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Review article

Anesthesia in pregnant patients for nonobstetric surgery

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Abstract Anesthesiologists in every subspecialty encounter, with varying regularity, patients presenting for surgery during the course of pregnancy. With the increasing sophistication of surgical and anesthetic techniques, increasingly complex surgeries are being undertaken. In this review, we address the fundamental physiologic principles central to the care of pregnant patients and fetuses in this difficult clinical situation.

1. Introduction

Patients presenting for surgery during the course of pregnancy carry a number of important challenges for anesthesiologists. Optimum management requires a thorough understanding of maternal and fetal physiology, altered drug pharmacodynamics and pharmacokinetics, and a sensitive approach to the parturient, who must be counseled carefully about the risks and benefits of intervention. The ultimate goal is to provide safe anesthesia to the mother while simultaneously minimizing the risk of preterm labor or fetal demise. Multidisciplinary input from surgeons, anesthesiologists, and obstetricians is essential to ensure fetal and maternal well-being throughout the perioperative period. A successful maternal and fetal outcome is dependent on expert management of both the surgical disease process and anesthesia.

2. Epidemiology

The frequency with which pregnancies are complicated by the need for nonobstetric surgical procedures is of the order of 0.75% to 2.0%. Of these procedures, approximately 42% are performed during the first trimester, 35% during the second, and 23% during the third [1]. The frequency with which nonobstetric surgery is performed in pregnant patients may be considerably higher in the first trimester as pregnancy may be undetected at the time of surgical intervention.

The range and incidence of nonobstetric surgical conditions encountered in pregnant patients are similar to those in the general population. Appendectomy is the most commonly performed nonobstetric surgical procedure in pregnancy, performed at a rate of 1 per 1500 to 2000 pregnancies [2]. Cholecystectomy ranks second, with between 1 and 8 being performed per 10 000 pregnancies. Pregnancy itself predisposes a patient to cholelithiasis. Increased bile lithogenicity and decreased gallbladder motility occur secondary to high circulating estrogen levels. However, whereas 3% of pregnant patients develop gallstones, only a limited number present with symptomatic biliary disease requiring surgery [3,4]. Adnexal disease is not uncommon during pregnancy. Surgery may be required for diagnosis or treatment of ovarian pathology, and the laparoscopic approach is increasingly being used in this situation [5]. Conservative management of adnexal pathology may allow disease progression. Between

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1% and 8% of adnexal masses diagnosed in pregnancy are malignant. In addition, complications such as torsion and rupture of ovarian cysts are more common in pregnancy, often rendering surgical intervention unavoidable [6]. The physiologic demands of pregnancy on the cardiovascular system may precipitate decompensation of cardiac valvular disease or aortic dissection in susceptible patients [7-9]. Similarly, lesions of the central nervous system may present during pregnancy and surgery may be required to alleviate dangerous elevations in intracranial pressure [10]. There are numerous reports in the literature of successful maternal and fetal outcomes after surgery for life-threatening cardiac and neurologic diseases [10,11].

3. Physiologic changes in pregnancy

During pregnancy, maternal physiology undergoes profound changes. Primary changes occur under the influence of gestational hormones, which are essential to ensure adequate supply of oxygen and nutrition to fetuses and to prepare for delivery. Secondary changes occur as a result of the mechanical effects of enlarging gravid uteri.

These changes are extensively reviewed in many textbooks [1], but only those most clinically relevant are briefly discussed in this article.

3.1. Respiratory system changes

Changes in respiratory physiology are of particular concern to anesthesiologists and are of substantial clinical relevance to the provision of anesthesia to pregnant patients. These alterations place patients at increased risk of developing hypoxemia and rapid desaturation when they are apneic [12]. Failed intubation is the leading cause of maternal death as caused by anesthesia [13].

Under the influence of progesterone, there is an early (first trimester) 25% increase in alveolar minute ventilation (MV) caused by increases in both respiratory rate (15%) and tidal volume (40%). At full term, MV increases 45% to 70% higher than nonpregnant values. This produces a slight chronic respiratory alkalosis ($PaCO_2$ = 28-32 mm Hg; pH = 7.44), which shifts the maternal oxyhemoglobin dissociation curve to the right, promoting oxygen delivery to fetuses. The increase in the arterial pH level is limited by an increase in renal bicarbonate excretion. Despite the expected pregnancy-induced increase in metabolic demand, PaO_2 remains normal or increases slightly during pregnancy [14].

Gravid uteri exert a restrictive effect on respiratory mechanics, with a reduction in functional residual capacity of 20% at term.

Airway management in pregnancy is further complicated by the anatomical changes related to both weight gain and edema of the upper airway and vocal cords, which occurs secondary to a generalized increase in capillary permeability [12]. There is a significant risk of failed intubation and airway trauma during instrumentation.

3.2. Cardiovascular system and hematologic changes

Cardiac output begins to increase early in the first trimester and peaks in the second trimester (up to 50% higher than the baseline value), at which time heart rate has increased by 25% and stroke volume has by 30% [14].

The increased metabolic demands of fetuses and the presence of placenta as a low-pressure system in parallel with systemic circulation necessitate this increase in cardiac output. Systemic and pulmonary vascular resistances decrease in response to increased synthesis of vasodilators such as prostacyclin [1].

Blood pressure undergoes minor changes during pregnancy, falling slightly in the first trimester, rising in the second, and approximating its prepregnancy level in the third. At 12 weeks' gestation, the uterus rises out of the pelvis to encroach upon the abdominal viscera. Aortocaval compression in the supine position becomes clinically relevant. Supine hypotensive syndrome is associated with cardiac output reductions of up to 20%. Inferior vena caval and aortic compression are demonstrable in the supine position and require left lateral tilts of 15° and 30°, respectively, to reliably restore adequate circulation [14].

Blood volume expansion occurs in the first trimester and increases by 35% to 50% at term [1]. The greater increase in plasma volume relative to red cell mass leads to dilutional anemia. This serves a protective physiologic function at birth where lost blood is relatively hemoglobin poor but leads to early compromise of oxygen-carrying capacity in acutely hemorrhaging patients. The reduction in blood viscosity improves flow through the uteroplacental circulation.

A benign leukocytosis up to 15 000 mm^{-3} during pregnancy and that up to 20 000 mm^{-3} during labor are commonly seen and can confound diagnosis of systemic infection. Increased circulating levels of clotting factors VII, VIII, X, and XII; enhanced platelet turnover; clotting; and fibrinolysis produce a hypercoagulable state that leaves pregnant patients at high risk of experiencing thromboembolic events [15]. This risk is further increased by immobility and the hypercatabolic state of the postoperative period.

3.3. Gastrointestinal system

In early pregnancy, the effects of circulating progesterone include a reduction in lower esophageal sphincter tone and a slight increase in gastric acidity. Gastrointestinal smooth muscle demonstrates dysrhythmias leading to nausea and vomiting [16]. Once the gravid uterus rises from the pelvis into the abdomen, it exerts a mechanical effect on the anatomical arrangement of the intraabdominal viscera. The angle of the anatomical gastroesophageal sphincter becomes less acute, exacerbating incompetence [1]. Parturient patients are therefore at increased risk of developing aspiration pneumonitis after 16 weeks' gestation [17]. The traditionally held view that gastric emptying is also delayed by progesterone has been disputed by studies on non–laboring pregnant

women [18]. Gastric emptying does, however, cease with the onset of labor. It is also reduced by pain, emotional distress, and opioid administration [19].

Intraabdominal pathologies are the most commonly encountered surgical emergencies in pregnancy, and accurate diagnosis is made difficult by a number of factors. Nausea, constipation, vomiting, abdominal distension, and pain are common in pregnancy; their significance may not be immediately appreciated, leading to delayed diagnosis. The position of the appendix changes throughout gestation as it gradually rises from the right iliac fossa to lie over the right kidney at term. It also undergoes rotation relative to the cecum and thus may no longer be in contact with the parietal peritoneum at term. Classical signs of peritonitis may therefore be reduced or absent. Increased systemic steroid levels limit inflammatory response and protective omental migration, increasing the risk of visceral perforation and generalized peritonitis [20].

3.4. Changes in central and peripheral nervous systems

Pregnant patients demonstrate a 30% reduction in the minimum alveolar concentrations of volatile anesthetic agents [21]. Superimposed upon the increase in alveolar MV, this leads to rapid induction of anesthesia if an inhalation induction technique is used.

Similarly, neural tissue demonstrates increased sensitivity to the effects of local anesthetic drugs. Both therapeutic doses and toxic plasma levels are reduced by approximately 30% in pregnancy [22].

The total volume of the epidural and subarachnoid spaces is reduced in pregnancy as inferior vena caval compression produces engorgement of the epidural venous plexus. This leads to more extensive spread of local anesthetic agents administered during central neuraxial blockade.

The response of the autonomic nervous system to hemodynamic changes is biphasic. In the first trimester, there is a shift toward increased vagal tone and decreased sympathetic activity in association with the increase in blood volume. A gradual transition in the second trimester leads to lower vagal tone and increased sympathetic activity by the third trimester, which helps overcome the mechanical effects of both aortocaval compression and low-resistance parallel placental circulation [23].

4. Drugs in pregnancy

4.1. Pharmacology

Pharmacokinetic and pharmacodynamic profiles are altered in pregnancy; therefore, drug administration must be titrated accordingly. Volume of distribution is increased secondary to pregnancy-induced increase in blood volume. The physiologic hypoalbuminemia of pregnancy is accompanied by increased α_{-1}-glycoprotein concentration. Altered plasma protein binding changes the free or unbound fraction of drugs and reduces the doses of drugs such as local anesthetic agents, at which toxicity is observed [1].

Alterations in individual drug pharmacokinetics and pharmacodynamics are however heterogeneous, reflecting different pregnancy-related changes in each of the metabolizing organ systems. Neuromuscular blocking agents illustrate the complexity of these changes. Plasma cholinesterase levels are decreased by 25% from early during pregnancy until the 7th day postpartum. Prolonged neuromuscular blockade with succinylcholine is uncommon, however, as the increased volume of distribution offsets the impact of decreased drug hydrolysis [24]. Vecuronium at a standard dose of 0.2 mg/kg has been shown to have a faster onset time and longer duration of action in pregnancy [25]. The onset time of rocuronium at a dose of 0.6 mg/kg is unchanged but also demonstrates a longer duration of action compared with nonpregnant patients [26]. Neuromuscular blocking agents whose elimination is organ independent also display altered pharmacokinetics. cis-Atracurium for example, which undergoes Hoffman's elimination in vivo, demonstrates a significantly more rapid onset and shorter duration of neuromuscular blockade in pregnant patients [27].

4.2. Teratogenicity

Teratogenicity is defined as the observation of any significant change in the function or form of a child secondary to prenatal treatment [28,29]. Perioperative events leading to severe maternal hypotension or hypoxemia pose the greatest risk to fetuses. Derangements in carbohydrate metabolism and hyperthermia have also been shown to be teratogenic, but hypothermia is not associated with any adverse fetal outcome.

The trophoblast acts as a lipid membrane across which lipid-soluble drugs and those with a low molecular weight move easily by passive diffusion. Any agent can be teratogenic in animals if sufficient exposure occurs at a sensitive developmental stage. The impact of any administered drug depends on the dose and the gestational age at which it is administered. A small dose of a given drug may be catastrophic to the early embryo, yet a large dose of the same drug may have no effect on a fetus at an advanced stage of development. Experimental models involving supraclinical drug doses do not necessarily indicate that a single short exposure would pose a significant risk in clinical practice. Most iatrogenic structural abnormalities have resulted from drug exposure during the period of organogenesis (days 31-71). Functional abnormalities are associated with drug exposure during late pregnancy [1].

The Shepherd Catalog, which lists agents or factors that are proven human teratogens, does not include anesthetic agents or any drug used routinely during the administration of anesthesia [29].

Polar molecules such as neuromuscular blocking agents do not cross the placenta in significant amounts. Fetal blood concentrations of muscle relaxants are 10% to 20% of

maternal concentrations. Nitrous oxide has been shown to be a weak teratogen in rodents after high concentrations are administered for prolonged periods. The required doses are extremely large, involving administration of 50% N_2O for more than 24 hours, and are not encountered in clinical practice. Current evidence does not support withholding nitrous oxide in clinical practice [29].

Concerns regarding an association between diazepam and craniofacial defects have been extensively researched and debated [30]. The evidence does not support this association [31], and, on occasion, it may be appropriate to provide judicious preoperative anxiolysis. This avoids increases in circulating catecholamine levels, which impair uteroplacental perfusion.

Large survey studies that considered outcomes in women who underwent surgery during pregnancy suggest no increase in congenital anomalies among their offspring but rather an increase in the risk for abortions, growth restriction, and increased frequency of low-birth-weight and very low–birth-weight neonates for reasons attributed to the requirement for surgery but not anesthetic administration [32].

4.3. Anesthetic management

Both general and regional anesthetic techniques have been successfully used for nonobstetric surgery in pregnant patients. No research to date has shown a definitive superiority of one technique over the other in fetal outcome. Regional anesthesia does avoid the potential risk of failed intubation and aspiration in addition to reducing the exposure of fetuses to potential teratogens.

During anesthesia and surgery, fetal well-being is best ensured by careful maintenance of stable maternal hemodynamic parameters and oxygenation. Close monitoring of fetal responses for signs of distress is strongly recommended [14].

At the preoperative assessment, premedication to allay anxiety may be considered for reasons already addressed. Prophylaxis against aspiration pneumonitis with H_2-receptor antagonists and nonparticulate antacids should be administered from 16 weeks' gestation [16]. From that time, patients should be considered to be at risk for both aortocaval compression and aspiration pneumonitis. Positioning must ensure a 15° left lateral tilt to facilitate uterine displacement. Changes in maternal position can have profound hemodynamic effects; therefore, Trendelenburg's or reverse Trendelenburg's position during anesthesia should be carried out slowly.

Rapid-sequence intravenous induction of general anesthesia should be preceded by meticulous denitrogenation with 100% oxygen for 5 minutes and application of effective cricoid pressure. Although endotracheal intubation is mandatory, in cases of failed intubation in pregnant patients, laryngeal mask airways have been used to ventilate successfully and safely in the reverse Trendelenburg's position for brief periods.

General anesthesia is most commonly maintained with volatile anesthetic agents in either an air/oxygen or N_2O/O_2 mixture. Studies to date do not support concerns regarding N_2O teratogenicity in clinical practice. The effects of light general anesthesia and its associated catecholamine surge with resulting impaired uteroplacental perfusion are considerably more dangerous to fetuses.

Positive pressure ventilation should be used with care and end-tidal carbon dioxide levels should be maintained within the limits seen normally in pregnancy. There is a linear relationship between maternal $PaCO_2$ and fetal $PaCO_2$ [14]. Maternal hypercarbia limits the gradient for CO_2 diffusion from fetal to maternal blood and can lead to fetal acidosis, increasing the risk of fetal loss. For this reason, regular arterial blood gas analysis has been advocated in laparoscopic surgery, where CO_2 is used to establish and maintain a pneumoperitoneum. A recent study however found a good correlation between end-tidal CO_2 and $PaCO_2$ in pregnancy and concluded that the former gradient could safely be used to guide ventilation during laparoscopy in pregnant patients [33,34].

Application of positive end expiratory pressure must give consideration to hemodynamic changes that would compromise placental perfusion.

Patients should be extubated fully awake in the lateral position after careful orogastric suctioning as the risk of aspiration persists until protective airway reflexes have returned.

4.4. Hypotension

Hypotension caused by hypovolemia, anesthetic drugs, central neuraxial blockade, or aortocaval compression poses a major risk to fetuses [14]. The uteroplacental circulation is not subject to autoregulation and perfusion is therefore entirely dependent on maintenance of adequate maternal systemic blood pressure [1].

There is a limited number of case reports of fetal preservation during hypotensive anesthesia when this has been a surgical requirement, in neurosurgical patients for example. The use of hypotensive anesthesia in such cases involves balancing risk to the fetus against risk of maternal death from excessive hemorrhage or stroke.

Intravenous fluid boluses can be used to ameliorate hypotension, but care is required as concomitant administration of tocolytics and increased capillary permeability predispose patients to pulmonary edema [1].

Ephedrine is widely used for the treatment of maternal hypotension unresponsive to intravenous fluid administration. Animal studies in the 1970s suggested that ephedrine better preserved uterine blood flow when compared with metaraminol and methoxamine [35]. Ephedrine is an indirectly acting sympathomimetic agent, releasing noradrenaline from postganglionic sympathetic nerve endings. Therefore, ephedrine has a relatively slow onset and long duration of action. In addition, tachyphylaxis is common, caused in part by depletion of noradrenaline from presynaptic nerve endings and prolonged blockade of receptors. These factors make titration of ephedrine doses difficult. Recent studies have challenged the superiority of ephedrine

as a vasopressor and suggest that the alpha agonists phenylephrine and metaraminol are more effective in maintaining maternal blood pressure and in preventing fetal acidosis [36,37].

4.5. Fetal monitoring

Continuous fetal heart rate (FHR) monitoring is feasible from 18 weeks' gestation. This may be limited by technical difficulties during abdominal surgery or in cases of maternal obesity. Fetal heart monitoring should be interpreted by an experienced operator with understanding of the changes encountered during surgery and anesthesia. When technically possible, fetal monitoring is mandatory as maternal hemodynamic stability alone is not an adequate indicator of fetal well-being.

Fetal heart rate variability is a useful indicator of fetal well-being and can be monitored from 25 to 27 weeks' gestation onward. Anesthetic agents reduce both baseline FHR and FHR variability, so readings must be interpreted in the context of administered drugs. The human fetus may respond to a number of environmental stimuli including noise, pressure, pain, and cold temperature. Noxious stimuli produce an autonomic response and a rise in stress hormones. Persistent fetal bradycardia generally indicates true fetal distress and should prompt swift remedial measures. One caveat is that neostigmine has been noted to cause fetal bradycardia when administered with glycopyrrolate because of the reduced placental transfer of the latter compound.

The value of intraoperative FHR monitoring is that it detects early compromise, allowing optimization of maternal hemodynamics and oxygenation with appropriate fluid therapy, vasopressors, blood product administration, hyperventilation, or position adjustment. During laparoscopic surgery, changes in the FHR may indicate the need for temporary deflation of the pneumoperitoneum [38,39]. Preoperative and postoperative liaisons with the obstetric team should establish a definitive plan should there be evidence of fetal distress unresponsive to conservative measures.

4.6. The postoperative period

If pregnancy continues beyond the first postoperative week, then the incidence of premature labor is no higher than that in nonsurgical pregnant patients [32]. Tocometry during this period is useful as postoperative analgesia may mask awareness of mild early contractions and delay tocolysis. The routine administration of prophylactic tocolytics is controversial and is generally limited to those patients in whom there has been manipulation of the uterus intraoperatively. Provision of adequate analgesia is also important in the postoperative period, as pain has been shown to increase the risk of premature labor [22].

As previously described, pregnancy induces a hypercoagulable state. The risk of thromboembolic disease is further increased by postoperative venous stasis. Therefore, administration of thromboprophylaxis with heparin is essential. Dextrans are contraindicated in pregnancy as an anaphylactoid reaction may precipitate acute fetal distress [39]. Although there are fewer experiences with low-molecular-weight heparins in pregnancy, small studies suggest that they are as safe and effective as unfractionated heparins in pregnancy [40-42]. Low-molecular-weight heparin is likely to be increasingly used as a result of its relative ease of administration.

4.7. Complex surgery

With advances in surgical technique and technology in addition to modern anesthetic practice, increasingly complicated cases are being undertaken during pregnancy. Although the basic principles of anesthesia in pregnant patients apply, some developments pose increasing challenges to anesthesiologists and warrant further discussion.

Laparoscopic management of appendicitis and gallbladder and adnexal diseases has an increasing role in the management of pregnant patients. Potential benefits include less postoperative pain, shorter recovery times, lower risks of thromboembolic complications, and reduced uterine manipulation (lowering the risk of premature labor). Establishment of a pneumoperitoneum has both mechanical and biochemical implications for mothers and, consequently, fetuses. Hemodynamic changes may impair uteroplacental perfusion, and this may be exacerbated by position changes. This is particularly marked when position changes are rapidly instituted. Movement to and restoration from Trendelenburg's positioning should therefore be carried out slowly, and administration of fluid boluses before movement may be helpful as hemodynamic changes will be exaggerated by reduced intravascular volume. The same principle applies to inflation and deflation of the pneumoperitoneum. Continuous fetal heart monitoring, when feasible, is advisable so that maternal hemodynamics may be optimized at the first indication of compromise [6,43,44].

During pregnancy, intracranial tumors may become symptomatic or there may be aggravation of presenting signs and symptoms necessitating intervention before term. Meningiomas have steroid receptors, and their enlargement during pregnancy is secondary to intracellular fluid retention and engorgement of tumoral vasculature. General anesthesia for tumor excision or shunt placement carries a number of conflicting concerns. In addition to the usual problems encountered in anaesthetizing pregnant patients, attention must be given to the prevention of elevations in intracranial pressure. Several authors have reported successful fetal outcomes after neurosurgery in such patients with the use of simple measures such as lidocaine and mannitol to control intracranial pressure accompanied by, when feasible, fetal echocardiographic monitoring [10,45].

Cardiac surgery for decompensated valve disease, coronary artery bypass grafting, atrial myxomata, and aortic dissection has been carried out safely in pregnant patients without fetal loss. Maternal mortality is low in this context,

no higher than that in nonpregnant patients and related to the severity of the underlying cardiac disease rather than pregnancy per se. Because of this, surgical intervention is undertaken before patients develop New York Heart Association class IV disability when possible. Fetal mortality is an issue but appears to be decreasing with improved techniques. Extracorporeal circulation causes profound derangements of multiple systems with alterations in coagulation, release of vasoactive mediators, activation of the complement system, air and particulate embolization, hypothermia, hypotension, and nonpulsatile flow. Despite limited experimental data, it appears that fetal outcome may be optimized by intervention before the development of NYHA class IV disease and by the use of normothermic, high-flow, high-pressure extracorporeal circulation. Hyperoxia should be maintained, and a hematocrit level higher than 25% is advised [46,47].

5. Conclusion

Successful outcomes after anesthesia administration for nonobstetric surgery in pregnant patients are dependent on comprehensive preoperative assessment, meticulous attention to detail in relation to maternal and fetal physiology perioperatively, and ongoing supportive care in the postoperative period. Maintenance of maternal stability, optimal timing of surgery, and appropriate selection of anesthetic technique are essential.

Although the chief goal in the management of anesthesia is maintenance of uteroplacental perfusion, the role of a multidisciplinary team in the care of high-risk parturient patients cannot be underestimated. Newer surgical techniques have implications for anesthesiologists, and close attention to maternal and fetal parameters is essential to ensure successful outcomes during nonobstetric surgery in pregnant patients. Close communication, especially in relation to timing of surgery and surgical techniques used during the course management, is essential.

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