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Comparison of the effects of sevoflurane and isoflurane anesthesia on the maternal-fetal unit in sheep

Toshiyuki Okutomi, Robert A. Whittington, Deborah J. Stein, and Hisayo O. Morishima

Departments of Anesthesiology and Obstetrics/Gynecology, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA

Abstract
Purpose. The aim of this study was to determine the hemodynamic and blood gas effects of inhalational anesthetics on the maternal-fetal sheep unit. The principal hypothesis, tested in chronically instrumented near-term pregnant ewes, was that sevoflurane anesthesia may be safe and useful for the mother and fetus during pregnancy, compared with isoflurane.
Methods. Six chronically instrumented pregnant and 3 nonpregnant ewes were tested repeatedly to establish the minimum alveolar concentration (MAC) for sevoflurane and isoflurane to be used in the hemodynamic and blood gas studies. Progressively increasing concentrations of sevoflurane or isoflurane in oxygen were administered to 12 pregnant ewes. Uterine blood flow, maternal and fetal heart rates, blood pressure, arterial blood gases, and intra-amniotic pressure were subsequently measured.
Results. The MAC of sevoflurane was 1.52 ± 0.15% and 1.92 ± 0.17% in pregnant and nonpregnant ewes, respectively; while the MAC of isoflurane in the pregnant and nonpregnant sheep was 1.02 ± 0.12% and 1.42 ± 0.19%, respectively. In both the sevoflurane and isoflurane groups, changes in maternal and fetal blood gases were minimal during exposure to low-dose (0.5–1.0 MAC) inhaled concentrations. Although uterine blood flow was maintained and the fetus remained well oxygenated at higher concentrations of both agents (2.0 MAC of either agent), the agents produced decreases in maternal and fetal arterial pressure.
Conclusion. A "low-dose" concentration (0.5–1.0 MAC) of sevoflurane may be safe and useful for both mother and fetus during near-term pregnancy. However, a high concentration (1.5–2.0 MAC) of sevoflurane or isoflurane may induce hemodynamic instability in the mother and fetus when administered.

Key words Pregnancy · Maternal-fetal hemodynamics · Sheep · Volatile anesthetics · Sevoflurane and isoflurane

Address correspondence to: T. Okutomi, Department of Anesthesiology, Kitasato University School of Medicine, 1-15-1 Kitasato, Sagamihara, Kanagawa 228-8555, Japan
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Introduction

When administering anesthesia for cesarean delivery, regional anesthesia is preferred to general anesthesia because the latter has higher risks of difficulty in instrumenting the maternal airway, leading to maternal hypoxia, aspiration pneumonia, and even increased maternal mortality [1,2]. However, general anesthesia is still frequently utilized for emergent cesarean delivery due to the shorter induction time associated with this modality of anesthetic administration. Furthermore, general anesthesia for cesarean delivery has some advantages over regional anesthesia, such as less hypotension and cardiovascular instability, and better control of ventilation. Because intravenous anesthetics administered to the mother prior to delivery may produce neonatal depression secondary to placental transfer of these agents, low to moderate concentrations (0.5–1.0 minimum alveolar concentration [MAC]) of inhalation anesthetics are often used during general anesthesia for cesarean delivery.

Fetal surgery, using ex-utero intrapartum treatment (EXIT), for some rare, potentially life-threatening fetal conditions, is becoming more popular due to rapidly advancing prenatal diagnostic techniques. General anesthesia with higher concentrations of inhalational anesthetic has been recommended for EXIT of the fetus, because uterine relaxation is required for this procedure [3–6]. Sevoflurane has been widely used as a general anesthetic agent because induction and recovery are faster than with halothane or isoflurane [7,8]. However, there is little information available regarding the effects of sevoflurane on the fetus [9–11].

Although the umbilical venous-to-maternal arterial concentration ratio of sevoflurane at birth is higher than that for halothane or enflurane [10], sevoflurane concentrations in the umbilical vein do not correlate with the newborn's condition as determined by Apgar score [9,10]. However, it is not known whether sevoflurane

alters utero-placental blood flow, which may then indirectly impact the fetal condition, or whether sevoflurane has direct effects on the fetal hemodynamics or acid-base status.

The aim of this study was to determine the MAC and the effects of sevoflurane and isoflurane in the ovine maternal-fetal unit, with emphasis on uterine blood flow and fetal hemodynamics and acid-base status. The principal hypothesis tested was that sevoflurane may be advantageous for general anesthesia during pregnancy and parturition, compared to isoflurane.

Materials and methods

The protocol was approved by the Columbia University Animal Care and Use Committee. Twelve near-term pregnant sheep with a mean (±SEM) weight of 56.3 ± 4.2 kg, carrying fetuses of 126 ± 6 days' gestation (term, 148 days) were used in these studies. Six of these pregnant sheep were repeatedly tested in the MAC study prior to being used for the hemodynamic studies. All 12 animals were used for 46 hemodynamic studies, 25 with sevoflurane and 21 with isoflurane. Three nonpregnant ewes, weighing 44.2 to 46.3 kg, were also included in the MAC studies of sevoflurane to test whether MAC is altered during gestation.

Surgical preparation

Animals were deprived of food but not water for a period of 24 h prior to surgery. Under halothane anesthesia, all ewes had catheters introduced into the carotid artery and jugular vein under sterile conditions. Pregnant animals also underwent laparotomy and hysterotomy for the insertion of catheters into the fetal abdominal aorta and inferior vena cava via the femoral vessels. After a polyethylene catheter was placed in the amniotic cavity, the uterine incision was closed. The main ascending branch of the uterine artery perfusing the pregnant horn was isolated and fitted with a 4-mm "R" series pulse transit-time ultrasonic transducer flow meter (Transonic Systems, Ithaca, NY, USA) that was anchored to the surrounding tissues. One liter of lactated Ringer's solution was administered intravenously during the operative procedure, and the estimated loss of amniotic fluid was replaced with an equal volume of warmed normal saline after the uterine and abdominal walls were closed.

All catheters and the transducer cable were tunneled subcutaneously to the flank of the ewe and secured in a pouch attached to the flank area. Intravascular catheters were flushed daily with heparinized saline. A tracheostomy was performed in all animals. Antibiotics (chloromycetin and penicillin) were administered intravenously to the adults and via intra-amniotic injection (for the fetuses) until the third postoperative day. The experiments were performed no earlier than 4 days after the surgery, due to the minimum time required for recovery.

Experimental procedures

Minimum alveolar concentration (MAC) study

The MAC study was performed in order to establish the appropriate sevoflurane (Maruishi, Osaka, Japan) and isoflurane (Anaquest, Liberty Corner, NJ, USA) concentrations to be used in the hemodynamic studies. With the animal standing in an enclosed study cart, the tracheostomy tube was connected to a semiclosed circuit, through which sevoflurane or isoflurane in oxygen was administered. The MACs of sevoflurane and isoflurane were determined repeatedly in six pregnant and three nonpregnant ewes. Using a gas analyzer (Datex Capnomatic; Datex-Ohmeda, Madison, WI, USA), the target expired sevoflurane or isoflurane concentration was measured and maintained for at least 15 min prior to each determination. The total fresh gas inflow rate into the semiclosed circuit was maintained at 5 $l \cdot min^{-1}$ or greater. The animal's response to gross noxious stimulus (earlobe clamping, using a rubber-covered hemostat for at least 60 s) was observed. If no movement was elicited in response to stimulation, the exhaled anesthetic concentration was lowered by 10% and the clamping was repeated. If the animal did react, the inhaled concentration was increased by 10%; 1.0 MAC was defined as the concentration, which prevented movement in 50% of tests.

Hemodynamic study

The awake animals breathed air for a 60-min period, during which baseline maternal and fetal blood pressure, heart rate, arterial pH, and blood gases (Pa_{O_2} and Pa_{CO_2}), as well as uterine blood flow measurements were obtained. Thereafter, the tracheostomy was connected to a semiclosed anesthesia circuit.

The animals were randomized in a nonblinded fashion, to receive either sevoflurane or isoflurane. The administration of the selected anesthetic was preceded by the inhalation of 100% oxygen for 15–30 min. The animals were then exposed to sevoflurane or isoflurane in oxygen delivered from an agent-specific vaporizer (Datex-Ohmeda). The inhaled anesthetic concentration was adjusted incrementally to 0.5, 1.0, 1.5, or 2.0 MAC, and each concentration was maintained for 15–20 min after the equilibration of the end expiratory and inhaled gas concentrations. Ewes were manually ventilated when the animals became unconscious. At the end of the 2.0-MAC exposure the animal was disconnected from the anesthesia circuit and allowed to

breathe room air. Two studies per day were performed on each animal, using either sevoflurane or isoflurane. Between the studies, the animal was allowed to recover completely from anesthesia for a period of at least 90 min. Maternal and fetal arterial samples were simultaneously obtained during the control period (baseline), prior to and at the end of each MAC period, and 15 min after discontinuation of anesthesia (recovery) for the determination of pH and blood gases.

Physiological measurements

Maternal and fetal arterial pressure and heart rate, as well as intra-amniotic pressure, were monitored continuously with Statham pressure transducers (Statham, Oxnard, CA, USA) and recorded on a multichannel Gould polygraph recorder (Gould, Valley View, OH, USA). Maternal and fetal heart rate was determined with a cardiotachometer, using the arterial pulse pressure. Uterine blood flow was measured using an ultrasonic flow meter (Transonic Systems) attached to the polygraph recorder.

Data analysis

Within-group comparisons were made with repeated measures analysis of variance, and between-group comparisons were performed by using Student's paired *t*-test.

Data are reported as means ±SEM, and a P value of less than 0.05 was considered statistically significant.

Results

On the day of the experiment, the pregnant ewes, weighing 58–71 kg, were at 129–143 days of gestation.

Minimum alveolar concentration (MAC) study

For sevoflurane, the MAC required to prevent movement in response to a painful stimulus was 1.92 ± 0.17% in nonpregnant sheep, and 1.52 ± 0.15% in pregnant sheep. The MAC of isoflurane was 1.02 ± 0.12% and 1.42 ± 0.19% in pregnant and nonpregnant ewes, respectively.

Hemodynamic study

Uterine blood flow and maternal and fetal arterial blood pressure and heart rate

Baseline values for uterine blood flow and maternal and fetal mean arterial pressure, heart rate, arterial pH, and blood gases are listed in Table 1. There were no significant differences in these measured variables between the sevoflurane and isoflurane groups.

Table 1. Baseline values for uterine blood flow and maternal and fetal mean arterial pressure, heart rate, pH, and blood gases in sevoflurane and isoflurane groups

	Sevoflurane	Isoflurane
Uterine blood flow (ml·min^{-1})	346 ± 33	368 ± 41
Mother		
Mean arterial pressure (mmHg)	84 ± 2	84 ± 2
Heart rate (bpm)	120 ± 6	114 ± 5
pHa	7.53 ± 0.01	7.53 ± 0.01
Pa_{CO_2} (mmHg)	29 ± 0.6	29 ± 0.8
Pa_{O_2} (mmHg)	107 ± 3	101 ± 4
Fetus		
Mean arterial pressure (mmHg)	52 ± 4	53 ± 3
Heart rate (bpm)	162 ± 4	161 ± 5
pHa	7.37 ± 0.01	7.35 ± 0.01
Pa_{CO_2} (mmHg)	42 ± 1.2	43 ± 1.4
Pa_{O_2} (mmHg)	18 ± 0.7	17 ± 1.0

Values are means (± SEM)
Differences between the groups are not statistically significant

Dose-related changes in uterine blood flow and maternal blood pressure and heart rate over the course of the experiment were not significantly different between the sevoflurane and isoflurane groups. Uterine blood flow remained essentially unchanged even at 2.0 MAC of sevoflurane or isoflurane (Fig. 1). Maternal arterial pressure also remained unchanged until the animals were exposed to the 2.0-MAC dose of either volatile anesthetic ($P < 0.02$), while the heart rate was unaffected throughout. This decrease in blood pressure was accompanied by a slight reduction in uterine blood flow compared to the baseline values (from 346 ± 33 to 300 ± 49 ml·min^{-1} for sevoflurane and 368 ± 41 to 329 ± 44 ml·min^{-1} for isoflurane); however, this change was not statistically significant in either group. All animals recovered from anesthesia rapidly, and an adequate breathing pattern was reestablished within 5 min after the anesthetic was discontinued. Compared to isoflurane, the emergence from anesthesia was more rapid in the sevoflurane group; the ewes regained consciousness within 2.2 ± 0.9 min after discontinuation of this agent compared with 5.7 ± 0.6 min with isoflurane. At the time when the recovery values were obtained, all animals were alert and their hemodynamic parameters had returned completely to the baseline values.

Fetal hemodynamic changes were similar in both the sevoflurane and isoflurane groups, However, unlike maternal arterial pressure, fetal blood pressure fell from a baseline value of 52 ± 4 to 42 ± 2 mmHg ($P < 0.05$) in the sevoflurane group, and from 53 ± 3 to 43 ± 2 mmHg ($P < 0.05$) in the isoflurane group at 1.5 MAC, while maternal blood pressure remained unchanged. As illustrated in Fig. 1, the decrease in fetal heart rate became

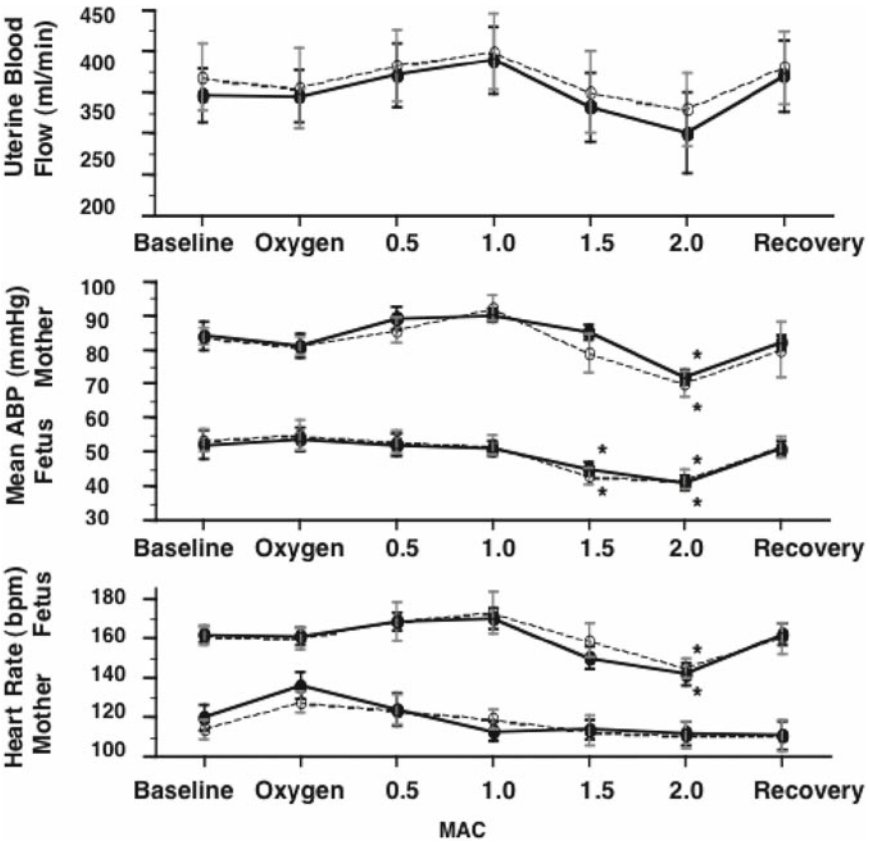

Fig. 1. Mean (±SEM) values of uterine blood flow and maternal and fetal mean arterial blood pressure (*ABP*) and heart rate prior to and at 0.5, 1.0, 1.5, and 2.0 minimum alveolar concentration (MAC) sevoflurane (*filled circles*) or isoflurane (*open circles*). *$P < 0.05$, significantly different from baseline value. All values were similar in the sevoflurane and isoflurane groups

more pronounced at 2.0 MAC with both anesthetics, with a significant decrease in heart rate from 162 ± 4.3 to 142 ± 5.7 beats·min^{-1} for sevoflurane and 161 ± 5.0 to 145 ± 5.0 beats·min^{-1} for isoflurane. These fetal changes were readily reversible within 15 min following discontinuation of the anesthetic.

pH and blood gases

Maternal and fetal arterial pH and Pa_{CO_2} values are depicted in Figs. 2 and 3, respectively. Based on our previous studies, the baseline values were within the normal range for sheep [12,13]. Maternal respiration became progressively more depressed when the inhaled concentration of either sevoflurane or isoflurane increased beyond 1.0 MAC. At 2.0 MAC, the pH values with sevoflurane and isoflurane were 7.45 ± 0.03 and 7.46 ± 0.02, respectively, with increased Pa_{CO_2} values. However, all changes from the baseline values were clinically insignificant, because respiration was assisted manually to attempt to maintain pH and Pa_{CO_2} values within normal ranges during this period of depressed spontaneous respiration.

A markedly elevated maternal arterial Pa_{O_2} due to the administration of 100% oxygen was also reflected in the fetal Pa_{O_2} (Fig. 4); both values returned to baseline levels shortly after the mother began to breathe room air.

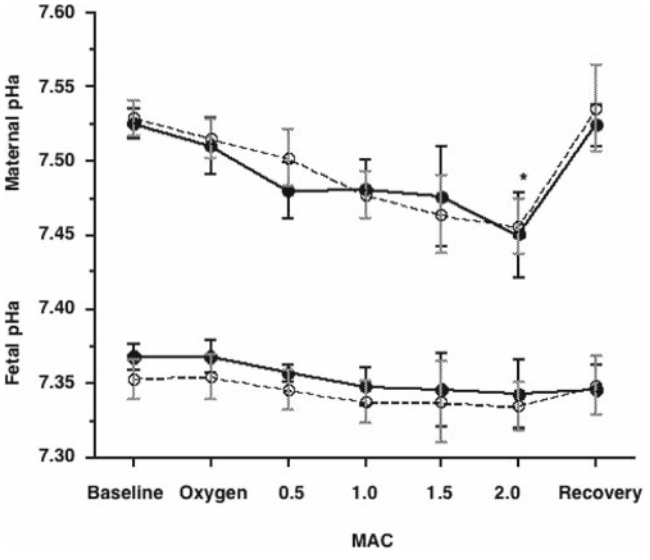

Fig. 2. Mean (±SEM) values of maternal and fetal arterial pH (*pHa*) prior to and at 0.5, 1.0, 1.5, and 2.0 MAC sevoflurane or isoflurane. *$P < 0.05$, significantly different from baseline value. All values were similar in the sevoflurane and isoflurane groups. *Symbols*, as in Fig. 1

Discussion

The present study indicates that, in sheep, the MACs of sevoflurane and isoflurane are lowered during pregnancy and that the hemodynamic changes induced by equally potent doses of sevoflurane and isoflurane are similar. No adverse effects were noted in the mother or fetus during the administration of low concentrations (0.5–1.0 MAC) of either agent, which are clinically relevant concentrations used during standard cesarean delivery under general anesthesia. However, higher concentrations of these drugs (1.5–2.0 MAC) caused a significant decrease in fetal blood pressure as well as heart rate.

The MAC of inhalation anesthetics varies between species and with age [14,15]. The MAC for sevoflurane in the nonpregnant human adult has been reported as 1.71% [16] and 2.05% [17]. However, the MAC of sevoflurane has not been established in pregnant women, but anesthetic requirements are known to be reduced during pregnancy. Indeed, in the present study the MAC of sevoflurane was 21% lower in the pregnant ewes than in the nonpregnant sheep. The same trend was observed with isoflurane, as reported previously [15].

In a clinical study, sevoflurane was administered to 16 pregnant women undergoing elective cesarean delivery [9]. Anesthesia was induced with 3%-4% sevoflurane and 60% nitrous oxide in oxygen and maintained with a gas mixture containing sevoflurane 0.5%-3%. During induction, arterial blood pressure fell by 18.3%. Similarly, in the present study, high concentrations of sevoflurane or isoflurane (2.0 MAC) resulted in a significant reduction in both maternal and fetal blood pressure (14% and 17% decreases from the baseline values, respectively) without a significant decrease in uterine blood flow. However, maternal heart rate was not significantly altered during deeper sevoflurane or isoflurane anesthesia. Observations similar to ours for sevoflurane were made in nonpregnant pigs [18]. During halothane anesthesia in the pregnant ewe, more profound maternal hypotension, with fetal hypoxemia and acidosis, was observed, compared with isoflurane [19].

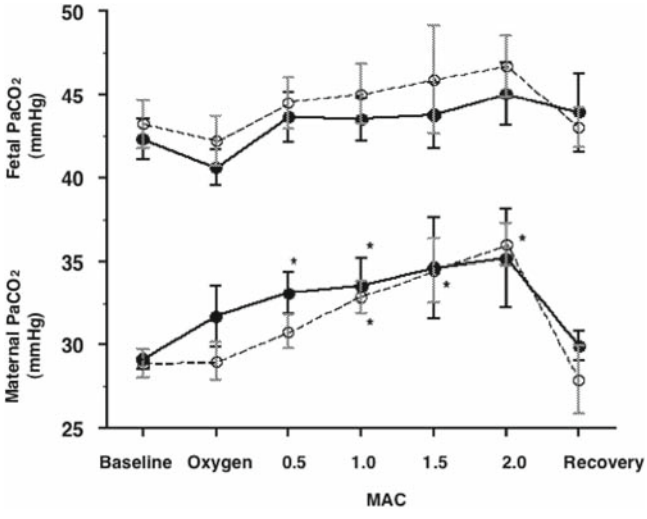

Fig. 3. Mean (±SEM) values of maternal and fetal Pa_{CO_2} prior to and at 0.5, 1.0, 1.5, and 2.0 MAC sevoflurane or isoflurane. *$P < 0.05$, significantly different from baseline value. All values were similar in the sevoflurane and isoflurane groups. *Symbols*, as in Fig. 1

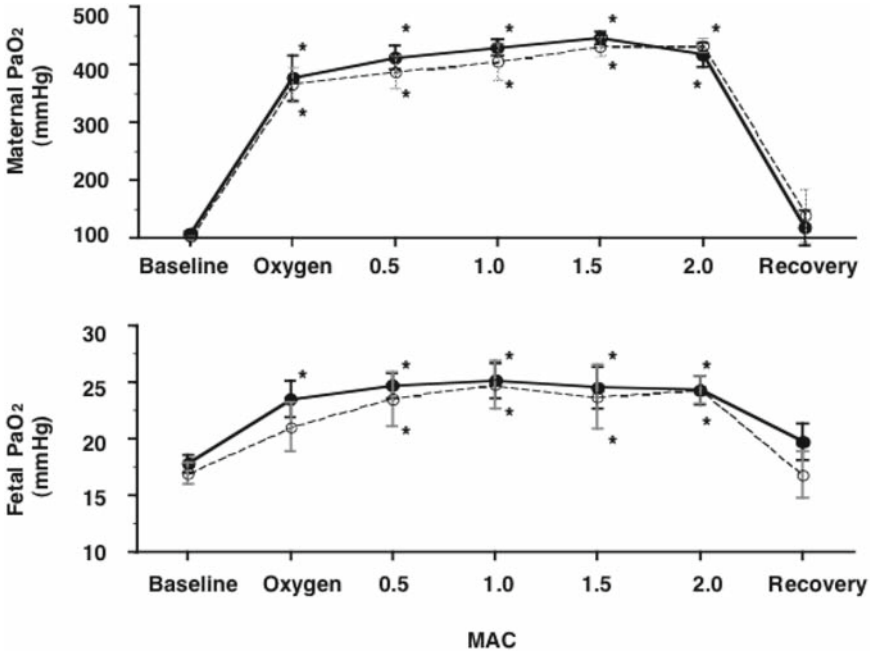

Fig. 4. Mean (±SEM) values of maternal and fetal Pa_{O_2} prior to and at 0.5, 1.0, 1.5, and 2.0 MAC sevoflurane or isoflurane. *$P < 0.05$, significantly different from baseline value. All values were similar in the sevoflurane and isoflurane groups. *Symbols*, as in Fig. 1

In the present study, we noted that fetal blood pressure decreased at 1.5 MAC with both isoflurane and sevoflurane, while maternal blood pressure did not change significantly at the same level of MAC. This was probably due to a direct cardiovascular depressant effect of the anesthetic only in the fetus. Thus, when either of these inhalation anesthetic agents is used in clinical practice at the time of delivery, or for intrauterine surgery, one should keep in mind that the concentration of these agents should be maintained at a minimum.

One might anticipate that the low concentrations of inhalational anesthetic agents utilized during an intrauterine surgical procedure may not block the fetal response to a painful stimulus. Although the MAC of these agents for the fetus has not been established, it has been reported that the concentration of inhalational anesthetic required to prevent movement in response to painful stimuli in the newborn lamb is 50% lower than that for adult sheep [20]. Given the need for uterine relaxation during intrauterine fetal surgery, other measures of tocolysis could be considered, e.g., nitroglycerin or terbutaline, combined with volatile anesthetic, has been recently recommended [6,21,22].

It has been postulated that in the gravid uterus the placental vasculature is maximally dilated, so that the perfusion pressure is a major determinant of uterine blood flow [18]. This was contradicted by a study [23] reporting that, during 1.0- to 1.5-MAC anesthesia with isoflurane, uterine blood flow increased slightly or remained unchanged, until 2.0 MAC of isoflurane was administered. These changes were attributed to the relaxing effect of the anesthetic on the myometrium [24–27], leading to a reduction in uterine vascular resistance. In the present study, uterine blood flow remained essentially unchanged. This difference from other studies may well be due to differences in experimental protocols. During a normal pregnancy, uterine blood flow fluctuates within a large range according to the circadian rhythm. The normal fetus can tolerate a reduction of approximately 50% in the utero-placental blood flow without ill effects [28]. However, an acutely or chronically compromised fetus may not be able to tolerate even a small decrease in uterine blood flow and oxygen supply. In our study, the decrease in arterial blood pressure at 1.5 MAC of either agent was more profound in the fetus than in the mother. This finding, together with the fact that fetal concentrations of volatile halogenated anesthetics remain lower than maternal concentrations [29,30], in spite of rapid placental transfer, suggests that the fetal vasculature state may be sensitive to inhalational agents. Although uterine blood flow in sheep is well maintained even at 2.0 MAC isoflurane or sevoflurane for 15–20 min, the fetal blood pressure may decrease further with prolonged exposure to inhalational anesthetic agents [29,31]. Therefore, our finding suggests that, should a high concentration of either agent be required in clinical practice, such as for intrauterine surgery, the duration of administration should be kept to a minimum. Experimental studies of the effect of maternally administered inhalational anesthetics on fetal hemodynamic and acid-base balance have demonstrated inconsistent results [19,23,29,30,32]. Fetal acidosis worsens following progressively decreases in arterial blood pressure as the anesthetic concentration increases. The primary purpose of our study was to determine whether the fetus maintains normal blood gas values with concentrations of anesthetic agents up to 2.0 MAC. Because we did not use a ventilator, mild maternal respiratory depression, as defined by a slowing of the respiratory rate, occurred when MAC was increased. However, blood gas values remained within the normal range. It should be noted that, in our study, the fetus remained well oxygenated. This finding is supported by a previous study, which showed that oxygenation remained constant even as fetal mean arterial pressure decreased significantly in both near-term and preterm fetal sheep [33,34].

We found that recovery from sevoflurane anesthesia was significantly faster compared with recovery from isoflurane, indicating that a decrease in the inspired concentration of sevoflurane results in a rapid decrease in its alveolar concentration. Thus, the present study showed that the advantage of sevoflurane, compared to isoflurane, is a more rapid emergence.

In summary, the hemodynamic responses to sevoflurane in pregnant ewes and their fetuses were similar to those with isoflurane. We conclude that the anesthetic concentrations used in clinical practice (0.5–1.0 MAC) are not likely to produce adverse effects in the mother or fetus. However, caution should be exercised when higher concentrations of volatile anesthetic may be required, such as during fetal surgery.

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