days required until delivery after stimulation, the gestational week at delivery, mode of
122 delivery, birth weight, Apgar score, and the umbilical artery pH.

123 Foetal Doppler measurements, foetal heart rates, and pregnancy outcomes were assessed as foetal physiological influences.
124 Maternal Doppler measurements, uterine contraction frequencies, VAS measurements of lower back pain, and pregnancy outcomes were
125 assessed as maternal physiological influences.

126

Statistical Analysis

Repeated measures ANOVA was used to compare data collected before and after stimulation. In repeated measures ANOVA, significant values were adjusted by Bonferroni correction for the groups. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using Easy R (EZR, the R Foundation for Statistical Computing, Vienna, Austria) for Windows (Kanda, 2013).

RESULTS

Ten pregnancies were analysed. Demographic data, characteristics, and pregnancy outcomes are shown in Table 1. The mean gestational age at delivery was 38.5 weeks; all pregnancies had vaginal deliveries. The mean Apgar score for 1 min and 5 min was 8.33 and 9.16, respectively, and the mean umbilical artery pH was 7.30. Foetal distress and neonatal asphyxia were not observed (Table 1). There were no cases of neonatal intensive care unit admission and respiratory support, the progress of all cases was good, and there was no problem found with both mothers and children on medical examination at 1-month follow up.

Table 1. Demographics, characteristics, and pregnancy outcomes of women who underwent sacral surface electrical stimulation.

Parameter	ss-ES

	(n = 10)
Age (years)[a]	32.7 ± 3.52
BMI (kg/m^2)[a]	20.2 ± 2.28
Primipara (%)	50 (5/10)
Days until delivery (days)[a]	16.8 ± 13.18
GA at delivery (weeks)[a]	38.5 ± 1.80
Vaginal delivery (%)	100 (10/10)
Birth weight (g)[a]	3079 ± 372
Apgar score (1 min)	8.33 ± 0.51
Apgar score (5 min)	9.16 ± 0.75
Umbilical artery pH[a]	7.30 ± 0.04

[a]Data are expressed as mean ± SD.

ss-ES, sacral surface electrical stimulation; BMI, body mass index; GA, gestational age; SD, standard deviation

Regarding lower back pain, we analysed seven cases with symptom. Some parameters could not be measured because of delivery or

146 foetal position. The measured parameters are shown in Figure 3-8.

147 No statistical differences were observed for the following foetal Doppler measurements: UA-PI ($p = 0.277$) (Figure 3 and Table 2)
148 and MCA-PI ($p = 0.895$) (Figure 4 and Table 2). However, a significant difference was observed for UVFV ($p = 0.013$); the value was
149 significantly higher immediately ($p < 0.001$) and 12 h ($p = 0.018$) after stimulation than before stimulation (Figure 5 and Table 2).

150 Regarding the maternal Doppler measurements, a statistical difference was observed for Ut-PI ($p < 0.001$); Ut-PI was significantly
151 lower immediately ($p = 0.020$) and 12 h ($p = 0.018$) after stimulation compared with before stimulation (Figure 6 and Table 2).

152 The CTG measurement of foetal heart rate showed that category I (normal) heart rate was consistently observed; category II
153 (indefinite) and category III (abnormal) heart rates were not observed at any time point.

154 A statistical difference was observed for uterine contraction frequency ($p < 0.001$); significant decreases in uterine contractions
155 were observed in the periods from before stimulation to immediately ($p = 0.029$), 1 day ($p = 0.002$), and 2 days ($p = 0.003$) after
156 stimulation (Figure 7 and Table 2).

157 A statistical difference was observed for the VAS scores of lower back pain ($p = 0.006$); significant decreases were observed
158 between before stimulation and 12 h ($p = 0.024$), 1 day ($p = 0.006$), 2 days ($p = 0.038$), and 7 days ($p = 0.005$) after stimulation (Figure 8
159 and Table 2).

160

161 Table 2. Comparisons of maternal and fetal blood flow velocities, uterine contraction frequency, and lower back pain.

	Before ss-ES	After ss-ES	*p* value	12 h	*p* value	1 day	*p* value	2 days	*p* value	7 days	*p* value
UA-PI *p* = 0.277	0.71 ± 0.11	0.68 ± 0.09	1	0.75 ± 0.14	1	0.69 ± 0.09	1	0.78 ± 0.11	0.30	0.75 ± 0.08	1
MCA-PI *p* = 0.895	1.68 ± 0.30	1.80 ± 0.31	1	1.81 ± 0.35	1	1.81 ± 0.31	1	1.70 ± 0.19	1	1.92 ± 0.36	1
UVFV (ml/min) *p* = 0.013	171.18 ± 58.32	244.03 ± 62.06	<0.001	211.87 ± 64.91	0.018	170.61 ± 69.78	1	164.14 ± 31.57	1	172.91 ± 19.66	1
Ut-PI *p* < 0.001	0.69 ± 0.18	0.61 ± 0.19	0.020	0.52 ± 0.06	0.018	0.52 ±0.08	0.214	0.56 ± 0.10	0.191	0.71 ± 0.21	1
UC (times/30 min) *P* < 0.001	9.90 ± 3.17	5.10 ± 2.46	0.029	6.00 ± 2.00	0.199	2.62 ± 1.92	0.002	1.87 ± 1.55	0.003	4.00 ± 3.09	0.231

Lower back pain (VAS 1–10) $p = 0.006$	3.42 ± 1.27	2.57 ± 1.39	1	1.14 ± 0.89	0.024	0.50 ± 0.54	0.006	0.40 ± 0.54	0.038	1.50 ± 1.73	0.005

A one-way repeated measures ANOVA was used to compare the data between groups, and significant values were adjusted using Bonferroni correction for the groups; Data are expressed as mean ± SD.

ss-ES, sacral surface electrical stimulation; UA-PI, umbilical artery pulsatility index; MCA, middle cerebral artery; UVFV, umbilical venous flow volume; Ut, uterine artery; UC, uterine contraction; VAS, visual analogue scale; SD, standard deviation.

We observed no significant adverse events, including skin conditions such as inflammation and redness, after stimulation.

DISCUSSION

We believe that this study was the first to investigate the impact of ss-ES on maternal and foetal physiology during pregnancy. Most importantly, this study demonstrated that ss-ES generated no harmful effect on pregnant women and foetuses at 36 weeks of gestation.

Hypoxia associated with placental insufficiency during pregnancy can affect foetal pulse Doppler findings due to the brain-sparing mechanism; MCA-PI and UA-PI have been shown to decrease and increase, respectively (Cheema et al., 2006). Moreover, CTG reflects

the present foetal condition (Macones et al., 2008). We found no statistical differences in terms of foetal UA-PI and MCA-PI; only category I (normal) foetal heart rates were observed. Therefore, ss-ES had no direct adverse effects on placental function or foetuses.

Regarding pregnancy outcomes, foetal distress and neonatal asphyxia were not confirmed. No pregnancies required caesarean sections. Therefore, there were no adverse effects on the foetuses in the short term or the long term prior to delivery. In addition, although the long-term prognosis could not be evaluated, but there were no obvious findings suggestive of brain damage at short-term evaluation.

Regarding maternal physiological effects, this study showed that ss-ES causes uterine relaxation during pregnancy. The ss-ES in non-pregnant patients has previously been reported to cause uterine relaxation during the menstrual period and the luteal phase of the menstrual cycle (Fujii et al., 2008; Ogura et al., 2006). The uterine muscle relaxation effects have also been shown to last for 2–4 days after single treatment sessions of the uteri of non-pregnant women (Ogura et al., 2006). In this study, all participants had histories of threatened premature labour; one patient delivered 1 day after stimulation and another patient delivered 3 days after stimulation. However, the other patients had significant decreases of uterine contraction frequency. Although the uterine relaxation mechanism is unclear, ss-ES is believed to facilitate the strengthening of the pelvic floor muscles, increase urethral pressure through activation of efferent fibres of the pudendal nerve, and cause an increase in bladder volume by activation of its afferent fibres (Alavi et al., 2015; Liu et al., 2017; Yokozuka et al., 2004). It has been reported that electrical stimulation of sacral spinal nerves also increases intra-rectal pressure and closure pressure of the anal canal (Damaser et al., 2015). Ss-ES can be a potential treatment for threatened premature labour.

The use of ss-ES also significantly improved lower back pain in patients for up to 7 days. Transcutaneous electrical nerve stimulation, an alternative therapy that differs from sacral neuromodulation in terms of stimulation location and method, has been reported to be as effective as acetaminophen for lower back pain during pregnancy, without affecting neonatal outcomes (Keskin et al., 2012). The possible mechanism of action is that electrical pulses stimulate the nerve pathways in the spinal cord, thereby blocking pain transmission (Keskin et al., 2012); this mechanism may also explain the pain-relieving effects of ss-ES. Many pregnant women have severe lower back pain that interferes with ordinary daily activities, exercise, rest, pelvic belts, compresses and acetaminophen often does not provide a therapeutic effect (Liddle & Pennick, 2015). Ss-ES can be a potential treatment for lower back pain during pregnancy.

These results show that administering ss-ES to pregnant women with gestation periods of at least 36 weeks might be safe based on physiological and biological clues. Electrical stimulation of the bilateral S1 dorsal roots in rats, where the parasympathetic nerves are located, showed no adverse effects on pregnant rats and foetuses (Wang & Hassouna, 1999). Two reviews (Mahran et al., 2017; Yaiesh et al., 2016) and one case series(Agnello et al., 2021) reported the use of sacral neuromodulation in pregnant patients with bladder dysfunction or faecal incontinence (Agnello et al., 2021; Mahran et al., 2017; Wang & Hassouna, 1999; Yaiesh et al., 2016) are consistent with the current study.

The current study suggests potential value for the use of ss-ES treatment of pregnant women. The use of ss-ES might decrease Ut-PI and uterine contraction frequency and temporarily increase UVFV, based on the measurement times used for evaluation of the technique

205 in this study. Uterine contractions cause a significant reduction in placental perfusion (Sinding et al., 2016), and a high Ut-PI has previously
206 been associated with utero-placental vascular insufficiency (Levytska et al., 2017). UVFV, which reflects vascular placental function, was
207 shown in that study to increase after ss-ES (Parra-Saavedra et al., 2013). Therefore, we speculate that the uterine relaxation caused by ss-ES
208 resulted in decreased Ut-PI, increased UVFV, and improved utero-placental perfusion. As the association between foetal hypoxia due to
209 impaired utero-placental perfusion and foetal growth restriction is well known (Moran et al., 2015), ss-ES might be a potential future
210 treatment for foetal growth restriction related to placental factors that cause foetal hypoxia (Pollack & Divon, 1992).
211 This is a preliminary study and therefore has several limitations. The sample size was small, ss-ES was performed only once per
212 patient, and a single gestational age group was evaluated. Therefore, we need to investigate foetal and maternal physiological changes that
213 may occur with multiple administrations of ss-ES at other gestational intervals. However, we reported this data because significant
214 differences were confirmed in this study. This study showed that ss-ES had no adverse effects on pregnant women or foetuses in the short
215 term at 36 weeks of gestation, although this was observed in a few cases. Moreover, ss-ES might cause decreased Ut-PI and increased
216 UVFV as the result of uterine relaxation and thereby improve utero-placental perfusion and improve lower back pain. In addition, ss-TES is
217 inexpensive and can be easily performed in an outpatient. Therefore, in the future, ss-TES might be a useful treatment in the management
218 of threatened premature labour, foetal growth restriction and lower back pain. However, this preliminary study is insufficient to clarify the

safety and efficacy of ss-ES during pregnancy; hence, further clinical research is necessary.

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Competing Interests

The authors declare no conflicts of interest.

Data Availability Statement

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

DK and TM designed and planned the study; DK wrote and managed the manuscript; DK, ST, KH, ST, TH, NK and TM contributed to sections of the manuscript; and DK and TM conducted data analysis.

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FIGURE LEGENDS

Figure 1. The pasting position of Electrodes.

Electrodes were placed on the skin bilaterally and symmetrically above the posterior sacral foramina between S2 and S4, 4 cm below the Jacoby line as the upper edge border and the apex of the sacrum as the lower edge border of the treatment zone.

Figure 2. An IFCα1 prototype (Nihon Medix, Chiba, Japan).

Main body and dedicated stand.

Figure 3. Comparison of UA-PI before and immediately after stimulation and 12 h, 1 day, 2 days and 7 days after ss-ES.

Comparison of data before and after the stimulation with repeated measures ANOVA. ss-ES, sacral surface electrical stimulation; UA-PI, umbilical artery pulsatility index.

Figure 4. Comparison of MCA-PI before and immediately after stimulation and 12 h, 1 day, 2 days and 7 days after ss-ES.

Comparison of data before and after the stimulation with repeated measures ANOVA. ss-ES, sacral surface electrical stimulation; MCA-PI, middle cerebral artery pulsatility index.

315

316 Figure 5. Comparison of UVFV (ml/min) before and immediately after stimulation and 12 h, 1 day, 2 days and 7 days after ss-ES.

317 Comparison of data before and after the stimulation with repeated measures ANOVA. ss-ES, sacral surface electrical stimulation; UVFV,

318 umbilical venous flow volume.

319

320 Figure 6. Comparison of Ut-PI before and immediately after stimulation and 12 h, 1 day, 2 days and 7 days after ss-ES.

321 Comparison of data before and after the stimulation with repeated measures ANOVA. ss-ES, sacral surface electrical stimulation; Ut-PI,

322 uterine artery pulsatility index.

323

324 Figure 7. Comparison of UC (times/30 min) before and immediately after stimulation and 12 h, 1 day, 2 days and 7 days after ss-ES.

325 Comparison of data before and after the stimulation with repeated measures ANOVA. ss-ES, sacral surface electrical stimulation; UC, uterine

326 contraction.

327

328 Figure 8. Comparison of lower back pain (VAS) before and immediately after stimulation and 12 h, 1 day, 2 days and 7 days after ss-ES.

329 Comparison of data before and after the stimulation with repeated measures ANOVA. ss-ES, sacral surface electrical stimulation; VAS, visual

analogue scale.