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Pregnancy Does Not Enhance Volatile Anesthetic Sensitivity on the Brain

An Electroencephalographic Analysis Study

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ABSTRACT

Backgrounds: Parturients are thought to be more sensitive to inhalational anesthetics because their minimum alveolar concentration is decreased. However, this conventional theory may be wrong, because, according to recent animal studies, minimum alveolar concentration indicates anesthetic effect on the spinal cord but not on the brain. The aim of this electroencephalographic study was to investigate the differences in the hypnotic effect of sevoflurane on parturients and nonpregnant patients.

Methods: Fifteen parturients undergoing cesarean section and 15 patients undergoing elective gynecologic surgery were enrolled. Anesthesia was induced with 4 mg/kg thiopental, 2 μg/kg fentanyl, and 2 mg/kg suxamethonium or 0.15 mg/kg vecuronium. Anesthesia was maintained with sevoflurane and fentanyl. The electroencephalographic signals, obtained from the bispectral index monitor, were recorded on a computer. We calculated 95% spectral edge frequency, amplitude, and bicoherence using custom software (Bispectrum Analyzer for bispectral index). After confirming that end-tidal sevoflurane had reached equilibrium, we measured electroencephalographic parameters of sevoflurane at 2.0 and 1.5% during surgery and at 1.0 and 0.5% after surgery.

Results: With the decrease of end-tidal sevoflurane concentration from 2.0 to 0.5%, 95% spectral edge frequency, amplitude, bispectral index, and bicoherence values changed dose-dependently in pregnant and nonpregnant women ($P < 0.0001$). However, there were no significant differences in those electroencephalographic parameters in pregnant and nonpregnant women.

Conclusions: This electroencephalographic study has shown that pregnancy does not enhance hypnotic effect of sevoflurane. These results suggested that the decrease in minimum alveolar concentration during pregnancy does not mean an enhanced volatile anesthetic effect on the brain.

What We Already Know about This Topic

- Minimum alveolar concentration (MAC) is decreased during pregnancy
- The incidence of intraoperative awareness is increased during cesarean section.

What This Article Tells Us That Is New

- No differences in electroencephalographic measures during sevoflurane anesthesia were found between end-term pregnant and nonpregnant patients.
- MAC may not be a correlate of anesthetic depth.

THE application of light general anesthesia has been encouraged in cesarean section to avoid neonatal depression and uterine atony,[1] because the supposition has been that minimum alveolar concentration (MAC) decreases during pregnancy. In 1974, Palahniuk and Shnider[2] found that MAC of halothane, methoxyflurane, and isoflurane in pregnant ewes decreased by 25–40% compared with that in nonpregnant ewes. From this finding, they proposed that parturients require a smaller amount of volatile anesthetics than do nonpregnant women. Thereafter, a 30% decrease in MAC of volatile anesthetics was identified in first trimester parturients.[3] The incidence of intraoperative awareness during cesarean section has been reduced by the improvement of anesthesia technique.[1] However, the incidence of intraoperative awareness during cesarean section performed under general anesthesia is still 0.4%,[4] which is

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higher than the rate in nonpregnant women undergoing general anesthesia for surgeries (0.2%).[5] Thus, patients undergoing cesarean section may have increased risk of intraoperative awareness, as occurs in patients having cardiac surgery and trauma surgery. However, it remains unknown why intraoperative awareness occurs commonly in parturients despite the fact that their MAC is low and anesthetic sensitivity is high.

MAC still does indicate anesthetic efficacy, but for movement,[6] however, this established theory has recently been challenged. Rampil *et al.*[7] showed no change in MAC before and after the removal of the forebrain in mice. Antognini *et al.*[8,9] reported a MAC of 0.8% in goats that had been administered isoflurane in the lower body using separate extracorporeal circulation, but a MAC of 2.9% (*i.e.*, greater than 3-fold increase) when isoflurane had been selectively given to the brain. These results suggest that the anesthetic efficacy indicated by MAC mainly reflects its effect on the spinal cord, not on the brain. Therefore, it is likely that MAC is not a good indicator of unconsciousness or amnesia. If the sensitivity to inhalational anesthetics on the brain is not enhanced by pregnancy, current general anesthetic procedures in cesarean section should be reviewed.

According to the current definition of anesthetic depth, anesthesia consists of hypnosis and analgesia.[10] Intravenous and inhalational anesthetics induce hypnosis, whereas opioid and local anesthetics induce analgesia.[10] Electroencephalographic monitoring techniques during anesthesia, such as the bispectral index (BIS), are considered an indicator of the hypnotic effect of volatile and intravenous anesthetics on the brain.[10] In patients who are awake, the electroencephalogram usually consists of low-amplitude fast waves. Clinical doses of volatile anesthetics induce dose-dependent decreases in the electroencephalogram frequency and the BIS and dose-dependent increases in the amplitude and bicoherence as a result of phase consistency (*i.e.*, enhanced synchrony).[11–13] In this study, electroencephalograms were obtained from parturients during cesarean section and from nonpregnant women during gynecological abdominal surgery at 2.0 to 0.5% sevoflurane expiratory concentrations. By comparing the electroencephalographic parameters in the two groups, we investigated whether a decreased MAC in parturients indicates an enhanced anesthetic effect on the brain or not.

Materials and Methods

Patients

The subjects were 15 full-term pregnant patients (aged 23 to 38 yr) who underwent a scheduled cesarean section under general anesthesia (pregnant group) and 15 patients (aged 21 to 41 yr) who underwent a scheduled gynecological surgery (nonpregnant group). All of the patients gave written informed consent and were approved by the institutional review board (Osaka University Hospital, Suita, Osaka, Japan). All of the patients had an American Society of Anesthesiologists physical status of I or II. Patients with a history of mental or neurologic disorders and patients treated with central nervous system drugs, such as sedatives and antidepressants, were excluded. Patients with multiple-fetus pregnancies, placenta previa, or other complications were also excluded. The pregnant group consisted of seven patients with idiopathic thrombocytopenia purpura: five were treated with steroids before surgery; four were given heparin for thrombosis in the lower extremity before surgery; two refused spinal anesthesia; and two patients has a history of spinal surgery. The nonpregnant group consisted of seven patients undergoing myomectomy, five patients undergoing ovarian cystectomy, and three patients undergoing hysterectomy. Patients who underwent laparoscopic surgery were excluded. For intraoperative monitoring, we used electrocardiogram, noninvasive blood pressure, pulse oximetry, and a respiratory monitor (M2360A; Hewlett Packard, Palo Alto, CA).

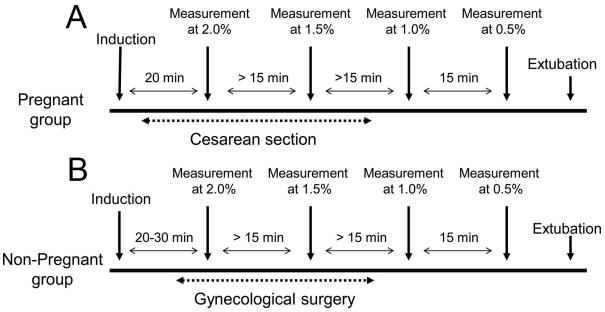

Fig. 1. A schematic summary of the study protocol in pregnant group (*A*) and nonpregnant group (*B*). Electroencephalographic measurements at sevoflurane concentration of 2.0 and 1.5% were done during surgery and at 1.0 and 0.5% after surgery.

Anesthetic Protocols

Pregnant Group (Cesarean Section). No premedication, except 150 mg of ranitidine orally the night before and on the morning of surgery, was administered. After preoxygenation, rapid-sequence induction with cricoid pressure was performed using 4 mg/kg thiopental, 2 μg/kg fentanyl, and 0.15 mg/kg vecuronium, or 2 mg/kg suxamethonium. After tracheal intubation, the patient was placed on mechanical ventilation with sevoflurane at an end-tidal concentration of 3% in 4 l of air and 2 l of oxygen. End-tidal carbon dioxide concentration was maintained between 30 and 35 mmHg. Immediately after tracheal intubation, cesarean section was started. After tracheal intubation, 3.0% sevoflurane was administered for 10 min, followed by 2 to 2.5% sevoflurane for 10 min to maintain end-tidal sevoflurane concentration at 2.0%. After that, 1.5 to 2.0% sevoflurane was administered to maintain end-tidal sevoflurane concentration at 1.5% for 15 min. The electroencephalographic parameters were recorded at the end of the 2.0 and 1.5% sevoflurane administration periods (fig. 1A). Nitrous oxide was not given. Patients who were given suxamethonium were administered 4 to 6 mg vecuronium after delivery. Immediately after delivery, 5 units of intravenous oxytocin and 2 μg/kg intravenous

fentanyl was administered for 5 min. We also administered 1 μg/kg additional fentanyl every 30 min during operation. Patients with hypotension were treated with intravenous ephedrine. After completion of surgery, we administered sevoflurane at expiratory concentrations of 1.0 and 0.5% for 15 min at each concentration (fig. 1A). Electroencephalographic parameters were recorded at the end of the 1.0 and 0.5% sevoflurane administration periods. Sevoflurane administration protocol was obtained from computer simulation using the software Gas Man® (Med Man Simulations, Boston, MA).

Nonpregnant Group (Gynecological Surgery). No premedication, except 150 mg of ranitidine orally the night before and on the morning of surgery, was administered. After establishing an intravenous route, 4 mg/kg thiopental, 2 μg/kg fentanyl, and 0.15 mg/kg vecuronium were administered for induction of general anesthesia. After tracheal intubation, sevoflurane, fractional inspired oxygen tension, and end-tidal carbon dioxide were maintained in the same manner as the cesarean section group. Surgery was started 10 to 15 min after tracheal intubation in all patients. We administered 2 μg/kg fentanyl before incision, and an additional 1 μg/kg fentanyl was given every 30 min during the operation. Electroencephalographic parameter recording was also performed at the end of the 2.0 and 1.5% sevoflurane administration period (fig. 1B). Patients with hypotension during surgery were treated with intravenous ephedrine. After completing surgery, sevoflurane was administered at an expiratory concentration of 1.0 and 0.5% for 15 min (fig. 1B). Electroencephalographic parameters were recorded at the end of each sevoflurane administration period.

Electroencephalographic Monitoring

For electroencephalographic recordings, we used the BIS® A-1050 monitor (Aspect Medical Systems, Natick, MA). Three-point electroencephalographic sensors were attached to the forehead. Automatic electrode impedance check was done in all subjects. Raw data, including electroencephalographic waveforms, BIS, and other parameters, were obtained from the BIS A-1050 monitor *via* a RS232 cable connected to a laptop computer and analyzed with custom software (Bispectrum Analyzer for BIS).[12,13] Using this software, we calculated the 95% spectral edge frequency (SEF95), amplitude, and bicoherence. Bicoherence is an indicator of electroencephalographic synchrony, and volatile anesthetics are known to increase the peak heights of bicoherence at 3–5 Hz (pBIC-low) and 5–10 Hz (pBIC-high) in a dose-dependent manner.[12,13] In this study, to evaluate the difference in response to sevoflurane, we compared the changes in electroencephalographic parameters (SEF95, amplitude, BIS, and bicoherence) in the pregnant and nonpregnant women at sevoflurane concentrations of 2.0 to 0.5%.

Statistical Analysis

A pilot study was performed in 10 patients (n = 5 for each group). The pilot study showed that BIS has a larger SD (50 ± 9 at 1.5% sevoflurane in nonpregnant group) than the other parameters (SEF and amplitude). Based on BIS data from the pilot study, a sample size of 13.75 in each group was considered to have 80% power to detect a difference in means of 20% (specifically, because BIS value mean in nonpregnant women was 50, the difference in mean was 10), assuming that the common SD was 9 using a two-group *t* test with a 0.05 two-sided significance level. Consequently, the number of subjects was specified to 15 patients per group. The patient characteristics, including age, height, weight, surgical time, and hemodynamic data, were compared using an unpaired *t* test. SEF95, amplitude, BIS value and bicoherence (pBIC-low and pBIC-high) at 2.0% to 0.5% concentrations of sevoflurane were analyzed by a two-way analysis of variance. The model included the main effects, group (pregnant/nonpregnant), and sevoflurane concentration (0.5, 1, 1.5, or 2%), and their interaction. These electroencephalographic parameters in the two groups were also compared using an unpaired *t* test. A *P* value of less than 0.05 was considered statistically significant (two-sided). All statistical analysis were performed by SAS Release 9.2 (SAS Institute Inc., Cary, NC).

Table 1. Patient Characteristics

Characteristic	Pregnant Group (n = 15)	Nonpregnant Group (n = 15)	*P* Value
Age (yr)	31 ± 6	32 ± 4	0.52
Height (cm)	160 ± 5	159 ± 5	0.72
Weight (kg)	64.5 ± 7.0	58 ± 8	0.78*
(Weight before pregnancy (kg))	(59 ± 8)	—	—
Gestational age (wk)	39 ± 0.4	—	—
Surgical time (min)	71 ± 17	77 ± 23	0.43

Data are expressed as mean ± SD.

* *P* value between weight before pregnancy in pregnant group and weight in nonpregnant group.

Results

The patient's characteristics are shown in table 1. No significant differences between the pregnant and nonpregnant groups were found in age, height, and nonpregnant weight. Maternal and neonatal data are shown in table 2. Table 3 shows the hemodynamic data in each group. In the pregnant group, heart rate was significantly higher than in the nonpregnant group ($P < 0.01$) during study period. The average ephedrine doses for treatment of hypotension in the nonpregnant and pregnant groups were 6.3 ± 2.5 (n = 4) and 7.0 ± 2.7 mg (n = 5), respectively. Seven parturients were given suxamethonium at induction of general anesthesia.

Typical electroencephalographic waveforms of the two groups are shown in figure 2. There was no problem in the quality of electroencephalographic signals in the two groups. The signal quality index was 0.8 or higher. Reducing the sevoflurane concentration in 0.5 percentage point increments (from 2.0 to 0.5%) decreased the electroencephalographic amplitude and increased the electroencephalographic frequency in both groups.

Table 2. Maternal and Neonatal Data

Maternal Data	n = 15
Uterine Incision Delivery Time (s)	91 ± 43
Blood Loss with Amniotic Fluid (ml)	1,130 ± 480
Umbilical A	
pH	7.32 ± 0.07
Pao_2 (mmHg)	27 ± 8.6
$Paco_2$ (mmHg)	52 ± 4.3
Base Excess (mM)	−1.1 ± 1.7
Apgar scores at 1 min	
8–10	10
<8	5
Apgar scores at 5 min	
8–10	13
<8	2

Data are expressed as mean ± SD except for Apgar scores.

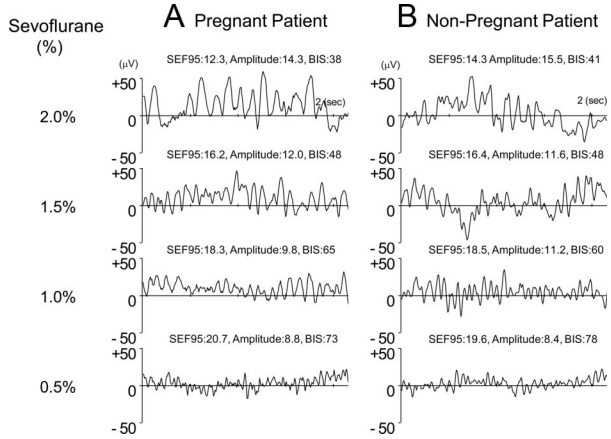

Fig. 2. The typical electroencephalographic wave forms at 2.0, 1.5, 1.0, and 0.5% sevoflurane concentration in the pregnant (*A*) and nonpregnant (*B*) groups. The reduction in sevoflurane concentration from 2.0 to 0.5% changes electroencephalograms from a high-amplitude slow wave to a low-amplitude fast wave. BIS bispectral index; SEF95 = 95% spectral edge frequency.

Table 4 shows the electroencephalographic parameters and the differences between the two groups at 2.0, 1.5, 1.0, and 0.5% sevoflurane concentrations. Figures 3, 4, and 5 show the changes in SEF95, amplitude, and BIS value at 2.0 to 0.5% sevoflurane concentrations, respectively. In the pregnant group, the reduction in sevoflurane concentration in 0.5 percentage-point decrements from 2.0 to 0.5% caused changes in the frequency, the BIS, and the amplitude. To be specific, SEF95 increased from (mean ± SD) 13.8 ± 2.2 to 19.7 ± 2. 6 Hz, the BIS increased from 40.7 ± 6.7 to 79.2 ± 6.2, and the amplitude reduced from 14.6 ± 2.8 to 7.6 ± 0.7 μV. In addition, in the nonpregnant group, the SEF95 increased from 13.4 ± 1.5 to 21.0 ± 2.7 Hz, the BIS increased from 37.8 ± 5.6 to 82.4 ± 6.7, and the amplitude reduced from 15.1 ± 2.4 to 7.1 ± 0.8 μV.

pBIC-low and pBIC-high (which indicate electroencephalographic synchrony) were 33.3 ± 7.7 and 37.9 ± 7.3, respectively, at 2.0% sevoflurane concentration in the pregnant group. They decreased to 20.7 ± 5.9 and 19.6 ± 6.2, respectively, at 0.5%. In the nonpregnant group, pBIC-low and pBIC-high were 36.4 ± 9.2 and 40.8 ± 6.8 at 2.0% sevoflurane concentration. This decreased to 17.3 ± 6.3 and 20.2 ± 6.2, respectively, at 0.5%.

The results of two-way analysis of variance showed that sevoflurane concentration effect was significant ($P < 0.0001$) for each electroencephalographic parameter (table 5). However, the group effect (pregnant/nonpregnant) and the interaction were not significant for each electroencephalographic parameter (table 5). The unpaired *t* test also showed that electroencephalographic parameters in the pregnant and nonpregnant groups at each sevoflurane concentration were not significantly different (table 4). These results imply that each electroencephalographic parameter changed dose-dependently according to sevoflurane concentration but was unaffected by pregnancy.

A BIS value greater than 60 at 1.5% sevoflurane concentration was observed in two patients (one each from the pregnant and nonpregnant groups). A BIS value greater than 60 at 1.0% sevoflurane concentration was observed in 10 patients from the nonpregnant group and 8 patients from the pregnant group. The patients from the two groups were interviewed on surgery day and the following day but none had intraoperative memory.

Discussion

During non–rapid eye movement sleep, as the stages of sleep progress, the electroencephalogram pattern changes from a low-amplitude fast wave to a high-amplitude slow wave.[14]

Table 3. Hemodynamic Data

Groups	Sevoflurane (%)				
	Control	2.0	1.5	1.0	0.5
Pregnant (n = 15)					
MBP (mmHg)	85.8 ± 8.2	95.3 ± 12.0	84.3 ± 10.3	81.0 ± 8.5	83.4 ± 12.3
HR (beats/min)	88.3 ± 16.7*	93.2 ± 14.3*	92.2 ± 13.3*	87.3 ± 10.2*	88.3 ± 11.2*
Nonpregnant (n = 15)					
MBP (mmHg)	87.2 ± 11.8	97.2 ± 11.5	85.3 ± 12.8	80.3 ± 7.8	80.2 ± 10.4
HR (beats/min)	73.2 ± 11.3	77.3 ± 13.5	72.3 ± 11.7	69.5 ± 10.5	71.5 ± 12.0

Data are mean ± SD.

* Significant difference from nonpregnant group ($P < 0.01$).

HR = heart rate; MBP = mean blood pressure.

Table 4. The Electroencephalographic Parameters and the Differences between Two Groups at 2.0, 1.5, 1.0, and 0.5% Sevoflurane Concentrations

Parameters and Sevoflurane Concentration	Pregnant Group (n = 15)	Nonpregnant Group (n = 15)	Difference	*P* Value
SEF95				
2%	13.8 ± 2.2Hz	13.4 ± 1.5Hz	−0.5	0.515
1.5%	16.1 ± 1.9Hz	16.5 ± 2.3Hz	0.4	0.571
1.0%	18.3 ± 3.0Hz	19.8 ± 2.3Hz	1.6	0.122
0.5%	19.7 ± 2.6Hz	21.0 ± 2.7Hz	1.4	0.179
Amplitude				
2%	14.6 ± 2.8μV	15.1 ± 2.4μV	0.5	0.579
1.5%	12.1 ± 2.0μV	12.7 ± 2.1μV	0.5	0.489
1.0%	9.5 ± 2.2μV	9.1 ± 1.4μV	−0.4	0.538
0.5%	7.6 ± 0.7μV	7.1 ± 0.8μV	−0.4	0.123
BIS				
2%	40.7 ± 6.7	37.8 ± 5.6	−2.9	0.211
1.5%	48.5 ± 8.4	50.2 ± 7.4	1.8	0.544
1.0%	59.5 ± 8.9	62.4 ± 5.0	2.9	0.277
0.5%	79.2 ± 6.2	82.4 ± 6.7	3.3	0.180
pBIC-Low				
2%	33.3 ± 7.7	36.4 ± 9.2	3.1	0.313
1.5%	30.3 ± 8.8	35.1 ± 10.9	−0.1	0.266
1.0%	24.6 ± 6.8	24.5 ± 9.7	4.8	0.969
0.5%	20.7 ± 5.9	17.3 ± 6.3	−3.3	0.142
pBIC-High				
2%	37.9 ± 7.3	40.8 ± 6.8	3.0	0.253
1.5%	37.8 ± 7.0	41.6 ± 6.9	3.8	0.146
1.0%	28.3 ± 12.0	29.3 ± 10.3	1.0	0.816
0.5%	19.6 ± 6.2	20.2 ± 6.2	0.5	0.842

Data are expressed as mean ± SD. There were no significant differences between the groups as determined by unpaired *t* test.
BIS = bispectral index; pBIC-high = peak heights of bicoherence at 5–10 Hz; pBIC-low = peak heights of bicoherence at 3–5 Hz; SEF95 = 95% spectral edge frequency.

Patients given volatile anesthetics at clinical concentration also reveal a similar electroencephalographic pattern. Therefore, the level of hypnosis can be presumed from these anesthetic-induced electroencephalographic changes.[10] From this aspect, electroencephalogram is thought to be a reliable monitor of the hypnotic effects of anesthetics.

In our study, values for the electroencephalographic parameters SEF95, amplitude, BIS, and bicoherence changed in a dose-dependent manner in the 2.0% to 0.5% sevoflurane concentration range in both the pregnant and nonpregnant groups. If pregnancy enhances the hypnotic effect of volatile anesthetics, electroencephalographic parameters of the pregnant group at respective sevoflurane concentrations would be expected to change more significantly than in the nonpregnant group. However, no significant differences were found in the SEF95, amplitude, BIS, and bicoherence values in the two groups.

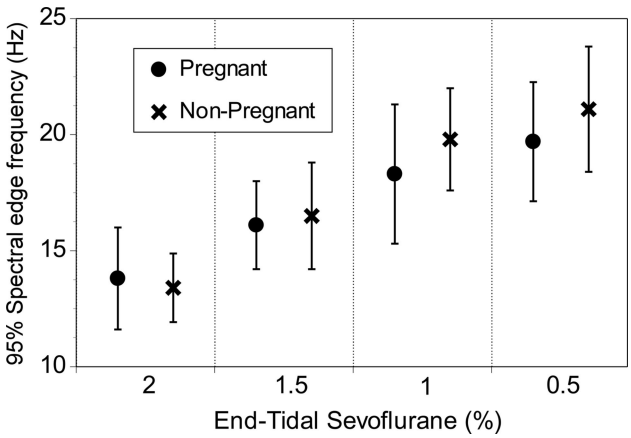

Fig. 3. 95% Spectral edge frequency at 2.0, 1.5, 1.0, and 0.5% sevoflurane concentrations in the pregnant and nonpregnant groups. Data are mean values with SD. There was no significant difference between groups.

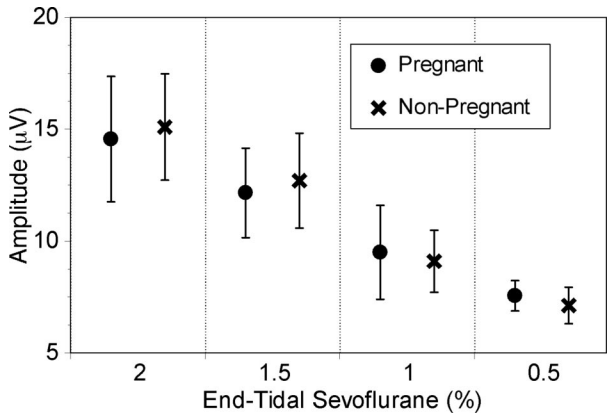

Fig. 4. Amplitude at 2.0, 1.5, 1.0, and 0.5% sevoflurane concentrations in the pregnant and nonpregnant groups. Data are mean values with SD. There was no significant difference between groups.

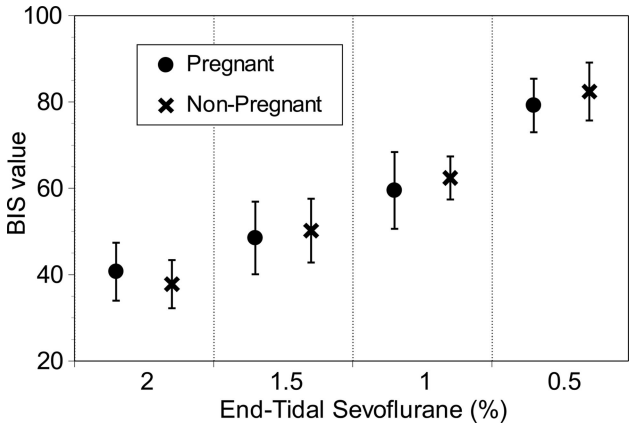

Fig. 5. Bispectral index (BIS) value at 2.0, 1.5, 1.0, and 0.5% sevoflurane concentrations in the pregnant and nonpregnant groups. Data are mean values with SD. There was no significant difference between groups.

Because sample size calculation was designed on the assumption of detecting 20% differences in mean value between two groups, we could have missed differences under 20%. In clinical studies, evaluating the difference often provides more information than statistical significance testing. Actually, the observed differences between electroencephalographic parameters in the two groups at each sevoflurane concentration were all less than the SD (table 4). Therefore, we believe that there are no clinically significant differences between the two groups. This consequently suggests that there is no important difference in the hypnotic effect of sevoflurane in pregnant and nonpregnant women.

Table 5. Results of Two-way Analysis of Variance

Parameter & Effect	NDF	DDF	*F*	*P* Value
SEF95				
Group	1	112	2.83	0.0953
Sevoflurane	3	112	49.17	< 0.0001
Group·Sevoflurane	3	112	1.16	0.3265
Amplitude				
Group	1	112	0.02	0.8777
Sevoflurane	3	112	88.71	< 0.0001
Group·Sevoflurane	3	112	0.61	0.6076
BIS				
Group	1	112	0.99	0.3224
Sevoflurane	3	112	195.89	< 0.0001
Group·Sevoflurane	3	112	1.25	0.2968
BIC-low				
Group	1	112	0.55	0.4593
Sevoflurane	3	112	23.4	< 0.0001
Group·Sevoflurane	3	112	1.42	0.2396
BIC-high				
Group	1	112	1.93	0.1672
Sevoflurane	3	112	41.7	< 0.0001
Group·Sevoflurane	3	112	0.29	0.8293

The group effect (pregnant/nonpregnant), sevoflurane concentration effect, and group·sevoflurane interaction for each electroencephalographic parameter.

BIS = bispectral index; DDF = denominator degrees of freedom; Group = pregnant *vs.* nonpregnant group; Group·Sevoflurane = interaction between group and sevoflurane; NDF = numerator degrees of freedom; pBIC-high = peak heights of bicoherence at 5–10 Hz; pBIC-low = peak heights of bicoherence at 3–5 Hz; SEF95 = 95% spectral edge frequency; Sevoflurane = sevoflurane concentration (0.5, 1.0, 1.5, and 2.0%).

Why did the electroencephalogram not indicate a difference in the hypnotic effect in the subjects in whom MAC was thought to be different? MAC represents the alveolar concentration of inhalational anesthetics that prevents 50% of subjects from moving in response to noxious stimuli.[6] Because such movement is considered an escape response from painful stimuli, MAC has been considered an indicator of the effect of anesthetics on the brain. However, as indicated in Introduction, animal studies have shown that MAC indicates the effect of anesthetics on the spinal cord,[7–9] whereas the electroencephalogram shows the anesthetic effect on the brain. Therefore, it is not surprising that hypnotic levels indicated by electroencephalogram are similar in pregnant and nonpregnant women, although MAC may differ between the two groups. The results of this study show that the decrease in MAC during pregnancy cannot validate the rationale that parturients require less volatile anesthetics.

Various factors affect the electroencephalographic waveforms during surgery, one being noxious stimuli. If analgesic dosage is insufficient, noxious stimuli can increase the frequency and decrease the amplitude of high-amplitude slow waves induced by anesthetics.[15] This phenomenon is called desynchronization,[15] in which consciousness likely returns by noxious stimuli reaching the brain. In this study, two types of operations (cesarean section in the pregnant group and gynecological surgery in the nonpregnant group) were performed. It remains possible that the intensity of noxious stimulus differed depending on the type of operation. One method to evaluate the intensity of the noxious stimulus is intraoperative hemodynamic changes. In our study, because both the preoperative and intraoperative heart rates were higher in the pregnant group, the hemodynamic values are not appropriate. Another method to evaluate the intensity of noxious stimuli is bicoherence, a parameter that indicates the hypnotic effect of anesthetics. Bicoherence disappears when a strong noxious stimulus is applied, because noxious stimuli induce an arousal electroencephalographic pattern.[16] It is restored or prevented by sufficient opioid analgesia.[16] In this study, bicoherence was similar in the pregnant and nonpregnant groups at 2 and 1.5% sevoflurane. We believe that fentanyl analgesia minimized the noxious stimuli, and the degree of noxious stimuli was equivalent in both groups.

Some drugs administered intraoperatively also affect the electroencephalographic waveforms. Thiopental is known to affect electroencephalogram; however, the duration is short. According to a previous report, nonpregnant patients recovered consciousness 330 ± 153 s after induction of 4 mg/kg thiopental.[17] At the time of return of consciousness, the BIS value was 81 ± 5.[17] Redistribution is the principal mechanism accounting for this early awakening. Approximately 10–15 min after 4–6 mg/kg thiopental administration, serum levels fall to 5 μg/ml, which is equivalent to 50% of awakening level in both parturients and nonpregnant patients.[18,19] Al-

though the dose requirement of thiopental in parturients is approximately 18% lower compared with nonpregnant women,[20] the blood concentration of thiopental at our study period (20–150 min after induction) is thought to be sufficiently low to affect the electroencephalogram. A muscle relaxant itself does not have an effect on electroencephalogram. However, electromyogram artifacts greatly change the electroencephalographic waveform. If an electromyogram is combined with the electroencephalogram, the electroencephalographic frequency increases, and it comes to show an arousal pattern. To prevent this, we administered muscle relaxant in all cases.

Some factors affect not only the electroencephalogram but also MAC. Drugs such as ephedrine increase MAC by increasing the catecholamine in the brain.[21] Such drugs are usually dose-related and require a very high dose.[22] The amount of ephedrine necessary to raise MAC by 50% has been reported to be as high as 0.04 mg/kg/min in a dog study.[21] Because the dosage of the ephedrine in our study was small (0.01 mg/kg, bolus), it was probably not enough to influence the MAC.

Hormonal changes associated with delivery also affect the MAC. According to previous human studies, the postpartum changes in MAC were as follows. During the first 1–12 h postpartum, the MAC of isoflurane was similar to the 0.775% measured in pregnant patients of 8–12 weeks' gestation.[3] MAC increased to 0.825% during the next 36 h, to reach normal values (1.125%) by 72 h postpartum.[23] Although MAC in the third trimester in parturients has not been examined because of ethical considerations, these results suggested that changes in MAC at the postpartum period are very slow. Therefore, we believe that rapid changes in MAC did not occur during our study period.

So how much volatile anesthetic should we administer during general anesthesia for cesarean section? It has been shown that the volatile anesthetic requirement for general anesthesia is lower than that required for prevention of body movements.[24] The results of this study showed that the BIS ranged from 40 to 60 in most patients in both groups at 1.5% sevoflurane concentration. By contrast, the BIS exceeded 60 in almost half of the patients in both groups at 1.0% sevoflurane concentration. The highest BIS value at 1.0% was 80. These results are almost the same as the BIS values for sevoflurane concentration determined by Katoh *et al.*[25] in nonpregnant patients and by Chin *et al.*[26] in pregnant patients.

Under the assumption that the BIS value for appropriate hypnosis during operation is less than 60,[10,27] approximately half of patients are insufficiently anesthetized at 1.0% sevoflurane concentration. Therefore, in cases without both electroencephalographic monitoring and nitrous oxide administration, at least 1.5% sevoflurane may be needed during maintenance of general anesthesia.

The dose requirements of inhalational anesthetics has been believed to be less for parturients because MAC is significantly decreased by pregnancy. To prevent undesired outcomes, such as neonatal suppression or uterine atony, parturients have routinely been administered volatile anesthetics at a lower concentration compared with nonpregnant women. However, our electroencephalographic study indicates that there is no difference between pregnant and nonpregnant women in the hypnotic effects of sevoflurane, despite the groups supposedly having different MAC values. These findings suggest that a decrease in MAC during pregnancy does not mean an enhanced volatile anesthetic effect on the brain. We believe that parturients should be given the same dose of anesthetics as nonpregnant women for prevention of intraoperative awareness. Thus, anesthesiologists should reconsider using MAC as an indicator of efficacy of volatile anesthetics.

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ANESTHESIOLOGY REFLECTIONS

The Schneider Brain Wave Synchronizer

After observing how some radar technicians had become "transfixed" by rhythmic flashing dots on their radar screens, inventor Sidney Schneider designed his Brain Wave Synchronizer (BWS) to hypnotize by visually stimulating subjects at frequencies mimicking those of their alpha, beta, or delta brainwaves. In 1959 Schneider and hypnotist-obstetrician William Kroger, M.D., published their use of the BWS in prenatal classes for thousands of women prior to its use as an "electronic aid for hypnotic induction" during labor and delivery. Four years later, Chicago anesthesiologist Max S. Sadove, M.D., published his work on how BWS-induced hypnosis could reduce anesthetic agent requirements during general anesthesia. By 1994 the BWS would be cited for causing epileptic seizures in a patient. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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