Maternal Insufflation during the Second Trimester Equivalent Produces Hypercapnia, Acidosis, and Prolonged Hypoxia in Fetal Sheep


Background: Anecdotal reports suggest that the second trimester is the safest time to conduct a laparoscopic procedure on a pregnant patient, but this supposition has not been tested empirically.

Methods: Previously instrumented preterm sheep (total n = 8) at gestational day 90 (term, 145 days) were anesthetized and then insufflated with carbon dioxide for 60 min at a pressure of 15 mmHg. Cardiovascular parameters were continuously recorded while blood gas status was determined before and at 15-min intervals during and up to 2 h after insufflation.

Results: Insufflation produced minimal maternal blood gas or cardiovascular changes except for a significant reduction in uterine blood flow. The decrease in perfusion increased fetal arterial blood partial pressure of carbon dioxide and decreased fetal pH, oxygen saturation, and oxygen content; there was also progressive fetal hypotension and bradycardia. After manually deflating the ewe, uterine blood flow returned to normal, and the fetal partial pressure of carbon dioxide and pH changes resolved within 1 h. However, fetal oxygen saturation and content remained depressed, and fetal cardiovascular status continued to decline during the 2-h postinsufflation monitoring period.

Conclusion: Previous studies with near-term sheep determined that carbon dioxide pneumoperitoneum produces respiratory acidosis but does not decrease fetal oxygenation. In contrast, the current findings indicate that in the preterm fetus, insufflation-induced hypercapnia and acidosis are accompanied by prolonged fetal hypoxia and cardiovascular depression. This result suggests that additional work should be conducted to confirm the presumed safety of conducting minimally invasive procedures during the second trimester.

THE use of minimally invasive surgical techniques to correct abdominal disorders continues to increase. For the general surgical population, the benefits of conducting a closed procedure over open surgery are reduced physiologic response to manipulation and decreased postoperative pain and analgesic use, leading to reductions in the duration of hospital stay. Various groups have proposed that gravid surgical candidates (and their fetuses) could derive these same benefits.

This positive recommendation was not always the case. During the late 1980s and early 1990s, when laparoscopy was becoming the technique of choice for many abdominal procedures, pregnancy was often stated to be a contraindication. Such statements were based on the belief that the combination of increased abdominal pressure through carbon dioxide insufflation and subsequent increased arterial blood partial pressure of carbon dioxide (Pco2) would pose an unacceptable risk to fetal wellbeing. Other surgeons felt differently, and reports of successful non–obstetric-related laparoscopic procedures were published as early as 1991. Since then, the outcomes of more than 200 laparoscopic patients and their fetuses have been described in a variety of single reports and small case studies. Appendectomy and cholecystectomy constitute the majority of surgeries conducted on gravid patients, but successful outcomes from other procedures, such as adrenalectomy, have also been reported. Immature of the pathology, the need for surgical exploration coupled with the desire to minimize fetal stress entails that the intervention be as minimally invasive as possible. With such constraints, diagnostic laparoscopy and laparoscopic surgery seem to be viable therapeutic tools for pregnant patients presenting with abdominal distress.

Despite what has become the generally accepted practice of conducting minimally invasive surgeries during pregnancy, the effects of insufflation on maternal/fetal well-being are poorly understood. Studies conducted by us and other investigators (e.g., Curet et al.) on instrumented near-term pregnant sheep have determined that maternal insufflation with carbon dioxide produces significant fetal acidosis and hypercapnia. Although the consequences of these changes in physiologic status to human fetuses are unknown, additional small animal experiments (in this case guinea pigs) suggest they may produce postnatal behavioral anomalies in the offspring. To date, the aforementioned large animal studies have been conducted toward the end of gestation. In
contrast, the Society of American Gastrointestinal Endoscopic Surgeons (Los Angeles, California) recommends that, when possible, operative interventions during pregnancy should be conducted in the second trimester§§. This policy statement is based on retrospective analyses and has not been evaluated in humans or animals in a prospective manner. To that end, the purpose of the current research was to determine the effects of carbon dioxide pneumoperitoneum on the preterm fetus. Studies were conducted on instrumented pregnant sheep at 90 days of gestation (term between 145 and 155 days), an experimental preparation that is used routinely as a model of human pregnancy.

Materials and Methods

Surgical Protocol

All aspects of the surgical and experimental protocols were approved by the Duke University Institutional Animal Care and Use Committee, Durham, North Carolina, and all experiments were conducted at this institution. Time-dated Q fever–negative pregnant ewes were obtained from a commercial supplier. On arrival at the Duke University Vivarium, each ewe received an intramuscular injection of procaine penicillin G (1,200,000 U). This penicillin regimen was repeated at 48-h intervals for the duration of the study. The animals were housed individually and were allowed ad libitum access to food and water except for a 12- to 14-h fasting period before fetal instrumentation.

Surgery and catheterizations were performed on ewes and preterm fetuses at a mean gestational age of 90 ± 1 day. After presedation with intramuscular midazolam (0.7–1.0 mg/kg), surgical anesthesia was induced with intravenous sodium thiopental (7.0 mg/kg), and the ewes’ lungs were intubated. Glycopyrrolate (0.5 mg intramuscular) was used to control mucosal secretions. Surgical anesthesia was maintained with 1–2% isoflurane in oxygen delivered by a Narkomed 2B ventilation system (North American Dräger, Telford, PA). To prevent aortocaval compression, ewes were placed (tilted) in the left semilateral position. Using a sterile technique, the maternal left femoral artery and left jugular vein were catheterized. Next, a laparotomy was performed to reveal the uterus, and the fetus was exteriorized through a small uterine incision. Both fetal femoral arteries were instrumented with polyethylene catheters (size 50; Intramedic; Clay Adams, Parsippany, NJ), and then the fetus was returned to the uterus. As the incisions were closed, a catheter was installed in the amniotic cavity, and an electromagnetic flow probe (Transonic Systems Incorporated, Ithaca, NY) was placed around the left uterine artery. On completion of the surgery (3–4 h), bupivacaine (0.25%) was infused around the incision sites, and the animal was returned to its pen. Nalbuphine hydrochloride, up to 1.0 mg/kg intramuscular (or similar opioid), was administered to the ewe as needed to control postsurgical pain. In addition to penicillin, prophylactic antibiotic therapy involved two doses of gentamicin (ewe, 80 mg intravenous; fetus, 40 mg via the amniotic catheter) and daily maternal intravenous infusions of sulfamethoxazole-trimethoprim (800 mg/160 mg in 5% glucose). All animals were allowed at least 72 h to recover from instrumentation before conducting the insufflation experiments.

Maternal Pneumoperitoneum

On the day of experimentation, anesthesia was again provided by the combination of midazolam, thiopental, and isoflurane in oxygen. (As before, the ewe was placed in the left-lateral tilt position.) In this setting, isoflurane concentration was kept at exactly 1.5% as measured by an airway gas monitor (Datex Instrumentation Corporation, Helsinki, Finland). The ewe’s ventilation was actively managed before, during, and after pneumoperitoneum to keep end-tidal carbon dioxide below 35 mmHg; other standard operative monitoring devices (e.g., pulse oximetry) were also used. Body temperature was maintained at 39.5°C with the use of a Bair Hugger body warming system (Arizant Healthcare Incorporated, Eden Prairie, MN). The arterial catheters were flushed with heparinized saline and then attached to force transducers (Transpac®; Abbott Laboratories, North Chicago, IL); maternal and fetal cardiovascular data along with uterine blood flow (UBF) were recorded using a 16-channel PowerLab system (ADInstruments, Colorado Springs, CO). Fetal arterial pressure measurements were corrected for variations in intrauterine pressure by subtracting simultaneously measured amniotic fluid pressure.

After a baseline recording period, 10-mm Versaport trocars (United States Surgical Corporation, Norwalk, CT) were inserted under direct vision into the four quadrants of the peritoneal cavity using an open technique for each placement (i.e., we did not preinsufflate with a Veress needle). The abdomen was then inflated with carbon dioxide at a rate of 1 l/min to a final pressure of 15 mmHg with a high-flow clinical insufflator (Stryker Endoscopy, Santa Clara, CA). After 60 min, the trocars were removed, and the abdomen was manually deflated. Each ewe was maintained on anesthesia for an additional 2 h. During the study, maternal and fetal arterial blood samples were obtained at regular intervals; blood gas status was quantitated with a Gem Premier 3000 blood gas analyzer (Instrumentation Laboratory, Lexington, MA).

Statistical Analysis

Arterial blood gas data are presented as group mean ± SD. After determining fetal arterial oxygen saturation and

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partial pressure, along with hemoglobin content, fetal arterial blood oxygen content was calculated using the formula\textsuperscript{12}

\[
\text{oxygen content} = (\text{Hemoglobin} \times \text{oxygen saturation} \times K_{\text{oxygen capacity}}) + (P_{O_2} \times 0.003),
\]

where \(P_{O_2}\) is partial pressure of oxygen. The constant 0.003 is the solubility coefficient for oxygen in blood. The oxygen capacity constant \(K\) is 1.36 for fetal sheep.\textsuperscript{13}

Maternal and fetal cardiovascular data (heart rate and mean arterial pressure [MAP]) were averaged at 2-min intervals for each animal and presented as group means. For the UBF data, a baseline value was calculated for each anesthetized animal by averaging the measurements taken during the prepneumoperitoneum period. Subsequent UBF measurements taken during and after insufflation were divided by this baseline UBF value and expressed as percent of baseline.

For all physiologic measurements, changes over the course of treatment were tested statistically with mixed-effects repeated-measures linear regression models (Proc Mixed; SAS, Cary, NC). Any differences/changes were assumed significant at \(P < 0.05\). This method treated sheep as random effects and accounted for the correlation of measures from the same sheep. Percent change in UBF during insufflation was compared to baseline and to deflation using all measurements. The other adult cardiovascular responses to insufflation have been well established, so maternal heart rate and MAP changes are described but were not analyzed. Maternal and fetal arterial blood gases at baseline (time 0, immediately before insufflation) were compared to the 60-min time point (immediately before deflation) and to the values at 120 and 180 min (1 and 2 h after deflation, respectively) using the Dunnett adjustment for multiple comparisons. Fetal heart rate and MAP after baseline were tested for significant change over time.

**Results**

A total of eight instrumented preterm sheep were used in this study. All of the ewes tolerated the procedure well, with no maternal intrainsufflation or postinsufflation complications.

The maternal physiologic responses to 60 min of carbon dioxide insufflation are presented in figures 1 and 2. Pneumoperitoneum produced moderate increases in maternal heart rate and MAP (fig. 1) that gradually resolved after the peritoneal cavity was deflated. More striking was the significant reduction in UBF that occurred within the first 10 min of insufflation and remained reduced for the ensuing 50 min. From an average starting point of 186 ± 101 ml/min, insufflation produced a mean decrease in UBF of 30.5% (SE = 3.5; \(P = 0.0001\) vs. baseline); median individual decreases ranged from 21 to 46% (the decrease in UBF was statistically significant for each animal). After deflation, UBF rapidly returned to, and at times exceeded, baseline; this represented a mean 32.4% increase over the rate of flow during insufflation (95% confidence limits, 28.9–35.9%; \(P < 0.0001\)). With respect to maternal arterial blood gas status (fig. 2), the ewes were well ventilated throughout the procedure, with average end-tidal carbon dioxide changing by only 1.75 units during insufflation (\(P < 0.05\)). In-sufflation did produce modest maternal arterial hypercapnia (an increase of 10.6 mmHg; \(P < 0.0001\) vs. baseline) and acidosis (a decrease in mean pH of 0.098; \(P < 0.0001\)). Before insufflation, the mean end-tidal/artrial carbon dioxide difference was 5.5 ± 3.9 mmHg. The difference peaked at the 60-min time point (11.3 ± 4.6 mmHg; \(P < 0.05\)) but resolved within 15 min of
deflation of the abdomen. Maternal arterial pH and $P_{CO_2}$ returned to baseline levels by the 120-min time point (i.e., within 1 h of desufflation). Maternal arterial blood oxygen saturation remained at 100% throughout the study, whereas arterial $PO_2$ fluctuated between 350 and 500 mmHg.

The fetal physiologic responses are presented in figures 3 and 4. Maternal pneumoperitoneum resulted in protracted decreases in fetal heart rate ($P = 0.0091$) and MAP ($P = 0.0103$). The decreases started shortly after insufflation and continued throughout the postinsufflation monitoring period (fig. 3). Heart rate reached a nadir of $146 \pm 22$ beats/min at the 180-min time point (2 h after deflation), whereas the nadir for fetal MAP was $28 \pm 2$ mmHg, reached at the 120-min time point (1 h after deflation); pressure remained at this level for the duration of the study. Commensurate with the cardiovascular changes, pneumoperitoneum also produced significant changes in fetal arterial blood gas status (fig. 4). Fetal $P_{CO_2}$ increased an average of 15.5 mmHg during insufflation ($P < 0.0001$) but returned to only slightly above baseline at 1 and 2 h after deflation ($P = 0.0944$). Fetal pH decreased an average of 0.08 units during insufflation ($P < 0.0001$) and then returned to baseline at the 120- and 180-min time points ($P = 0.0944$). Fetal arterial blood oxygen saturation decreased an average of 9.05 units during insufflation ($P < 0.0001$) and remained significantly below baseline by an average of 10.05 units at both 120 and 180 min (1 and 2 h after deflation; $P = 0.0001$). From a starting point of $2.9 \pm 0.7$ ml $O_2/100$ ml, fetal oxygen content mirrored the saturation decrease (fig. 4, bottom panel), albeit in this case reaching its nadir ($2.0 \pm 0.9$ ml $O_2/100$ ml) at the 15-min point. Fetal hemoglobin concentration stayed constant throughout the experimental period (data not shown).

**Discussion**

Current Society of American Gastrointestinal Endoscopic Surgeons guidelines for conducting minimally invasive non-obstetric-related surgery during pregnancy recommend that, when possible, the procedure be conducted during the second trimester. However, the empirical evidence to support this stance is not strong...
because it is based mainly on case reports and small serial studies. One exception is a retrospective analysis of the Swedish Health Registry. Between 1973 and 1993, 2,181 women with singleton pregnancies underwent a laparoscopic procedure while 1,522 underwent an open procedure; for both groups, the reasons for surgery were not related to pregnancy status. Group comparisons determined that there were no differences in fetal outcome when the procedure was conducted between the 4th and 20th weeks of gestation. Unfortunately, questions about the safety of later term procedures were left unanswered because of insufficient numbers. Conversely, the experimental animal studies conducted to date have focused on a distinct (i.e., ± 1 gestational day) second trimester time point.

In general, the maternal physiologic responses to pneumoperitoneum mimicked those reported for near-term sheep. The principal findings were the 30% reduction in UBF (despite increases in both maternal heart rate and MAP) and the appearance of modest hypercapnia and acidosis. These effects result from the combination of increased intraperitoneal pressure and the presence of carbon dioxide in the peritoneal space. Currently, carbon dioxide is the most frequently used gas for insufflation because it is noncombustible and has a high plasma solubility. However, as noted, carbon dioxide is not physiologically inert with respect to its actions on a patient’s respiratory and circulatory status. Researchers have evaluated the use of other gases (e.g., helium, argon) with varying results. In one study with near-term sheep, insufflation with helium produced less maternal hypercapnia and acidosis compared with carbon dioxide, but there was a similar degree of impaired fetal perfusion (i.e., reduction in UBF). As a result, it is uncertain whether use of a different insufflation gas would offer substantive benefits to the mother and the fetus, especially because the gases studied to date have higher risks of gas emboli development (compared with carbon dioxide) because of their decreased solubility.

One maternal observation of note was the significant difference between the end-tidal and arterial blood carbon dioxide levels. Previous animal studies have reported a similar finding, but the clinical significance of this difference is unclear. An increase in the end-tidal/arterial carbon dioxide gradient has been observed in healthy laparoscopic cholecystectomy patients, but some have suggested that this does not apply to gravid humans. Because other researchers have argued that capnography is an inaccurate means of assessing changes in arterial PCO2 concentration, various organizations continue to recommend both end-tidal carbon dioxide and arterial blood gas monitoring for pregnant patients undergoing a minimally invasive surgical procedure (e.g., The European Association for Endoscopic Surgery, Eindhoven, The Netherlands). Our data support this recommendation.

We have determined that maternal pneumoperitoneum has profound effects on the preterm fetus. Collectively, the responses to insufflation were indicative of an episode of fetal distress. The decrease in perfusion (i.e., UBF) was no doubt a precipitating factor in the fetal cardiovascular and blood gas changes that also occurred during the 60 min of carbon dioxide pneumoperitoneum. Of particular concern was that the decrease in fetal oxygenation along with the fetal bradycardia and hypotension persisted long after deflation and resolution of the hypercapnia and acidosis. Near-term animals were not used in the current experiment, but one can make qualitative comparisons between our preterm observa-
tions and previous reports on the effects of maternal insufflation on the older fetus. Reviewing results from several different research groups \(^6,^{14-17}\) (and allowing for procedural differences), the general responses to near-term carbon dioxide insufflation are maternal and fetal respiratory acidosis, and some have reported decreases in perfusion \((i.e., \text{decreased UBF})\). However, no group (including our own \(^7\)) has reported a decrease in fetal oxygenation. As a result, we are led to conclude that the preterm fetus exhibits an increased sensitivity to maternal carbon dioxide pneumoperitoneum.

Different factors may contribute to the preterm fetal responses. Certainly the reduction in UBF was an initiating event, and there is the possibility that the 60 min of pneumoperitoneum produced placental injury. However, perfusion changes alone cannot account for the continued decrease in fetal oxygenation because UBF was at or above baseline during the postinsufflation period. Instead, the initial physiologic changes (including our own \(^7\)) has reported a decrease in fetal oxygenation. As a result, we are led to conclude that the preterm fetus exhibits an increased sensitivity to maternal carbon dioxide pneumoperitoneum.

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The current fetal sheep study is not without its limitations. Principal among these is the absence of an anesthetic control group that would have allowed us to separate out any isoflurane-specific effects on the ewe and fetus. Although earlier sheep work has suggested that the actions of this volatile anesthetic are modest at the concentration we used, \(^{28,29}\) the potential for isoflurane to augment the pneumoperitoneum-induced responses cannot be excluded. Regional anesthetic techniques have been used for a variety of different laparoscopic procedures, \(^{30}\) but the fetal responses to maternal pneumoperitoneum under this method of pain control have yet to be evaluated. A second limitation is that we did not extend the monitoring period or recover the ewes to ascertain how long fetal oxygenation remains depressed. At some later point, in the face of adequate UBF and normal nutrient exchange, fetal blood oxygen levels would be expected to return to baseline. Coincident with this is that the long-term significance of the observed midterm changes in blood gas status remains to be determined. A prolonged or severe episode of hypoxia has long been recognized as a major cause of intrauterine brain injury, but, to some extent, the younger fetus is more resistant to neurologic damage than the older conceptus. \(^{21}\) This resiliency not withstanding, we previously determined that insufflation of pregnant guinea pigs at an equivalent midgestational time point produced behavioral anomalies in the offspring. \(^9\) For the current study, we were not in a position to conduct outcome or histologic assessments of the sheep to establish a causal relation between pneumoperitoneum-induced hypoxia and subsequent neurologic injury; this is a focus of current investigations along with testing methods for improving fetal physiologic status during insufflation.

In conclusion, maternal carbon dioxide pneumoperitoneum during the second trimester equivalent produces significant hypercapnia and acidosis, along with prolonged hypoxia. Collectively, the fetal effects of insufflation at this gestational age seem more severe than at near term, but the clinical importance of these observations remains unclear. At a minimum, the current findings suggest that additional work should be conducted to confirm the presumed safety of conducting minimally invasive procedures during the second trimester.

References


