Decreased Minimum Alveolar Concentration of Isoflurane in Pregnant Humans


Background: Minimum alveolar concentration (MAC) is decreased in pregnant animals, but this change has not been demonstrated in humans, probably because of ethical considerations. It is less problematic to determine MAC in pregnant women undergoing termination of pregnancy, however, and therefore we compared the MAC of isoflurane in these women with the MAC in matched nonpregnant women.

Methods: Patients underwent inhalational induction of anesthesia with isoflurane and tracheal intubation. MAC was determined in each patient by testing the response to a 10-s, 50-Hz, 80-mA transcutaneous tetanic electrical stimulus to the ulnar nerve at varying concentrations of isoflurane. The end-tidal concentration of isoflurane was kept constant for 10 min before each stimulus and the concentration of isoflurane ultimately varied in steps of 0.05% until we obtained a sequence of three alternate responses (move, not move, move) or (not move, move, not move). MAC for each patient was taken as the mean of the two concentrations just permitting and just preventing movement. MAC for the group was taken as the median of the individual MAC values. A blood sample was taken immediately before induction of anesthesia for measurement of progesterone concentrations. Data were compared between groups by the Mann–Whitney test.

Results: The median (range) MAC for isoflurane in the pregnant group, 0.775% (0.675–0.825), was less than that in the nonpregnant group, 1.075% (1.025–1.175) ($P < 0.001$). The median (range) plasma progesterone concentration in the pregnant group, 53.4 (8.8–106) nm, was greater than that in the nonpregnant group, 8.4 (0.7–66) nm ($P < 0.02$).

Conclusions: The MAC of isoflurane was reduced by 28% in pregnant women at 8–12 weeks’ gestation compared with that of nonpregnant controls. (Key words: Anesthesia: obstetric; Anesthetics, volatile: isoflurane. Hormones: progesterone. Potency: minimum alveolar concentration.)

PREGNANCY is associated with many physiologic changes that may affect the pharmacologic profile of drugs given to the mother. Animal studies have shown a decreased maternal anesthetic requirement during pregnancy. The minimum alveolar concentration (MAC) for inhalational agents was reduced by 25–40% in pregnant ewes and by 16–19% in pregnant rats. A study in rabbits suggested that this reduction may be caused by progesterone. One study found no difference in MAC between pregnant and nonpregnant rats, but the adjustment of the halothane concentration in steps of 0.2–0.25% would have precluded accurate determination of the changes in MAC with pregnancy.

For ethical and practical reasons, the decrease in MAC has not been confirmed in pregnant women despite the important implications of a change in anesthetic requirement of 16–40%. However, it is possible to study women undergoing termination of pregnancy at 8–12 weeks’ gestation with the provision that the results may not reflect what occurs at other stages of pregnancy. This study set out to determine, in humans, the change in anesthetic requirement associated with pregnancy. We compared the MAC of isoflurane in patients undergoing termination of pregnancy with the MAC in nonpregnant women undergoing elective gynecologic surgery.

Materials and Methods

The study was approved by the local clinical research ethics committee, and ten patients were recruited for each group. Patients were eligible for the study if they were ASA physical status 1 and required tracheal intubation for elective gynecologic surgery. Pregnant patients were undergoing termination of pregnancy with laparoscopic sterilization, and nonpregnant patients were scheduled for laparoscopic surgery. Patients were excluded if they had symptoms of esophageal reflux or were taking any medications, including oral contraceptive agents. Pregnant patients had a positive result on pregnancy testing and ultrasonic confirmation of pregnancy. Nonpregnant patients had a negative result on pregnancy testing and reported menstruation in the

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previous 5 weeks. Written informed consent was obtained from all patients.

No premedication was given. Patients were anesthetized by inhalation of isoflurane in oxygen using a Magill anesthetic circuit. The trachea was intubated with a 7.5-mm (ID) gas monitoring tracheal tube (Portex, Hythe, England). Inspired and expired concentrations of isoflurane, carbon dioxide, and oxygen were measured with a photoacoustic and magnetoacoustic gas monitor (type 1304, Brüel and Kjær, Nærum, Denmark). The end-tidal carbon dioxide concentration was held constant at 5.0% by adjusting the fresh gas flow to the Magill circuit.

MAC was determined by observing the successive responses to tetanic electrical stimuli to the ulnar nerve at varying concentrations of isoflurane. A 10-s, 50-Hz, 80-mA transcutaneous tetanic stimulus to the ulnar nerve at the wrist was delivered in 200-μs pulses by a constant-current peripheral nerve stimulator (NS252, Fisher & Paykel Healthcare, Auckland, New Zealand). This machine delivers a monophasic, unidirectional square wave with a rising time of less than 5 μs, has a maximum output of 350 V, and alarms if the current is more than 5 mA different from that selected. After cleaning the arm, one silver–silver chloride electrode (Medtronic, Haverhill, MA) was placed over the ulnar nerve at the proximal skin crease of the wrist and the other electrode placed 5 cm proximally. A positive response was recorded if there was movement in one of the nonstimulated limbs during the tetanus. Swallowing and coughing were not considered positive responses. The same investigator determined all MAC values and was blinded to the study group.

The end-tidal concentration of isoflurane was held constant at each desired level for a 10-min equilibration period. At an initial end-tidal isoflurane concentration of 1% the tetanic stimulus was applied. If there was no response, isoflurane was decreased by 0.2% and then in steps of 0.1% until a response was noted. The isoflurane was then increased in steps of 0.05% until there was no response and then decreased by 0.05% until the response returned. A reverse sequence was applied if there was a response to the initial stimulus at 1%. MAC for each patient was taken as the mean of the two concentrations just permitting and just preventing movement. The MAC for each group was calculated as the median of the individual MAC values.

A blood sample was taken immediately before induction of anesthesia for measurement of the plasma concentration of progesterone by solid-phase iodine 125 radioimmunoassay (Coat-A-Count, Diagnostic Products, Los Angeles, CA). The interassay coefficient of variation was 10% at 5.0 nm and 7.2% at 47.0 nm, and the limit of detection was 0.2 nm (where 1 nm = 3.18 ng·ml⁻¹).

Data were compared between groups by using the Mann–Whitney test. In each group, MAC was compared with progesterone concentrations by Kendall rank correlation. P < 0.05 was considered significant. Results are presented as medians (with ranges in parentheses).

**Results**

Demographic characteristics of the nonpregnant patients (age 34.5 [31–45] yr, weight 54 [48–67] kg, and height 1.62 [1.51–1.70] m) were similar to those of the pregnant group (35.5 [21–46] yr, 59 [41–65] kg, and 1.60 [1.50–1.69] m). The pregnant patients were 10 (8–12) weeks pregnant by dates, and pathologic examination confirmed a fetus in all women.

The MAC in the pregnant group, 0.775% (0.675–0.825), was less than that in the nonpregnant group, 1.075% (1.025–1.175) (P < 0.001) (fig. 1). Plasma progesterone concentration in the pregnant group, 63.4 (0.8–106) nm, was greater than that in the non-

![Fig. 1. Minimum alveolar concentrations (MAC) for isoflurane (percentage) and plasma progesterone concentrations (nanomolar) in ten nonpregnant women (open circles) and ten pregnant women at 8–12 weeks' gestation (filled circles). Number 3 = three overlapping data points in the nonpregnant group.](image-url)
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pregnant group, 8.4 (0.7–66) nm (P < 0.02) (fig. 1). One pregnant woman, age 45 yr, whose MAC was 0.675%, had a very low progesterone concentration, 0.8 nm. The Kendall rank correlation between MAC and progesterone concentrations was not significant in either the nonpregnant (P = 0.09) or the pregnant group (P = 0.32).

Discussion

The MAC of isoflurane determined by tetanic stimulation for our nonpregnant patients is similar to that (1.03%) determined by Zbinden et al., using a similar technique, although Zbinden et al. found that this MAC value was slightly less than the MAC (1.16%) determined by surgical incision in the same patients. The MAC of nitrous oxide determined by tetanic stimulation was similar to that determined by skin incision. However, the MAC of desflurane determined by tetanic stimulation (4.58%) was decreased when compared with that determined by skin incision. The results obtained from tetanic stimulation may be discrepant because studies use different electrical stimuli. It is important to use a supramaximal stimulus and avoid desensitization after repeated stimulation. The use of a constant-current nerve stimulator is desirable; tetanic stimulation is advantageous in that it is easy, is harmless and repeatable in each patient, and gives reproducible results.

MAC was decreased by 28% in our patients, who were at 8–12 weeks' gestation, but we cannot speculate as to what may occur at other stages of pregnancy. The original work by Palahniuk et al. in ewes within 3 weeks of term found a 40% reduction for isoflurane and a 25% reduction for halothane, whereas in rats, Strout and Nahrwold found MAC for halothane decreased by 19% on the 10th day of pregnancy and by 16% at term (days 21–23).

Progesterone concentrations in the pregnant patients were generally in accord with previous measurements of progesterone in pregnancy. However, these concentrations are much less than those expected at term and raise doubt about a linear correlation between increased progesterone and decreased anesthetic requirement throughout pregnancy. Plasma progesterone concentration is approximately 1 nm during the follicular phase of the menstrual cycle, is 60 nm in the midluteal phase or at 24 h postpartum, starts to increase by the 10th week of pregnancy to 100 nm at 12 weeks, and reaches 500 nm at term but with considerable individual variation. Strout and Nahrwold found no correlation between MAC and progesterone, and although Datta et al. concluded that there was an inverse linear correlation, the fit was poor (r = 0.53), and they had excluded four rats with high progesterone concentration and high MAC. It is possible that only a threshold concentration of progesterone is necessary to reduce MAC or that the relation between the two is nonlinear. Further studies throughout pregnancy are required but would be feasible only in animals. Therefore there is no definitive evidence that the increased progesterone in pregnancy causes the reduction in MAC.

Recent work suggests that anesthetics act principally at the spinal cord, and it may be more important to determine the unbound concentration of progesterone in the cerebrospinal fluid, which does not parallel the changes in unbound plasma concentration. The ratio of unbound plasma progesterone to unbound CSF progesterone was 2:1 in nonpregnant patients, 15:1 in those at term pregnancy, and 6:1 in women in the immediate postpartum period. We are unaware of any data on the unbound CSF progesterone concentrations in early pregnancy.

Tetanic current and surgical incision are painful stimuli used to determine MAC, and pregnancy-induced analgesia may affect the response to these painful stimuli and hence MAC. Endorphins and dynorphins mediate an increase in pain threshold during pregnancy in rats, and pregnancy-induced analgesia to visceral stimulation in rats could be reversed by naloxone. There may be interactions between progesterone and opioids; intrathecal progesterone has been observed to potentiate spinal sufentanil in rats. Although some researchers have not found increased tolerance to thermal stimuli in pregnant humans, others have shown pregnancy-induced analgesia.

The MAC for isoflurane was decreased by 28% in pregnant women at 8–12 weeks' gestation compared with that of nonpregnant women. This finding is in agreement with MAC studies in animals, but the underlying cause of this reduction remains unclear.

References


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