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Anaesthetic considerations for non-obstetric surgery during pregnancy

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Editor's key points

- Anaesthetic management of pregnant patients requires balanced consideration of both maternal and fetal physiology and pharmacology.
- Potential and real adverse effects dictate avoidance of general anaesthesia when possible.
- Tailored approaches are necessary in managing pregnant patients for cardiac, neuro-, and laparoscopic surgery.

Summary. Surgery during pregnancy is complicated by the need to balance the requirements of two patients. Under usual circumstances, surgery is only conducted during pregnancy when it is absolutely necessary for the wellbeing of the mother, fetus, or both. Even so, the outcome is generally favourable for both the mother and the fetus. All general anaesthetic drugs cross the placenta and there is no optimal general anaesthetic technique. Neither is there convincing evidence that any particular anaesthetic drug is toxic in humans. There is weak evidence that nitrous oxide should be avoided in early pregnancy due to a potential association with pregnancy loss with high exposure. There is evidence in animal models that many general anaesthetic techniques cause inappropriate neuronal apoptosis and behavioural deficits in later life. It is not known whether these considerations affect the human fetus but studies are underway. Given the general considerations of avoiding fetal exposure to unnecessary medication and potential protection of the maternal airway, regional anaesthesia is usually preferred in pregnancy when it is practical for the medical and surgical condition. When surgery is indicated during pregnancy maintenance of maternal oxygenation, perfusion and homeostasis with the least extensive anaesthetic that is practical will assure the best outcome for the fetus.

Keywords: non-obstetric surgery; obstetric anaesthesia

Non-obstetric surgery during pregnancy is not uncommon and can have excellent outcomes with proper planning. Between 0.75% and 2% of pregnant women require non-obstetric surgery. In the USA, ~75 000 pregnant women undergo non-obstetric surgery each year.[1] The most common indications not related to pregnancy are acute abdominal infections (acute appendicitis incidence 1:2000 pregnancies and cholecystitis 6:1000 pregnancies), maternal trauma, and surgery for maternal malignancy.[2]

Surgery can be required during any stage of pregnancy depending on the urgency of the indication. In the largest single series concerning surgery and anaesthesia during pregnancy, 42% of surgery during pregnancy occurred during the first trimester, 35% during the second trimester, and 23% during the third.[3] When caring for pregnant women undergoing non-obstetric surgery, safe anaesthesia must be provided for both the mother and the child. Thorough understanding of the physiological and pharmacological adaptations to pregnancy is required to insure maternal safety. Fetal safety requires avoidance of potentially dangerous drugs at critical times during fetal development, assurance of continuation of adequate uteroplacental perfusion, and avoidance and/or treatment of preterm labour and delivery.[4]

Physiological changes of pregnancy

The pregnant woman undergoes well-known physiological adaptations to pregnancy. The earliest of these changes are hormonally driven, while changes that occur later in pregnancy are associated with mechanical effects of the enlarging uterus, increased metabolic demands of the fetus, and the low resistance placental circulation.

Some of the most noteworthy changes are in the respiratory system, which include a 20% increase in oxygen consumption and a 20% decrease in pulmonary functional residual capacity both of which contribute to the rapid decrease in maternal Pa_{O_2} that is observed even during

brief apnoea.[5] Maternal obesity, pre-eclampsia, or both can accentuate the risk of hypoxaemia associated with induction of and emergence from general anaesthesia. Other respiratory changes include mild maternal hyperventilation mediated by progesterone-enhanced brainstem sensitivity to Pa_{CO_2}. This effect is counteracted in the anaesthetized patient by greater central nervous system sensitivity to general anaesthetics.

Airway changes include swelling and friability of oropharyngeal tissues that contribute to a reduced size of the glottic opening. These changes are most pronounced near the end of pregnancy but can be present from the mid-second trimester onwards. Physiological changes in the maternal airway during pregnancy can lead to difficulty in ventilating and intubating the trachea of the unconscious pregnant patient. In a study of 1500 parturients undergoing Caesarean section with general anaesthesia, Rocke and colleagues[6] calculated the relative risk of difficult intubation in women with Mallampati class III and IV airways to be 7.5 and 11.3 compared with those with class I airways. The authors concluded that Mallampati classification is more predictive of difficult intubation in pregnancy than in non-pregnant women. Pilkington and colleagues photographed oral airway exams in 242 pregnant women and found that from 12 to 38 weeks of gestational age, the incidence of class IV airways increased by 34%. These findings were also correlated with maternal weight gain.[7] The higher incidence of failed intubation during induction of anaesthesia in pregnant women has been debated in the literature. Clearly not all pregnant women are difficult to intubate. Several audits have evaluated the rate of failed intubation in pregnant patients. There is some concern that as the field has moved away from routine general anaesthesia in pregnancy, the incidence of failed intubation has risen.[8–12] Whether or not failed intubation is becoming more frequent, the loss of airway control is the most common cause of anaesthesia-related maternal mortality.[13] Steps to decrease the risk of maternal airway loss during anaesthesia include increased use of regional anaesthesia, better clinical training with simulation, well-rehearsed airway emergency algorithms with ready availability of advanced airway devices, and experienced anaesthesia personnel available on labour floors at all times.[14]

Haemodynamic changes during pregnancy include a 40–50% increase in blood volume and cardiac output and a 20% reduction in haematocrit due to dilution.[15] Physiological anaemia begins during the first trimester of pregnancy and is most extreme in the mid-second trimester after which it is mitigated to some extent by enhanced red blood cell production if iron stores are adequate.[16] Aortocaval compression is of concern to the anaesthesiologist during and after the second trimester.[17 18] Particularly, in the presence of neuraxial anaesthesia, the supine position can predispose the mother to hypotension, especially after the 20th week of gestation. In addition, the growing uterus can lead to reduced venous return from the lower extremities predisposing to pedal oedema and increasing the already elevated risk for deep vein thrombosis. These considerations underscore the need for left uterine displacement in later pregnancy during surgery and anaesthesia.[14]

Table 1 Drugs associated with teratogenicity

ACE inhibitors	Valproic acid
Alcohol	Lithium
Androgens	Phenytoin
Antithyroid drugs	Streptomycin
Carbamazapem	Tetracycline
Chemotherapy agents	Thalidomide
Cocaine	Trimethadione
Warfarin	Diethylstilbestrol

The risk of gastric contents aspiration is increased in pregnancy. Although gastric emptying has recently been shown to be normal during pregnancy and right before labour, the risk of aspiration is still increased because of reduced pressure at the level of the lower oesophageal sphincter.[19–21] After 20 weeks of gestation, caution regarding the unprotected airway should be exercised. For maternal airway protection and to reduce the exposure of the fetus to general anaesthetic drugs, regional anaesthesia is preferred when possible. When general anaesthesia is required, a mask or laryngeal mask airway should be used only judiciously in carefully chosen patients. A history of active reflux or obesity adds additional risk for regurgitation and aspiration which can cause a life-threatening event or simply increase the risk of postoperative pulmonary infection. It is incumbent on the anaesthetist to protect the high-risk airway in the best way possible during general anaesthesia, especially in pregnancy.[22]

Teratogenicity of anaesthetic drugs

Anaesthetic drugs affect cell signalling, mitosis, and DNA synthesis,[23–25] which are involved in cellular differentiation and organogenesis. As such, any drug given during pregnancy could potentially negatively affect the development of the fetus depending on the dose administered, the route of administration, and the timing of exposure with respect to development (Table 1). Concerns about anaesthetic effects on the developing human fetus have been considered for many years. Despite years of animal studies and observational studies in humans, no anaesthetic drug has been shown to be clearly dangerous to the human fetus and there is no optimal anaesthetic technique. The search for a clear answer is hampered by the fact that it would not be ethical to conduct a randomized trial on pregnant patients and no animal model perfectly mimics human gestation.

Timing of exposure is crucial because during the first 15 days of human gestation, an all-or-nothing phenomenon occurs: the embryo is typically lost or preserved fully intact. Tuchmann-Duplessis[26] in the 1960s found that major congenital malformations were most likely to occur from exposures between days 13 and 60 in human embryos. Multiple case–control studies have investigated the risk for birth defects in

the offspring of women who had surgery and anaesthesia during pregnancy. While the anaesthetic drugs used and the stage of gestation varied, overall no study has shown excess birth defects in children of women who underwent surgery during pregnancy, but most have shown a small increase in the risk of miscarriage or preterm delivery.[3 27 28] It is not possible from these studies to conclude whether the increase in risk of preterm delivery is related to the anaesthesia, surgery, or the condition that compelled the surgery. However, the enhanced risk of preterm labour after abdominal and pelvic surgeries suggests that mechanical perturbation, local inflammation, or both are risk factors.[29]

The largest retrospective study of exposure to surgery and anaesthesia in pregnancy was conducted by Mazze and Källén[3] in which they evaluated data from three Swedish health-care registries for the years 1973–1981. Of 720 000 pregnant women, 5405 (0.75%) had non-obstetric surgery, including 2252 who had procedures during the first trimester. Of women who had surgery, 54% received general anaesthesia, which included nitrous oxide in 97% of cases. There was no difference between surgical and control patients with regard to the incidence of stillbirth or the overall incidence of congenital anomalies. However, there was an increased incidence of low birth weight (<1500 g), as a result of prematurity and intrauterine growth restriction in the surgical group and an increased rate of neural tube defects with exposure in the first trimester. Clearly, only necessary surgery should be done during pregnancy. When possible, a regional technique is preferred due to consideration of the maternal airway and limiting fetal drug exposure.

Nitrous oxide affects DNA synthesis and has teratogenic effects in animals.[30] Case–control studies in the 1970s suggested a link between occupational exposure to nitrous oxide in early pregnancy with pregnancy loss and birth defects. These studies were highly confounded and the quantity of exposure was not known. Two studies have made a more convincing link between exposure to unscavenged nitrous oxide and reduced fertility in medical personnel.[31 32] A secondary analysis of this data set analysed by Rowland and colleagues in 1992 also identified an increased risk of spontaneous abortion with exposure to unscavenged nitrous oxide in the dental setting.[33] Modern scavenging techniques can reduce exposure to nitrous oxide by more than 90%. Several studies of nitrous oxide exposure in modern hospital settings with scavenging systems in place have failed to show an association between nitrous oxide use and adverse pregnancy outcome.[34 35]

Small case–control studies of benzodiazepine use in pregnancy suggested an association with cleft palate and cardiac anomalies; however, more recent, better controlled studies have refuted this association.[36 37] Most other anaesthetic medications, including propofol, barbiturates, opioids, neuromuscular blocking agents, and local anaesthetics have a good safety record for use during pregnancy. However, subtle associations cannot be ruled out. A recent meta-analysis evaluated 54 of 4052 publications that met their inclusion criteria, which included 12 452 women having surgery during pregnancy. They found (i) that maternal mortality was less than 1/10 000, (ii) non-obstetric surgery did not increase the risk of major birth defects, and (iii) surgery and general anaesthesia were not major risk factors for spontaneous abortion; (iv) however, acute appendicitis with peritonitis posed a risk for fetal loss.[38]

Recent studies showing accelerated neuronal apoptosis in immature rodent brains exposed to anaesthetic agents with associated behavioural anomalies in the offspring has raised considerable concern about the standard practice of anaesthesia.[39 40] Most commonly, administered anaesthetic agents have either *N*-methyl-D-aspartate (NMDA)-type glutamate receptor blocking or γ-aminobutyric acid (GABA) receptor-enhancing properties. NMDA and GABA receptors are widely distributed throughout the central nervous system and are necessary for neuronal synaptogenesis, differentiation, and survival during development.

Although evidence for anaesthetic-induced neuronal apoptosis in rodents is convincing, it is less clear that these data can be extrapolated to humans.[41–43] Peak vulnerability to anaesthetic-induced apoptosis in animals coincides with a period of vigorous brain development and activity-dependent synaptogenesis. General anaesthetic drugs inhibit synaptic transmission.[44] Reduced synaptic activity at a critical period could result in inappropriate apoptosis and abnormal developmentally important synaptic connections. However, this phase of rapid synaptogenesis occurs in rodents shortly after birth, but in humans, it extends from mid-gestation to several years after birth. The extended period of synaptogenesis in humans could confer protection against persistent behavioural effects of perinatal anaesthetic exposure because the duration of anaesthetic exposure is only for a brief fraction of the vulnerable period. From a developmental perspective, exposing an infant rat to isoflurane for 6 h is roughly the equivalent of producing general anaesthesia for several weeks in a human neonate.

Avoidance of fetal asphyxia

Consulting perioperative physicians commonly concludes with a recommendation to avoid hypoxia and hypotension. While this imperative is a foundation of anaesthetic practice, it is particularly important to the maternal–fetal unit during non-obstetric surgery. Short periods of mild hypoxaemia are well tolerated,[45] but prolonged or serious maternal hypoxaemia causes uteroplacental vasoconstriction and decreased uteroplacental perfusion that can result in fetal hypoxaemia, acidosis, and death.[46] Maternal hypercarbia directly results in fetal respiratory acidosis. Severe fetal respiratory acidosis causes myocardial depression. Hypercapnia also causes uterine artery vasoconstriction and reduced uterine blood flow.[47] Similarly, hypocapnia results in reduced uterine blood flow and can ultimately cause fetal acidosis.

Maintenance of normal maternal systemic arterial pressure is of great importance because of the relative passive dependence of the uteroplacental circulation. Under normal circumstances, the spiral arteries are maximally dilated.[48] As such a

reduction in maternal arterial pressure causes reduced uteroplacental blood flow and fetal ischaemia. Except under unusual circumstances such as severe maternal renal or cardiac disease, i.v. fluid administration can be generous and appropriate to the surgical blood loss requirements. Contrary to past recommendations, both ephedrine and phenylephrine are considered safe and effective pressors for control of maternal arterial pressure during pregnancy.[49] For decades, ephedrine was the drug of choice for the treatment of maternal hypotension based on classic studies in sheep that suggested deleterious effects of pure α-adrenergic agonists on uteroplacental blood flow.[50] However, multiple clinical trials conducted in the 1990s and early twenty-first century[51–54] have demonstrated that phenylephrine or other α-agonists (e.g. metaraminol) are safe and generally more effective than ephedrine alone to prevent maternal hypotension and its sequelae (e.g. nausea and vomiting). Furthermore, ephedrine use is associated with lower neonatal pH and a higher incidence of neonatal acidosis than the use of phenylephrine or other pure α-agonists.[55]

Fetal monitoring

From 18 to 22 weeks, fetal heart rate monitoring is practical, and from 25 weeks, heart rate variability can be readily observed. Outcome data supporting continuous monitoring in normal delivery are not yet available. Nevertheless, the American College of Obstetrics and Gynaecology Committee opinion on 'Non-Obstetric Surgery in Pregnancy' states that 'although there are no data to support specific recommendations regarding non-obstetric surgery and anaesthesia in pregnancy, it is important for non-obstetric physicians to obtain obstetric consultation before performing non-obstetric surgery. The decision to use fetal monitoring should be individualized and each case warrants a team approach for optimal safety of the woman and her baby'.[56] All general anaesthetic drugs cross the placenta to some extent at equilibrium conditions. In the setting of general anaesthesia, loss of fetal heart rate variability is not always an indicator of fetal distress, but may simply be an indication of expected anaesthetic effects on the fetal autonomic nervous system. Slowing of the fetal heart rate in the operative setting is more concerning for fetal hypoxaemia and acidosis, but could also be related to a decrease in temperature, maternal respiratory acidosis, or the administration of drugs, anaesthetic agents, or both, which tend to slow the heart rate.[57]

Cardiac surgery

The cardiovascular changes of pregnancy include a 30–50% increase in blood volume and cardiac output. These effects peak at 24–28 weeks of gestation and are maintained until parturition when even greater alterations can be observed. Thus, patients with pre-existing cardiac disease are exposed to major cardiac stress in the second and third trimesters through delivery. Although pregnant patients with heart disease are usually managed with medical therapy, in some settings, those with severe decompensation and surgically correctable lesions might come to surgery, in particular those with severe mitral or aortic valvular obstruction.[57 58] New techniques in percutaneous cardiac intervention create the potential for valvular repair during pregnancy. Percutaneous balloon valvuloplasty seems to be a better alternative than surgical repair and is associated with a significant reduction in fetal and neonatal mortality.[59–61]

Table 2 Factors important during cardiopulmonary bypass in maternal cardiac surgery

High pump flows (30–50% increase over non-pregnant state)
Mean arterial/perfusion pressure >65 mm Hg for optimal uteroplacental perfusion
Haematocrit >28%
Limit hypothermia (<32°C associated with higher fetal mortality)
Monitor fetal heart rate continuously
Optimize acid–base, glucose, Pa_{O_2}, and Pa_{CO_2}

The use of cardiopulmonary bypass increases perioperative risk, particularly for the fetus. Factors related to cardiopulmonary bypass that can adversely affect fetal oxygenation include non-pulsatile perfusion, inadequate perfusion pressures, inadequate pump flow, embolic phenomena to the uteroplacental bed, and the release of renin and catecholamines.[57] The use of intraoperative fetal monitoring can decrease the high fetal mortality rate. During cardiopulmonary bypass, a high pump flow (>2.5 litre min^{-1} m^{-2}) and perfusion pressure (>70 mm Hg) are recommended to maintain uteroplacental blood flow.[15] It is recommended that the maternal haematocrit be maintained >28% to optimize oxygen-carrying capacity.[62 63] Normothermic bypass might be beneficial to the fetus. In one series, fetal mortality was 24% with hypothermic compared with 0% with normothermic cardiopulmonary bypass,[58 64] which is recommended when feasible.[64] Although controversial, pulsatile flow might also better preserve uteroplacental blood flow.[65] Finally, changes in P_{CO_2} also affect uteroplacental blood flow. Specifically, hypocapnia causes uteroplacental vasoconstriction, and hypercapnia increases uteroplacental blood flow but is associated with fetal acidosis and reduced cardiac function. During hypothermic cardiopulmonary bypass, acid–base disturbances can be more pronounced and there is no consensus regarding pH management during pregnancy. It is a good practice to manage pH according to α-stat pH management,[66] or direct measurement of sample pH after warming to 37°C rather than back calculating the pH to the temperature of the patient (pH stat). This might be advantageous for CO_2 homeostasis which is important for uteroplacental blood flow (Table 2).[58 62]

Neurosurgery

Haemorrhage from intracranial saccular aneurysm or arteriovenous malformation is unfortunately not uncommon during pregnancy.[67–69] Although there is no clear correlation

between pregnancy and increased risk of vascular rupture, stress induced by the increased cardiac output, blood volume, and the softening of vascular connective tissue by the hormonal changes of pregnancy could predispose to such an event. The risk of intracranial haemorrhage is increased by hypertensive conditions of pregnancy and their associated risk factors. The usual neurosurgical anaesthetic treatment of these patients can include controlled hypotension, hypothermia, hyperventilation, and diuresis, which must be undertaken carefully in the pregnant patient.

Controlled hypotension can be induced with high-dose volatile anaesthetic, sodium nitroprusside, or nitroglycerin. Each carries its own potential hazards in addition to reduction in uteroplacental blood flow. All of these drugs cross the placenta and can induce hypotension in the fetus.[67] Reduction in systolic arterial pressure of 25–30% or a mean arterial pressure <70 mm Hg generally leads to reduced uteroplacental blood flow. Nitroprusside is converted to cyanide and then to thiocyanate by the hepatic enzyme rhodanase. Cyanide accumulation in the fetus has been observed with significant toxicity and fetal death in pregnant patients treated for long periods 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^{-1} h^{-1}, if maternal metabolic acidosis ensues, or if resistance to the agent is apparent. Inhalation agents (isoflurane and sevoflurane) provide the benefit of being both hypnotic and hypotensive agents at clinical concentrations where they reduce metabolic activity and potentially provide preconditioning. They are used alone or in combination with adjuvant agents to limit tachycardia and rebound hypertension. Nitroglycerin has yet to be associated with adverse fetal effects and can be used as an adjuvant to reduce required doses of nitroprusside. Nitroglycerin is metabolized to nitrites, which have produced methaemoglobinaemia experimentally. Induced hypotension is used less frequently when vascular clips are used proximal to the lesion, so this technique might be considered in the setting of pregnancy to avoid the need for induced maternal hypotension. When induced hypotension is deemed necessary, fetal heart rate monitoring should be used and the period of hypotension.

Hypothermia is occasionally used in neurosurgical anaesthesia to decrease metabolic requirements in the brain and other organs and to reduce cerebral blood flow. The usual goal is to achieve a temperature of 30°C, which will induce similar changes in the fetus and fetal bradycardia. Fetal heart rate will increase again with rewarming.[70 71]

Hyperventilation is commonly used in neuroanaesthesia to reduce Pa_{CO_2} and cerebral blood flow. As a result of increased ventilation during pregnancy, normal Pa_{CO_2} at steady state is 4–4.2 kPa. Although the clinical effects on placental blood flow are arguable, extreme hyperventilation (Pa_{CO_2}<3.3 kPa) can cause uterine artery vasoconstriction and leftward shift of the maternal oxyhaemoglobin dissociation curve. Indeed, prophylactic hyperventilation of head-injured patients to Pa_{CO_2} values <3.3 kPa has been shown to have a negative impact on outcome.[72] However, 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, that is, to a Pa_{CO_2} of 3.3–4.0 kPa. Fetal heart rate monitoring should alert the anaesthesiologist to compromises in fetal condition and adjustments to maternal ventilation should be made accordingly.[67]

Diuresis is often accomplished with osmotic agents or loop diuretics to shrink the brain both intraoperatively and after operation. These can cause significant negative fluid shifts for the fetus. Mannitol given to a pregnant woman slowly accumulates in the fetus, and fetal hyperosmolality leads to physiological changes such as reduced fetal lung fluid production, reduced renal blood flow, and increased plasma sodium concentration.[73] In animal models, a net transfer of water from the fetus to the mother occurs over time, raising concern about fetal dehydration. However, in individual case reports, mannitol in small doses of 0.25–0.5 mg kg^{-1} has been used without ill effect to the fetus and appears safe if required.[74] A loop diuretic provides an alternative but should also be used cautiously with fetal monitoring and only if necessary.

Laparoscopy

There are questions about fetal wellbeing during laparoscopic surgery. Direct fetal and uterine trauma and fetal acidosis from absorption of insufflated carbon dioxide are potential mechanisms of injury. With increased intra-abdominal pressure, maternal cardiac output and uteroplacental perfusion can decrease. Animal data have supported these concerns.[75 76] However, clinical experience, using careful surgical and anaesthetic technique, has been favourable. A comparison of laparotomy and laparoscopy performed in pregnancy in over 2 million pregnancies in Sweden over a 20 yr period found no difference in fetal outcome between the two techniques.[77] Thus, the following guidelines were issued by the Society of American Gastrointestinal Endoscopic Surgeons regarding laparoscopic surgery during pregnancy. Whenever possible, surgery should be deferred to the second trimester. Fetal and uterine status should be monitored and also end-tidal P_{CO_2} and maternal arterial blood gases. An open technique should be used to enter the abdomen. Aortocaval

Table 3 Factors important in maternal laparoscopy

Use an open technique to enter the abdomen
Monitor maternal end-tidal P_{CO_2} (4–4.6 kPa range) with or without arterial blood gas to avoid fetal hypercarbia and acidosis
Maintain low pneumoperitoneum pressure (1.1–1.6 kPa) or use gasless technique
Limit the extent of Trendelenburg or reverse Trendelenburg positions and initiate any position slowly
Monitor fetal heart rate and uterine tone when feasible

compression should be avoided. Finally, low pneumoperitoneal pressure (<1.6 kPa) should be used (Table 3).

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