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Minimum Alveolar Concentration of Halothane and Enflurane Are Decreased in Early Pregnancy

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Background: **Minimum alveolar concentration (MAC) of isoflurane is decreased in early pregnancy but it is not known whether this occurs to the same extent with other inhalational anesthetics. The MAC of halothane and enflurane were compared in pregnant women undergoing elective termination of pregnancy and in nonpregnant women.**

Methods: **We studied 16 pregnant women scheduled for termination of pregnancy at 8 to 13 weeks gestation and 16 nonpregnant patients undergoing laparoscopic sterilization. Eight patients in each group received halothane and the others received enflurane. After inhalational induction of anesthesia and tracheal intubation, MAC was determined in each patient by observing the motor response to a 10-s, 50-Hz, 80-mA transcutaneous electric tetanic stimulus to the ulnar nerve at varying concentrations of either halothane or enflurane. The end-tidal concentration of inhalational anesthetic was kept constant for at least 15 min before each stimulus and the concentration was varied ultimately in steps of 0.05 vol% (halothane) or 0.10 vol% (enflurane) until a sequence of three alternate responses (move, not move, move) or (not move, move, not move) was obtained. Minimum alveolar concentration for each person was taken as the mean of the two concentrations just permitting and just preventing movement, and MAC for the group was the median of individual MAC values. Confidence intervals were calculated for the percentage decrease in MAC for pregnant women compared with nonpregnant women.**

Results: **The median (range) MAC of halothane, 0.58 vol% (0.53 to 0.58), and enflurane, 1.15 vol% (0.95–1.25), in the pregnant women were less than those in the nonpregnant women, 0.75 vol% (0.70 to 0.78), $P = 0.0005$ and 1.65 vol% (1.45 to 1.75), $P = 0.0007$, respectively. The percentage decrease (95% CI) in MAC for pregnant women was 27% (20 to 27%) for halothane and 30% (24 to 36%) for enflurane.**

Conclusions: **The MAC of halothane and enflurane were reduced by a similar degree in pregnant women at 8 to 13 weeks gestation compared with nonpregnant women. (Key words: Anesthesia, obstetric. Anesthetics, volatile: halothane, enflurane. Potency, anesthetic: minimum alveolar concentration.)**

THE minimum alveolar concentration (MAC) of isoflurane in pregnant women (at 8 to 12 weeks gestation) is 28% less than the MAC measured in nonpregnant controls.[1] In pregnant ewes, MAC of halothane, methoxyflurane, and isoflurane are decreased by 25%, 32%, and 40%, respectively.[2] The purpose of the present study was to quantify the changes of MAC during pregnancy for different inhalational anesthetics and to present a method to compare the differences in MAC among different agents. We measured the MAC of halothane and enflurane in pregnant women scheduled for termination of pregnancy between 8 and 13 weeks gestation and in nonpregnant women undergoing elective laparoscopic sterilization.

Materials and Methods

The study was approved by the clinical research ethics committee. Written informed consent was obtained from all patients. Sixteen pregnant patients at 8 to 13 weeks gestation and 16 matched nonpregnant controls were included in the study. All patients were classified as American Society of Anesthesiologists physical status 1. Exclusion criteria were history of esophageal reflux, opioid or alcohol abuse, and recent use of any medication, including oral contraceptives. Nonpregnant patients were scheduled for elective laparoscopic tubal ligation, tested negative for urinary human chorionic

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gonadotrophin using a qualitative immunoassay (Abbott TestPack Plus; Abbott Laboratories, Abbott Park, IL), and had normal menstruation within the previous 4 weeks. Pregnant patients were scheduled for termination of pregnancy with laparoscopic sterilization, had a positive pregnancy test, and ultrasonic confirmation of a viable fetus immediately before surgery. Patients were allocated randomly so that eight patients from each group received halothane and eight from each group received enflurane. Investigators were blinded to the patient group, but it was not feasible to blind the investigators to the inhalational anesthetics because of their characteristic odor.

All measurements were conducted in the anesthesia room before surgery. Patients received no preanesthetic medication. After intravenous access was established, anesthesia was induced by inhalation of either halothane or enflurane in oxygen via a tight-fitting face mask. Fresh gas flow was delivered through a standard Magill breathing system. The trachea was intubated with a 7.5-mm (inner diameter) cuffed gas monitoring endotracheal tube (Portex Limited, Hythe, UK) without using a muscle relaxant. End-tidal gas was aspirated from the distal sampling port. Inspired and expired concentrations of halothane, enflurane, carbon dioxide, and oxygen were measured continuously using a calibrated photoacoustic and magnetoacoustic gas monitor (type 1304; Brüel and Kjaer, Naerum, Denmark).[3] Patients were allowed to breathe spontaneously and fresh gas flow was adjusted and ventilation assisted manually to maintain an end-tidal carbon dioxide concentration of 4.5 to 5.5 vol%.

Minimum alveolar concentration was determined by testing the motor responses to successive tetanic stimuli applied to the ulnar nerve[1] at varying concentrations of halothane or enflurane. The volar surface of the right forearm was cleaned with alcohol; a silver-silver chloride electrode (Medtronic, Haverhill, MA), the cathode, was placed over the ulnar nerve at the proximal skin crease of the wrist; and the anode was placed 5 cm proximally along the nerve. A standardized transcutaneous electrical tetanus of 10-s, 50-Hz, 80-mA, 200-μs square pulses was delivered using a constant-current peripheral nerve stimulator (NS252; Fisher & Paykel Healthcare, Auckland, New Zealand). A positive response was defined as any purposeful movement of the head, neck, or limbs apart from the stimulated arm. Delayed movements within 60 s after the stimulus were regarded as a positive response, but frowning, bucking, coughing, or swallowing were not.

The initial target end-tidal concentrations for halothane and enflurane were 0.65 vol% and 1.50 vol%, respectively. If a positive response was observed in the halothane group, the concentration of halothane was increased by 0.10 vol% and then in steps of 0.05 vol% until the response disappeared. The concentration of halothane was then reduced by 0.05 vol% and the tetanic stimulus repeated to confirm consistency of response. Similarly, for patients receiving enflurane, end-tidal concentration was increased by 0.20 vol% and then in steps of 0.10 vol% until there was no response. The concentration of enflurane was reduced by 0.10 vol% to confirm consistency of response. A reverse sequence was done if there was no response to the initial target end-tidal concentrations for halothane or enflurane. At each step change, the end-tidal concentration of halothane or enflurane was held constant for at least 15 min before the stimulus was repeated. The MAC for each patient was the concentration midway between the lowest concentration preventing and the highest concentration permitting a positive response. Minimum alveolar concentration for each group was taken as the median of the individual MAC values.

Patient data were compared among groups using the Kruskal-Wallis test or Mann-Whitney U test. Probability values less than 0.05 were considered statistically significant. To compare the changes in anesthetic requirements among different anesthetic agents, the 95% confidence interval (CI) was calculated for the percentage decrease in MAC between pregnant and nonpregnant groups for each agent. This was derived from the general method used to calculate a CI for the difference between the medians of two unpaired samples.[4] Briefly, for n_1 observations in the first sample and n_2 observations in the second sample, the difference between the two population medians is estimated by the median of all the possible $n_1 \times n_2$ differences that are calculated between all possible pairs of observations in one sample with observations in the other sample. This procedure may give a different value from that calculated by just subtracting the median in one sample from the median in the other sample. The approximate 95% CI for the difference between population medians is also calculated from these $n_1 \times n_2$ differences using the distribution of the Mann-Whitney U test statistic.[4] The difference between population medians and the 95% CI was then divided by the nonpregnant MAC

Table 1. Patient Characteristics

	Halothane		Enflurane	
	Pregnant (n = 8)	Nonpregnant (n = 8)	Pregnant (n = 8)	Nonpregnant (n = 8)
Age (yr)	35 (15–39)	30 (29–34)	36 (25–40)	34 (32–37)
Weight (kg)	54.5 (44–76)	53.5 (42–69)	50.8 (45–85)	57.5 (44–67)
Height (cm)	154 (142–160)	156 (148–160)	156 (148–167)	157 (151–163)
Gestation (wk)	11 (9–13)		9.8 (8–13)	

Values are median (range).

value to give the percentage decrease (with 95% CI) in MAC for the pregnant patients compared with the nonpregnant patients. This percentage decrease may be different from that calculated by just simply comparing the MAC values for the pregnant and nonpregnant groups.

Results

Table 1 summarizes patient characteristics. Age, weight, height, and gestation did not differ among groups. All studies were completed within 2 h, and there were no anesthetic complications.

In each patient, the expired gas wave form demonstrated an early plateau and the inspired-to-expired concentration difference was less than 0.05 vol% and 0.10 vol% for halothane and enflurane, respectively. Involuntary movements unrelated to tetanic stimulus were observed in 14 of the 16 patients receiving enflurane at end-tidal concentrations greater than the individual MAC. No patient remembered the tetanic stimuli applied during the study.

Responses to tetanic stimulation were consistent, and individual MAC values were determined easily except in two patients. One nonpregnant patient in the halothane group showed a positive response twice at 0.65 vol%, one positive and one negative response at 0.70 vol%, and two negative responses at 0.75 vol%, and MAC was recorded as 0.70 vol%. One pregnant patient in the enflurane group showed a positive response twice at 1.10 vol%, one positive and one negative response at 1.20 vol%, and two negative responses at 1.30 vol%, and MAC was recorded as 1.20 vol%.

Figure 1 shows individual MAC values. The median MAC values of halothane and enflurane in the pregnant groups were less than those in the nonpregnant groups (P = 0.0005 and P = 0.0007, respectively). Table 2 lists the difference (95% CI) in MAC between pregnant and nonpregnant women and the corresponding percentage decrease (95% CI) for halothane and enflurane.

Discussion

The reduction in MAC of halothane during human pregnancy confirms the results of earlier animal studies with halothane. The MAC of halothane was reduced by 25% in pregnant sheep[2] and by 16 to 19% in pregnant Sprague-Dawley rats.[5] No data exist for the MAC of enflurane during pregnancy.

The MAC of halothane (0.75 vol%) and enflurane (1.65 vol%) determined by transcutaneous tetanic nerve stimulation in the nonpregnant women we studied are similar to MAC values obtained by the standard skin incision method (0.73 to 0.77 vol%[6–8] and 1.68 vol%,[9] respectively). Other studies have shown that the MAC of isoflurane[10] and nitrous oxide[11] determined by the two methods are also similar. Transcutaneous tetanic nerve stimulation is a simple, easy, harmless, and repeatable alternative to the standard surgical incision.

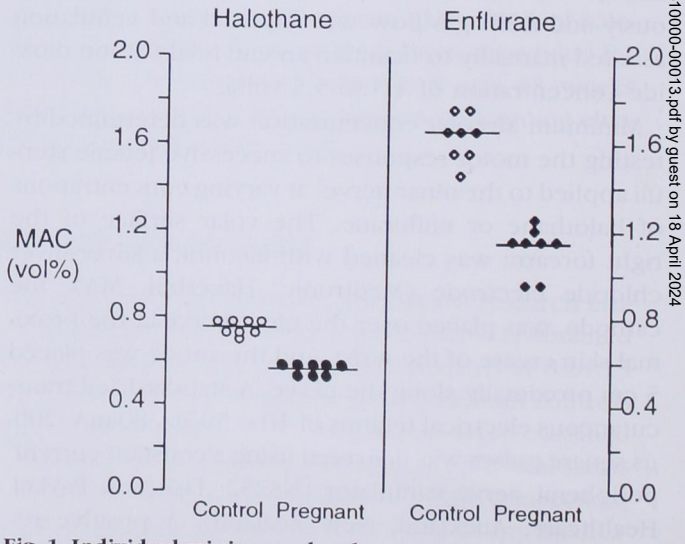

Fig. 1. Individual minimum alveolar concentrations (MAC) for halothane in pregnant women (●) and nonpregnant women (○), and enflurane in pregnant women (♦) and nonpregnant women (◇).

Table 2. Median (Range) of Individual Minimum Alveolar Concentration (MAC) Values for Pregnant and Nonpregnant Women, and Differences (95% CI) in MAC between Pregnant and Nonpregnant Women

	Halothane		Enflurane	
	Pregnant (n = 8)	Nonpregnant (n = 8)	Pregnant (n = 8)	Nonpregnant (n = 8)
MAC (vol%)	0.58* (0.53–0.58)	0.75 (0.70–0.78)	1.15* (0.95–1.25)	1.65 (1.45–1.75)
Difference in MAC (vol%)	0.20 (0.15–0.20)		0.50 (0.40–0.60)	
Percentage decrease in MAC (95% CI) for pregnant group versus nonpregnant group	27 (20–27)		30 (24–36)	

Differences in MAC are also expressed as the percentage decrease (95% CI) in MAC for pregnant women compared with nonpregnant women.

* $P < 0.001$ *versus* MAC in nonpregnant group.

We maintained constant end-tidal concentrations of halothane and enflurane for more than 15 min. Theoretically, the time required for the brain to reach the same partial pressures as that in blood depends on the blood–brain partition coefficient. Based on laboratory investigations on tissue homogenates,[12] 95% equilibration between arterial blood and brain partial pressures for halothane and enflurane should be completed in 14.4 and 7.9 min, respectively. In our healthy young patients, 15 min of steady-state end-tidal concentrations of halothane and enflurane should allow adequate equilibration between the lung, the arterial blood, and the brain. The similarity of our MAC values to those found in other studies and the consistency of response shown by nearly all patients are also evidence that the equilibration time is adequate.

With the current study design, it was difficult to directly compare the changes in MAC for different anesthetic agents. We used a method that calculated the 95% CIs for nonparametric data, because MAC is normally defined as the median rather than the mean. Another study design permitting more direct comparison would be to determine MAC in the same patient during early pregnancy and again when she is no longer pregnant, but this was impractical in our setting.

Data analysis from our earlier study[1] showed that the difference (95% CI) in MAC for isoflurane between pregnant (n = 10) and nonpregnant women (n = 10) was 0.35 vol% (0.30 to 0.40). This corresponded to a percentage decrease (95% CI) in MAC of 33% (28 to 37%). Examining the 95% CIs for the percentage decrease in MAC, there is no difference between halothane and enflurane. The CIs were narrow for both anesthetic agents and we believe there is no additional benefit in trying to reduce the confidence limits further by recruiting more patients. The 95% CIs for the isoflurane (28 to 37%) and halothane (20 to 27%) do not overlap, and this would suggest that pregnancy reduces the MAC of isoflurane to a greater extent than of halothane. However, the data for isoflurane were taken from a previous study. Although all measurements in both studies were performed by the same investigators under identical conditions, unknown factors may explain the modest discrepancy. The small differences observed between the agents (33% for isoflurane, 27% for halothane, and 30% for enflurane) are not important clinically.

The underlying mechanism for the decreased anesthetic requirements during pregnancy is unclear. Exogenously administered progesterone can reduce anesthetic requirements in animals,§[13,14] but human data are lacking.[1] Increased concentrations of endorphins and dynorphins in pregnant rats mediate an increase in pain threshold,[15,16] and this could also affect anesthetic requirements.

Although MAC is decreased during early pregnancy, we cannot extrapolate these findings to other stages of pregnancy. The MAC of halothane was reduced by 19% in rats at 10 days (mid-term) and by 16% at 21 to 23 days (full term).[5] In humans, the MAC of isoflurane was also reduced in the immediate postpartum period.[17,18]

In pregnant women at 8 to 13 weeks gestation, the median percentage decreases in MAC for halothane

§Tanifuji Y, Yasuda N, Kobayashi K, Eger EI II: Effect of progesterone and estrogen on halothane MAC in dogs (abstract). ANESTHESIOLOGY 1986; 65:A351.

and enflurane were 27% and 30%, respectively, compared with those in nonpregnant women.

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