CHAPTER 3

ANESTHESIA MANAGEMENT IN PREGNANCY

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INTRODUCTION

Pregnant patients applying for any non-obstetric surgery during the course of their pregnancy present a number of challenges for anesthesiologists. A detailed insight into fetal and maternal physiology, changes in several systems, pharmacokinetics and pharmacodynamics are needed for an ideal anesthesia management.

Optimum anesthesia in pregnancy aims to reduce the risks of preterm labour while at the same time. This can be achieved with a multidisciplinary approach with the involvement of surgeons, anesthesiologists, and obstetricians. Maternal and fetal outcomes become successful depending on the skilled and experienced management of surgical disease and anesthetic management. In this chapter, anesthesia management in pregnancy is discussed from all aspects.

EPIDEMIOLOGY

The incidence of non-obstetric surgical procedures needed during pregnancy is between 0.75% and 2.0%. These operations are carried out during the first trimester by 42%, during the first trimester, in the second trimester by 35% and during the third trimester by 23% (1). The higher frequency of surgical procedures during the first trimester might be due to the fact that pregnancy might be not noticed at the time of the surgical operation.

The percentage of non-obstetric surgery performed during pregnancy is similar to the percentage of the general population. The most commonly performed non-obstetric procedure during pregnancy is appendectomy with 1 per 1500-2000 pregnancies followed by cholecystectomy with 1-8 per 10000 pregnancies (2). In addition, surgery may also be needed for detection and intervention to numerous

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ovarian pathologies and the laparoscopic method is now used as the gold standard for these procedures (3). Adnexal masses detected during pregnancy are malignant between 1-8 %. Some other conditions such as ruptured ovarian cysts and torsion are commonly seen during pregnancy and require surgical intervention (4). Physiological demands of pregnancy in susceptible pregnant women, can lead to aortic dissection and cardiac valvular disease. In addition, central nervous system lesions may require surgery to reduce life-threatening elevation in intracranial pressure (5).

PHYSIOLOGICAL CHANGES IN PREGNANCY

Pregnant women undergo well-established physiological adaptations to pregnancy. The first changes are hormone-induced, while the later changes have resulted from mechanical effects of the enlarging uterus, low resistance placental circulation, and increased metabolic demands of the fetus. There is a 60% increase in oxygen demand and mechanical displacement of the abdominal organs leads to a reduction in residual volume. The increased O_2 consumption and increased minute ventilation decreases tidal volume by about 40%, which increases PO_2 during apnea (6). Significant changes occur during pregnancy in several systems including respiratory, cardiovascular, gastrointestinal and central venous systems. The combined changes in physiological factors during pregnancy predispose the pregnant woman to higher risk when general anesthesia is performed and thus, local or regional anesthesia is more suitable when it is possible. The most clinically relevant changes in these systems during pregnancy are discussed below briefly.

CHANGES IN RESPIRATORY SYSTEM

Alterations in the respiratory system during pregnancy are of particular interest for anesthesiologists. The changes in the respiratory system put the pregnant woman at risk of developing rapid desaturation and hypoxemia (7). Airway management becomes increasingly demanding with the progression of pregnancy due to increased body weight, enlarged breasts, short neck, nasopharyngeal edema and capillary engorgement (8, 9). Functional capacity decreases by approximately 20%.

Decreased functional capacity and increased oxygen consumption make the pregnant woman prone to hypoxia (10). Because hypercarbia or low carbon dioxide will compromise uteroplacental perfusion, physiological mild alkalosis should be maintained during artificial ventilation (11).

CARDIOVASCULAR SYSTEM CHANGES

Plasma volume increases by 45% and a state of hypercoagulopathy occurs. Heart rate, stroke volume and cardiac output increase during pregnancy. During the second trimester, maternal cardiac output increases by 50% and peaks by the end of the trimester. This is thought to be resulted from a combination of stroke volume (30%) and increased heart rate (25%). Estrogen and progesterone in the circulation lead to a decreased systemic vascular resistance as a result of a reflex response in the heat rate. In addition, systemic vascular resistance decreases (12). The enlarged uterus leads to compression of the aorta and inferior vena cava, resulting in hypotensive syndrome. The risk of caval compression increases and thus, it is important to use a left lateral tilt position. Pregnant women are more susceptible to thromboembolic complications and therefore appropriate prophylactic measures such as administration of low-molecular weight heparin should be taken (13).

GASTROINTESTINAL CHANGES

The enlarged uterus leads to an increase in intragastric pressure. The risk of gastric regurgitation increased due to the combination of decreased lower esophageal sphincter tonus and increased gastric acid secretion. To reduce gastric secretion and increase gastric pH, acid aspiration prophylaxis is recommended (14).

In early pregnancy, gastric emptying remains the same. With the progression of pregnancy, higher intra-abdominal pressure and decreased pressure of the lower esophageal sphincter may increase the risk of aspiration. Although gastric emptying time is not prolonged during pregnancy, overall gastrointestinal time is prolonged (15).

It is recommended to administer prophylaxis against aspiration pneumonitis from 16 weeks gestation to pregnant women undergoing general anesthesia. Some anesthetists may prefer to give a prokinetic such as metoclopramide.

CENTRAL NERVOUS NERVE SYSTEM CHANGES

The depression of the central nervous system is seen due to increased progesterone levels. Enlarged epidural venous plexus reduces the epidural space capacity. Pregnancy is associated with decreased alveolar levels of volatile anesthetics and a higher sensitivity to local anesthetics (16). The minimum alveolar volatile agents levels decrease in pregnant women by 30%.

By the same way, neural tissues exhibit increased sensitivity to the influences of local anesthetics agents. Both toxic and therapeutic plasma levels of these agents decrease down to nearly 30% during the course of pregnancy (5).

The autonomic nervous system has two-stage hemodynamic changes to these decreases. The increased blood volume leads to decreased sympathetic activity during and shifting toward increased vagal tone and during the first trimester. A gradual shift occurring in the second trimester causes an increase in sympathetic activity in the third trimester.

PRE-ANESTHETIC ASSESSMENT

Regardless of the gestational period, the most important step is a thorough pre-operative assessment. Verbal reassurance is usually preferred to pharmacological pre-medication. Preanesthetic evaluation should always involve close collaboration with the obstetricians and should include an ultrasound examination of the fetus when delivery is closed. Neonatologists also should be engaged in the consultation. During these discussions, gestational age should be noted and the possibility of preterm labour and miscarriage should be addressed. Numerous signs and symptoms that are often related to cardiac diseases such as dyspnea, peripheral edema, heart murmurs, are commonly faced symptoms during normal pregnancy, but can be confusing for the anesthesiologists regarding suspicion of underlying comorbidity (17).

Alterations in ECG during pregnancy include nonspecific ST and T-wave changes, premature beats, and left axis deviation. Fetal exposure should be minimized during a radiological examination. Outcomes of the relevant biochemical tests should be ready at hand and blood must be available for all surgeries for urgent need of transfusion If required, resuscitation must be carried out in accordance with the principles of the advanced trauma life support (ATLS) or advanced life support (ALS) or protocols. In order to avoid supine hypotension, the resuscitation procedure should be performed in the left lateral tilt position.

Particular attention must be paid to airway examination because pregnant women have edema of the airway as a result of the hormonal impact. Edema and breast engorgement can lead to difficulties during bag-mask ventilation and laryngoscopy. In such cases, nasal intubation should be avoided and small-size tubes should be preferred. Pre-oxygenation with 100% oxygen for 3-5 minutes will enable airway securing under general anesthesia, which should be performed through rapid sequence induction and intubation (17). However, in the case

of failed intubation, a laryngeal mask airway is used successfully to reverse Trendelenburg's position for a short time safely and for ventilation.

Premedication should include aspiration of prophylaxis such as metoclopramide, sodium citrate or ranitidine. To prevent stress on the mother and fetus, analgesia should be administered when appropriate. Because premature closure of ductus arteriosus can occur, NSAIDs should be avoided. In this condition low-dose aspirin appears to be safe. Deep venous thrombosis prophylaxis should always be considered. Considering the duration of gestation and type of surgery, analgesics and sedatives should be used reasonably (18).

MATERNAL CONSIDERATIONS

American College of Obstetricians and Gynecologists' Committee on Obstetric Practice recommends that regardless of trimester, pregnant women should not be denied indicated surgery. Physiological changes in pregnancy and the effects of drugs on mothers should be well-understood. Maternal physiology changes in the second trimester with the impact of the hormonal activities including increasing progesterone production and metabolic demands, and from the second trimester due to the mechanical effects of the enlarging uterus. Positioning of the mother during anesthesia is of crucial importance, because even small changes in maternal position can have significant hemodynamic effects.

A positive pressure ventilation should be utilized with caution and $ETCO_2$ values should be maintained within the normal limits. Because there is a good correlation between $PaCO_2$ and $ETCO_2$ and in pregnancy, $ETCO_2$ can be used as a guide in ventilation of pregnant patients (19).

FETAL CONSIDERATION

Fetal heart rate can be monitored continuously from the 18th week of gestation. This may be limited in cases of maternal obesity or abdominal surgery. An experienced specialist should monitor fetal heart monitoring during surgery and anesthesia. In fact, continuous fetal monitoring is essential as maternal hemodynamic stability is not always an indicator of fetal well-being.

Anesthetic agents reduce both reference fetal heart rate and its variability, and thus readings must be interpreted taking into account the anesthetic agents administered. The benefits of intraoperative fetal heart monitoring include detection of early compromise, position adjustment, or hyperventilation (20).

DRUGS DURING PREGNANCY

Pharmacology

Drug administration must be titrated as pharmacokinetics and pharmacodynamics change in pregnancy. Pregnancy increased the distribution volume. The doses of local anesthetic agents are reduced because of changes in plasma protein binding (21).

However, changes in pharmacodynamics and pharmacokinetics are heterogenous and reflect pregnancy-related changes in all organ systems. Neuromuscular blocking agents indicate the complexity of these pregnancy-related alterations.

Between the 15th and 56th days of gestation, the human embryo is most susceptible to the teratogenic effects of drugs (22). The Swedish Catalogue of Registered Pharmaceutical Specialities (FASS) has given codes to the most drugs used in medicine and anesthesia since 1978. These codes serves as a guide to choose drugs appropriately regarding their effects on uteroplacental blood flow, the placenta, and the fetus. Studies have reported that problems include a higher risk of abortion, low birth weight and growth restriction resulting from the surgical procedure itself and not from exposure to anesthesia. Today, there is a consensus that benzodiazepines are not teratogenic and a single dose appears to be safe. However, regular use of these agents particularly in the first trimester should be avoided because of the risk of developing cleft palate (23).

Nitrous oxide

Nitrous oxide is known as a teratogen in mammals, which rapidly crosses the human plasma (24). The teratogenicity of nitrous oxide is believed to be resulted from its oxidation with vitamin B12, which cannot function for the enzyme methionine synthetase in this case. Thymidine, which is a subunit of DNA requires methionine synthetase. Nitrous oxide is not associated with congenital abnormalities in humans (25).

Benzodiazepines

Benzodiazepines exert their effects by the inhibition of gamma-aminobutyric acid (GABA) receptors in the central nervous system. GABA has been proven to cause cleft palate formation. In human retrospective studies, it has been found that there was an association between diazepam ingestion in the first 6 weeks of pregnancy and cleft palate (26).

Classification of Anesthetic Agents

The United States of America published category ratings of specific anesthetic agents in 2015. Accordingly, the following classification of drugs has been made:

- **Category A: No risk.** Well-controlled studies in humans have not shown a risk to the fetus.
- **Category B: No evidence of risk in humans.** While animal studies have found a risk, human studies have not.
- **Category C: Risk can not be ruled out.** Human studies have not been adequately performed and potential benefits may justify the risk.
- **Category D: Potential evidence of risk.** Confirmed evidence of human risk.
- **Control X: Contraindicated in pregnancy.** Human and animal studies have clearly demonstrated that fetal risk that clearly overweighs the benefit to the patient in the use of Control X.

A list of anesthetic agents according to the above classification is given in Table 1.

Table 1. Risk classification of Anesthetic Agents

Anesthetic Agents	Classification	Anesthetic Agents	Classification
Induction agents		**Opioids**	
Etomidate	-C-	Alfentanyl	-C-
Ketamine	-C-	Fentanyl	-C-
Methohexital	-B-	Sufentanyl	-C-
Propofol	-B-	Meperidine	-B-
Thiopental	-C-	Morphine	-C-
Inhaled agents		**Benzodiazepines**	
Desflurane	-B-	Diazepam	-D-
Enflurane	-B-	Midazolam	-D-
Halothane	-C-		
Isoflurane	-C-	**Neuromuscular blocking agents**	
Sevoflurane	-B-	Atracurium	-C-
Local anesthetics		Cisatracurium	-B-
2-chloroprocaine	-C-	Curare	-C-
Bupivacaine	-C-	Mivacurium	-C-
Lidocaine	-B-	Pancuronium	-C-
Ropivacaine	-B-	Rocuronium	-B-
Tetracaine	-C-	Succinylcholine	-C-
		Vecuronium	-C-

TERATOGENICITY OF ANESTHETIC DRUGS

Any significant alteration in the function or form of an infant due to prenatal treatment is referred to as teratogenicity (5). The teratogenicity of a drug is dependent on the several factors depicted in Figure 1.

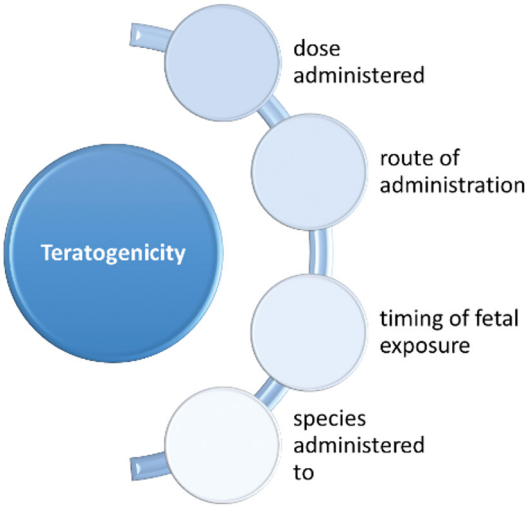

Figure 1. Factors affecting teratogenicity

Perioperative events that cause hypoxemia and hypotension pose the greatest risk for the fetus. Any agent, which produces sufficient exposure during the developmental stage can be teratogenic. The impact of any drug will depend on the week of gestation and the dose ingested. Whereas a small dose given in an early period may have significant adverse effects on the embryo, a large dose of a small drug might not have any impact on the fetus at an advanced stage. Studies have shown that a supra-clinical drug does not necessarily indicate that a short exposure will produce a significant risk in clinical practice. The majority of iatrogenic changes occur during the period of organogenesis, which involves 31th to 71th days.

Some polar molecules including neuromuscular blocking agents can not cross the placenta in considerable amounts. Fetal blood concentration is 10-20% of maternal levels. The correlations between craniofacial defects and diazepam have been well-addressed in the literature (27). Surveys that investigated outcomes in

women who underwent surgery during their pregnancy suggested the risks of increased frequency of low-birth-weight, abortion, growth restriction, but did not show increased i congenital abnormalities (28).

ANESTHESIA MANAGEMENT

In pregnant women, non-obstructive surgeries have been performed successfully with regional and general anesthesia. So far, there is no study showing the superiority of an anesthetic technique over others in terms of fetal outcomes. Regional anesthesia prevents the risk of failure in intubation and aspiration. Careful maintenance of maternal hemodynamics and oxygenation during surgery and anesthesia is the best way to monitor fetal well-being. monitoring of fetal responses to maternal surgery and anesthesia is also strongly recommended (29).

Prophylaxis for aspiration pneumonitis should be administered with H_2-receptor antagonists from the 16th gestational week. From the 16th week, pregnant patients should be considered at risk for developing aspiration pneumonitis. In order to ensure uterine displacement, positioning must be made as a left lateral tilt. Alteration in maternal position intraoperatively can have significant hemodynamic effects and thus, Trendelenburg position should be carried out with attention during anesthesia. Although endotracheal intubation is necessary, in pregnant women with failed intubation, laryngeal mask airways have been successfully used in order to provide adequate ventilation.

Maintenance of general anesthesia is usually provided using volatile anesthetic agents such as air/oxygen or N_2O/O2 mixture. There is no study supporting concern regarding the use of N_2O/O_2 mixture in clinical practice. $ETCO_2$ levels should be maintained within the normal ranges seen in pregnancy, and positive pressure ventilation should be used carefully in these patients. CO_2 diffusion gradient from fetal blood to maternal blood is limited by the maternal hypercarbia, increasing the risk for fetal loss. Therefore, arterial blood gas analysis should be performed during laparoscopic surgery. Therefore, in this case pregnant women should be extubated fully awake in the lateral position until protective airway reflexes return to normal.

FIRST TRIMESTER CONSIDERATIONS

Elective surgery should not be performed during the whole pregnancy period. Only tubal ligation should be permitted during the first six gestational weeks

in order to allow physiological changes of pregnancy to resolve. If it is possible, surgery should be postponed until the second trimester to reduce the risk of physiological changes (30).

Many women receive intravenous sedation and anesthesia for IVF. The anesthesia method used should not interfere with early development of the embryo. The use of propofol should always be supervised by an anesthetist, because it requires continuous monitoring. Animal studies have shown that nitrous oxide should be avoided, because it is a potent inhibitor of methionine synthase. Fetal well-being should be checked-up by Doppler before and after anesthesia and surgery. Regional anesthesia should be preferred over general anesthesia due to the increased risk of difficult intubation ,acid aspiration, hypoxemia, risk to the fetus (31).

COMPLICATIONS IN OBSTETRIC ANESTHESIA

In obstetric anesthesia, patients' expectations are high, and many interventions performed by anesthetists are carried out emergently or urgently. The complications encountered during obstetric anesthesia are not unique to this field of medicine, but physiological and anatomical changes during pregnancy can affect the frequency of adverse events. Some commonly faced complications during anesthesia in pregnancy are listed below:

- Inadequate block for cesarean section
- Nerve injury
- Accidental awareness under general anesthesia
- Post-dural puncture headache
- Failed tracheal intubation
- Aspiration

POSTOPERATIVE CONSIDERATIONS

After the postopertative first week The frequency of premature labour is not higher in pregnant women undergoing surgery compared to those who do not undergo (32). However, the routine application of prophylactic tocolytics is controversial in this condition. Since postoperative pain has been shown to increase the risk of premature termination, adequate analgesia is crucial in this period (33).

Postoperative venous stasis further increases the risk of thromboembolic disease. For this reason, the application of thromboprophylaxis with heparin is necessary in this case. Studies have reported that low-molecular weight heparins are as effective as unfractionated heparins during pregnancy (34).

CONCLUSION

In pregnant patients, successful outcomes depend on detailed preoperative assessment, close monitoring of the maternal and fetal physiology perioperatively, and continuous supportive care in the postoperative period. Optimal timing for surgery, appropriate selection of anesthetic techniques, and maintaining maternal stability are essential for successful anesthesia management. In addition, close communication between multidisciplinary teams involving surgeons, anesthetists, and neonatologists is one of the key points to successful outcomes.

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