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Nonobstetric Surgery During Pregnancy: What Are the Risks of Anesthesia?

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The need for anesthesia and surgery during pregnancy occurs in 1.5% to 2.0% of all pregnancies. Each year, over 75,000 pregnant women in the United States undergo nonobstetric surgery. The operations include those directly related to pregnancy (e.g., cerclage), those indirectly related to pregnancy (e.g., ovarian cystectomy), and those unrelated to gestation (e.g., appendectomy, cholecystectomy). The diagnosis of any medical condition requiring surgical intervention in pregnancy often raises questions about the safety of both surgery and anesthesia in these patients. This controversy was primarily attributed to the lay press speculations that surgery and anesthesia in pregnancy could pose hazards to the mother and fetus. Despite these concerns, the safety of nonobstetric surgery and anesthesia in pregnancy has been well established, and many pregnant women are safely anesthetized everyday without ill effects for the mother or fetus.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this article, the reader should be able to list the mechanisms of teratogenicity, to describe the intraoperative monitoring of a pregnant patient undergoing surgery, and to outline the particular issues associated with providing anesthesia to a pregnant patient undergoing cardiac and neurosurgical procedures.

GENERAL CONSIDERATIONS

The need for anesthesia and surgery during pregnancy occurs in 1.5% to 2.0% of all pregnancies (1–3). Each year, over 75,000 pregnant women in the United States undergo nonobstetric surgery (4). The operations include those directly related to pregnancy such as cerclage, those indirectly related to pregnancy such as ovarian cystectomy, and those unrelated to gestation such as appendectomy. When a pregnant woman presents for surgery, it is a stressful event for everyone involved. Issues about the surgical problem itself often seem secondary to maternal (and physician) concerns about the effect of surgery and anesthesia on the developing fetus or the potential to trigger preterm labor. The hazards to the fetus could come from teratogenic effects of drugs administered in the perioperative period, including anesthetic agents, from premature labor, from alterations in uteroplacental blood flow, and from maternal hypoxia and/or acidosis. Because the period of organogenesis is during the first trimester of pregnancy, it is commonly advised that all but truly emergent surgery be postponed until later in pregnancy to avoid potential teratogenicity and intrauterine fetal death. Premature labor is more likely in the third trimester. Although the risks to the fetus are quite real, careful management should minimize potential fetal harm (1–4).

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TERATOGENICITY

One of the major concerns among patients and physicians when faced with the possibility of surgery

during gestation is what effect the anesthetic and adjuvant drugs will have on the developing fetus (5). Numerous studies fill the literature, which relate to this question, and virtually every drug we use can be found to possess teratogenic characteristics in some species under some set of circumstances at some particular point in time during gestation (6–12). When evaluating such information, the following principles of teratology need to be kept in mind (Table 1):

1. The specificity of the substance could be quite broad or limited to an effect in a single species.
2. The dosage of the agent reaching the conceptus will determine the degree of teratogenic effect, if any, that will be manifest. This is also dependent on those factors governing placental transfer, e.g., some of the neuromuscular-blocking agents are teratogenic to the chick embryo when directly injected, but cross the placenta in such miniscule amounts when injected maternally as to not be a hazard in the clinical setting.
3. The time during embryogenesis at which exposure takes place is critical. For instance, a specific drug could either kill the blastocyst or allow it to develop entirely normally if exposure occurs during the first 2 weeks of gestation, because the cells are totipotent at this point. If given after 12 weeks, organogenesis is complete and only organ size or perhaps brain development could be effected. The mechanisms of teratogenicity include (Table 2) mutation, chromosomal dysjunction, interference with substrate precursors, depletion of energy sources, enzyme inhibition, altered membrane characteristics, or osmolar imbalance (8–11). These can result in excessive cell death, reduced proliferation, decreased cellular interactions, impaired morphogenic movements, reduced biosynthesis, or mechanical cellular disruption. To establish proof of teratogenicity, one must look at both retrospective and prospective evidence. Retrospectively, there should be a sudden increase in an anomaly beginning at the time of the drug's introduction. The exposure should have occurred at the appropriate point in time during development and a reasonable dose-response curve might be evident. Prospectively, confirmatory animal studies need to be undertaken, realizing that the population size might need to be enormous to definitively identify the reality of teratogenicity.

TABLE 1 **Critical factors in teratology**

1. Specificity
2. Dosage
3. Time of exposure during embryogenesis

TABLE 2 **Mechanisms of teratogenicity**

1. Mutation
2. Chromosomal dysjunction
3. Interference with substrate precursors
4. Depletion of energy sources
5. Enzyme inhibition
6. Altered membrane permeability
7. Osmolar imbalance

Because it is clear that virtually every drug and every inhalation anesthetic is teratogenic to some species under certain conditions, there is no "best" anesthetic agent (1–3, 6, 7). None has, as yet, been identified as a definite human teratogen. Some attention has been focused on the action of nitrous oxide on intracellular metabolism. Although it remains the backbone of general anesthesia for obstetrics and in the past was used as an analgesic in labor, concerns have been raised over its demonstrated ability to oxidize cobalamin (vitamin B_{12}) and thus inhibit methionine synthase activity (9, 10). This activity is a key link in the synthesis of S-adenosyl methionine and in the tetrahydrofolic acid cycle. Ultimately, DNA production, myelin deposition, and other folate and methylation process-dependent reactions might be affected. This could be of particular concern when administering nitrous oxide for a nonobstetric operation during pregnancy. In a study using human lymphoblasts exposed to N_2O, decreased methionine and serine synthesis was observed (11). Purine synthesis was more rapidly reduced in the absence of folate than in its presence. Others have found that nitrous oxide did not impair the ability of the rat liver to repair hepatic injury induced by hypoxia and halothane. They hypothesize that although DNA production has been shown to be impaired by nitrous oxide, in humans it might not be critically impaired. Several authors note that although methionine synthase inactivation occurs with N_2O, prophylaxis with methionine, folinic acid, and vitamin B_{12} seems to be feasible, although yet to be proven clinically effective.

Although the evidence currently remains encouraging, we cannot assume that some potential for teratogenicity does not exist. It is therefore most prudent to postpone elective surgical procedures until after pregnancy (1–4, 6, 7, 13). If this is not possible, then the first trimester should be avoided. It is of

more than parenthetical interest that many women who present for elective surgery could be in the early phase of gestation and not yet fully aware of it. It behooves the surgeon and the anesthesiologist to establish the presence or absence of pregnancy before proceeding with surgery. The choice of anesthetic agents should be limited to those with a strong background of success. A healthy mother is essential to preserve a fetus. Nitrous oxide can best be avoided during the first trimester, and if used at other stages of pregnancy, pretreatment of the patient with folic or folinic acid could offer some additional benefit (2, 3, 11). Whenever possible, regional anesthesia should be entertained. Spinal anesthesia offers the least drug transfer for the degree of anesthesia achieved. Hypotension, aortocaval compression, maternal hypoxia, and acidosis need to be avoided and/or treated promptly. Other forms of regional anesthesia such as epidural, combined-spinal epidural (if epidural catheter is activated) anesthesia, or brachial plexus block do yield higher local anesthetic blood levels and thus more placental transfer. There has been no association with teratogenic effects in humans from reasonable levels of local anesthetics, and recent animal studies tend to confirm human observations.

INTRAOPERATIVE MONITORING

The overall goal when managing a pregnant patient undergoing surgery is to maintain the mother and fetus in the best possible physiological condition. Therefore, as always, we must meticulously protect the patient from the usual stresses encountered in the operating room such as anxiety, pain, positioning, temperature changes, fluid and blood losses (1–3, 13). This requires that we effectively monitor the patient and, whenever possible, the fetus and uterine activity. Essential monitoring includes blood pressure, pulse rate, electrocardiogram, respirations, temperature, and pulse oximetry (Table 3). Aortocaval compression becomes a significant issue after 24 weeks gestation and must be prevented with a left uterine displacement device such as a wedge (2, 3). The effectiveness of displacement can be assessed by palpating the quality of the right femoral pulse, taking the blood pressure in the right leg, and perhaps by observing the waveform from a pulse oximeter or plethysmograph sensor on the right foot. Hyperventilation should be avoided, because maternal respiratory alkalosis is easy to produce because resting CO_2 is already reduced to 32 mm Hg and functional residual capacity (FRC) is reduced by approximately 20% during pregnancy. Respiratory alkalosis shifts the oxyhemoglobin dissociation curve to the left and thus could impair transfer of oxygen across the placenta. Umbilical blood flow is also decreased with alkalosis. End-tidal CO_2 ($ETCO_2$) monitoring can help avoid both over- and underventilation (3).

TABLE 3 **Intraoperative monitoring**

1. Blood pressure, heart rate, respiratory rate
2. Electrocardiogram
3. Oxygen saturation
4. End-tidal carbon dioxide
5. Fetal heart rate
6. Uterine activity (when feasible)

Fetal heart rate monitoring could prove useful at identifying intraoperative conditions leading to impaired uteroplacental blood flow and fetal oxygenation (4). This can be reliably accomplished with the current generation of external sensors. A normal fetal heart rate (FHR) is between 120 and 160 beats/min with 3 to 7 beats variability. Variability is decreased by hypoxia and by sedative drugs as well as periods of fetal sleep. Slowing of the fetal heart rate in the operative setting suggests hypoxemia, but could be related to a fall in temperature or the administration of drugs and/or anesthetic agents, which tend to slow the heart rate (1–3). Because the fetus has little ability to adjust its stroke volume, cardiac output is rate-dependent. If the heart rate falls to 80 beats/min, cardiac output is significantly reduced and at a rate of 60 beats/min, the fetus is in jeopardy. Although fetal bradycardia has alerted anesthesiologists in the past to unrecognized maternal hypoxemia, this should not occur in today's setting. Fetal tachycardia occurs with maternal fever, maternal/fetal sepsis, and with drug administration, eg, atropine. Uterine activity can be monitored with an external tocodynamometer. If premature labor occurs, tocolysis will be necessary to preserve the pregnancy. Some authors have suggested using the potent volatile anesthetics because they relax the uterus. This could prove effective intraoperatively, but other drugs will be required postoperatively. The beta-adrenergic agents ritodrine and terbutaline are commonly used to suppress labor but do have numerous side effects, including cardiac arrhythmias under anesthesia and pulmonary edema (1, 2). This underscores the need for careful maternal cardiovascular monitoring.

CARDIAC SURGERY DURING PREGNANCY

The cardiovascular changes of pregnancy include a 30% to 50% increase in blood volume and a similar

increase in cardiac output. These effects peak at 24 to 28 weeks of gestation and are maintained until parturition when even greater alterations could be observed. Thus, the patient with preexisting cardiac disease is exposed to a major stress as she enters the second and third trimesters of gestation. Although pregnant patients with heart disease are usually managed with medical therapy, including long periods of bed rest if necessary, those with severe decompensation and surgically correctable lesions will come to the operating room. These patients are usually those with rheumatic valvular disease, particularly mitral stenosis (13, 14). The first operations were closed mitral commissurotomies and carried a low maternal and fetal mortality rate, particularly when compared with medical therapy. However, the use of cardiopulmonary bypass increases the risks, particularly for the fetus. Several factors related to cardiopulmonary bypass, which can adversely affect fetal oxygenation, are nonpulsatile perfusion, inadequate perfusion pressures, inadequate pump flow, embolic phenomena to the uteroplacental bed, and the release of renin and catecholamines in response to cardiopulmonary bypass. The use of intraoperative fetal monitoring can decrease the high mortality rate (13). Several reports of its use have indicated that persistent fetal bradycardia occurs during bypass even with good maternal oxygenation and satisfactory acid-base status. The heart rate is usually between 80 and 100 beats/min and resolves with termination of bypass. This could be the result of moderate hypothermia. A recent review suggests that warm cardiopulmonary bypass could benefit the fetus (13). If the heart rate falls below 80 beats/min, increasing pump flow could improve the situation. The use of pump flows 30% to 50% greater than usual is recommended, and perfusion pressure should be maintained at or above 60 mm Hg to ensure adequate uteroplacental perfusion. Acid-base status, oxygenation, and ventilation should be monitored carefully with arterial blood gases. Table 4 summarizes the current recommendation regarding management of cardiopulmonary bypass in pregnant patients undergoing open heart surgery.

TABLE 4 **Cardiopulmonary bypass**

1. Avoid aortocaval compression
2. Maintain pump flows at 40% to 50% above usual
3. Maintain mean arterial pressure at 60 mm Hg
4. Optimize acid-base status

NEUROSURGERY DURING PREGNANCY

Subarachnoid hemorrhage from intracranial saccular aneurysm or arteriovenous malformation is not uncommon during pregnancy (3). Although there is no clear correlation with pregnancy and increased risk of rupture, it is possible that the stress induced by the increased cardiac output and blood volume and the softening of vascular connective tissue by the hormonal changes of pregnancy could predispose to such an event. The decision to operate on such lesions is made independent of pregnancy and is influenced by the site and type of lesion, the clinical condition of the patient, and the presence or absence of vasospasm (1, 3). The usual neurosurgical anesthetic approach to patients with these types of lesions includes controlled hypotension, hypothermia, hyperventilation, and diuresis.

Controlled hypotension could be induced with a volatile anesthetic, sodium nitroprusside, nitroglycerin, or trimethaphan. Each carries its own potential hazards in addition to reduction in uteroplacental blood flow. It is generally acknowledged that a reduction in systolic blood pressure of 25% to 30% or a mean blood pressure of less than 70 mm Hg will lead to reductions in uteroplacental blood flow. All of these drugs cross the placenta and can induce hypotension in the fetus (3). Nitroprusside is converted to cyanide and then to thiocyanate by the hepatic enzyme rhodanese. Cyanide accumulation in the fetus has been observed with significant toxicity and fetal death in the pregnant ewe made hypotensive with sodium nitroprusside. If this agent is used, it should be for only a short time and should be discontinued if the infusion rate exceeds 0.5 mg/kg per hour, if maternal metabolic acidosis ensues, or if resistance to the agent is apparent. Nitroglycerin has yet to be associated with adverse fetal effects. It is metabolized to nitrites, which have experimentally produced methemoglobinemia. Trimethaphan often leads to tachyphylaxis and interacts with neuromuscular-blocking agents, thus making it a poorer choice. Fetal heart rate monitoring should be used and hypotension limited to the least period of time possible. Successful neonatal outcome after induced hypotension with careful control is not unusual.

Hypothermia is occasionally used to decrease metabolic requirements in the brain and other organs and reduces cerebral blood flow. The usual goal is to achieve a temperature of 30°C. This will induce similar changes in the fetus and, as outlined earlier, a fetal bradycardia. The heart rate will increase again

with rewarming. This should not be harmful and does not appear to increase the risk of fetal morbidity.

Hyperventilation is commonly used during neuroanesthesia because the decrease in carbon dioxide reduces cerebral blood flow. The normal flow of 50 mL/100 g per minute is reduced by 1 mL/100 g per minute for each 1-mm Hg reduction in CO_2. This is effective until the CO_2 reaches approximately 20 mm Hg. The potential adverse effects on the fetus of decreased placental oxygen transfer and umbilical vessel vasoconstriction should not be a problem to a healthy fetus whose mother receives moderate hyperventilation, ie, to a CO_2 of approximately 25 mm Hg. Fetal heart rate monitoring should alert the anesthesiologist to compromises in fetal oxygenation and adjustments should be made accordingly (3).

Diuresis is often accomplished with osmotic agents or loop diuretics to shrink the brain both intraoperatively and postoperatively. These can cause significant negative fluid shifts for the fetus. Obviously, these agents should be used only as necessary and not strictly by protocol when caring for the pregnant patient.

An interesting issue has been identified with the reversal of muscle relaxants. Most anesthesiologists use glycopyrrolate to prevent the muscarinic effects of neostigmine. Because the former does not cross the placenta and the latter does to some degree, fetal bradycardia has resulted and led to cesarean section in some cases in which the fetus was of viable age. It is, therefore, highly recommended that atropine be used instead of glycopyrrolate.

CONCLUSIONS

The major considerations for providing anesthesia care for the pregnant patient undergoing nonobstetric surgery should include 1) understanding the physiological changes of pregnancy and their influence on the patient; 2) maintaining an adequate uteroplacental perfusion by avoiding and treating hypotension and avoiding aortocaval compression; 3) selecting anesthetic drugs and techniques that have a good track record for safety; 4) using regional anesthesia whenever possible; 5) remembering that no anesthetic agent or adjuvant drug has as yet been proven to be teratogenic in humans (This information should be transmitted to the patient before administering anesthesia.); 6) providing fetal surveillance with external fetal heart rate monitoring and uterine activity monitoring whenever feasible; and 7) making appropriate adjustments in technique as guided by the results (1–4, 15–17).

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