17
Anesthesia for Nonobstetric Surgery During Pregnancy

It has been estimated that every year in the United States about 50,000 pregnant women (0.5–2.2%) will receive anesthesia for various surgical indications during their pregnancy. The purpose of this surgery may be (1) to prolong gestation, (2) unrelated to the pregnancy, or (3) to correct fetal anomalies. Hence, an understanding of the effects of different anesthetic drugs and techniques on the mother and fetus is essential to the safe administration of anesthesia to pregnant women undergoing surgery. Recently, a question of preoperative pregnancy testing in adolescents has been raised. The authors observed retrospectively 412 adolescent women undergoing surgery. The overall incidence of a positive test was 1.2%. The authors concluded that mandatory pregnancy testing is advisable in all adolescent surgical candidates aged 15 years and older.[1] However, compulsory pregnancy testing is not practiced in all hospitals; a

S. Datta et al., *Obstetric Anesthesia Handbook*,
DOI 10.1007/978-0-387-88602-2_17,
© Springer Science+Business Media, LLC 2006, 2010

hospital policy should be established after a discussion with the obstetric as well as anesthesia divisions.

Ideal anesthetic consideration for pregnant women undergoing surgery should include maternal safety, fetal well-being, and continuation of pregnancy.

Maternal Safety

A thorough understanding of physiological changes during pregnancy is very important. This has been discussed in Chapter 1. The most important points will be reiterated here.

I. Respiratory system changes
   A. Capillary engorgement of respiratory mucous membrane
   B. Increased minute ventilation due mainly to an increase in tidal volume and to a lesser extent to an increase in respiratory rate
   C. Decreased end-tidal CO_2 and arterial CO_2 and decreased arterial to end-tidal CO_2 difference
   D. Decreased functional residual capacity
   E. Increased oxygen demand
II. Cardiovascular system changes
   A. Increased cardiac output
   B. Increased blood volume
   C. Aortocaval compression from the gravid uterus
III. Gastrointestinal system changes
   A. Decreased lower gastroesophageal sphincter pressure
IV. Central and peripheral nervous system changes
   A. Decreased anesthetic requirement both for general, epidural, and spinal anesthesia

Fetal Well-Being

Avoidance of the teratogenic effects of anesthetics on the fetus is paramount in the care of pregnant women undergoing nonobstetric surgery. One should also try to avoid derangement of fetal homeostasis, which can be affected directly and indirectly by anesthetic drugs and techniques.

The teratogenic effect of anesthetic drugs is a very controversial issue that has no clear-cut answer. Exposure to anesthetic agents may be either acute during surgery – sedatives, hypnotics, narcotics, muscle relaxants, local anesthetics, oxygen and carbon dioxide, or inhalational anesthetics – or chronic because of occupational exposure to inhalational anesthetics.

Acute Exposure to Anesthetics

Even though human studies of the effect of acute exposure of anesthetics demonstrated an increased incidence of spontaneous abortion, they failed to show any teratogenic effects on the fetus.[1–5] In 1986 Duncan and colleagues retrospectively reviewed the incidence of congenital anomalies and spontaneous abortions in 2,565 pregnant women who underwent surgery.[6] These women were matched with a control group consisting of a similar number of pregnant women with similar maternal ages as well as areas of residence. *No significant differences in the rate of congenital anomalies were observed between the study and control groups. However, there was a significant increase in spontaneous abortions in women who underwent surgery during their first and second trimesters. One of the drawbacks of this study was that the vast majority of surgeries were performed with the woman under general anesthesia, so one could not differentiate the effect of regional or general anesthesia on the incidence of spontaneous abortion.* Mazze and Kallen retrospectively analyzed pregnant women from Swedish health care registries (1973–1981).[7] Out of 720,000 cases, 5,405 underwent surgery. The incidence of congenital malformation was not different between the group that underwent surgery and the one that did not; however, there was a slightly higher incidence of prematurity and intrauterine growth retardation in the group that had surgery. The authors did not observe any association of this adverse outcome with the anesthetic used or the operation the woman underwent.

Chronic Exposure to Anesthetics

Several reports of increased congenital anomalies as well as spontaneous abortions among anesthesiologists and other operating room personnel have been published.[8,9] An important

report regarding this issue was published by an ad hoc committee of the American Society of Anesthesiologists.[10] They found an increased risk of congenital anomalies and spontaneous abortions in women working in operating room areas when compared with non-operating room female hospital employees. In a separate study, an increased rate of spontaneous abortions was reported among female dentists and assistants who used inhalational anesthetics as compared with those who used local anesthetics in their practice.[11,12] On the other hand, in a different study, Ericson and Kallen were unable to demonstrate an increased risk of adverse fetal outcome in operating room or anesthesia nurses as compared with a control group of medical floor nurses.[13]

Until now, no causal relationship has been proved between the chronic exposure to inhalational anesthetics and fetal anomalies. However, the importance of the scavenging system has been stressed in the operating room environment. Rowland et al. observed the effect of nitrous oxide on pregnancy in 459 dental assistants and divided them into five groups: (1) unexposed, (2) low scavenged, (3) high scavenged, (4) low unscavenged, and (5) high unscavenged. The mean time to conception was significantly higher in the high unscavenged group.[14]

Effect of Anesthetics on the Fetus

Teratogenic studies of different anesthetic agents have been studied mainly in animals. It is very difficult as well as impractical to extrapolate these results to humans. Fortunately, no commonly used anesthetics, when given acutely are known teratogens. Subtle effects on the fetal brain are the subject of intense investigations at present.

Sedative and Hypnotic Agents

Barbiturates have been used in humans as induction agents for many years. Although there is a conflicting report in animals regarding the teratogenic effect of barbiturates, in pregnant women these agents have been found to be safe.[15] Phenothiazines have also been observed to be without any

adverse effect in humans.[16] The association of minor tranquilizers with teratogenicity is controversial, although retrospective studies have shown diazepam and chlordiazepoxide to be associated with congenital malformations.[17,18] On the other hand, more recent studies did not find any increased risk of congenital anomalies following use of diazepam.[19] Midazolam has not been observed with any teratogenicity. Recently published literature on women attempting to commit suicide during pregnancy by taking large doses of drugs such as diazepam, medazepam, promethazine, and meprobamate did not show that these drugs were fetotoxic.[20–22]

Opioids

Geber and Schramm observed the teratogenicity of a wide variety of narcotics administered to pregnant hamsters at critical periods of fetal central nervous system development.[23] Comparative studies using single or multiple doses showed increased fetal anomalies with diacetylmorphine, thebaine, pentazocine, morphine, hydromorphone, as well as meperidine. On the other hand, other authors observed that the chronic administration of morphine, fentanyl, sufentanil, or alfentanil in pregnant rats was not associated with any teratogenic effect.[24–26] There is also no evidence that these opioids are associated with teratogenicity in humans.

Muscle Relaxants

There is no evidence of an adverse effect in fetal development following the use of muscle relaxants.

Local Anesthetics

In a very large study by the Collaborative Perinatal Project, and in other studies, no evidence of teratogenicity was found in pregnant rats following the administration of benzocaine, procaine, tetracaine, or lidocaine.[27–29] *In contrast, the use of cocaine is associated with fetal congenital malformations both in humans and animals.*[30] *This may be explained by cocaine-mediated vasoconstriction and, hence, fetal tissue hypoxia.*

Oxygen and Carbon Dioxide

Hypoxia as well as hypercarbia have been associated with teratogenicity in animal species.[31,32] Although a high concentration of inspired oxygen at atmospheric pressure does not produce any adverse effects,[33] hyperbaric oxygen exposure is associated with fetal anomalies in animals.[34]

Inhalation Anesthetics

The addition of inhalational anesthetics such as nitrous oxide or halogenated agents to oxygen has become a routine practice when administering general anesthesia. Some of these agents have been implicated in the development of fetal anomalies as well as in premature births.

Nitrous Oxide. Interest in the teratogenic effect of nitrous oxide has grown significantly among anesthesiologists since Nunn and colleagues observed the effect of the short-term nitrous oxide anesthetic administration on plasma concentrations of methionine, tryptophan, phenylalanine, and *S*-adenosylmethionine in humans.[35] The authors observed a 15% reduction in tryptophan concentration after exposure to 60–70% nitrous oxide for a mean duration of 88 min. The plasma methionine concentration decreased significantly following exposure to 50% nitrous oxide for up to 11 days in rats.[36] Using nitrous oxide during surgery and up to 24 h postoperatively, Skacel and colleagues observed a significant decrease in the plasma methionine concentration following major vascular surgery in humans.[37] Recovery took place following discontinuation of nitrous oxide administration. The main reason for the decreased plasma methionine concentration is related to inhibition of enzyme methionine synthetase.[35] Thus the teratogenic effect of nitrous oxide may be related to the interference with DNA synthesis by altering folate metabolism[35] (Fig. 17-1). Keeling and colleagues observed the effect of pretreatment with folinic acid on the teratogenic effect of nitrous oxide in rats.[38] Major skeletal abnormalities in the group receiving nitrous oxide without pretreatment increased five times as compared with the control group, whereas the group that was pretreated with folinic acid was not significantly

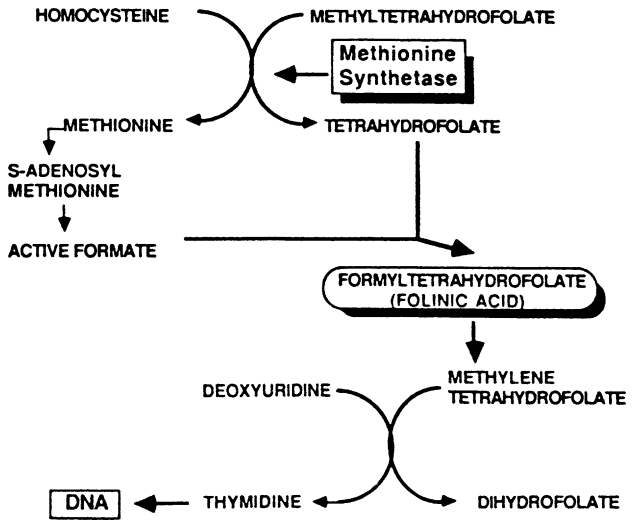

Figure 17–1. Mechanisms of the interference of nitrous oxide in DNA synthesis. Nitrous oxide directly blocks the transmethylation reaction by which methionine is synthesized from homocysteine and methyltetrahydrofolate. Nitrous oxide oxidizes vitamin B_{12}, the cofactor of the enzyme methionine synthetase. (From Levinson and Shnider.[55] Used with permission.)

different from controls. Mazze et al. also observed teratogenicity in rats after exposure to 50% or more of nitrous oxide for 24 h on day 8 of pregnancy.[39] Interestingly, the teratogenic effect was prevented by the addition of fentanyl or halogenated anesthetics with nitrous oxide.[40,41] Hence the authors concluded that the mechanism of teratogenicity following nitrous oxide exposure may not be related to interference in DNA synthesis but rather to a physiological effect of nitrous oxide, such as reduction in uterine blood flow due to increased sympathetic activity.[41] However, when an α-antagonist like phenoxybenzamine was used, the investigators could not completely abolish the teratogenic effect of nitrous oxide.[42] In summary, although in rats there is a relationship between the use of nitrous oxide

and teratogenicity, the exact mechanism is not clear at the present time. In humans, short exposures to nitrous oxide during the second trimester were not associated with any adverse effect.[43]

Halogenated Anesthetics. Halothane, enflurane, and isoflurane at physiological minimum alveolar concentrations are not associated with any teratogenicity in rats,[41] nor has evidence of teratogenicity been seen in humans with these agents.[19] The newer inhalational agents desflurane and sevoflurane are also not associated with any teratogenicity.[44]

Effects on the Fetal Brain: Behavioral Teratogenicity

The brain continues to develop throughout gestation and after birth.[45] Enduring change in behavior without obvious structural abnormalities has been termed behavioral teratogenicity. It is believed that compounds that interact with NMDA (*N*-methyl-D-aspartate) and GABA (gamma aminobutyric acid) receptors can trigger programmed cell death, or apoptosis, in developing brain.[45] Although apoptosis is a normal part of embryogenesis, some animal experiments have demonstrated functional or behavioral abnormalities accompanying an increase in cell death, such as impaired maze learning. These changes may persist at least into young adult life.[46] Because many anesthetic agents are NMDA antagonists or potentiators of GABA transmission, it is conceivable that anesthetic exposure during brain development could lead to neurodegeneration.

In a study of neonatal rats, Jovtovic-Todorovic et al.[46] observed significant increases in staining for apoptosis throughout the brain when the rats were exposed to 6 h of midazolam, N_2O, and isoflurane anesthesia at 7 days of age (which corresponds to the peak of synaptogenesis in the rat, a period likely to span many weeks from midgestation to the postnatal period in humans). The authors, however, used doses that produce a surgical plane of anesthesia in the rat, which were substantially larger than those commonly employed in humans. They also observed evidence of impaired synaptic function in the

hippocampus, important for memory formation. Studies in animals allowed to mature into young adulthood showed impaired learning in various maze tests, compared to air- and vehicle-treated controls. Subsequent investigations by these and other laboratories have demonstrated similar results with other anesthetics, including ketamine and propofol, in both anesthetic and even subanesthetic doses.[45,47,48] Guinea pigs exposed to isoflurane -nitrous oxide -midazonlam for 4 h in utero also demonstrated increased apoptosis and neuronal cell loss throughout the brain.[48] There is even some preliminary data in non-human primates that GABA-mimetic agents can induce apoptosis in developing brain.[47]

As with all non-human animal studies, extrapolation is difficult to determine the degree of risk anesthetics pose to humans undergoing general anesthesia, or fetuses exposed in utero to maternal anesthesia. Hopefully, in future, a better understanding of the mechanism of toxicity will also point to strategies to block the harmful effects. While laboratory and eventual clinical investigations proceed, it is prudent to assume that general anesthetics are potentially toxic to the developing fetal brain, and their use in obstetric anesthesia should continue to be a rare event reserved for emergencies.

Continuation of the Pregnancy

Surgery during pregnancy is associated with a higher incidence of premature labor and spontaneous abortion. The incidence is higher in lower abdominal, pelvic, and cervical surgery. Tocolytic drugs, both for prophylactic and therapeutic reasons, are used quite often to prevent premature delivery.

Recommendations for Minimizing Chances of Abortion or Premature Labor

Elective surgery should be postponed until after delivery. In semielective cases, it is best if surgery can be postponed until after the first trimester. In emergency cases, the anesthetic of choice should depend on the site and extent of the

surgery to be performed. If possible, regional anesthesia, e.g., spinal, epidural, or nerve block, is advisable. However, general anesthesia can be administered if necessary.

Preoperative medications, if necessary, may include benzodiazepines and opioids. Routine, nonparticulate antacid should be used, and rapid-sequence induction is often selected. *Although there is no general consensus, it is reasonable to use an endotracheal tube for longer or more extensive procedures.* Depending on the duration of surgery, one can use either depolarizing or nondepolarizing muscle relaxants. Anesthesia can be maintained with nitrous oxide, oxygen, and halogenated anesthetics. Morphine, fentanyl, sufentanil, or alfentanil can be used as analgesics. *Hyperventilation should always be avoided because it can reduce uteroplacental perfusion as well as shift the maternal hemoglobin dissociation curve to the left.*

For regional anesthesia, maintenance of normal blood pressure is absolutely necessary, and the routine use of oxygen by face mask is recommended. *Whether general or regional anesthesia has been chosen, left uterine displacement from the mid second trimester onward is mandatory.*

Routine monitoring should include blood pressure, electrocardiogram, oxygen saturation, capnograph, and temperature. In addition, fetal heart rate monitoring, if possible, should be performed from 24 weeks onward. Close communication between the anesthesiologist and obstetrician regarding fetal heart rate monitoring is necessary as well as interpretation of the tracings. Because most of the medications used for general anesthesia can abolish the fetal heart rate variability, the baseline fetal heart rate should be the main indicator of fetal well-being during general anesthesia. Depending upon the location of surgery, tocodynamometry can be used to monitor uterine contractions. This obviously becomes routine in the postoperative period when treating pregnant women with preterm contractions with tocolytics.

Recently, laparoscopic surgery during pregnancy has been used with success. One must have a basic knowledge of physiological changes during pregnancy. During laparoscopic cholecystectomy, women are placed in a head-up position during dissection and in a head-down position for irrigation. In parturients, these positions may have significant cardiovascular

and respiratory effects. Peritoneal insufflation pressure should be kept low because of the possibility of aortocaval compression. Ventilation should be optimal to maintain end-tidal PCO_2 at 32–34 mmHg. Bhavani Shankar et al. prospectively evaluated the $PaCO_2$–$ETCO_2$ difference in eight parturients undergoing laparoscopic cholecystectomy with CO_2 pneumoperitoneum. The intra-abdominal pressures were maintained around 15 mmHg. These women underwent surgery with general anesthesia during the second and third trimester of their pregnancies. Adjusting minute ventilation to maintain the $ETCO_2$ at 32 mmHg, the arterial blood gases (alpha-stat method) were measured at fixed surgical phases: preinsufflation, during insufflation, postinsufflation, and after completion of surgery.

We found no significant differences in either mean $PaCO_2$–$ETCO_2$ gradient or $PaCO_2$ and pH during the various phases of laparoscopy. During the surgical phase (i.e., preinsufflation, insufflation, and postinsufflation), the maximal $PaCO_2$–$ETCO_2$ difference detected was 3.1 mmHg (range, 1.1–3.1 mmHg). It appears that $ETCO_2$ correlates well with arterial CO_2, and adjusting ventilation to maintain $ETCO_2$ also maintains optimal maternal arterial CO_2.[49,50] We also showed that cardiac output decreases by about 30% during laparoscopy surgery in pregnant subjects and therefore vasopressors (ephedrine) should be administered to maintain blood pressures within 20% of the baseline.[51]

Intrauterine Surgery

Intrauterine surgery is becoming popular for treating fetal congenital anamolies.[52–55] In the majority of cases the pregnancy is continued, whereas for the ex-utero intrapartum treatment (EXIT) surgery is performed on the fetus on placental support followed by delivery (Fig. 17-2). Maternal and fetal considerations for anesthetic implications have already been discussed. The minimum alveolar concentration for halothane has been observed to be 50% lower in the fetal lamb as compared with the pregnant ewe (0.33% vol. vs. 0.69% vol, so the fetus will be anesthetized if the mother is)[52]. In case of EXIT

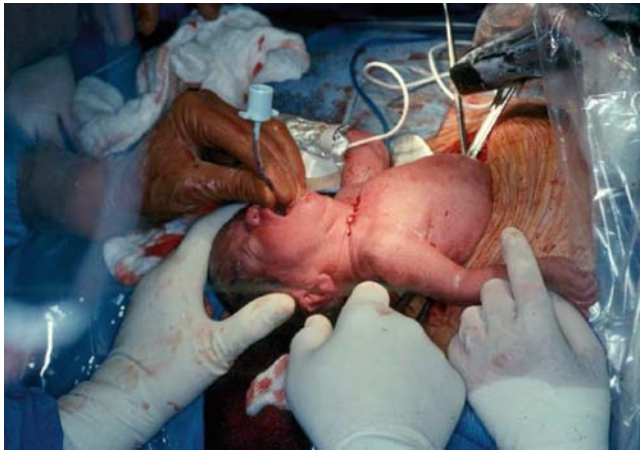

Figure 17–2. A fetus with a neck tumor. Airway being secured before disrupting uteroplacental–umbilical cord blood flow.

procedure, uterine relaxation is also important to prevent uterine contraction and separation of placenta. This is achieved by 1.5–2.0 MAC inhalational agents. Ephedrine or phenylephrine is used for maintenance of baseline blood pressure to maintain uteroplacental blood flow. Following delivery of the infant, inhalation anesthetic should be discontinued and use of uterotonic drugs is mandatory.

In intrauterine surgery, fetal movements are to be avoided. This can be accomplished by administering anesthetics and opioids to the mother, which will ultimately reach the fetus via the placenta in varying concentrations. Epidural or combined spinal-epidural can also be used for the surgery, and uterine relaxation can be achieved with nitroglycerin. Muscle relaxants and opioids can be directly administered to the fetus. Pancuronium maintains better fetal cardiovascular stability than does curare; vecuronium can also be used.[53] To prevent hypothermia of the fetus, the operating room should be kept as warm as possible and the uterus should be irrigated with a warm solution. Fetal monitoring will depend on the surgery and will vary from continuous fetal heart rate monitoring to

pulse oximetry and transcutaneous electrode measurement of blood pH and PO_2 if a body part is accessible.

Following surgery, monitoring of the fetal heart rate and uterine contractions should be routine because of the possibility of the onset of premature labor. Tocolytic drugs like magnesium sulfate are used for the prevention of preterm labor following discontinuation of the inhalation anesthetic at the conclusion of the surgery. For postoperative pain relief, patient-controlled intravenous analgesia can be used. If an epidural catheter is present, use of epidural morphine will be ideal.

Recently, percutaneous fetal aortic valve and pulmonary valve dilatations are being performed for hypoplastic ventricles via ultrasound guidance. These procedures can be performed under general or regional anesthesia. If general anesthesia is contemplated, the authors do not generally use more than 1 MAC of inhalational agent as uterine relaxation is not preferred in this approach. It is preferred that the fetus does not change positions as a result of uterine relaxation. Fetal analgesia and paralysis is provided by ultrasound-guided fetal intramuscular injections of fentanyl (30 μg) and vecuronium. Maternal depth of anesthesia is monitored via BIS. Maintenance of maternal paralysis is necessary to avoid unexpected maternal movements. An additional advantage of not using excessive maternal inhalational agents is that it avoids undue hypotension, and thus maintains uteroplacental blood flow. The recovery of the mother is quick and minimal postoperative analgesia is required.[54]

References

1. Azzam FJ, Padda GS, DeBoard JW, Krock JL, Kolterman SM. Preoperative pregnancy testing in adolescents. *Anesth Analg*. 1996;82(1):4–7.
2. Shnider SM, Webster GM. Maternal and fetal hazards of surgery during pregnancy. *Am J Obstet Gynecol*. 1965;92:891–900.
3. Brodsky JB, Cohen EN, Brown BW, Jr., Wu ML, Whitcher C. Surgery during pregnancy and fetal outcome. *Am J Obstet Gynecol*. 1980;138(8):1165–1167.

4. Smith BE. Fetal prognosis after anesthesia during gestation. *Anesth Analg*. 1963;42:521–526.
5. Kennedy RL, Miller RP, Bell JU, et al. Uptake and distribution of bupivacaine in fetal lambs. *Anesthesiology*. 1986;65(3):247–253.
6. Duncan PG, Pope WD, Cohen MM, Greer N. Fetal risk of anesthesia and surgery during pregnancy. *Anesthesiology*. 1986;64(6): 790–794.
7. Mazze RI, Kallen B. Reproductive outcome after anesthesia and operation during pregnancy: a registry study of 5405 cases. *Am J Obstet Gynecol*. 1989;161(5):1178–1185.
8. Vaisman AI. [Working conditions in the operating room and their effect on the health of anesthetists]. *Eksp Khir Anesteziol*. 1967;12(3):44–49.
9. Knill-Jones RP, Rodrigues LV, Moir DD, Spence AA. Anaesthetic practice and pregnancy. Controlled survey of women anaesthetists in the United Kingdom. *Lancet*. 1972;1(7764):1326–1328.
10. Occupational disease among operating room personnel: a national study. Report of an Ad Hoc Committee on the Effect of Trace Anesthetics on the Health of Operating Room Personnel, American Society of Anesthesiologists. *Anesthesiology*. 1974;41(4):321–340.
11. Cohen EN, Gift HC, Brown BW, et al. Occupational disease in dentistry and chronic exposure to trace anesthetic gases. *J Am Dent Assoc*. 1980;101(1):21–31.
12. Cohen EN, Brown BW, Jr. Occupational hazards of anaesthesia. *Br Med J*. 1980;281(6254):1568–1569.
13. Ericson HA, Kallen AJ. Hospitalization for miscarriage and delivery outcome among Swedish nurses working in operating rooms 1973–1978. *Anesth Analg*. 1985;64(10):981–988.
14. Rowland AS, Baird DD, Weinberg CR, Shore DL, Shy CM, Wilcox AJ. Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. *N Engl J Med*. 1992;327(14):993–997.
15. Heinonen OP, Slone D, Shapiro D, eds. *Birth Defects and Drugs in Pregnancy*. Littleton, MA: Publishing Sciences Group; 1977.
16. Slone D, Siskind V, Heinonen OP, Monson RR, Kaufman DW, Shapiro S. Antenatal exposure to the phenothiazines in relation to congenital malformations, perinatal mortality rate, birth weight, and intelligence quotient score. *Am J Obstet Gynecol*. 1977;128(5):486–488.
17. Safra MJ, Oakley GP, Jr. Association between cleft lip with or without cleft palate and prenatal exposure to diazepam. *Lancet*. 1975;2(7933):478–480.

18. Milkovich L, van den Berg BJ. Effects of prenatal meprobamate and chlordiazepoxide hydrochloride on human embryonic and fetal development. *N Engl J Med*. 1974;291(24):1268–1271.
19. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. *N Engl J Med*. 1998;338(16):1128–1137.
20. Gidai J, Acs N, Banhidy F, Czeizel AE. No association found between use of very large doses of diazepam by 112 pregnant women for a suicide attempt and congenital abnormalities in their offspring. *Toxicol Ind Health*. 2008;24(1–2):29–39.
21. Petik D, Acs N, Banhidy F, Czeizel AE. A study of the potential teratogenic effect of large doses of promethazine used for a suicide attempt by 32 pregnant women. *Toxicol Ind Health*. 2008;24 (1–2):87–96.
22. Timmermann G, Acs N, Banhidy F, Czeizel AE. A study of teratogenic and fetotoxic effects of large doses of meprobamate used for a suicide attempt by 42 pregnant women. *Toxicol Ind Health*. 2008;24(1–2):97–107.
23. Geber WF, Schramm LC. Congenital malformations of the central nervous system produced by narcotic analgesics in the hamster. *Am J Obstet Gynecol*. 1975;123(7):705–713.
24. Zagon IS, McLaughlin PJ. Effects of chronic morphine administration on pregnant rats and their offspring. *Pharmacology*. 1977;15(4):302–310.
25. Fujinaga M, Stevenson JB, Mazze RI. Reproductive and teratogenic effects of fentanyl in Sprague-Dawley rats. *Teratology*. 1986;34(1):51–57.
26. Fujinaga M, Mazze RI, Jackson EC, Baden JM. Reproductive and teratogenic effects of sufentanil and alfentanil in Sprague-Dawley rats. *Anesth Analg*. 1988;67(2):166–169.
27. Nicholls EA, Louie GL, Prokocimer PG, Maze M. Halothane anesthetic requirements are not affected by aminophylline treatment in rats and dogs. *Anesthesiology*. 1986;65(6):637–641.
28. Fujinaga M. Assessment of teratogenic effects of lidocaine in rat embryos cultured in vitro. Anesthesiology. 1998; 89(6): 1553–1558.
29. Kitson K, Ormond K, Pergament E. *Surgery in Pregnancy*; 2000.
30. Bingol N, Fuchs M, Diaz V, Stone RK, Gromisch DS. Teratogenicity of cocaine in humans. *J Pediatr*. 1987;110(1):93–96.
31. Haring OM. Effects of prenatal hypoxia on the cardiovascular system in the rat. *Arch Pathol*. 1965;80(4):351–356.
32. Haring OM. Cardiac malformations in rats induced by exposure of the mother to carbon dioxide during pregnancy. *Circ Res*. 1960;8:1218–1227.

33. Fujikura T. Retrolental fibroplasia and prematurity in newborn rabbits induced by maternal hyperoxia. *Am J Obstet Gynecol*. 1964;90:854–858.
34. Ferm VH. Teratogenic Effects of Hyperbaric Oxygen. *Proc Soc Exp Biol Med*. 1964;116:975–976.
35. Nunn JF, Sharer NM, Bottiglieri T, Rossiter J. Effect of short-term administration of nitrous oxide on plasma concentrations of methionine, tryptophan, phenylalanine and *S*-adenosyl methionine in man. *Br J Anaesth*. 1986;58(1):1–10.
36. Lumb M, Sharer N, Deacon R, et al. Effects of nitrous oxide-induced inactivation of cobalamin on methionine and S-adenosylmethionine metabolism in the rat. *Biochim Biophys Acta*. 20 1983;756(3):354–359.
37. Skacel PO, Hewlett AM, Lewis JD, Lumb M, Nunn JF, Chanarin I. Studies on the haemopoietic toxicity of nitrous oxide in man. *Br J Haematol*. 1983;53(2):189–200.
38. Keeling PA, Rocke DA, Nunn JF, Monk SJ, Lumb MJ, Halsey MJ. Folinic acid protection against nitrous oxide teratogenicity in the rat. *Br J Anaesth*. 1986;58(5):528–534.
39. Mazze RI, Wilson AI, Rice SA, Baden JM. Reproduction and fetal development in rats exposed to nitrous oxide. *Teratology*. 1984;30(2):259–265.
40. Mazze RI, Fujinaga M, Baden JM. Reproductive and teratogenic effects of nitrous oxide, fentanyl and their combination in Sprague-Dawley rats. *Br J Anaesth*. 1987;59(10): 1291–1297.
41. Mazze RI, Fujinaga M, Rice SA, Harris SB, Baden JM. Reproductive and teratogenic effects of nitrous oxide, halothane, isoflurane, and enflurane in Sprague-Dawley rats. *Anesthesiology*. 1986;64(3):339–344.
42. Fujinaga M, Baden JM, Suto A. Preventive effects of phenoxybenzamine on N2O induced reproductive toxicity in Sprague-Dawley rats (abstract). *Anesthesiology*. 1990; 73:920.
43. Aldridge LM, Tunstall ME. Nitrous oxide and the fetus. A review and the results of a retrospective study of 175 cases of anaesthesia for insertion of Shirodkar suture. *Br J Anaesth*. 1986;58(12):1348–1356.
44. O'Leary G, Bacon CL, Odumeru O, et al. Antiproliferative actions of inhalational anesthetics: comparisons to the valproate teratogen. *Int J Dev Neurosci*. 2000;18(1):39–45.
45. Loepke AW, Soriano SG. An assessment of the effects of general anesthetics on developing brain structure and neurocognitive function. *Anesth Analg*. 2008;106(6):1681–1707.

46. Jevtovic-Todorovic V, Hartman RE, Izumi Y, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci*. 2003;23(3):876–882.
47. Jevtovic-Todorovic V, Olney JW. PRO: anesthesia-induced developmental neuroapoptosis: status of the evidence. *Anesth Analg*. 2008;106(6):1659–1663.
48. Rizzi S, Carter LB, Ori C, Jevtovic-Todorovic V. Clinical anesthesia causes permanent damage to the fetal guinea pig brain. *Brain Pathol*. 2008;18(2):198–210.
49. Bhavani-Shankar K, Steinbrook RA, Brooks DC, Datta S. Arterial to end-tidal carbon dioxide pressure difference during laparoscopic surgery in pregnancy. *Anesthesiology*. 2000;93(2):370–373.
50. O'Rourke N, Kodali BS. Laparoscopic surgery during pregnancy. *Curr Opin Anaesthesiol*. 2006;19(3):254–259.
51. Steinbrook RA, Bhavani-Shankar K. Hemodynamics during laparoscopic surgery in pregnancy. *Anesth Analg*. 2001;93(6):1570–1571, table of contents.
52. Gregory GA, Wade JG, Beihl DR, Ong BY, Sitar DS. Fetal anesthetic requirement (MAC) for halothane. *Anesth Analg*. 1983;62(1):9–14.
53. Moise KJ, Jr., Carpenter RJ, Jr., Deter RL, Kirshon B, Diaz SF. The use of fetal neuromuscular blockade during intrauterine procedures. *Am J Obstet Gynecol*. 1987;157(4 Pt 1):874–879.
54. Silva V, Tsen LC, Wilkins-Haug L, Kodali BS. A Womb with a view: anesthetic, obstetric, and neonatal care issues for in-utero fetal surgery. *Anesthesiology*. 2006;104(Supp):A12.
55. Levinson G, Shnider SM. *Anesthesia for Obstetrics*. Baltimore: Williams & Wilkins; 1987:188.